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

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KUSP/TREC Brownbag Lunch Session – Mar 9, 2018

Alberta SPOR SUPPORT Unit | Pragmatic Clinical Trials Platform

Strategy for Patient-Oriented Research SPOR Putting Patients First

CIHR IRSC

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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

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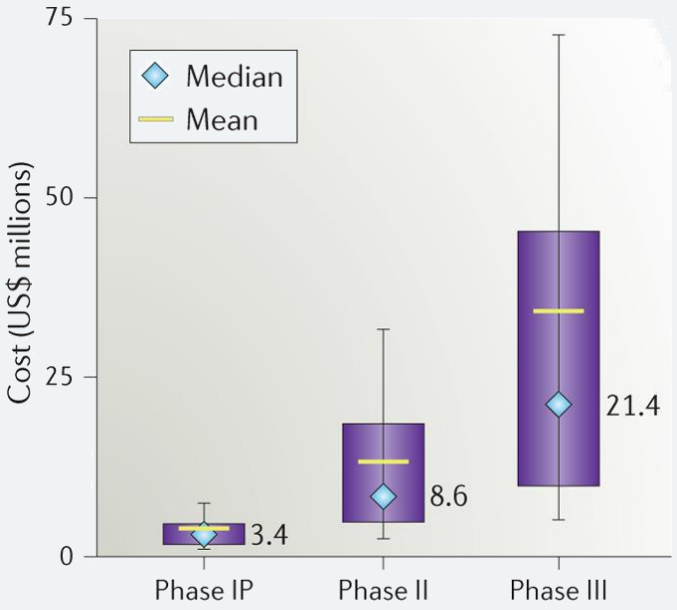
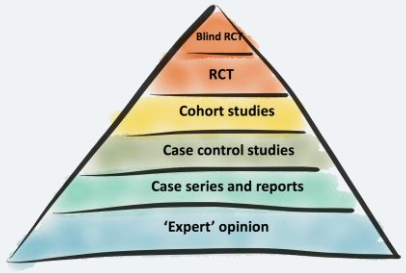


Martin L, Hutchens M, Hawkins C, Radnov A. How much do clinical trials cost? Nature Publishing Group. 2017 Jun;16(6):381–2.

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 set- ting not representative of general practice)
- Discomfort with randomization to placebo
- Sluggish knowledge translation

Angus DC. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? JAMA. American Medical Association; 2015 Aug 25;314(8):767–8.

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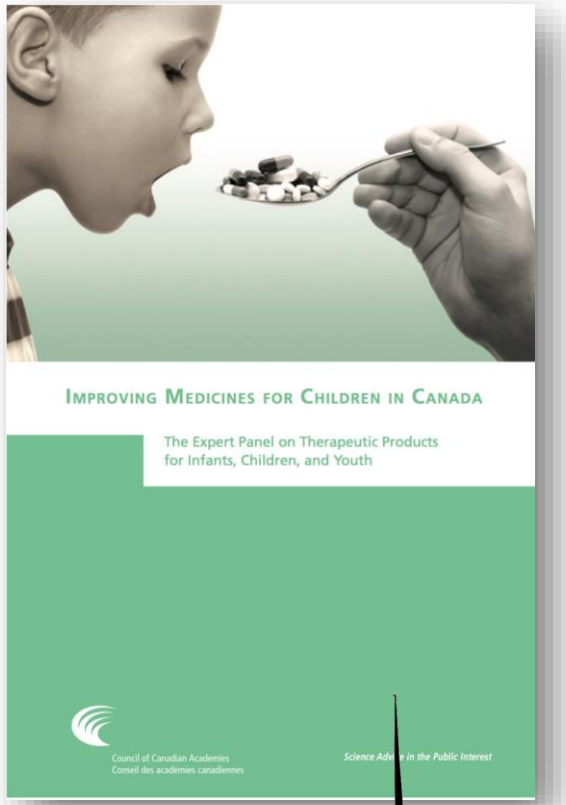
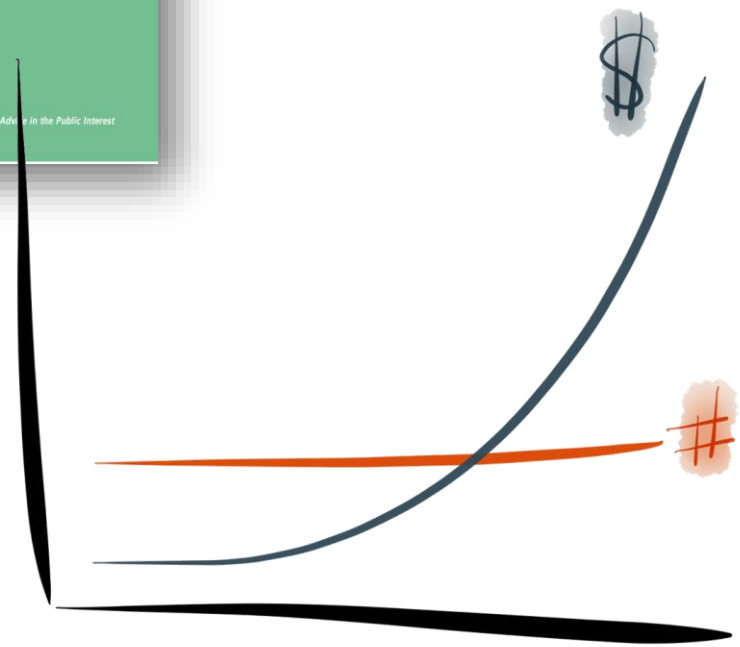


