

Embedded Pragmatic Clinical Trials and Hybrid Effectiveness-Implementation Trials: Similarities and Differences

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**NIH PRAGMATIC TRIALS
COLLABORATORY**

Rethinking Clinical Trials®

Disclosures

- Hayden Bosworth reports research funding through his institution from BeBetter Therapeutics, Boehringer Ingelheim, Esperion, Improved Patient Outcomes, Luminate Insights, Merck, Cleery, NHLBI, Novo Nordisk, Otsuka, Sanofi, Veterans Administration, Elton John Foundation, Hilton foundation, Pfizer.
- He also provides consulting services for Boehringer Ingelheim, Esperion, Elevance Health, Sanofi, Walmart, Webmed, Janssen. He was also on the board of directors of Preventric Diagnostics.

Learning goals

- Consider the importance of ePCTs, implementation science, and learning health system principles
- Identify key similarities and differences between ePCTs and hybrid trials
- Discuss advantages and disadvantages of ePCTs and hybrid trials and when they can be used to answer research questions

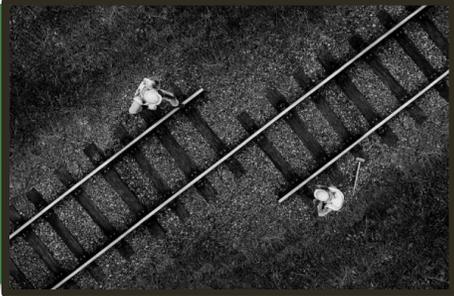


Getting the right evidence to decision-makers



Research timelines vs community needs

- First submission to publication ~6 years at least
- Decisions are made without waiting for research



Mismatched priorities and incentives

- Leaders want specific and timely answers
- Lack of incentives for community engagement



Lack of planning for future scale-up for interventions

- What is the “value proposition”?
- Avoiding “helicopter research”

