From Efficacy to Effectiveness: The Pragmatic Clinical Trial

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RSNA 2017
Acknowledgements

• NIH: UH2 AT007766-01; UH3 AT007766
• AHRQ: R01HS019222-01; 1R01HS022972-01
• PCORI: CE-12-11-4469

Disclosures

Physiosonix (ultrasound company): Founder/stockholder
UpToDate: Section Editor
Evidence-Based Neuroimaging Diagnosis and Treatment (Springer): Co-Editor
The Big Picture

Comparative Effectiveness

Evidence Based Practice

Health Policy
In a learning health care system, research influences practice and practice influences research.

**EVALUATE**
Collect data and analyze results to show what works and what doesn’t.

**IMPLEMENT**
Apply plan in pilot and control settings.

**DESIGN**
Design care and evaluation based on evidence generated here and elsewhere.

**ADJUST**
Use evidence to influence continual improvement.

**DISSEMINATE**
Share results to improve care for everyone.

**INTERNAL AND EXTERNAL SCAN**
Identify problems and potentially innovative solutions.
So we need to generate evidence
Challenge #1: Clinical research is slow

- Traditional RCTs are slow and expensive—and rarely produce findings that are easily put into practice.
- In fact, it takes an average of 17 years before research findings lead to widespread changes in care.
Challenge #1: Clinical research is slow

“...rarely produce findings that are easily put into practice.”
Efficacy vs. Effectiveness
Efficacy vs. Effectiveness

• Efficacy: can it work under ideal conditions
• Effectiveness: does it work under real-world conditions
Challenge #2: Clinical research is not relevant to practice

- Traditional RCTs study efficacy of txs for carefully selected populations under ideal conditions.
- Difficult to translate to real world.
- When implemented into everyday clinical practice, often see a “voltage drop” — dramatic decrease from efficacy to effectiveness.

“If we want more evidence-based practice, we need more practice-based evidence.”
Challenge #3: The evidence paradox

• >18,000 RCTs published each year—plus tens of thousands of other clinical studies.

• Yet systematic reviews consistently find not enough evidence to effectively inform clinical decisions providers and patients must make.
The solution?
A solution?
An approach?
The solution?
A solution?
An approach?

Pragmatic Trials
Pragmatic vs. Explanatory Trial

• Explanatory trials
  – Examine efficacy
  – Conducted under ideal conditions
  – Explain mechanisms

• Pragmatic trials
  – Determine comparative effectiveness (CER)
  – Routine practice
  – Aim to help providers, patients, and policy makers choose between interventions
Pragmatic Trials
Large Simple Trials
Effectiveness Trials
Explanatory Trials

• If and how an intervention works
• Control for as many biases and confounders as possible
• Maximize intervention’s effect
Pragmatic Trials

- Size: huge n→ robust estimates, heterogeneity
- Endpoints: patient oriented with minimal adjudication
- Setting: integrated into real world
  - Non-academic centers
  - Leverage digital data
  - Patients as partners
MYTHBUSTERS.

DON'T TRY THIS AT HOME!*
DO

TRY THIS AT HOME!*
Key features of most PCTs

Use of electronic health records (EHRs)
- EHRs allow efficient and cost-effective, recruitment, participant communication & monitoring, data collection, and follow up

Randomization at clinic or provider level
- Protocols can be tailored to local sites and can adapt to changes in a dynamic healthcare environment
But EMRs Have Their Limitations
Data Quality Issues with Death

• Unambiguous - should be easy
• Pts died prior to index visit
• Pts had visits after death
  – 1.4% of those who died subsequently had visits
A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe MMath, Merrick Zwarenstein MD MSc, Andrew D. Oxman MD, Shaun Treweek BSc PhD, Curt D. Furberg MD PhD, Douglas G. Altman DSc, Sean Tunis MD MSc, Eduardo Bergel PhD, Ian Harvey MB PhD, David J. Magid MD MPH, Kalipso Chalkidou MD PhD

Published at www.cmaj.ca on Apr. 16, 2009. An abridged version of this article appeared in the May 12 issue of CMAJ. This article was published simultaneously in the May 2009 issue of the Journal of Clinical Epidemiology (www.jclinepi.com).
Eligibility – Who is selected to participate in the trial?

Primary analysis - To what extent are all data included?

Recruitment - How are participants recruited into the trial?

Primary outcome - How relevant is it to participants?

Setting - Where is the trial being done?

Follow-up - How closely are participants followed-up?

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

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

Flexibility - How should the intervention be delivered?
Pragmatic vs. Explanatory

1. Eligibility
2. Recruitment
3. Setting
4. Organization
5. Flexibility-intervention
6. Flexibility-adherence
7. Follow-up
8. Primary outcome
9. Primary analysis (includes all data?)
Example of Pragmatic Trial-
Lumbar Imaging with Reporting of
Epidemiology (LIRE)
LIRE (pronounced leer)- From the French verb, “To Read”
LIRE Funded by NIH Health Care Systems Research Collaboratory
• Supported by the NIH Common Fund
• Goal: improve the way (pragmatic) clinical trials conducted
• Build infrastructure for CER
Rethinking Clinical Trials

Supported by the Common Fund at the National Institutes of Health, the Health Care Systems Research Collaboratory is intended to improve the way clinical trials are conducted by creating a new infrastructure for collaborative research. The ultimate goal is to ensure that healthcare providers and patients can make decisions based on the best available clinical evidence.