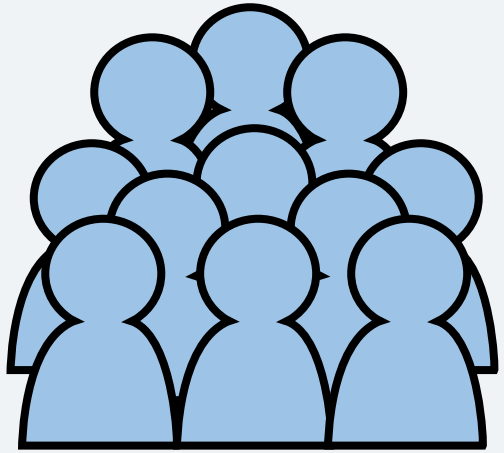


Up to 80% of medications used in children have not been tested in children

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

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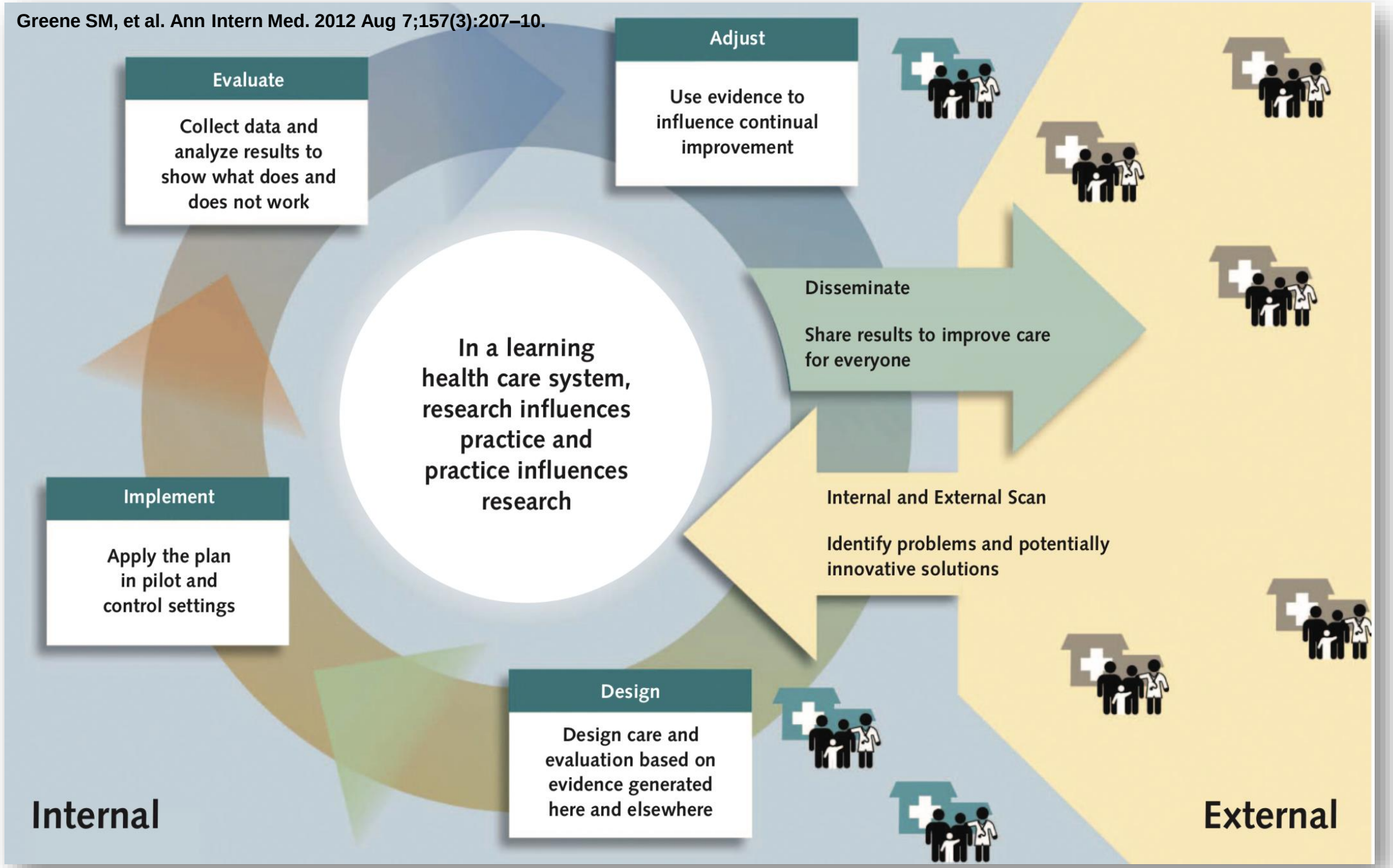
Greene SM, et al. Ann Intern Med. 2012 Aug 7;157(3):207–10.