Important things to know about ePCTs



ePCTs are designed to answer important, real-world clinical questions

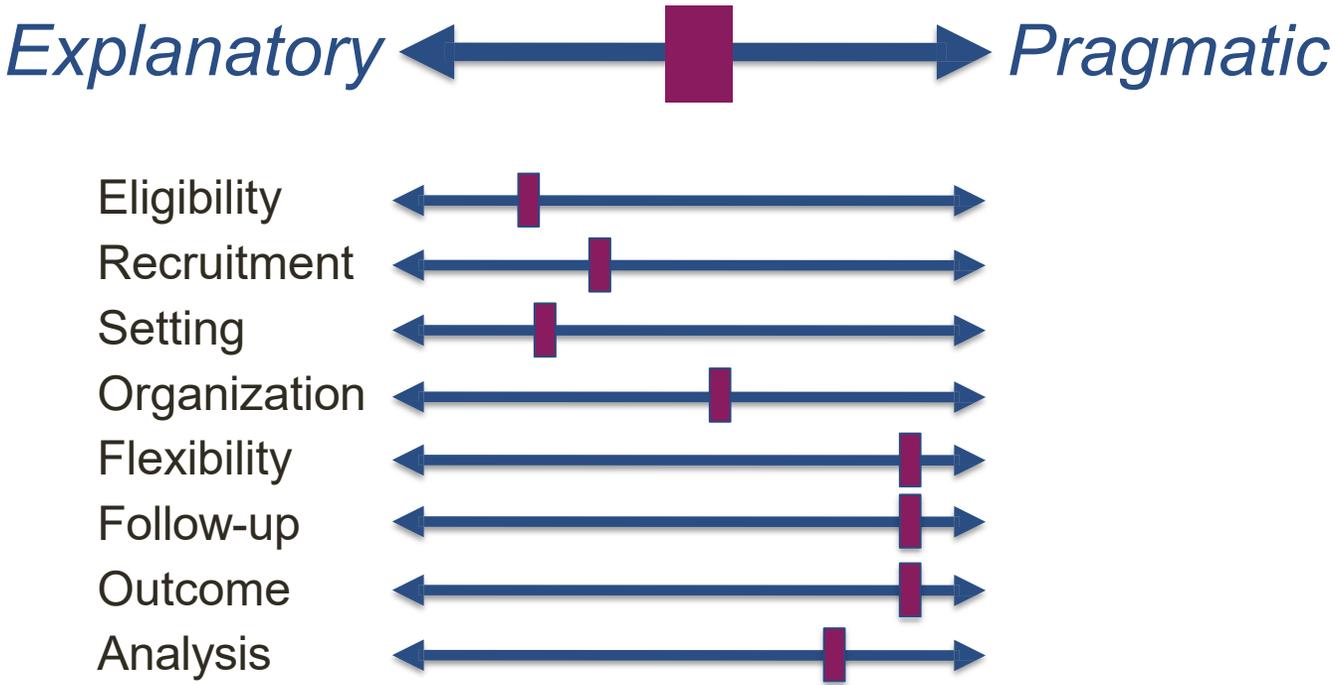


Broad engagement and support are essential from beginning to end



Trade-offs in flexibility, adherence, and generalizability are inevitable

Trials elements vary across a spectrum



Why conduct ePCTs?

- ✓ Potential to inform policy and practice with high-quality evidence



vs traditional trials

ePCT characteristics

Conducted within
healthcare systems

Use streamlined procedures
and existing infrastructure

Answer important
medical questions



Why Do an ePCT? The 5 Rs



Relevant Question

The question is pressing, and healthcare system leaders, patients, and front-line clinicians care about the answer.



Real-World Setting

Desire to test in diverse healthcare delivery settings with the hope of implementing findings widely.



Representative Population

Ability to recruit a population reflective of patients with the condition, including those from minoritized communities.



Routinely Collected Data

Can use data collected as part of healthcare delivery to answer the question, supplemented by data from other sources.



Rigorous Methods

Randomized research is needed to answer the question and inform changes in care, policy, or reimbursement.

Why pragmatic implementation trials?

Answering the right questions for decision-makers

An effective treatment or practice is only as good as how and whether...

