From Explanatory to Pragmatic Clinical Trials: A New Era for Effectiveness Research

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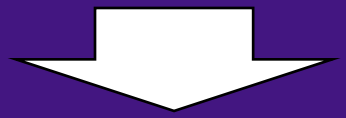
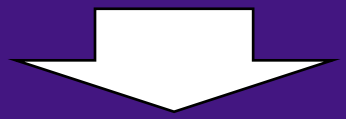
The Big Picture

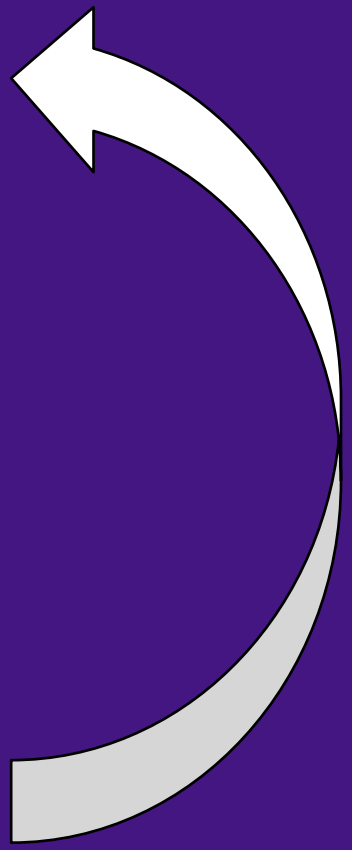
Comparative Effectiveness



Evidence Based Practice

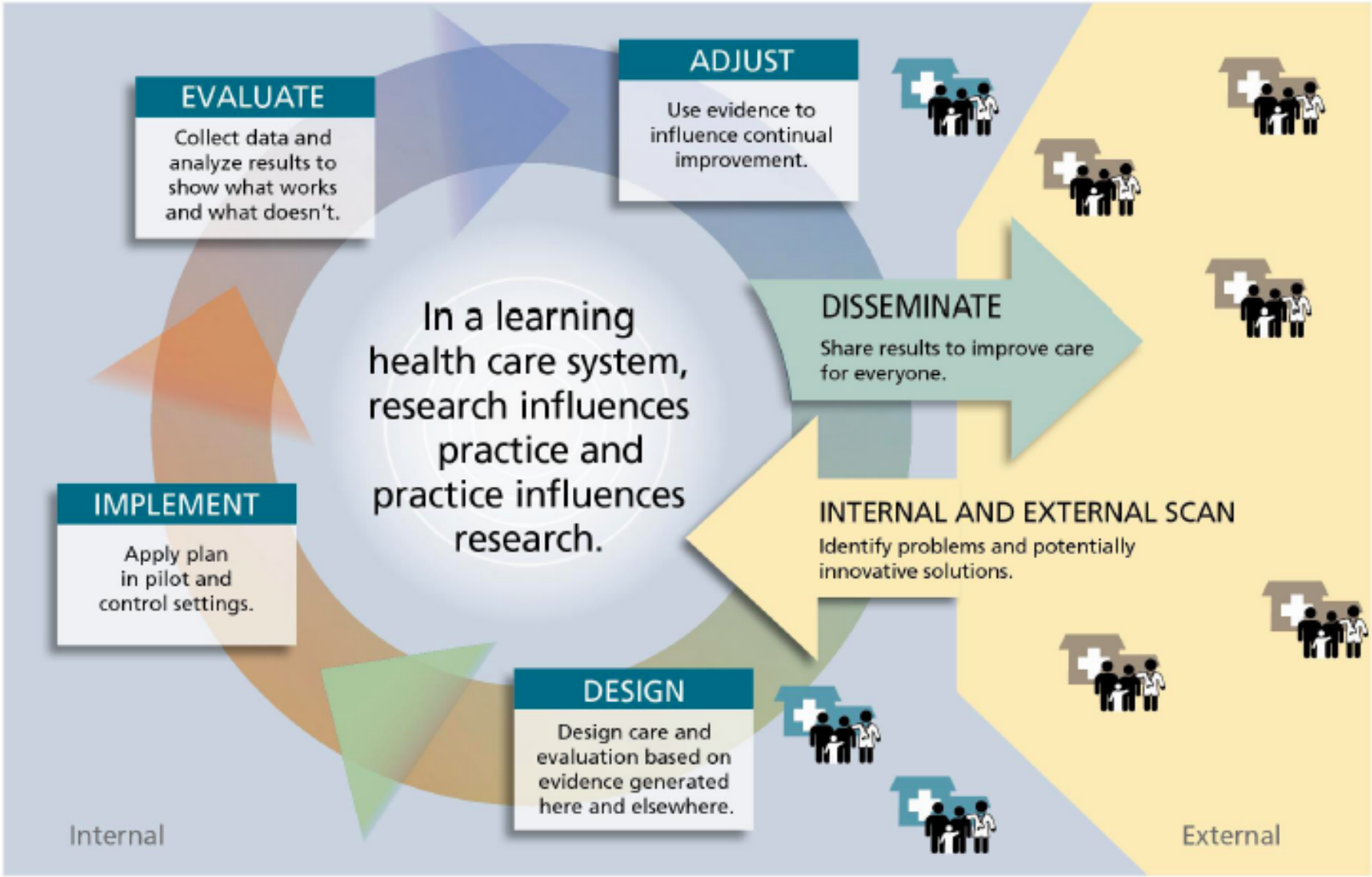


Health Policy



Learning health care systems

GroupHealth.



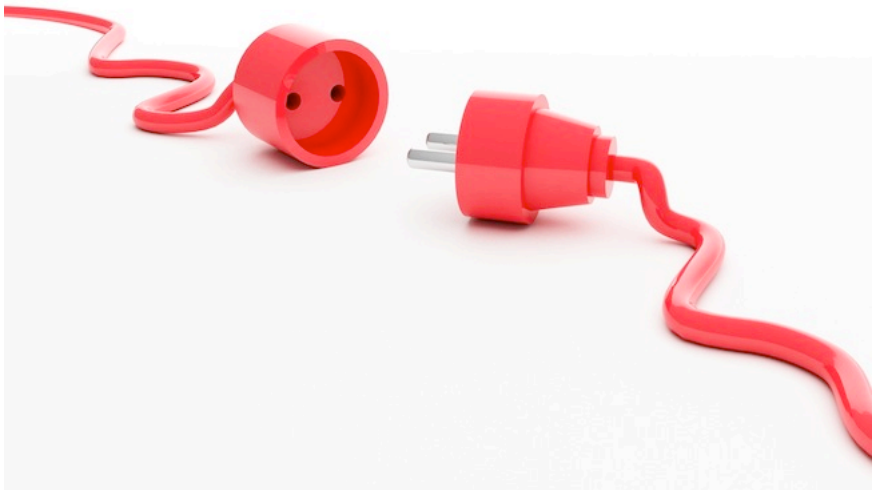
So we need to generate evidence

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."



NIH Collaboratory

Health Care Systems Research Collaboratory

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

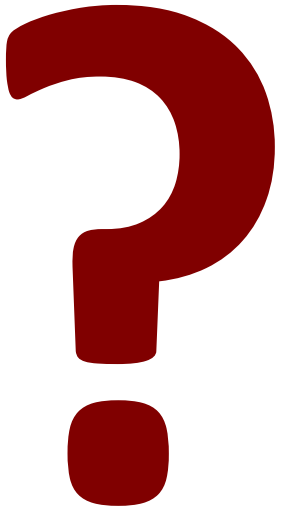
- Traditional RCTs study efficacy of txs for carefully selected populations under ideal conditions.
- Difficult to translate to real world.
- When implemented into everyday clinical practice, often see a "voltage drop"— dramatic decrease from efficacy to effectiveness.

"If we want more evidence-based practice, we need more practice-based evidence."