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***

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‘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

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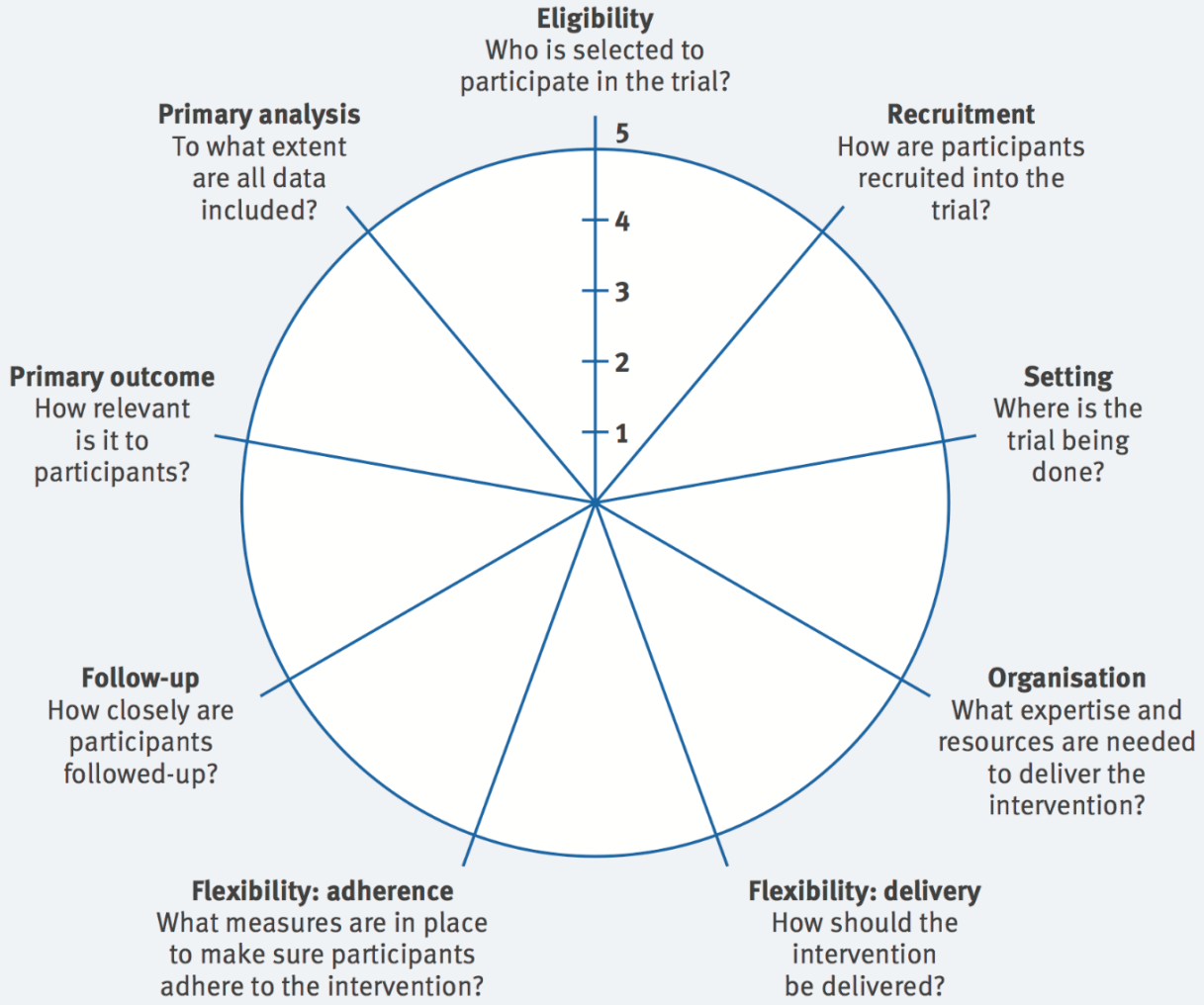
Pragmatic clinical trials