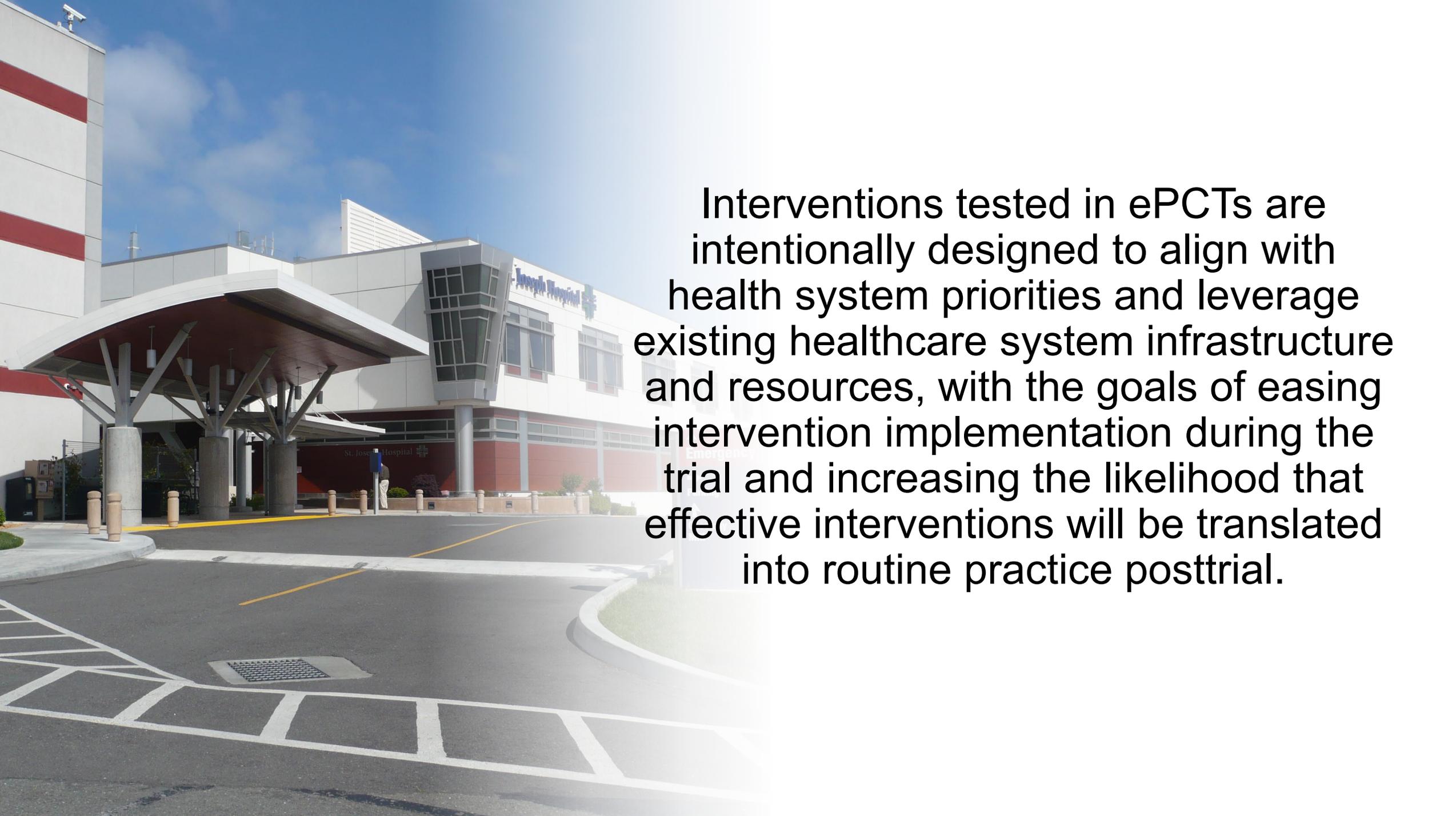
- It is adopted?
- Practitioners are trained to use it?
- Trained practitioners choose to use it?
- Eligible populations/patients benefit from it?

If we assume 50% threshold for each step...

Even with perfect access, adherence, dosage, and maintenance...

Clinical impact

$50\% \times 50\% \times 50\% \times 50\% = 6\% \text{ benefit}$



Interventions tested in ePCTs are intentionally designed to align with health system priorities and leverage existing healthcare system infrastructure and resources, with the goals of easing intervention implementation during the trial and increasing the likelihood that effective interventions will be translated into routine practice posttrial.