The NIH HCS Research Collaboratory includes a Coordinating Center that provides national leadership and technical expertise in all aspects of research with healthcare systems. The Coordinating Center will make data, tools, and resources from these projects available to the greater research community to facilitate a broadened base of research partnerships with healthcare systems.

The NIH HCS Research Collaboratory also supports the design and rapid execution of several high-impact Pragmatic Clinical Trial Demonstration Projects (listed below) that will address questions of major public health importance that engage health care delivery systems in research partnership.

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Project</th>
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NIH CommonFund New Innovator, Dr. Sabeti! MT
Background and Rationale

• Lumbar spine imaging frequently reveals incidental findings
• These findings may have an adverse effect on:
  – Subsequent healthcare utilization
  – Patient health related quality of life
Disc Degeneration in Asx
Hypothesis

• Inserting benchmark information into reports will influence subsequent management of primary care patients with LBP
  – Fewer subsequent imaging tests
  – Fewer referrals for minimally invasive pain treatment
  – Fewer referrals to surgery
  – Less narcotic use
LIRE PRECIS

Diagram showing the following categories:
- Eligibility
- Analysis
- Recruitment
- Setting
- Organization
- Delivery
- Adherence
- Follow Up
- Outcome
The following findings are so common in normal, pain-free volunteers that while we report their presence, they must be interpreted with caution and in the context of the clinical situation. Among people between the age of 40 and 60 years who do not have back pain, a plain film x-ray will find that about:

- 8 in 10 have disk degeneration
- 6 in 10 have disk height loss

Note that even 3 in 10 means that the finding is quite common in people without back pain.
## Participating Systems

<table>
<thead>
<tr>
<th>Name</th>
<th># Primary Care Clinics (Randomized)</th>
<th># PCPs (Randomized)</th>
</tr>
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<tbody>
<tr>
<td>Kaiser Perm. N. California</td>
<td>20</td>
<td>865</td>
</tr>
<tr>
<td>Henry Ford Health System, MI</td>
<td>26</td>
<td>228</td>
</tr>
<tr>
<td>Group Health Coop of Puget Sound</td>
<td>19</td>
<td>245</td>
</tr>
<tr>
<td>Mayo Health System</td>
<td>36</td>
<td>345</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>101</strong></td>
<td><strong>1683</strong></td>
</tr>
</tbody>
</table>
LIRE: Enrollment

<table>
<thead>
<tr>
<th>Clinics (n = 100)</th>
<th>Providers (n = 3,195)</th>
<th>Patients (n = 245,586)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>GHC</td>
<td>HFHS</td>
</tr>
<tr>
<td>Percentage</td>
<td>Percentage</td>
<td>Percentage</td>
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<tr>
<td>(%)</td>
<td>(%)</td>
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<tr>
<td>34%</td>
<td>13%</td>
<td>5%</td>
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<tr>
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<td>11%</td>
<td>6%</td>
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<tr>
<td>26%</td>
<td>6%</td>
<td>7%</td>
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<tr>
<td>21%</td>
<td>70%</td>
<td>81%</td>
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</tbody>
</table>
LIRE- Primary Outcome

• What we want to know: how patient’s back pain is doing
  – Back pain-related disability: Roland-Morris Disability Questionnaire
  – Back and leg pain: pain NRS
  – HRQoL

• How do we get this data?
  – Ask the patient: Pt Reported Outcome
Are PROs Pragmatic?

• Barriers:
  – Time to get
  – # of personnel
  – Finding and contacting
  – $$

• For 100s -> 😊

• For 1,000s -> 😞

• For >100,000s - > 😞
LIRE- Primary Outcome

• A single metric of overall intensity of resource utilization for spine care based on CPTs converted to RVUs
• Passively collected from EHR
Key Pragmatic Aspects of LIRE

• Broad inclusion criteria
• Waiver of consent/minimal risk
• Simple, easily implementable intervention
• Passive collection of outcomes
Examining Coordinated Care

Do patient outcomes improve when care providers team up in a coordinated program?

SEE WHAT RESEARCHERS ARE LEARNING
PCORI

• Independent non-governmental organization
• Goal to help patients, clinicians, purchasers and policy makers make better informed health decisions
• Spearheading CER and pragmatic trials
PCOR Trust Fund

• 2010-2012: $210 million
• 2013: ~$320 million
  – $150 million general revenues
  – $1/Medicare beneficiary + private plans
• 2014-2019: ~$650 million/yr
  – $150 million general revenues
  – $2/beneficiary
• PCORTF not authorized after 2019
PCORI National Priorities

- Comparative Assessments of Prevention, Diagnosis, and Treatment Options
- Improving Healthcare Systems
- Addressing Disparities
- Accelerating Patient-Centered and Methodological Research
Stakeholder Engagement Essential
What Is Stakeholder Engagement?

• Participation in formulation of research questions
• Defining essential characteristics of study participants, comparators, and outcomes
• Monitoring of study conduct and progress
• Interpretation/dissemination of results
Take Home Points

• Pragmatic vs. Explanatory trials and the PRECIS tool
• NIH Health Care Systems Collaboratory
• PCOR and PCORI
Explanatory vs. Pragmatic Trials

The Great Zeferelli’s chair worked a lot better in controlled conditions.