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.

Richesson RL, Green BB, Laws R, Puro J, Kahn MG, Bauck A, et al. Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory. Journal of the American Medical Informatics Association : JAMIA. 2017 Sep 1;24(5):996–1001.

Measuring pragmatism in trials



https://www.precis-2.org

PRECIS

Pragmatic

Explanatory

Continuum

Indicator

Summary

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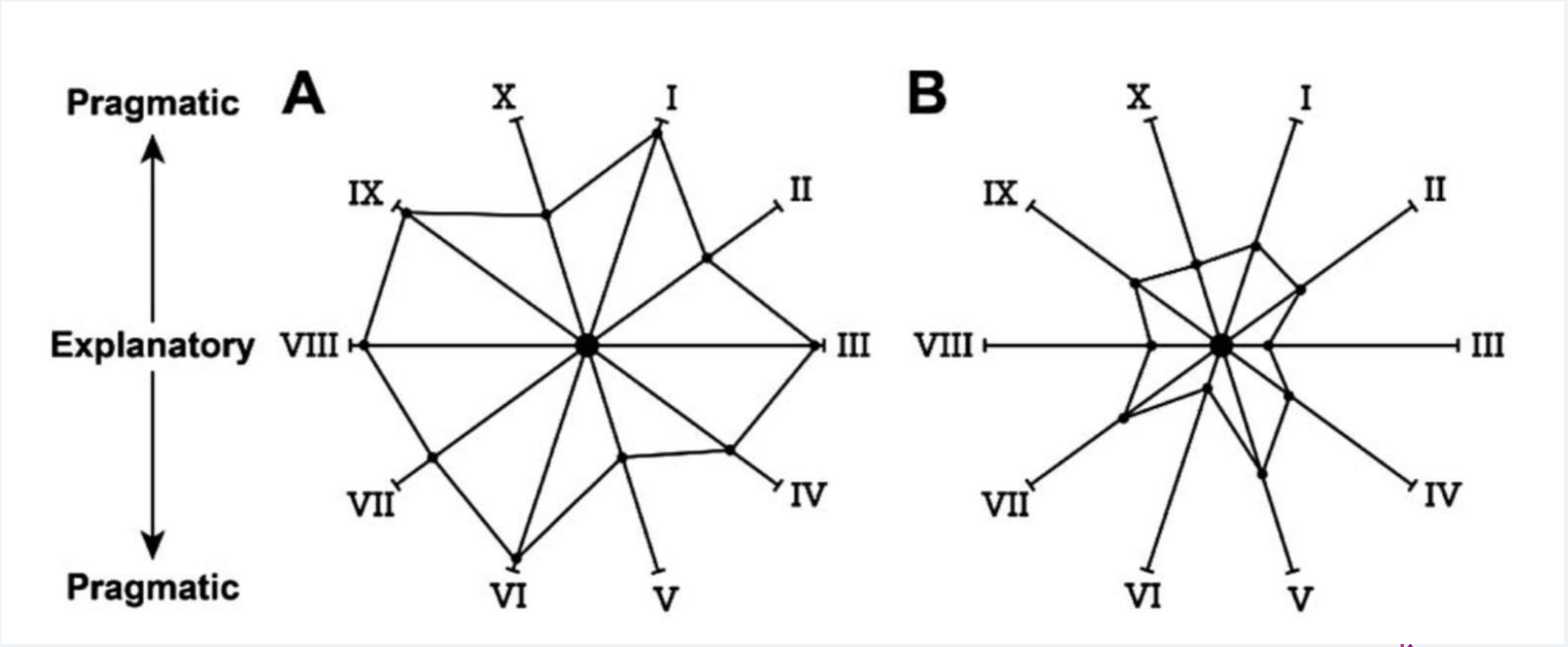
Pragmatic versus Explanatory