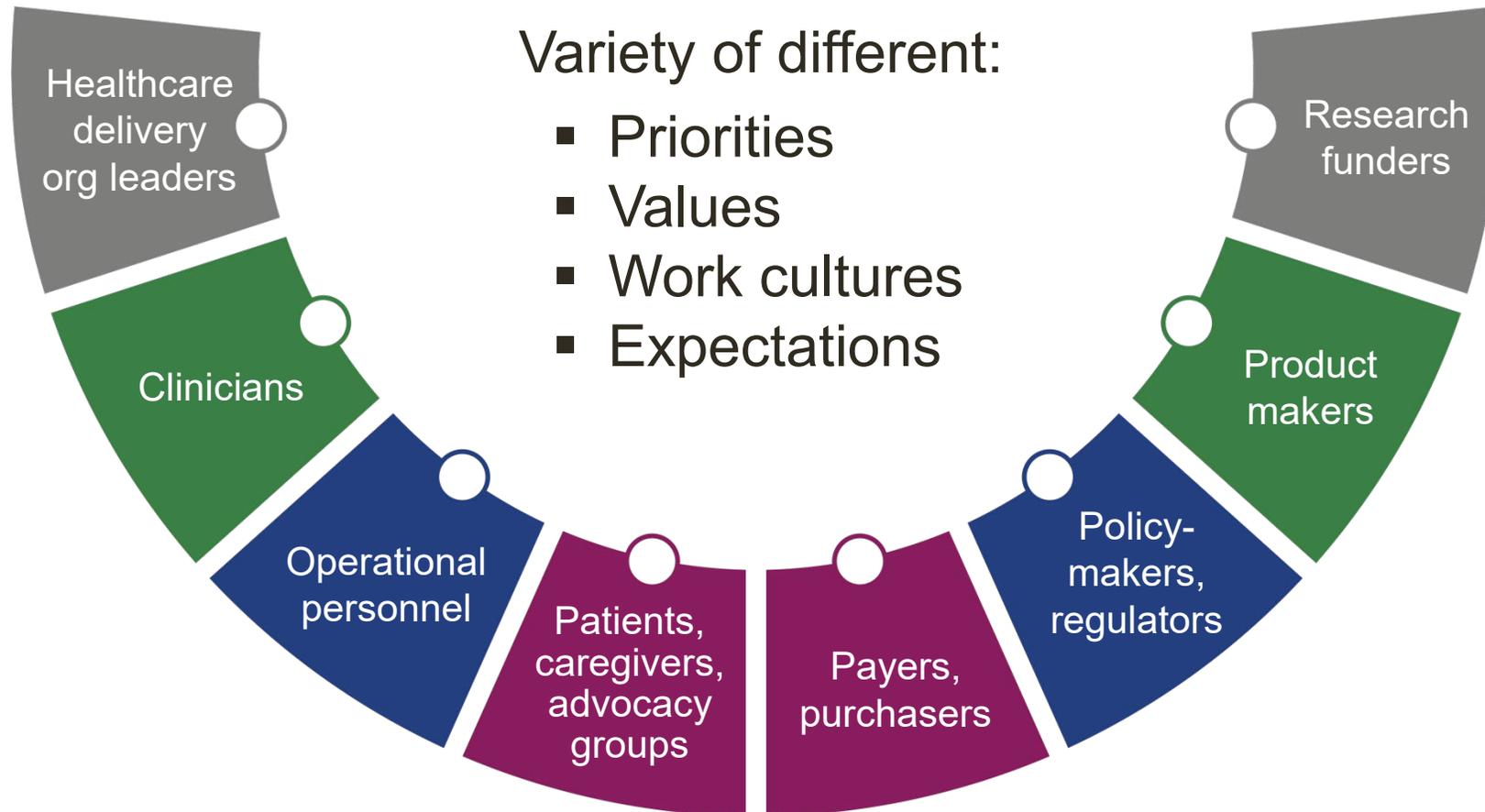
Problems



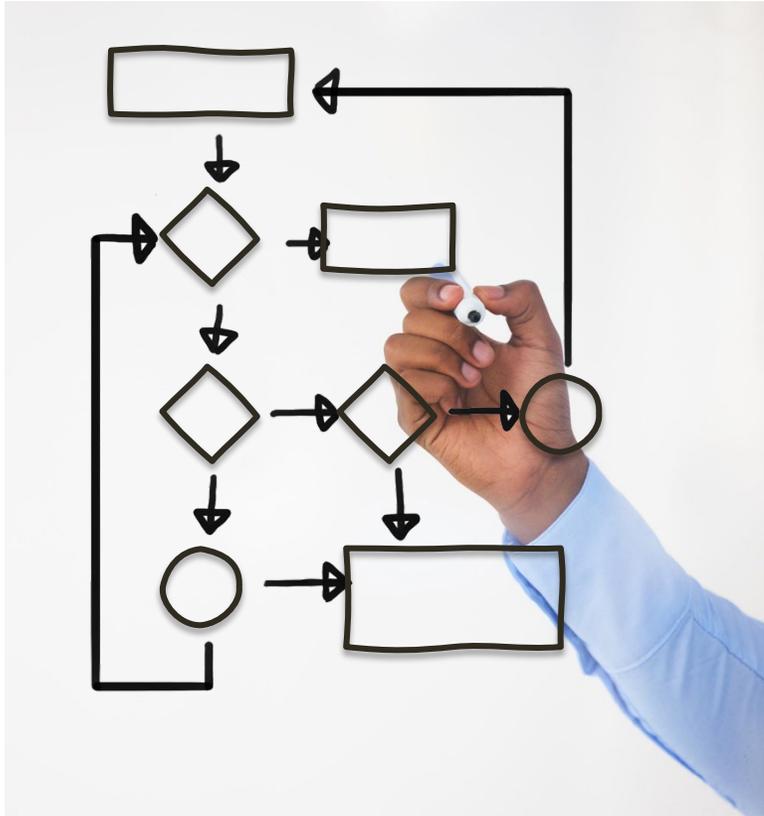
While many effective therapies exist, implementation is slow, ineffective, and unequal