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

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

Explanatory vs. Pragmatic Trial

- Efficacy
- Ideal conditions
- Explain mechanisms

- Effectiveness
- 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

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

But EMRs Have Their Limitations

Data Quality Issues: e.g. 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

Pragmatic vs. Explanatory Trials

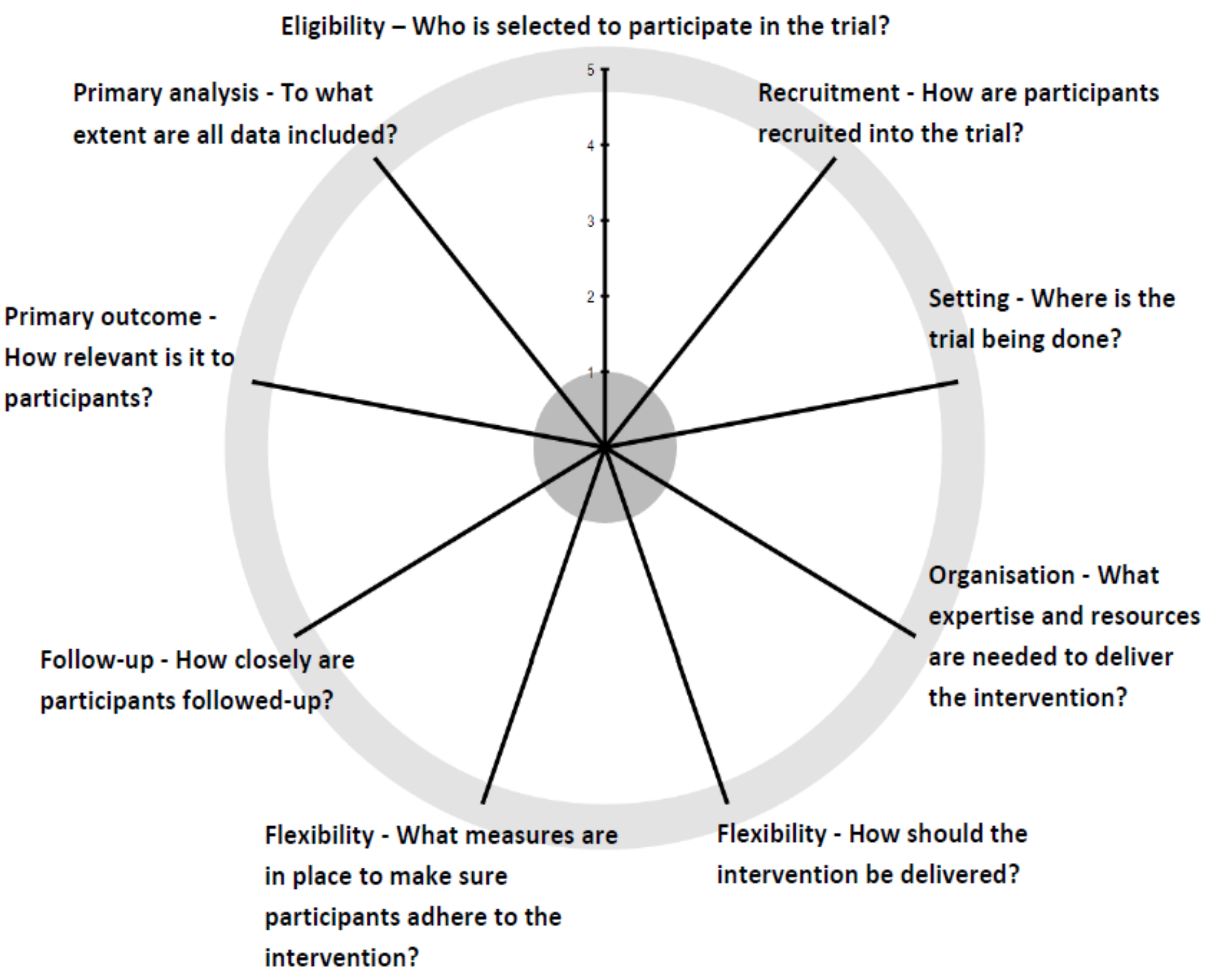
CMAJ

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

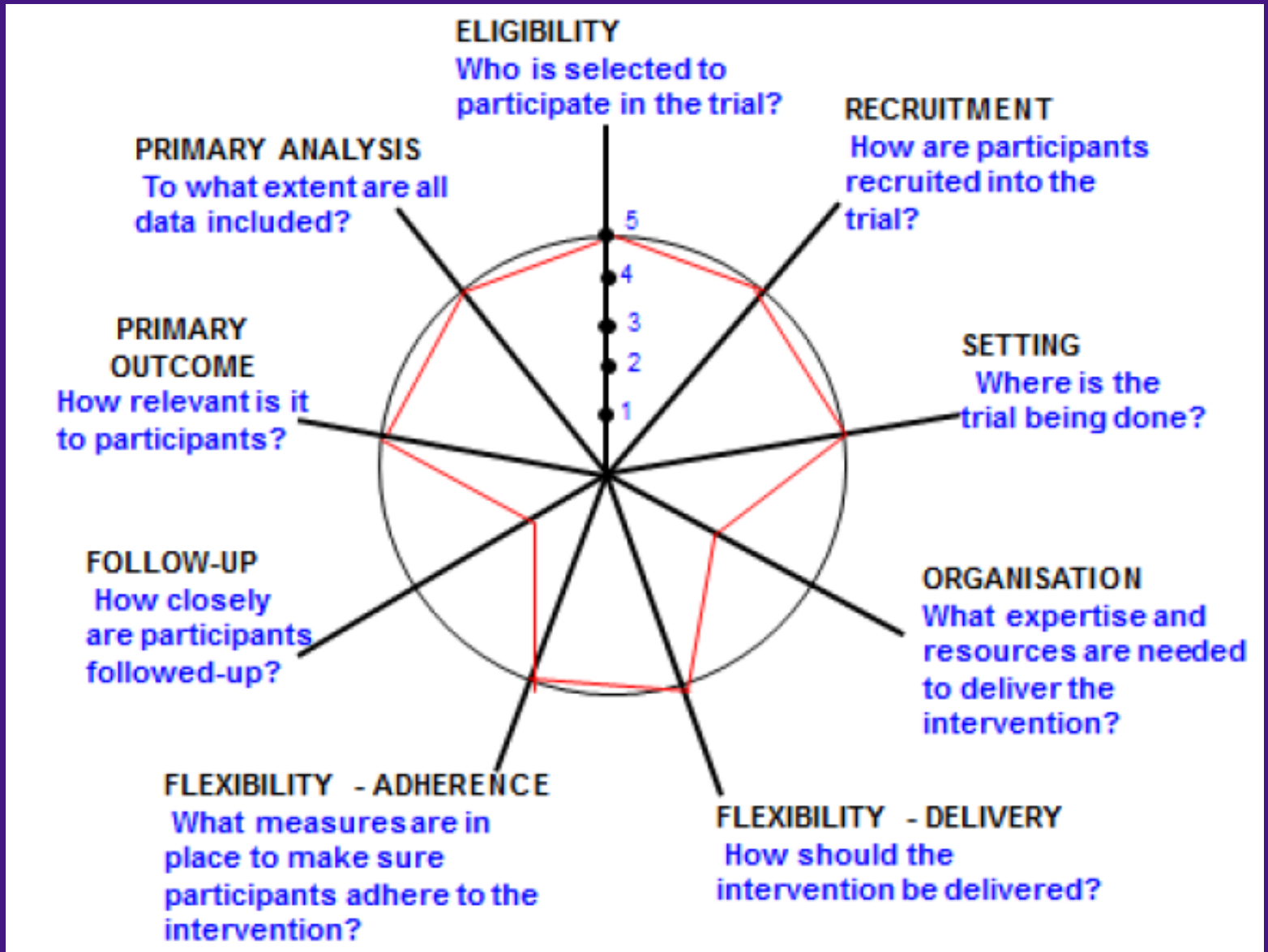
Published at www.cmaj.ca on Apr. 16, 2009. An abridged version of this article appeared in the May 12 issue of *CMAJ*. This article was published simultaneously in the May 2009 issue of the *Journal of Clinical Epidemiology* (www.jclinepi.com).


