Pragmatic Trials: What the Heck Are They and Why Should You Care?

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Explanatory vs. Pragmatic Trials

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Take Home Points

- Pragmatic vs. Explanatory trials and the PRECIS tool
- NIH Health Care Systems Collaboratory

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Clinical Trials- The Big Picture

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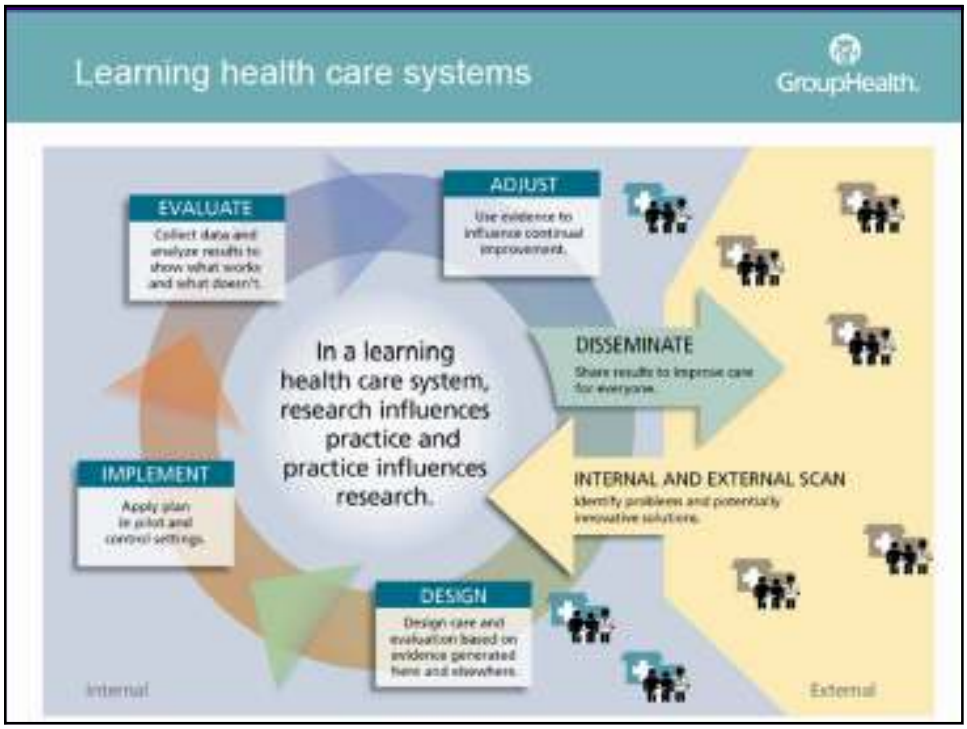

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So we need to generate evidence

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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.

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Challenge #1: Clinical research is slow

"…rarely produce findings that are easily put into practice."

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Efficacy vs. Effectiveness

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Efficacy vs. Effectiveness

- Efficacy: can it work under ideal conditions
- Effectiveness: does it work under real-world conditions

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Challenge #2: Clinical research is not relevant to practice

- Traditional RCTs study efficacy 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."

Green, LW. *American Journal of Public Health*, 2006.

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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.

?

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The solution?
A solution?
An approach?

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The solution?
A solution?
An approach?

Pragmatic Trials

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Pragmatic vs. Explanatory Trial

- Explanatory trials
  - Examine efficacy
  - Conducted under ideal conditions
  - Explain mechanisms
- Pragmatic trials
  - Determine comparative effectiveness (CER)
  - Embedded in routine practice
  - Aim to help providers, patients, and policy makers choose between interventions

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Pragmatic Trials
Effectiveness Trials
Embedded Clinical Trials
Large Simple Trials

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Pragmatic Trials
Effectiveness Trials
Embedded Clinical Trials
~~Large Simple Trials~~

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Explanatory Trials

- If and how an intervention works
- Control for as many biases and confounders as possible
- Maximize intervention's effect

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Pragmatic Trials

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

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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

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EMRs Have Their Limitations

- Don't necessarily contain outcomes of interest

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"It's fine to know your ABCs and your colors, but really you just have to be able to sit still and control your bladder."

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EMRs Have Their Limitations

- Don’t necessarily contain outcomes of interest
- Data quality issues

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Data Quality Issues

- Take death (please)
- Unambiguous- should be easy

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Data Quality Issues

Mr X had MRI of L-spine on 3/17/15. But when we got their EMR data, it indicated that he died 1 year before.

