Pragmatic Trials and Comparative Effectiveness Research (CER)

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Basic Idea

‘The importance of an idea or action lies in whether it makes a difference in everyday life. Ideas or actions that correspond to attractive explanations (e.g., metaphysical theories), but make no difference to outcomes, are problematic.’

– Charles Peirce, Popular Science Monthly, 1878.
Main Difference

• A pragmatic trial is a real-world test in a real-world population, whereas an explanatory trial is a specialized experiment in a specialized population
  – Maclure M. CMAJ 2009;180:1

• Pragmatic does not mean being less rigorous
Formulating a Question: PICOT

- **P:** population or characteristics of the implicated subjects
- **I:** intervention or exposure that the person or population experiences
- **C:** control to which the exposure is compared
- **O:** outcome measures of interest
- **T:** target of the trial (is the intervention better or as good); can also refer to time!
• Among families in a Canadian town, can receiving primary care from a nurse-practitioners (compared to a family physician) produce high levels of physical, social, and emotional function (as good as those achieved by a family physician)?
PICOT question

• P: among families in a Canadian town
• I: can receiving primary care from a nurse practitioner (NP)
• C: compared to a family physician
• O: produce high levels of physical, social and emotional function
• T: as good as those achieved by a family physician – non-inferiority
• Can nurse practitioners produce good health outcomes under IDEAL circumstances
  – Super-special training of the trial nurses, with frequent refresher courses and close monitoring
  – Who are caring for highly compliant patients
  – Who see their patients very frequently, offer long visits and out of hours care etc.
Conclusions from an explanatory trial

• A ‘no’ answer is informative BUT,

• A ‘yes’ answer doesn’t settle the pragmatic issue:
  – Would NPs be effective under the usual circumstances (less intensive training and monitoring, caring for typical patients, and seeing them only during illnesses or for routine preventive care)?
A pragmatic question

• Will NPs produce good health outcomes under usual circumstances?
  – Routine training of the trial nurses with no refresher courses or monitoring
  – Who are caring for typical patients
  – Who are seen only when ill or for routine preventive care
Conclusions from a pragmatic trial

• A ‘yes’ answer is informative BUT,

• A ‘no’ answer does not settle the question:
  – Are NPs not capable or was their training defective, their patients noncompliant, or their patients subjected to an unusually high burden of illness?
• PCTs are not an abandonment of the scientific methods that have led to countless breakthroughs.
• They don’t take away from basic science or diminish the importance of traditional RCTs—we just need a balance.
• No clinical trial is completely explanatory or pragmatic. RCTs and PCTs exist on a continuum.

The RCT-PCT Continuum

- **Explanatory Trial**
  - Can an intervention work under ideal conditions?
- **Pragmatic Trial**
  - Does an intervention work under usual conditions?
Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2)
Lessons from PRECIS (1)

• No trial is completely explanatory or pragmatic

• PRECIS can be used to reliably rate protocols and completed studies

• The PRECIS figure is a concise way of representing pragmatism across dimensions

• Some aspects of key characteristics of pragmatic trials were not included-
What’s new/different in PRECIS 2?

<table>
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<tr>
<th>PRECIS-1</th>
<th>PRECIS-2</th>
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<td>Eligibility</td>
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<td>Flexibility (Intervention)</td>
<td>Flexibility (Delivery compare to usual care)</td>
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<td>Flexibility (Control)</td>
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<tr>
<td>Practitioner Expertise (Intervention)</td>
<td>Organization – resources, expertise, training vs. usual care</td>
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<td>Follow-up intensity</td>
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<td>Outcomes</td>
<td>Primary Outcome relevant to patients</td>
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<td>Primary analysis</td>
<td>Primary analysis</td>
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<td>Recruitment – added effort to recruit</td>
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<td>Setting – vs. usual care or single center</td>
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Key Changes in PRECIS 2

- Rate compared to usual care
- No explicit ratings of control conditions
- Added ratings related to external validity - recruitment and settings

PRECIS 2 Toolkit at
https://crs.dundee.ac.uk/precis/Help/Documentation/Toolkit
• Consider the Trial

• For the PRECIS-2 domains including Eligibility, Flexibility (delivery), and Primary Outcome how would you rate each from 1 to 5
  – 1 = entirely explanatory, and
  – 5 = entirely pragmatic
Eligibility

• To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?

• For example, score 5 for very pragmatic criteria essentially identical to those in usual care; score 1 for a very explanatory approach with lots of exclusions (e.g. those who don’t comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care.
• How different is the flexibility in how the intervention is delivered and the flexibility likely in usual care?

• For example, score 5 for a very pragmatic choice with identical flexibility to usual care; score 1 for a very explanatory approach if there is a strict protocol, monitoring and measures to improve compliance, with specific advice on allowed co-interventions and complications.
• To what extent is the trial's primary outcome relevant to participants?
• For example, score 5 for a very pragmatic choice where the outcome is of obvious importance to participants; score 1 for a very explanatory approach using a surrogate, physiological outcome, central adjudication or use assessment expertise that is not available in usual care, or the outcome is measured at an earlier time than in usual care.
Summary

Pragmatic Study Methods: Key Characteristics

- Questions from and important to stakeholders
- Multiple, heterogeneous settings
- Diverse populations
- Comparison conditions are real-world alternatives
- Multiple outcomes important to decision and policy makers

Thorpe KE et al., Can Med Assoc J, 2009;180:E47-57
Tunis SR et al. Practical clinical trials…JAMA 2003;290:1624-1632
Comparative Effectiveness Research (CER)

• “The conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnosis, treat and monitor health conditions in ‘real world’ settings. (IOM)

• Patient Oriented Outcomes Research Institute (PCORI) states that “Patient-Centered Outcomes Research helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options.

• CER uses many of same approaches, philosophy and designs as pragmatic approaches

• ALWAYS compares real world alternatives:
  – Some (Russ) argue that comparison could be Minimal Interventions Needed to Change (MINC)
    • Are more expensive/intensive interventions more effective or cost-efficient than a “low dose” option that has clinically significant outcomes?
  – Some argue- and others disagree- that costs, resources, and value are important aspects of CER

Glasgow et al. The minimal intervention needed for change. Translational Behavioral Medicine, (2014)
Other CER Issues

• Are many appropriate designs - RCTs, natural experiments; observational data, time series, stepped wedge, adaptive designs, simulation models, mixed methods.....

• Consider the science
  and

• The pool of reviewers / culture of the funder
Key CER Issues

• CER can be comparison of drugs and devices but ALSO used to study system changes, behavioral interventions, multi-level interventions and policies

• Key stakeholders are 1) ‘patients’ and families; and 2) those staff who have to implement or deliver programs and policies
  – Range of relevant outcomes
  – Accounting for different perspectives...what are the core care decisions the study will inform?
CER-T: CER that will Translate *

• “The study of complex patients with complex problems and complex health care (or public health) teams embedded in complex systems whose goal is to evaluate complex and multifaceted outcomes (intended and unintended) of complex interventions**”
  – Representative participation
  – Cost data
  – Range of outcomes: health indicators, QoL, Behavioral change—system, provider, patient....

*Glasgow and Steiner- chapter in your text;
**Medical Research Council, 2008:
http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC004871
Key Take Home Points

• Many similarities: pragmatic research and CER-T

• Stakeholder perspective is central
  – Who are your key stakeholders?
  – Questions and outcomes that are relevant
  – How to keep stakeholders engaged over time?

• Real world—settings, participants, approaches, interventionists

• YOU will have a role in defining what the field is and is not...what you submit, publish, teach and review