Pragmatism in Clinical Trials - Exploring the challenges and opportunities with pragmatic clinical trials

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Objectives

• Review the similarities and differences between pragmatic and traditional clinical trials

• Discuss the challenges and opportunities for pragmatic clinical trials in Alberta

• Discuss how Precision Health will increase the need for pragmatic clinical trials and other innovative trial designs
Challenges

- Cost of clinical trials
- Efficacy data may not be sufficient for decision-making
- Fewer comparisons with existing treatments
- Too →
  - broad (average treatment effect not representative of benefit for individual)
  - narrow (trial population and setting not representative of general practice)
- Discomfort with randomization to placebo
- Sluggish knowledge translation

Up to 80% of medications used in children have not been tested in children

Less than 25% of guidelines in cardiology have high level evidence to support the guideline

Drug safety monitoring relies entirely on voluntary reporting
Traditional vs. Pragmatic Clinical Trial

**Traditional Clinical Trial**

- Efficacy
- Ideal conditions
- Ideal comparators/outcomes
- Less generalizable

**Pragmatic Clinical Trial**

- Effectiveness
- ‘Real-world’ conditions
- Relevant comparators/outcomes
- More generalizable
In a learning health care system, research influences practice and practice influences research.

**Internal**
- **Design**: Design care and evaluation based on evidence generated here and elsewhere.
- **Implement**: Apply the plan in pilot and control settings.

**External**
- **Disseminate**: Share results to improve care for everyone.
- **Adjust**: Use evidence to influence continual improvement.

**Evaluate**
- Collect data and analyze results to show what does and does not work.
Randomization
Comparability between intervention groups and decreased selection bias

- Explanatory (traditional) clinical trial
- Pragmatic (exploratory) clinical trial
- Observational study

Real World Evidence
Effectiveness in regular clinical practice = better evidence for clinicians and policy-makers
‘Real World’ Outcomes

• Studies (messy) real world experience
• Faster and much less expensive than experimental studies
  • Data accrued in other research (e.g. clinical trials) can be re-examined
  • Often can be performed when controlled trials are simply not possible
• May detect unexpected phenomena or subpopulations
• Even when not statistically definitive
  • Can refine questions and hypotheses
  • Identify potential recruits
  • Inform the design of future experimental research
Pragmatic clinical trials (PCTs) are research investigations embedded in health care settings designed to increase the efficiency of research and its relevance to clinical practice.

Measuring pragmatism in trials

PRECIS
Pragmatic Explanatory Continuum Indicator Summary

https://www.precis-2.org
Pragmatic versus Explanatory
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?

- Co-morbidities
- Other medications
- Age (young and old)

Recruitment

How much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients?

- Screening whole populations for eligibility
- Web-based approaches to consent
- Point of care tools
Setting

How different is the setting of the trial and the usual care setting?

• Tertiary hospital versus community clinics
• Affects eligibility (rural versus urban)
• Can remotes areas participate?

Organization

How different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care?

• Do interventions require additional training?
• Do measurements require additional training?
Flexibility: delivery

How different is the flexibility in how the intervention is delivered and the flexibility likely in usual care?

• Strict protocol that does not integrate well with usual care versus protocol designed with input about usual care
• Per-protocol flexibility based on normal variation of usual care in various settings
• Issues with flexibility anticipated and planned for in analysis

Flexibility: adherence

How different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care?

• Level of effort used to maintain adherence (e.g. standard verbal reminders at follow-up or extensive efforts outside of scheduled visits)
• Adherence will introduce post-randomization variables
  • Stopping a medication for side-effects
  • Stopping a medication for low effect
  • Stopping a medication for lack of interest
Follow-up

How different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care?

• Long questionnaires may affect adherence
• Schedule of follow-up visits
• Location of follow-up

Primary outcome

To what extent is the trial's primary outcome relevant to participants?

• Endpoints that matter to patients and decision makers
• Source of data from point-of-care systems
• Standard measures that are routinely used in care
  • Value of setting those standards where they do not exist
Primary analysis

To what extent are all data included in the analysis of the primary outcome?

• Intention to treat versus per-protocol analysis
• Risk modifiers controlled for in analysis – not design
• Benefit from explicit definition of the per-protocol effect, including plans to measure adherence and post-randomization variables, and specifications of the statistical analysis plan (Hernán MA, et al. NEJM 2017)
Quality

Pragmatic ≠ biased, poor quality, or irreproducible

https://www.precis-2.org
SPOR Pragmatic Clinical Trials Platform
What does the PCT Platform do?

• Not a service platform

• Build or support infrastructure or address gaps in the conduct of PCTs
  • Capacity building – PCT Coordinator Training Program
  • Consensus statement of Registry-Based Clinical Trials
  • Enrolment -> BeTheCure.ca to improve discoverability of clinical trials for all Albertans and to support direct patient engagement efforts
  • Enrolment -> direct communication with all potentially eligible participants in AB
  • Consent -> support opinion survey on waiver of consent for cluster PCT
  • Data management -> support REDCap Cloud for province-wide collaboration
  • Clinical Data -> support deployment of Connect Care to include key health outcome measures in multiple therapeutic domains as well as a Common Data Model
Learn from Experts
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YOU CAN HELP FIND NEW CURES.

GIVE YOUR TIME TO HEALTH RESEARCH.

PARTICIPATE IN A TRIAL
GET EMAIL UPDATES
CONNECT ON SOCIAL
VISIT OUR BLOG
Promote routine collection of standardized health outcome measures at point of care

Utilize common data model to maximize data interoperability
Registry-based trials

Lower cost (outside of registry costs)
Enhanced generalizability of findings
Rapid consecutive enrolment
Potential completeness of follow-up

Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research?

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