- The delay comes at enormous cost to patients, payers, and manufacturers
- If Implementation is considered, it is late in the development process
- If implementation is not done well, it can make healthcare inequities worse

Who is interested and involved?



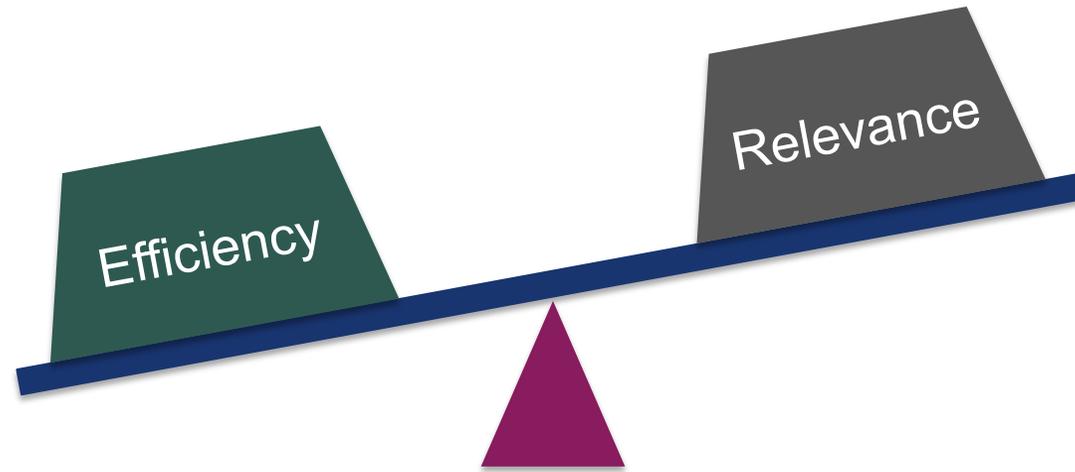
Use existing workflows



“The more complicated the intervention is to the existing workflow, the more difficult it is to get compliance—you can’t just add on a new thing, you have to change what happens on the floor.”

—Vincent Mor, PhD (PROVEN)

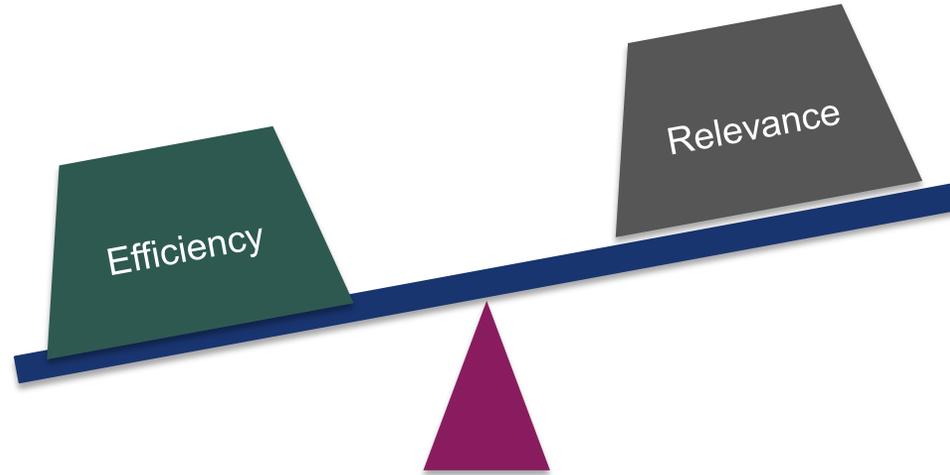
It's a balancing act



ePCTs want to achieve both

But...high relevance to real-world decision-making
may come at the expense of trial efficiency