We found in LIRE that 1.4% of those who died subsequently had visits

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Sites should be happy about 1.4% regeneration rate

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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 health care environment

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Pragmatic vs. Explanatory Trials

CMAJ ANALYSIS

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).

the bmj | BMJ 2015;350:h2147 | doi: 10.1136/bmj.h2147 RESEARCH METHODS & REPORTING

The PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon,[1] Shaun Treweek,[1] Frank Sullivan,[2] Peter Donnan,[3] Kevin E Thorpe,[4] Merrick Zwarenstein[5]

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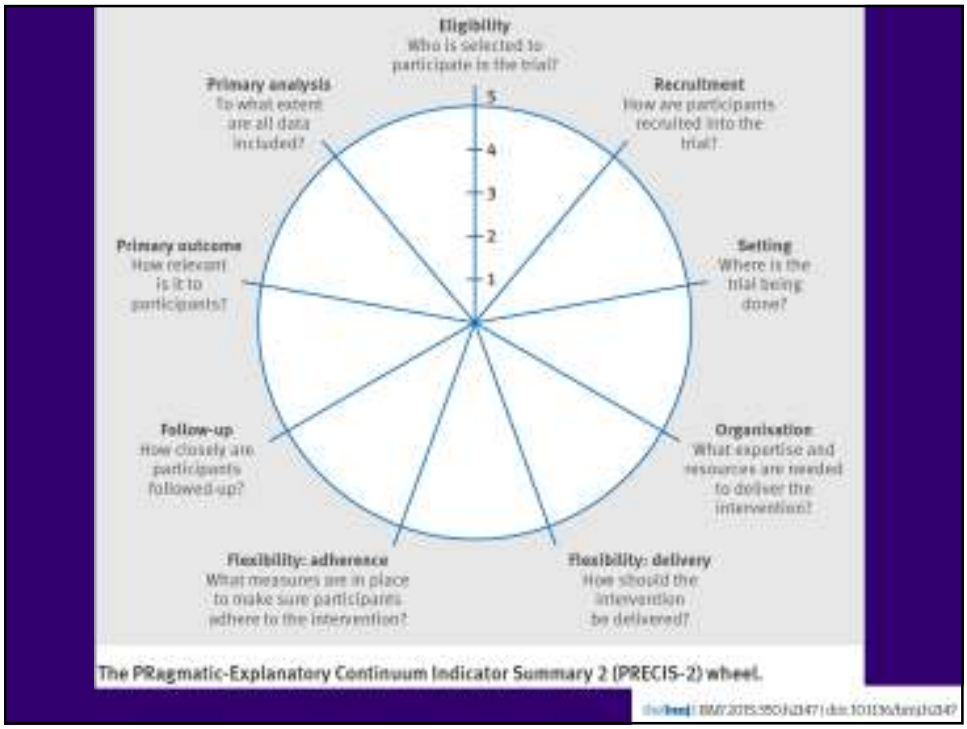

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Pragmatic vs. Explanatory

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?)

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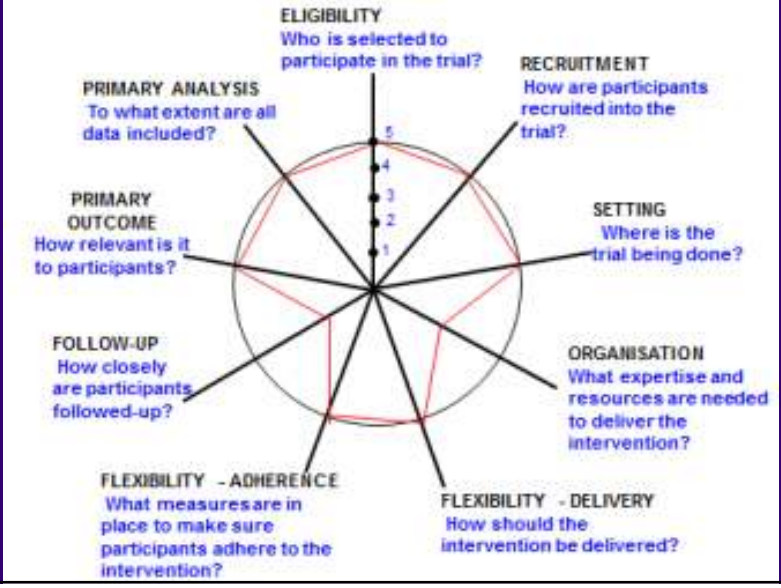
Example from: Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, Mullee M, Stuart B: Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. BMJ 2013, 347:f6041.