Eligibility – Who is selected to participate in the trial?
Recruitment - How are participants recruited into the trial?
Setting - Where is the trial being done?
Organisation - What expertise and resources are needed to deliver the intervention?
Flexibility - How should the intervention be delivered?
Flexibility - What measures are in place to make sure participants adhere to the intervention?
Follow-up - How closely are participants followed-up?
Primary outcome - How relevant is it to participants?
Primary analysis - To what extent are all data included?
5
4
3
2
1

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?)

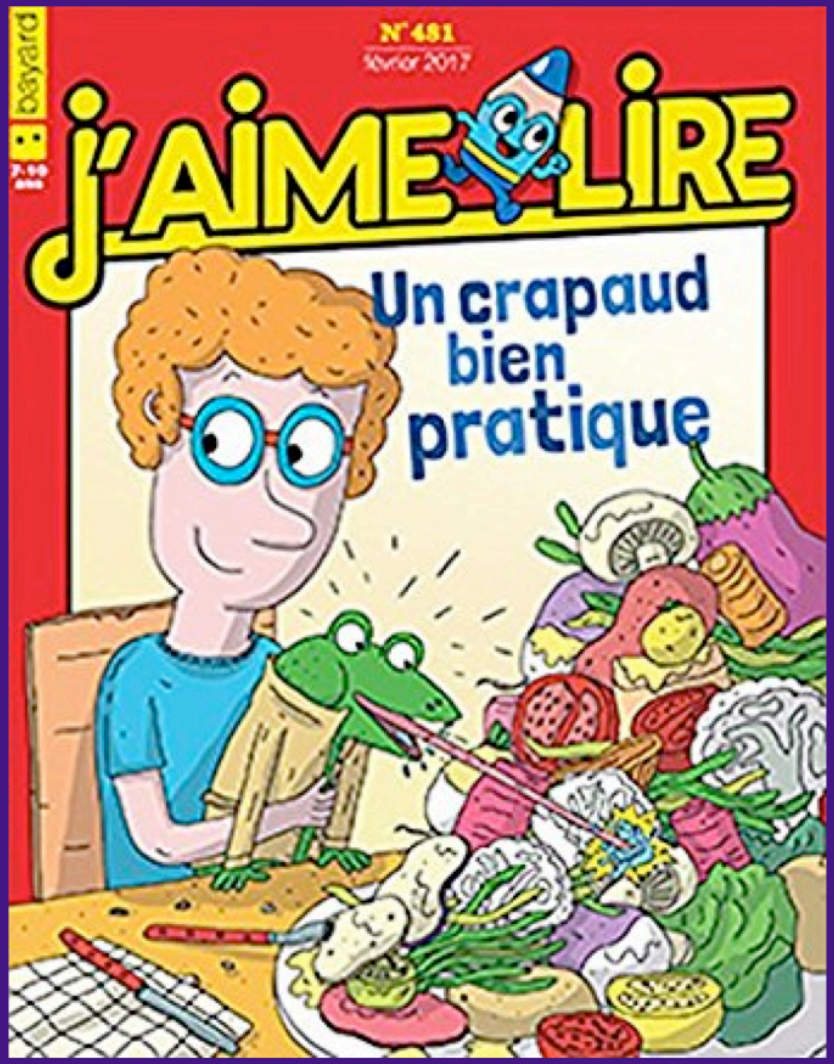
Example from: Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, Mullee M, Stuart B: Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. BMJ 2013, 347:f6041.



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

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

LIRE (pronounced *leer*) from the French verb, ‘to read’.



LIRE Funded by NIH Health Care Systems Research Collaboratory

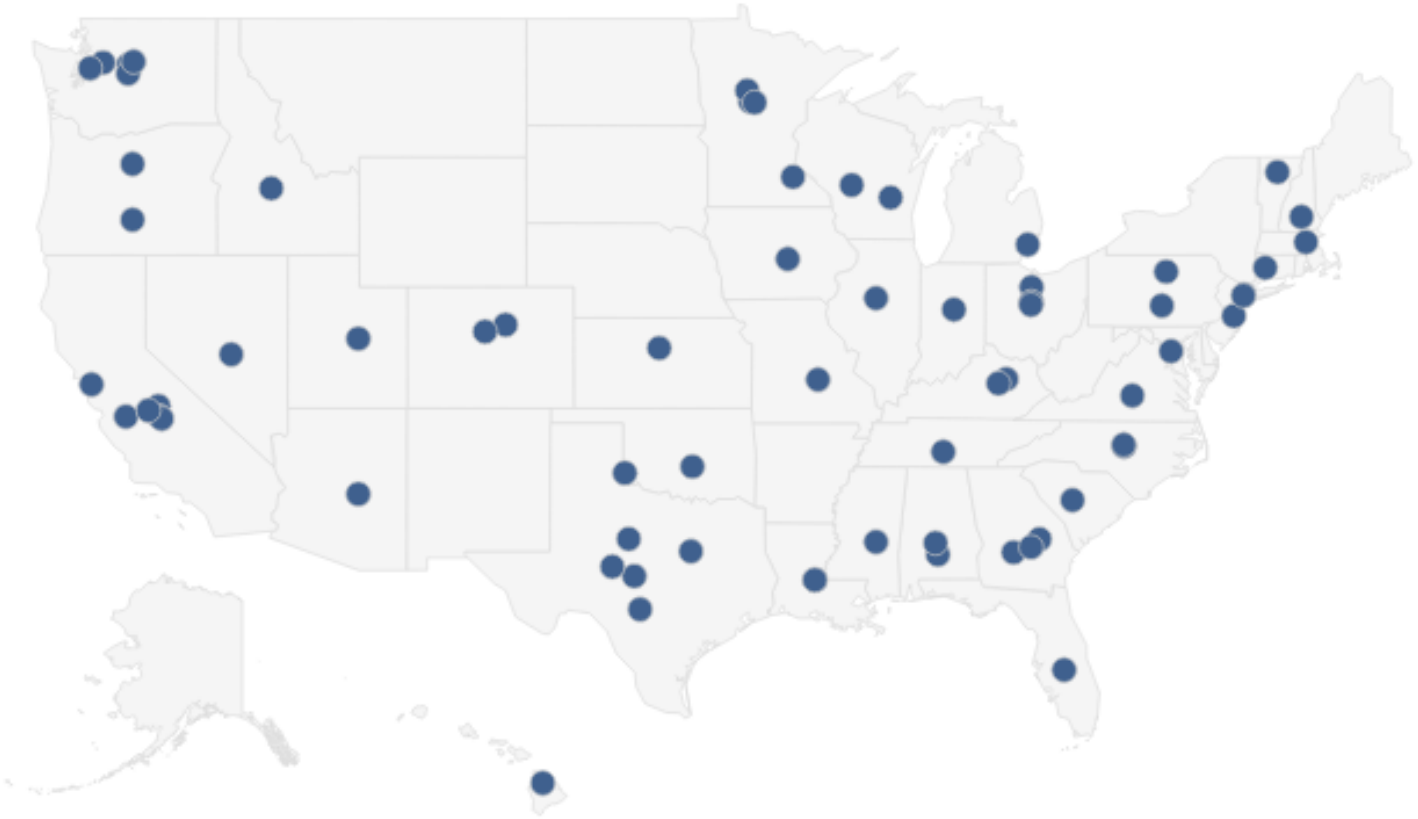
- Supported by the NIH Common Fund
- Goal: improve the way (pragmatic) clinical trials conducted
- Build infrastructure for CER

rethinkingclinicaltrials.org

NIH Collaboratory Demonstration Project Site Distribution

NIH Collaboratory Demonstration Projects are active in health systems across the United States, as shown in the map below. Hover over a pin for more information.

*Please note that pins may represent more than one site per state, and the pin location is not an exact representation.