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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

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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?

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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

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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

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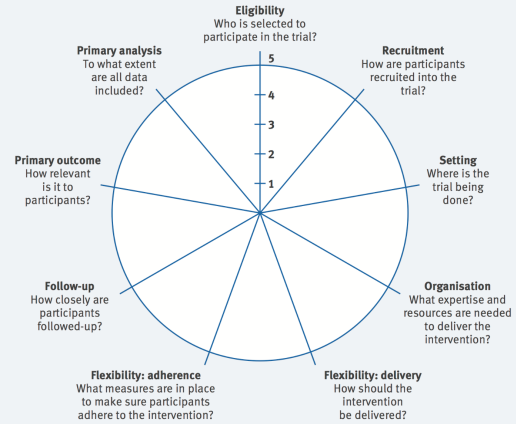
Primary analysis

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)

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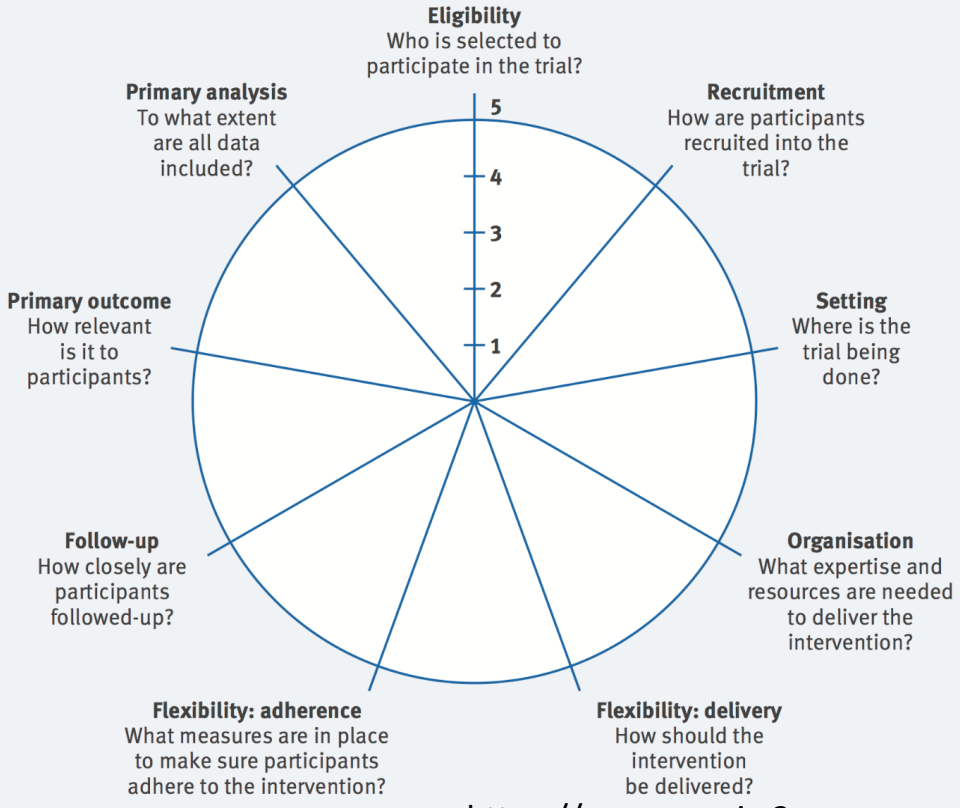
Quality