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Example of Pragmatic Trial- Lumbar Imaging with Reporting of Epidemiology (LIRE)

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LIRE (pronounced leer)- From the French verb, “To Read”

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LIRE Funded by NIH Health Care Systems Collaboratory

- Supported by the NIH Common Fund
- Goal: improve the way (pragmatic) clinical trials conducted
- Build infrastructure for CER

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rethinkingclinicaltrials.org

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Projects

Title	Investigator	Collaboratory Affiliation	Name
UH3 Project: Time to Reduce Mortality in End-Stage Renal Disease (TIME)	Dember, Laura	University of Pennsylvania	TIME
UH3 Project: Suicide Prevention Outreach Trial (SPOT)	Simon, Gregory	Group Health Cooperative; Group Health Research Institute	SPOT
UH3 Project: Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC)	Coronado, Gloria	Kaiser Foundation Research Institute	STOP CRC
UH3 Project: Pragmatic Trial of Video Education in Nursing Homes (PROVEN)	Mor, Vincent; Volandes, Angelo; Mitchell, Susan	Brown University School of Medicine	PROVEN
UH3 Project: Lumbar Imaging with Reporting of Epidemiology (LIRE)	Jarvik, Jeffrey	University of Washington	LIRE
UH3 Project: Improving Chronic Disease Management with Pieces (ICD-Pieces)	Vazquez, Miguel	UT Southwestern Medical Center	ICD-Pieces
UH3 Project: Collaborative Care for Chronic Pain in Primary Care (PPACT)	Deßar, Lynn	Kaiser Foundation	PPACT
UH3 Project: Active Bathing to Eliminate (ABATE) Infection	Huang, Susan	University of California, Irvine	ABATE
UH3 Project: A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity (Trauma Survivors Outcomes and Support [TSOS])	Zatzick, Douglas	University of Washington	TSOS
UH2 Project: A Blood Pressure Medication Timing Study (BPMedTime)	Rosenthal, Gary	University of Iowa	BPMedTime

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Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM)

PRISM UG3 Projects

Title	Principal Investigator	Sponsoring Institution	Phase
Fibromyalgia TENS in Physical Therapy Study (FM TIPS)	Kathleen Sluka; Leslie Crofford	University of Iowa	UG3
Group-based Mindfulness for Patients with Chronic Low Back Pain in the Primary Care Setting (OPTIMUM)	Natalia Morone	Boston Medical Center	UG3
Non-pharmacological Options in Postoperative Hospital-based and Rehabilitation Pain Management (NOHARM)	Andrea Cheville; Jon Tilburt	Mayo Clinic Rochester	UG3
Pragmatic Trial of Acupuncture for Chronic Low Back Pain in Older Adults (AcuOA)	Karen J Sherman; Lynn DeBar	Kaiser Foundation Research Institute	UG3

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Collaboratory Map

NIH Collaboratory Demonstration Projects are active in health systems across the United States, as shown in the map below.

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LIRE 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

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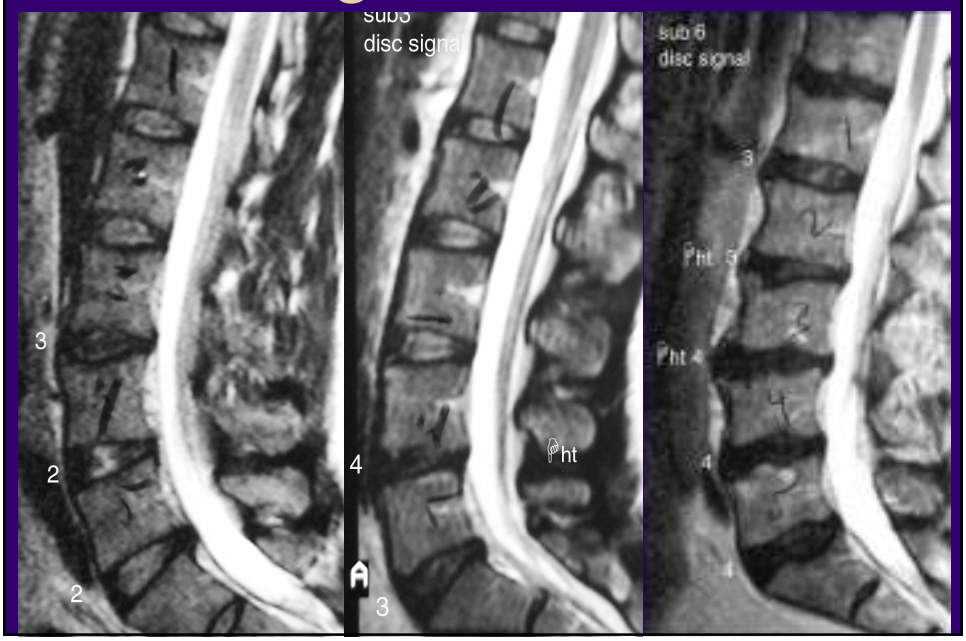
Disc Degeneration in Asx