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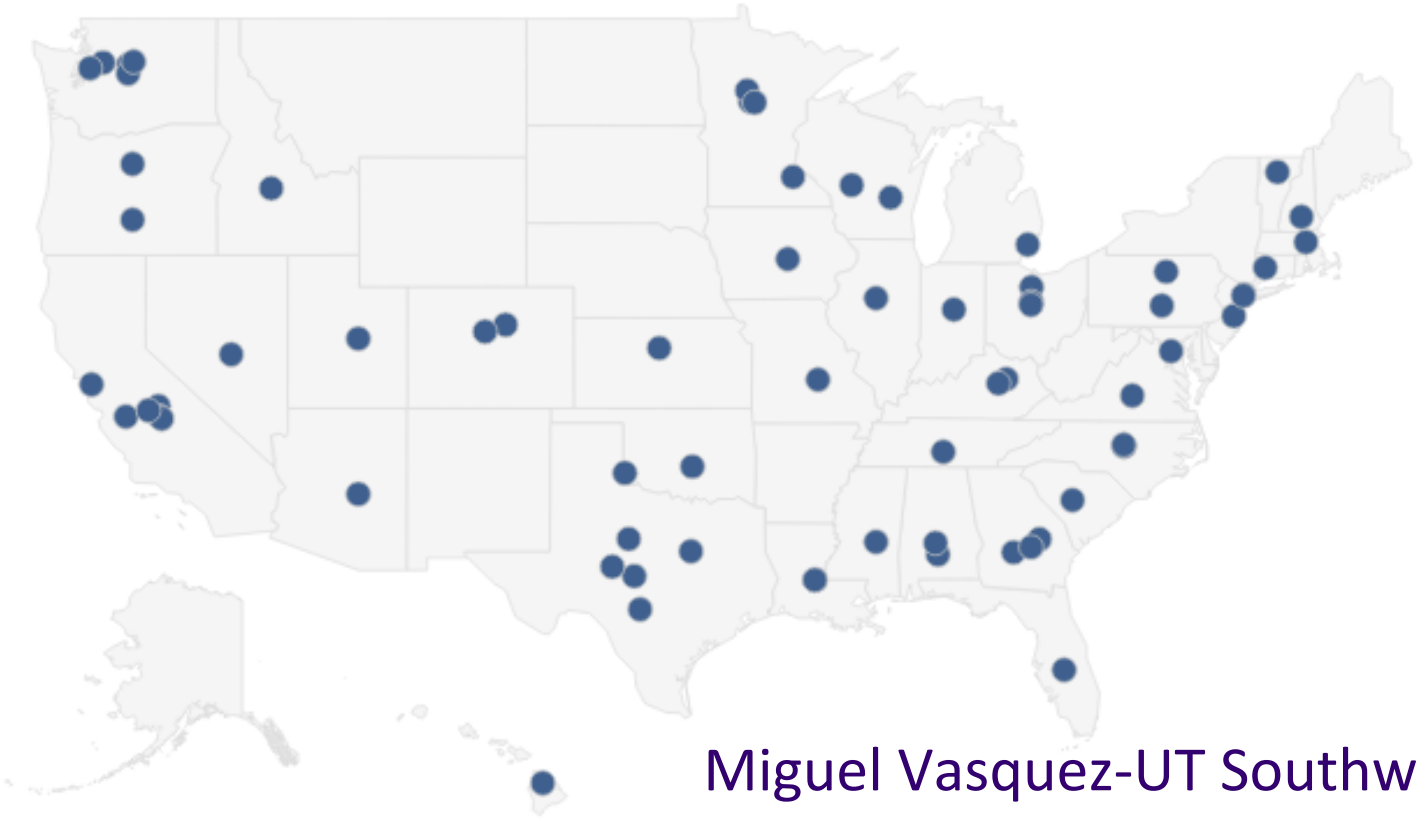
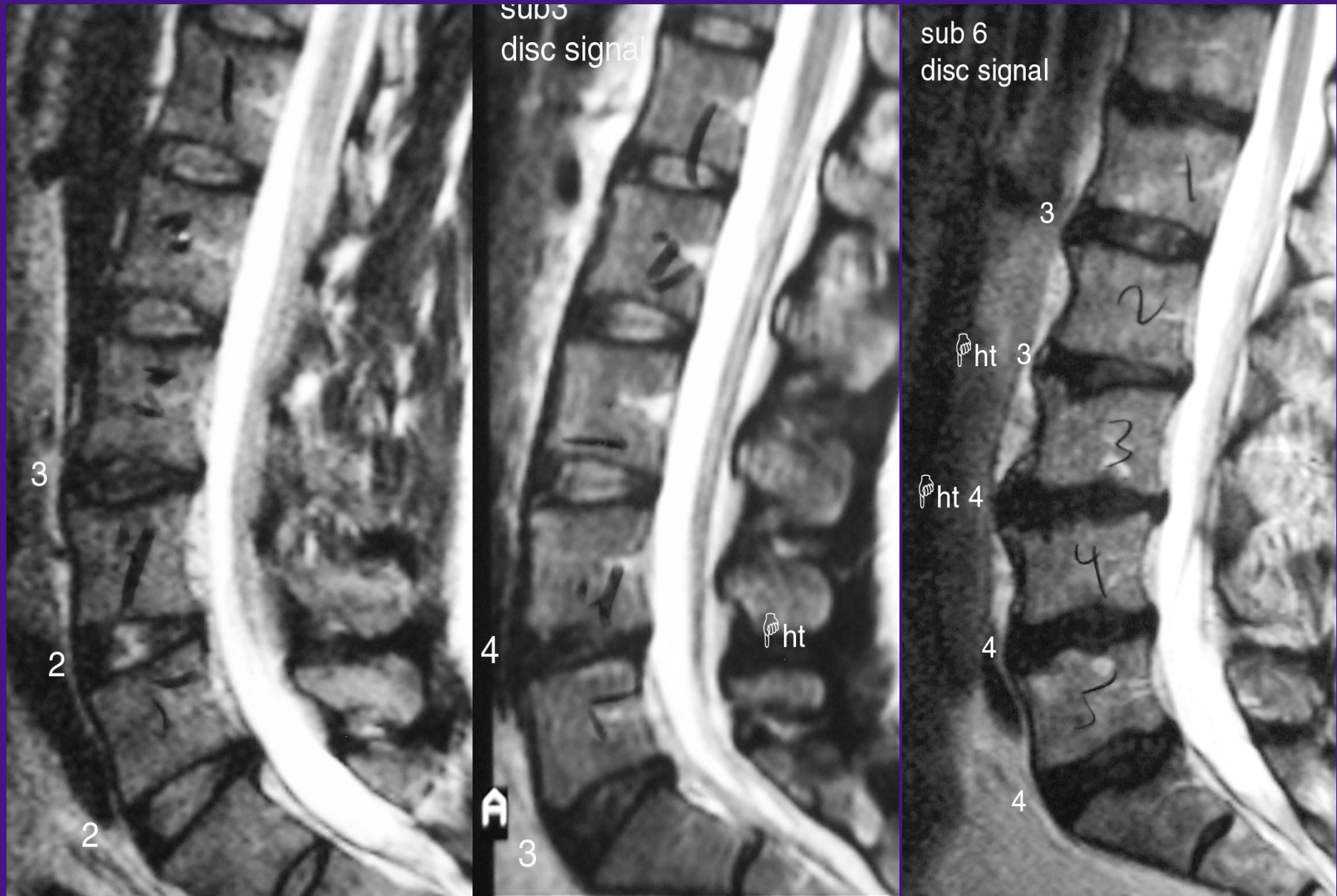