Pragmatic ≠ biased, poor quality, or irreproducible



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SPOR Pragmatic Clinical Trials Platform

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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

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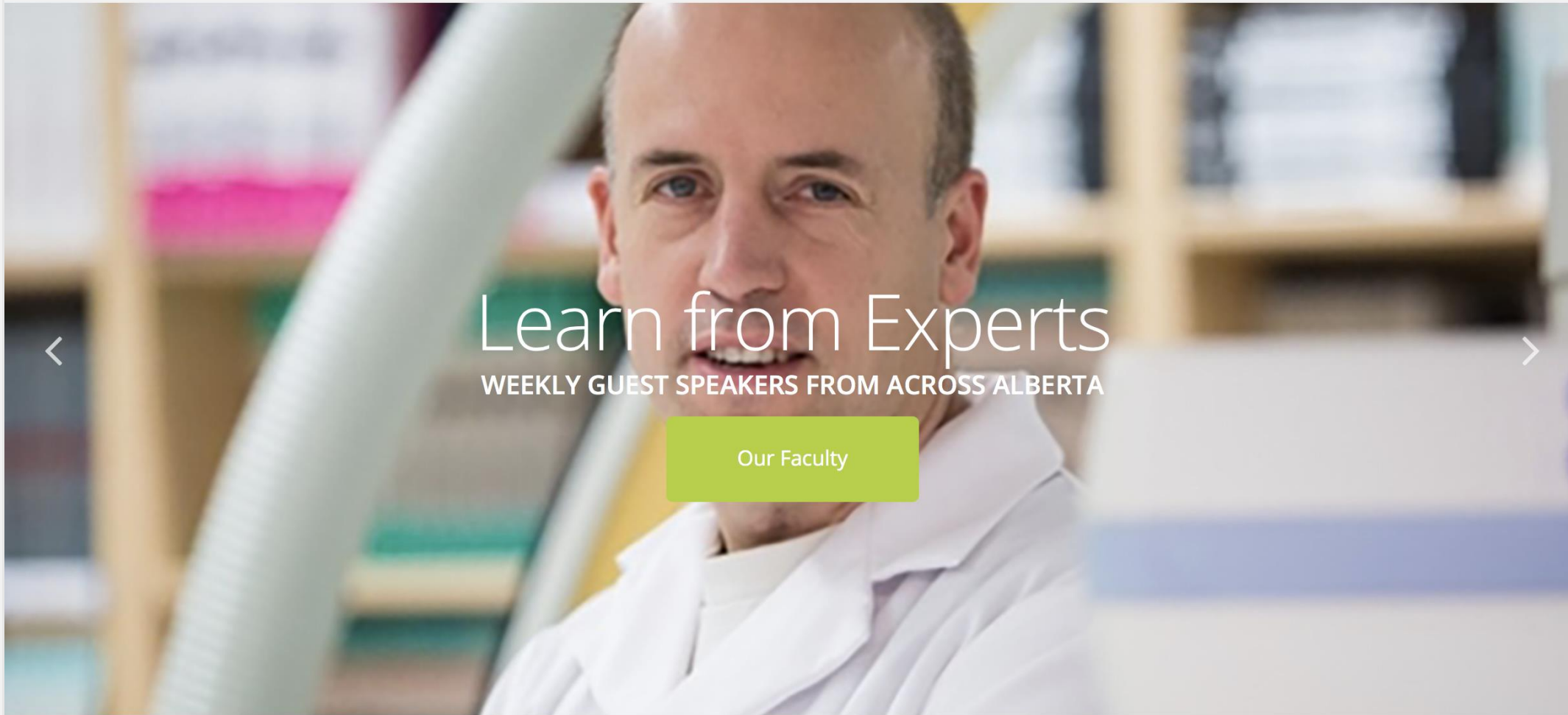
Leadership in
Patient-Oriented Research:
Pragmatic Clinical Trials Certificate