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Hypothesis

- The benchmark information 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

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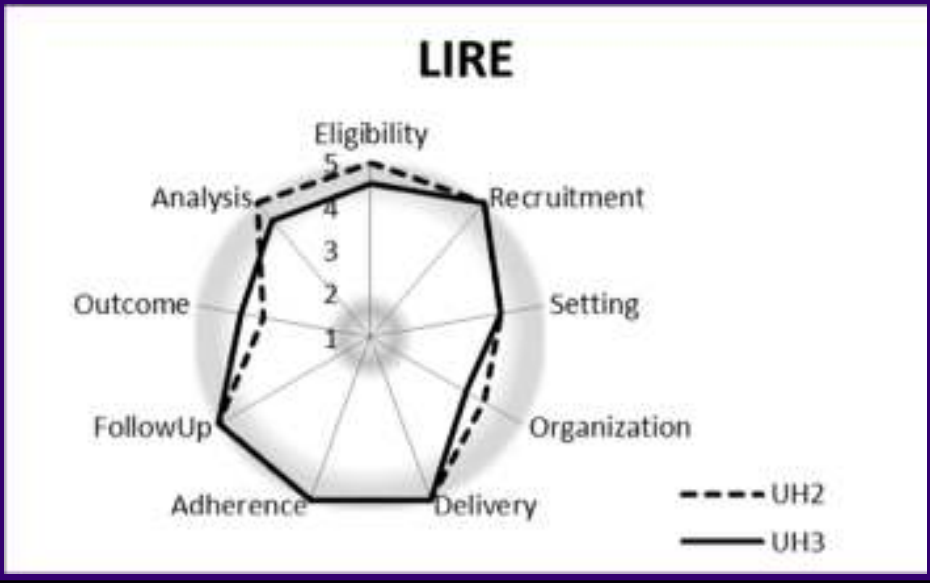
LIRE PRECIS



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The Intervention: KPWA Test Template

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The Intervention: KPWA Test Template

Comment

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.

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Participating Systems

- Kaiser Perm N. California
- Henry Ford Health System, MI
- Kaiser Perm WA (formerly Group Health Coop) WA & ID
- Mayo Health System, MN & WI

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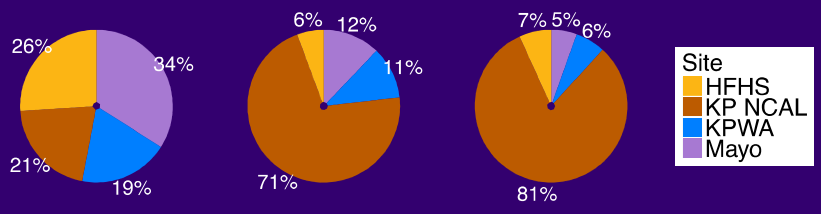
LIRE: Enrollment

Clinics	PCPs	Pts
n=98	n=3304	n=250,876



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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: PROMs

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Are PROMs Pragmatic?

- Barriers:
  - Time to get
  - # of personnel
  - Finding and contacting
  - $$
- For 100s- ☺
- For 1,000s- 😐
- For >100,000s- ☹

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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

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All Data Passively Collected (from EHR and VDW)

- CPT codes
- ICD10 codes
- Unique patient ID
- Unique provider ID
- Unique clinic ID
- Dates of service
- Limited patient demographics
- Imaging test results (text)
- Pharmacy data (medications, dose, etc)

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Key Pragmatic Aspects of LIRE

- Broad inclusion criteria
- Waiver of consent/minimal risk
- Simple, easily implementable intervention
- Passive collection of outcomes
- Stepped wedge for implementation