Miguel Vasquez-UT Southwestern

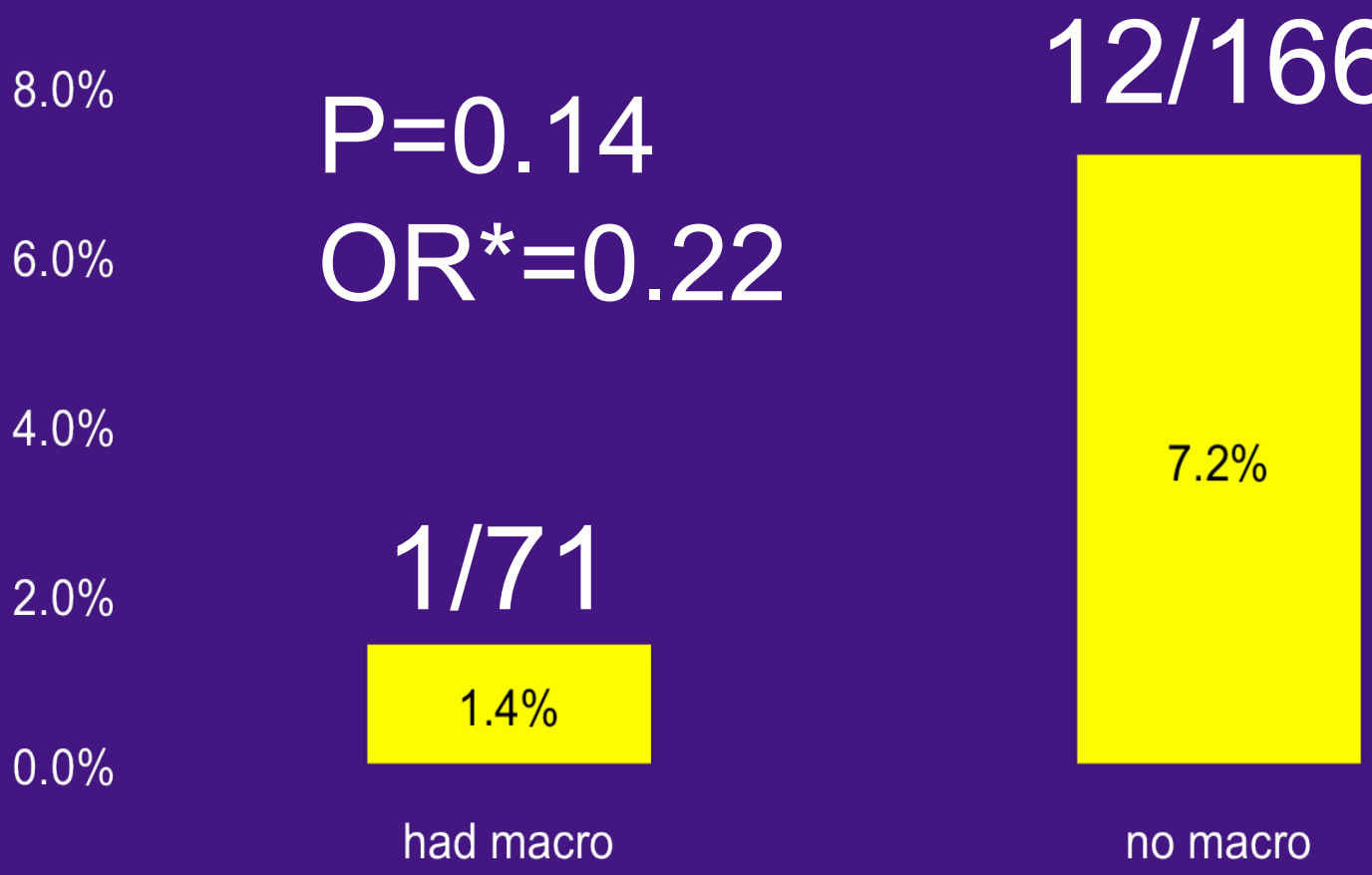
Background and Rationale

- 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

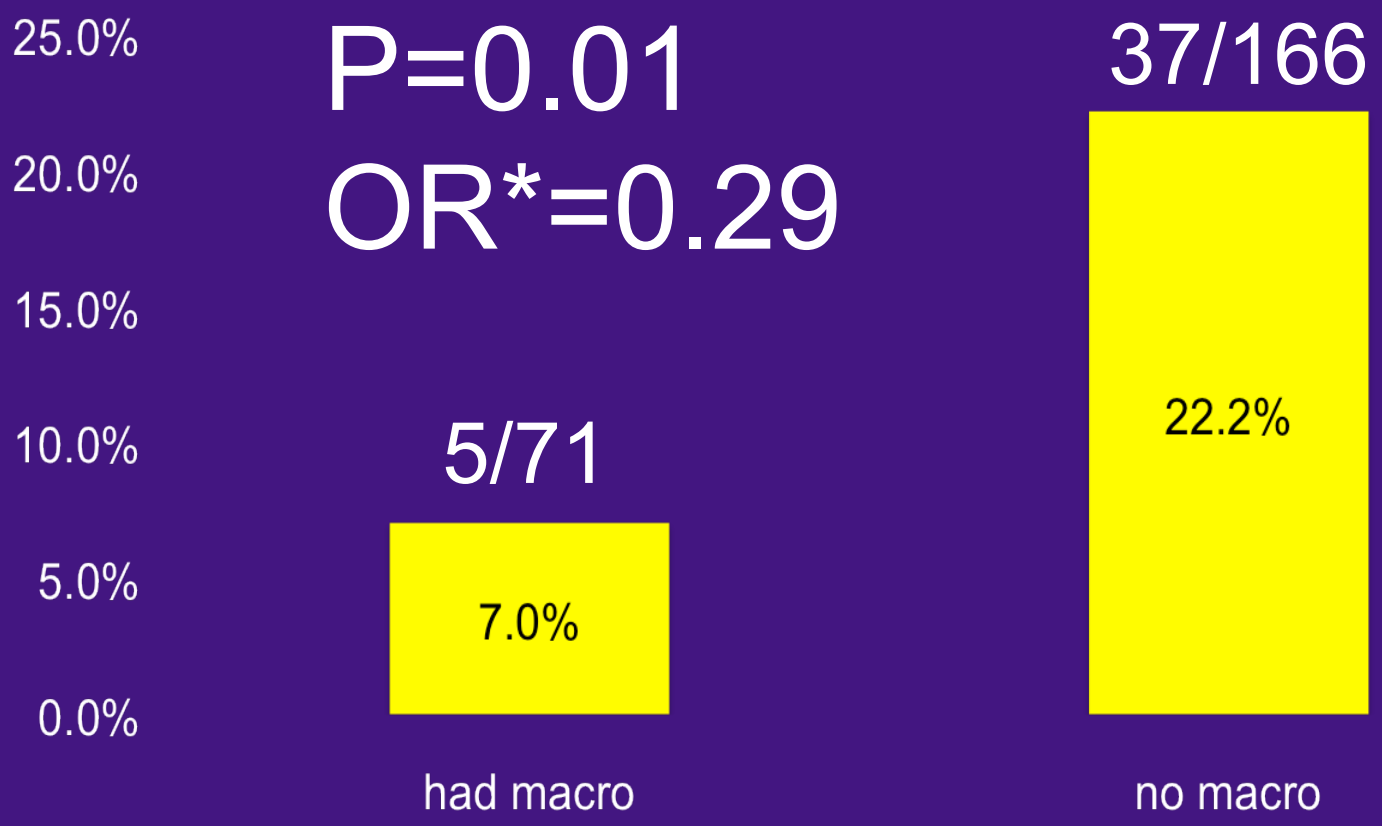


Retrospective Pilot Results: Subsequent Imaging Within 1 Yr



* Adjusted for imaging severity

Retrospective Pilot Results: Narcotic Rx Within 1 Yr



Published this year (Penn+Dartmouth)

Radiology

Jessica G. Fried, MD
Angeline S. Andrew, PhD
Natalie Y. Ring, BS
David A. Pastel, MD

Changes in Primary Care Health Care Utilization after Inclusion of Epidemiologic Data in Lumbar Spine MR Imaging Reports for Uncomplicated Low Back Pain[1]