Background Certificate Info How to Apply Who We Are Contact



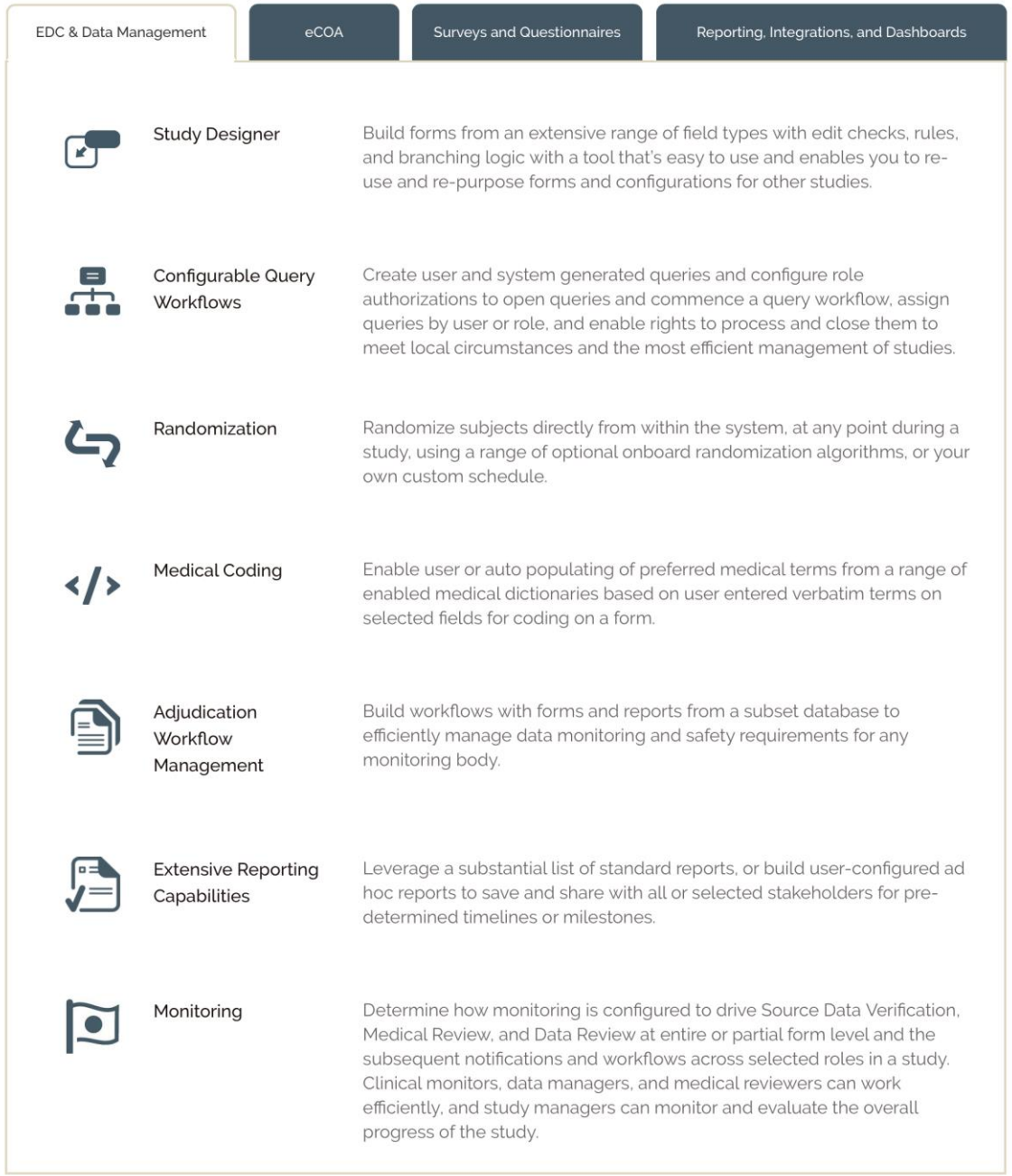
Pragmatic Clinical Trials Certificate

Apply Today

REDCAP CLOUD

Meets Health Canada regulatory requirements

Easier provincial collaboration

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UNIVERSITY OF CALGARY
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SEARCH FOR TRIALS
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GIVE YOUR TIME TO HEALTH RESEARCH.
PARTICIPATE IN A TRIAL
GET EMAIL UPDATES
CONNECT ON SOCIAL
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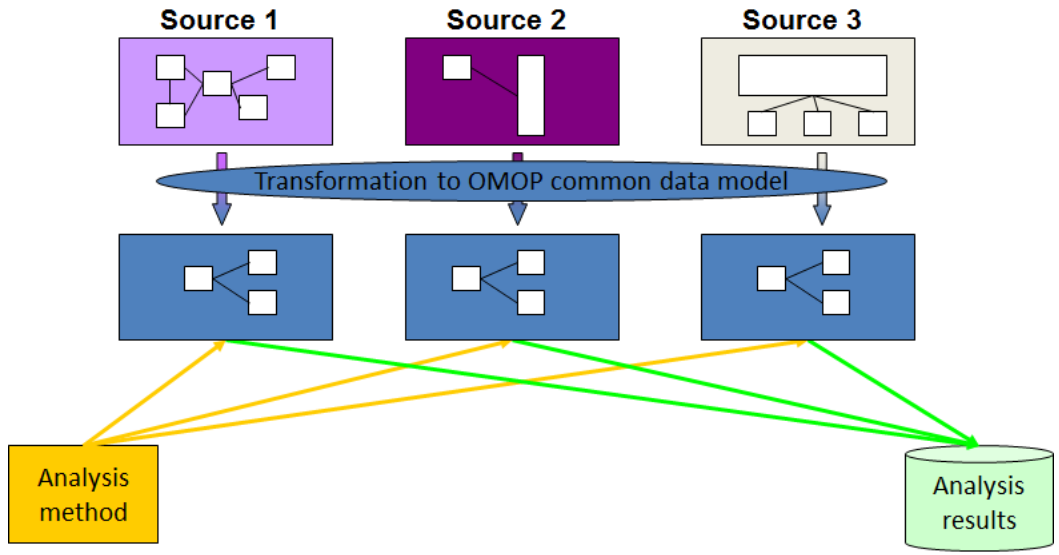