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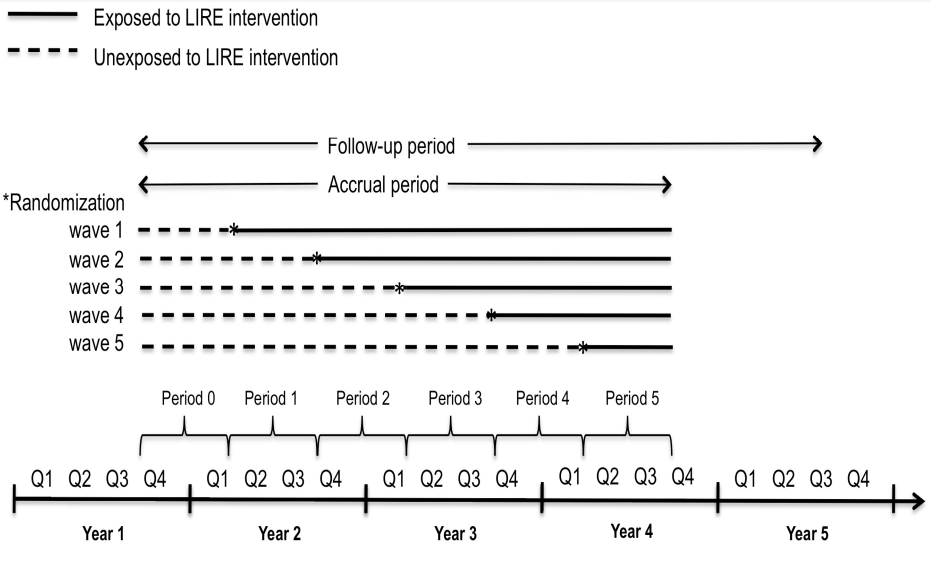
Stepped Wedge RCT



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Advantages of SW Design

- More efficient than parallel design since have both between and within group comparisons
- Assures all sites receive intervention → Participation more palatable for interventions viewed as desirable

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Disadvantage of SW Design

- Temporal changes that impact outcome can be problematic confounders since randomization is also based on time
- For example,
  - Opioid Rxs: LIRE 2^{o} outcome
  - External factors decreasing opioid Rxs independent of intervention

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Another Disadvantage of SW

- Delay in implementation leads to non-adherence/cross-over
- The tyranny of the waves…

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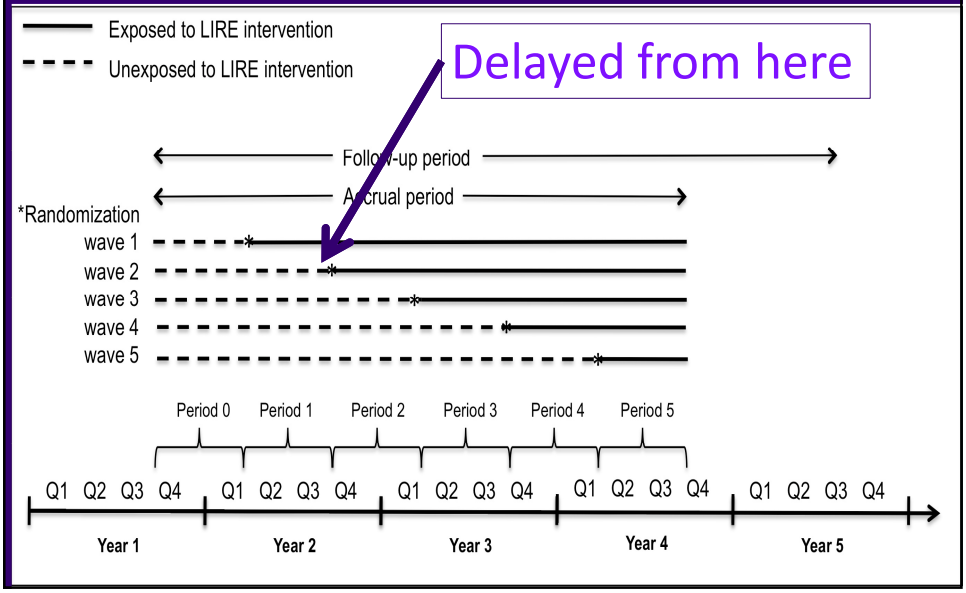
Stepped Wedge RCT