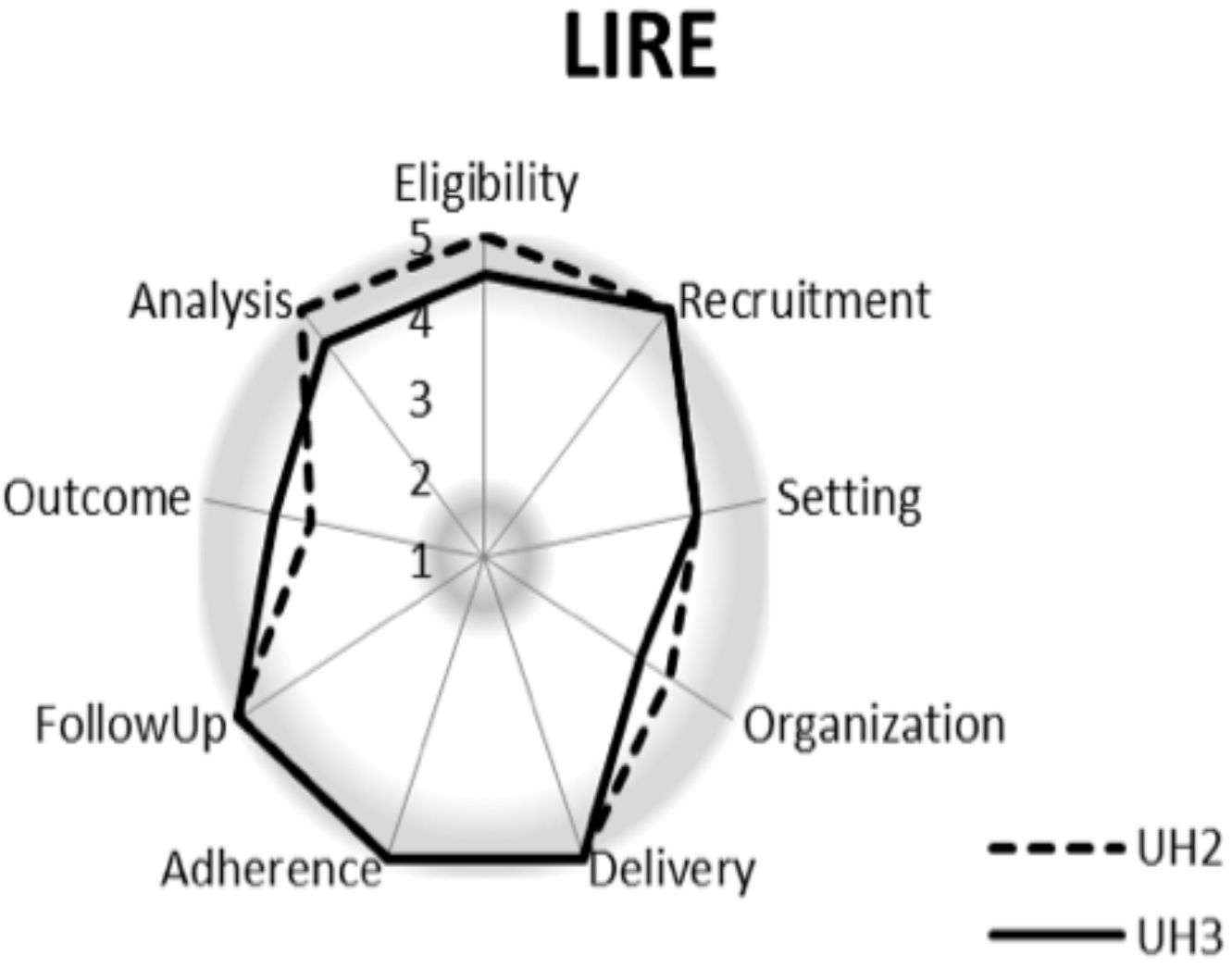
Results: Patients in the statement group were 12% less likely to be referred to a spine specialist (137 of 187 [73%] vs 159 of 188 [85%]; $P = .007$) and were 7% less likely to undergo repeat imaging (seven of 187 [4%] vs 20 of 188 [11%]; $P = .01$) compared with patients in the nonstatement group. The intervention was not associated with any change in narcotic prescription (53 of 188 [28%] vs 54 of 187 [29%]; $P = .88$) or with the rate of low back surgery (24 of 188 [13%] vs 16 of 187 [9%]; $P = .19$).

Conclusion: In this study, inclusion of a simple epidemiologic statement in lumbar MR imaging reports was associated with decreased utilization in high-cost domains of low back pain management.

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


LIRE
Eligibility
5
4
3
2
1
Recruitment
Setting
Organization
Delivery
Adherence
FollowUp
Outcome
Analysis
UH2
UH3

The Intervention

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.

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 - > ☹

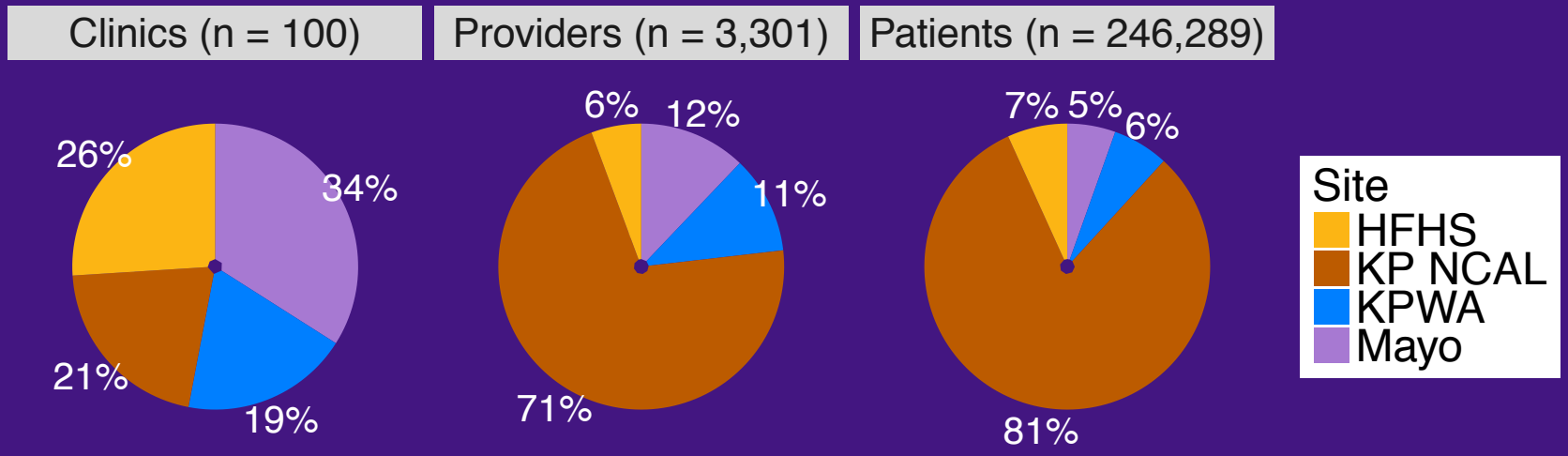
LIRE- Primary Outcome

- A single metric of overall intensity of resource utilization for spine care based on CPTs converted to RVUs
- Passively collected from EHR