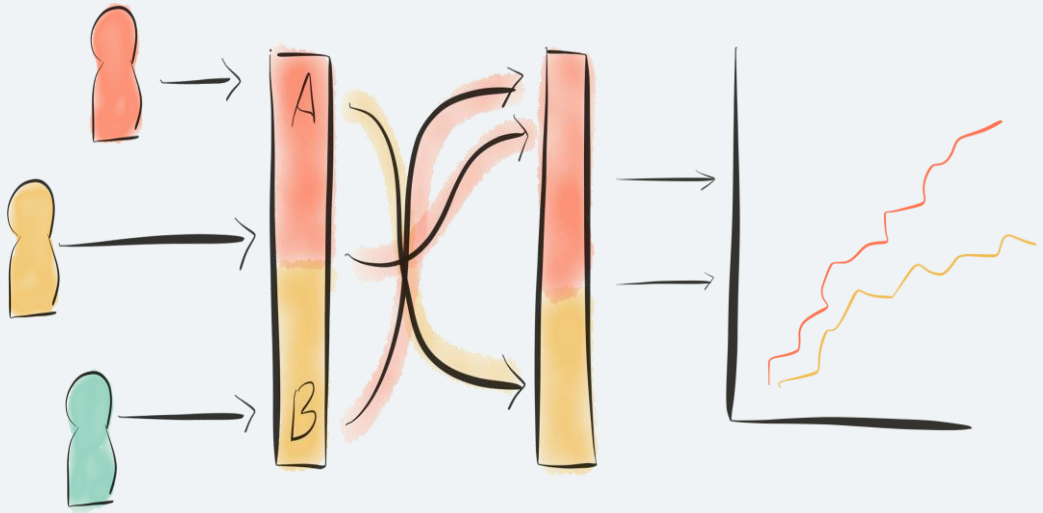
Connect Care

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?

Guowei Li[a,b], Tolulope T. Sajobi[c,d,e], Bijoy K. Menon[c,d,e], Lawrence Korngut[d,e], Mark Lowerison[c], Matthew James[c,f], Stephen B. Wilton[g], Tyler Williamson[c], Stephanie Gill[d,e], Lauren L. Drogos[g], Eric E. Smith[d,e], Sunita Vohra[h], Michael D. Hill[c,d,e], Lehana Thabane[a,b,*], on behalf of 2016 Symposium on Registry-Based Randomized Controlled Trials in Calgary

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