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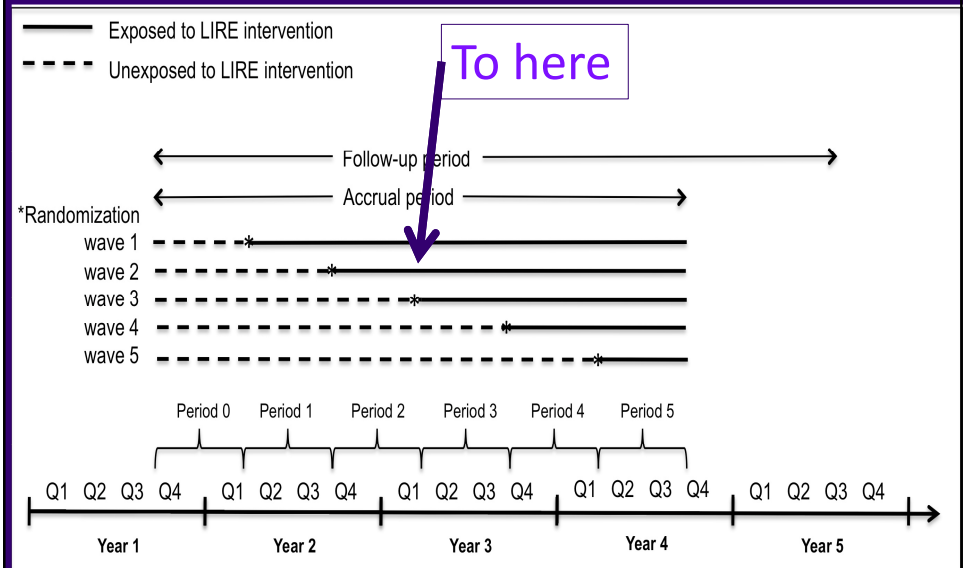
Stepped Wedge RCT



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Another Disadvantage of SW

- Delay in implementation leads to non-adherence/cross-over
- Delay in parallel design is annoying, potentially costly
- In intention-to-treat analysis, delay means non-adherence to random assignment

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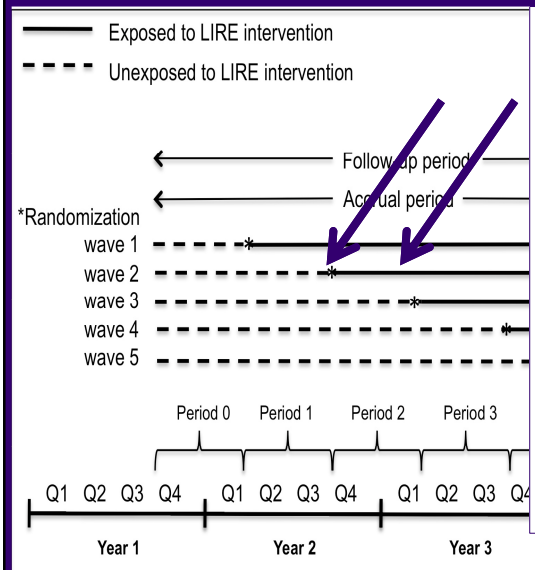
Stepped Wedge RCT



All pts enrolled from delayed site treated as if assigned to intervention, even though they received control! NON-ADHERENCE

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Take Home Points

- Pragmatic vs. Explanatory trials and the PRECIS tool
  - –LEVI (Large, Embedded, Valuable, Innovative)

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- **L**
  - Large
  - LEveraged
- **E**
  - Embedded
- **V**aluable
- **I'**
  - Inexpensive
  - Innovative
- **S**
  - Sound Science

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NIH National Heart, Lung, and Blood Institute

Stolen from M. Lauer- Deputy Dir, NIH Extramural Research (http://mdepinet.org/wp-content/uploads/D1_PS_1_Lauer_v2for-posting.pdf)

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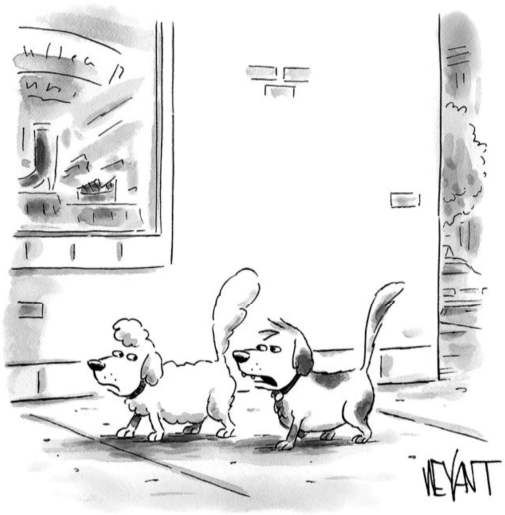

"I bark and I bark but I never feel like I effect real change."

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