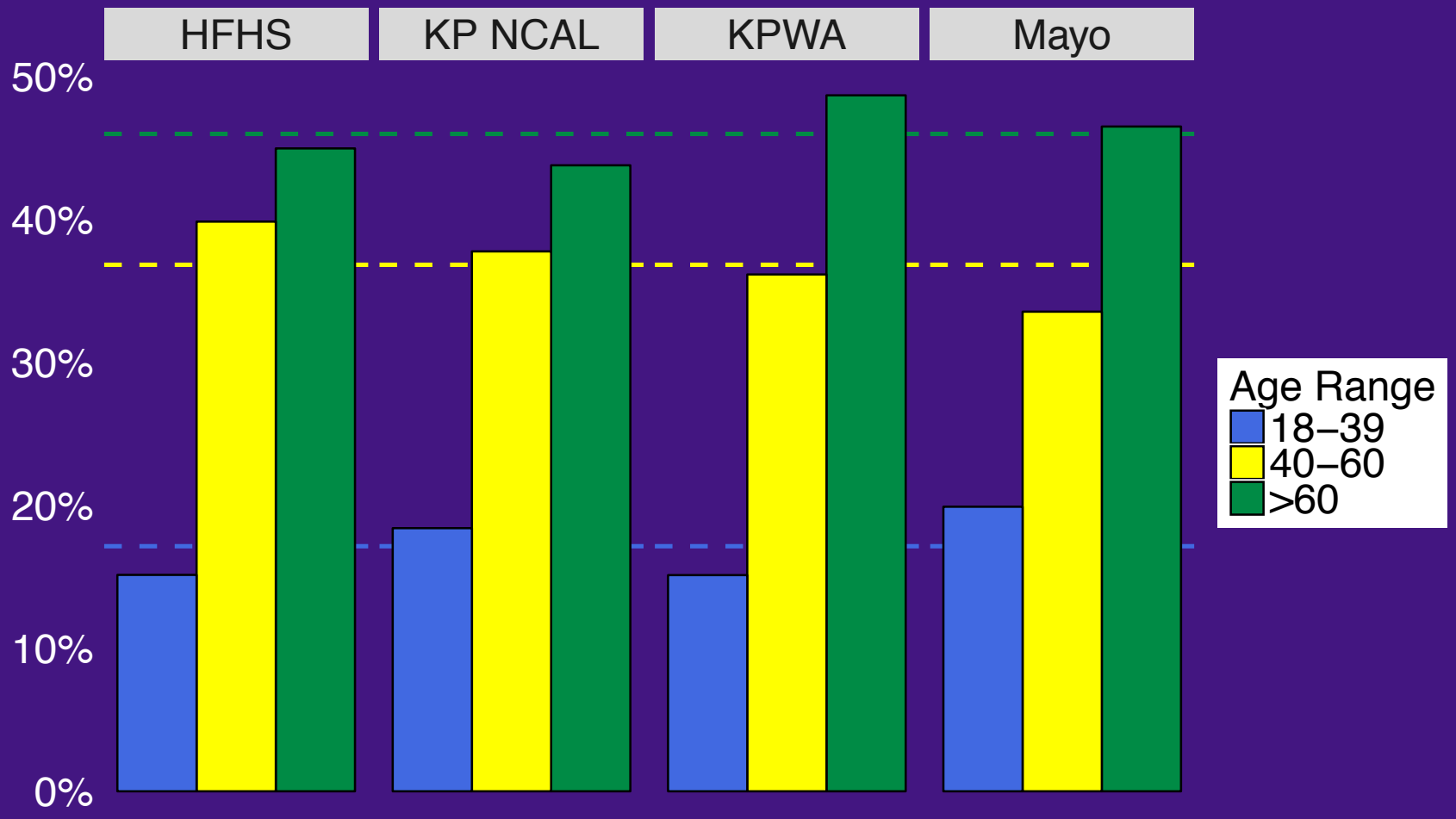
Participating Systems

Name	# Primary Care Clinics (Randomized)	# PCPs (Randomized)
Kaiser Perm. N. California	21	2,349
Henry Ford Health System, MI	26	187
Kaiser Permanente of Washington	19	365
Mayo Health System	34	400
Total	100	3,301

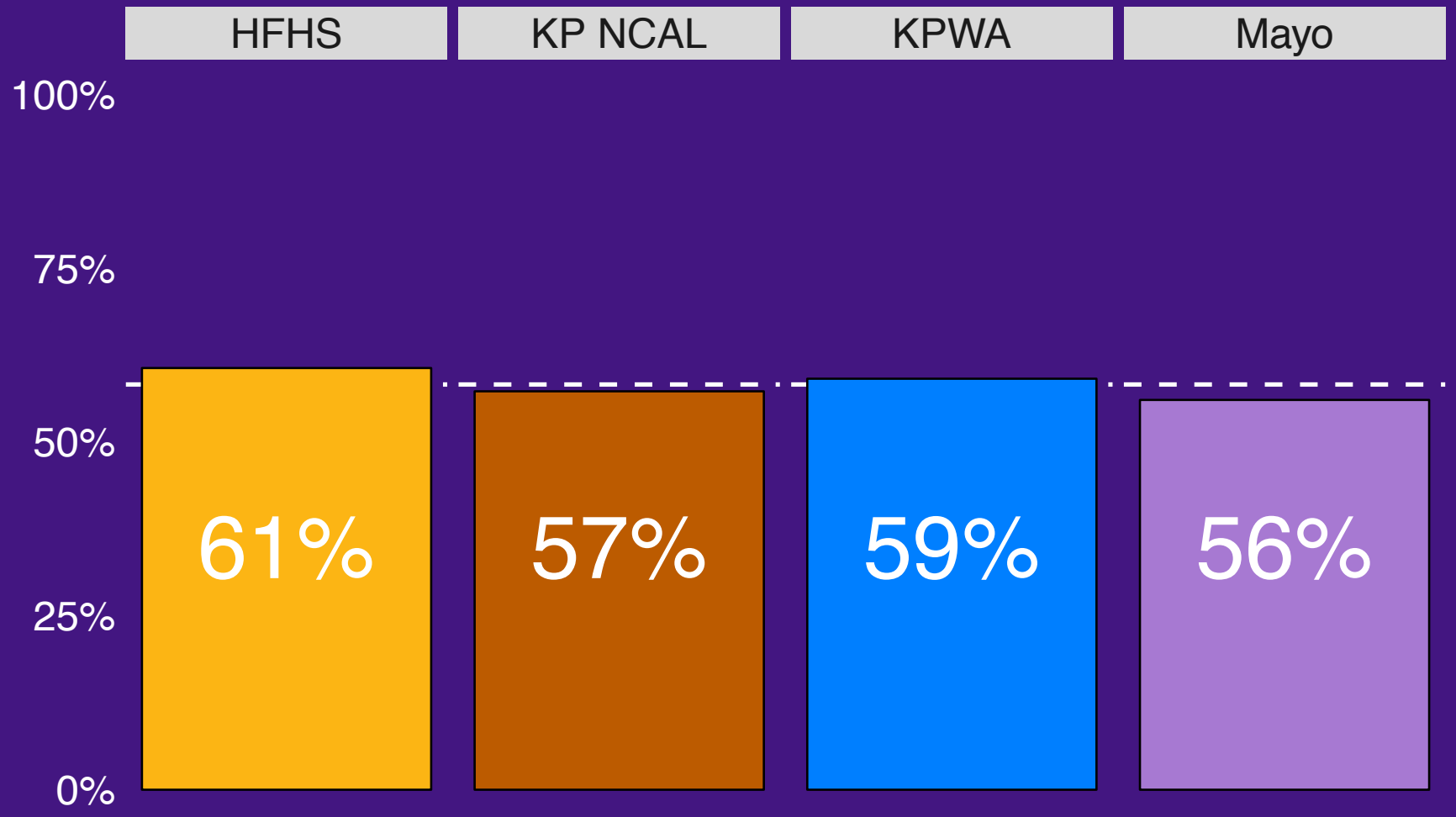
LIRE: Enrollment



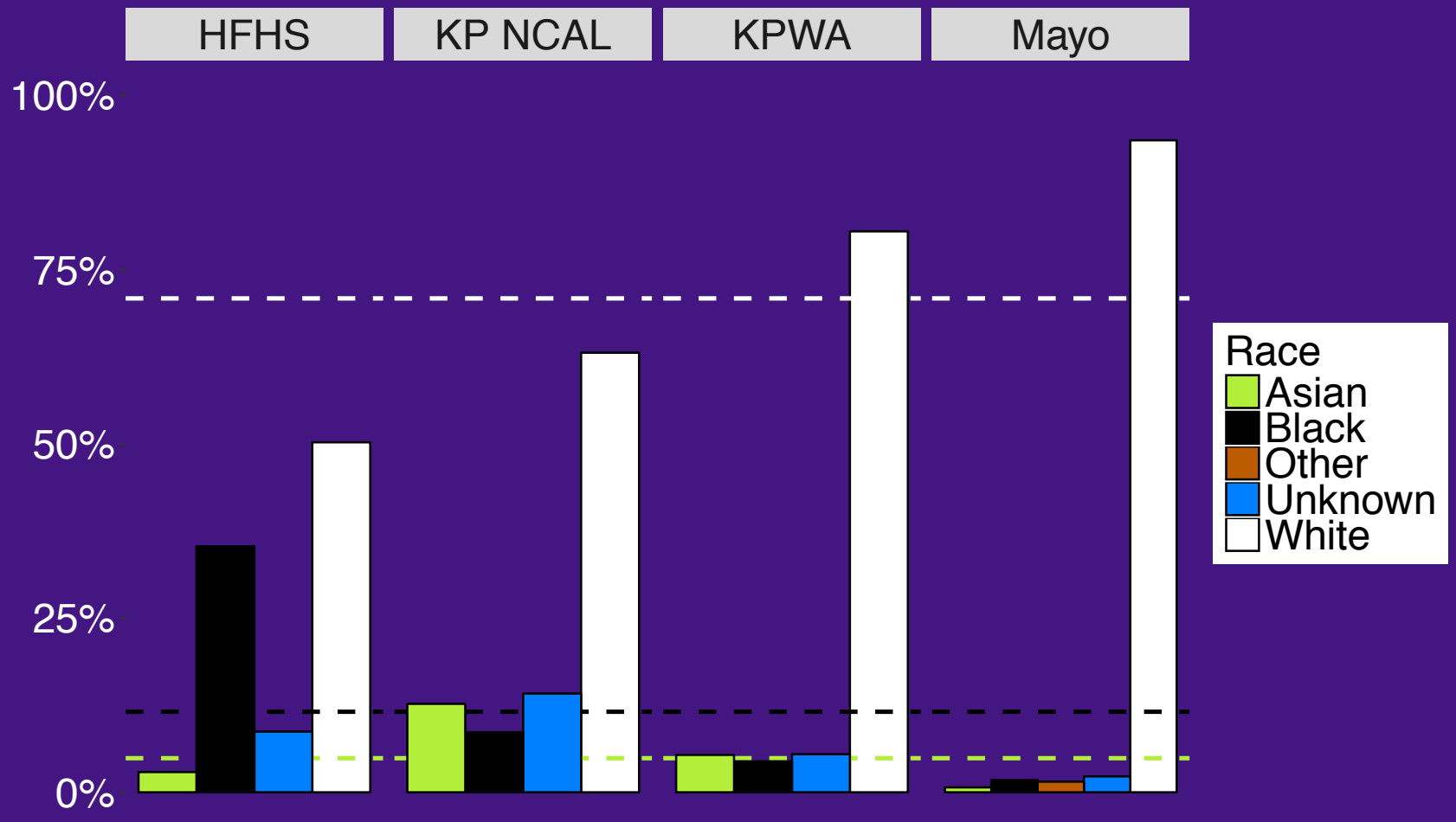
Patient age at index image



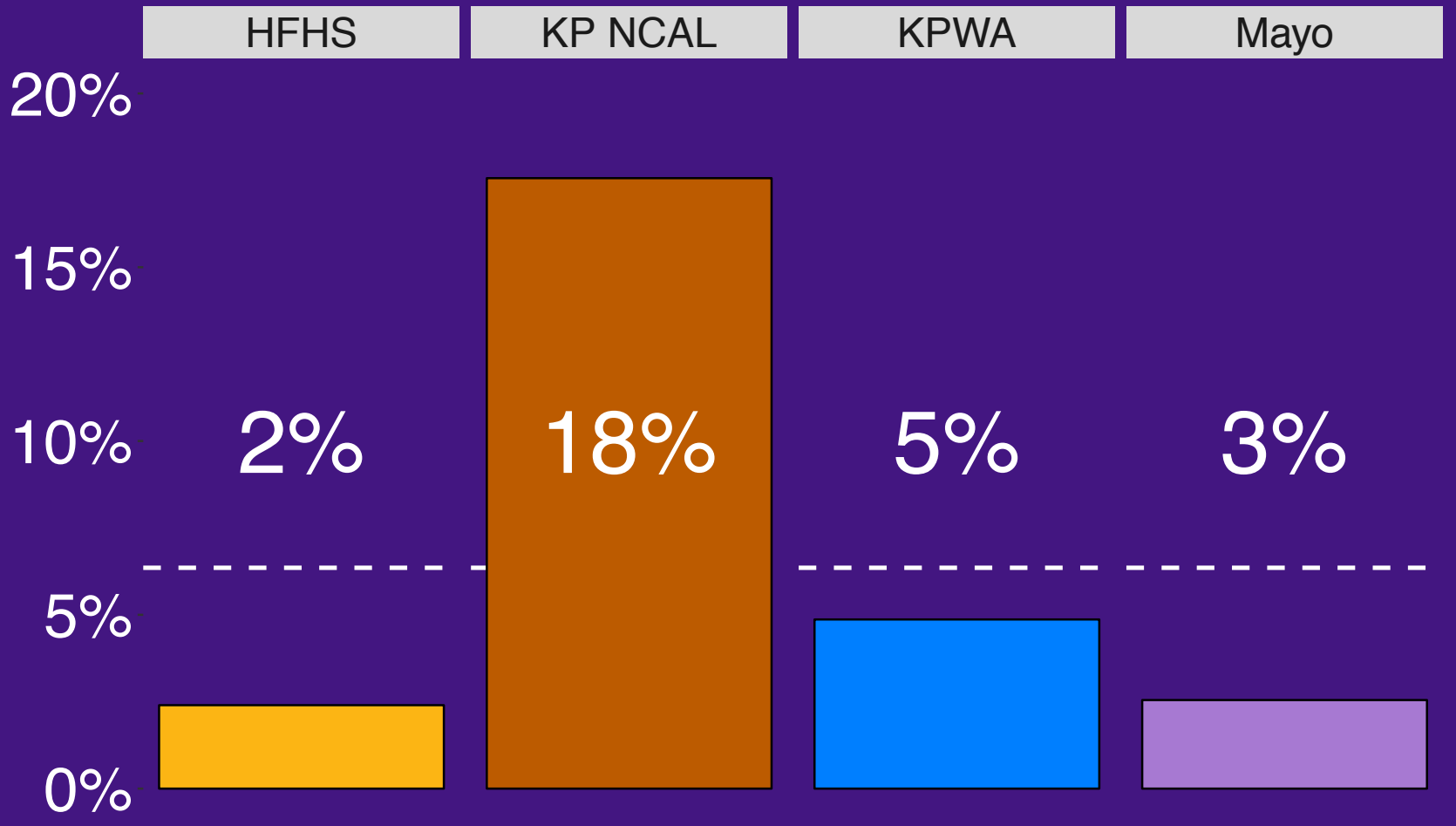
Female



Race


HFHS
KP NCAL
KPWA
Mayo
100%
75%
50%
25%
0%
Race
Asian
Black
Other
Unknown
White

Hispanic Ethnicity



Key Pragmatic Aspects of LIRE

- Broad inclusion criteria
- Waiver of consent/minimal risk
- Simple, easily (relatively) implementable intervention
- Passive collection of outcomes

Barriers Scorecard

Barrier	Level of Difficulty 1 = little difficulty 5 = extreme difficulty				
	1	2	3	4	5
Enrollment and engagement of patients/subjects	X				
Engagement of clinicians and Health Systems		X			
Data collection and merging datasets			X		
Regulatory issues (IRBs and consent)	X				
Stability of control intervention		X			
Implementing/Delivering Intervention Across Healthcare Organizations		X			

Lessons Learned

- top barriers/ challenges
  - –Site programmer engagement
  - –Heterogeneity of data extraction
  - –Getting dates

Advice for Potential PCT Investigators

- Budget for changes
- Be ready to drop/add sites, early on
- Importance of stakeholders; success depends mostly on people and less technology
- Pilot data collection at all sites
- Be sure communication flows through all level of personnel (PIs, programmers, coordinators, etc)
- Get cumulative vs. serial data for QC checks
- Get schematic of data sources feeding into study
- Work w/experienced team (e.g. Miguel Vasquez)

Patient-Centered Outcomes Research Institute

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

www.thecleareenter.org

UW Clinical Learning, Evidence And Research (CLEAR) Center for Musculoskeletal Disorders

- New UW NIH/NIAMS P30 Center
- Focused on transforming clinical → research data
- Data sets available for MSKresearchers
  - Claims (Marketscan, CMS)
  - Observational cohort (BOLD)
  - RCT (not yet…) LESS, LIRE
- Pilot $$ for faculty ($20k/project)

Take Home Points

- Pragmatic vs. Explanatory trials and the PRECIS tool
- NIH Health Care Systems Collaboratory
- PCOR and PCORI
- UW CLEAR Center

Explanatory vs. Pragmatic Trials