Example



Trial seeks to measure outcomes that matter most to patients and health systems

+

Information needed not available from the EHR

=

Must assess patient-reported outcomes, which are more expensive and less efficient

Important things to do

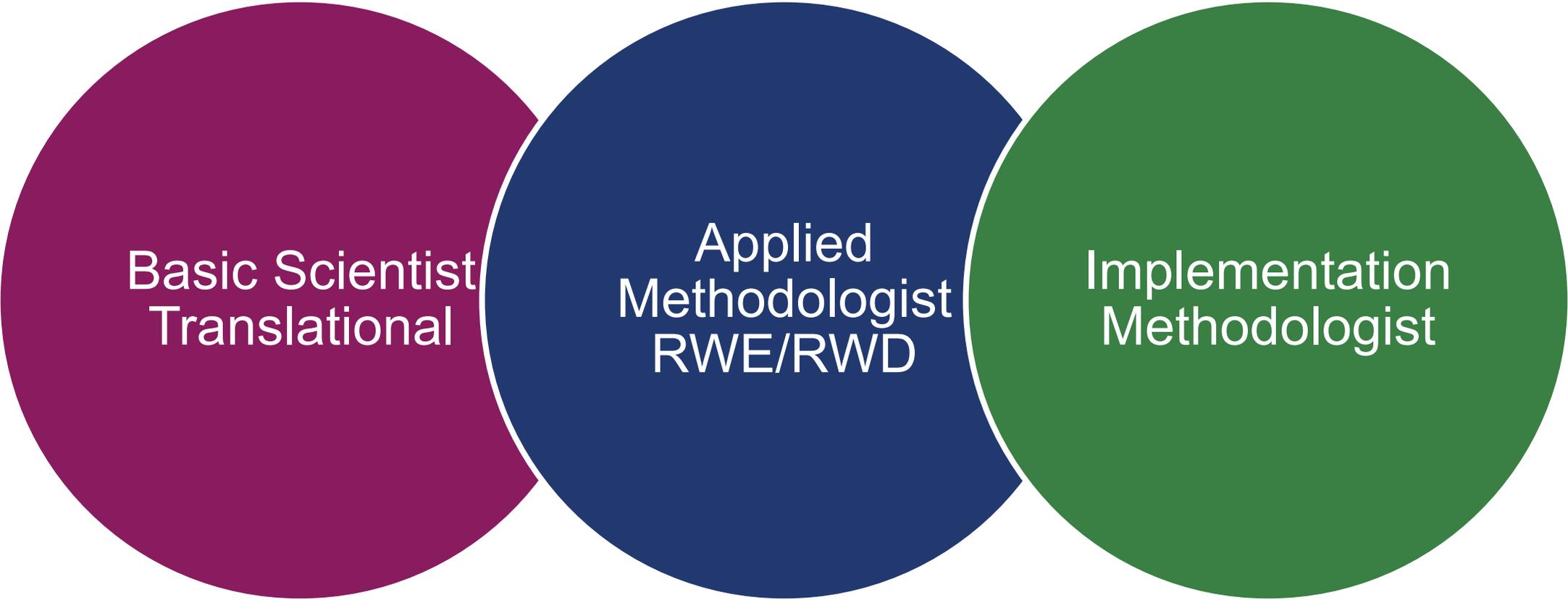


- Set expectations to work collaboratively and build trust from the beginning
- Get to know your partners' values, priorities, and expectations
- Assess your partners' capacity and capabilities
- Track goals reached, challenges, and adaptations throughout the life cycle of your ePCT
- Show appreciation and celebrate accomplishments early and often to have sustained partnerships

Why the increased focus on implementation science?

- “If you build it, they will come” is no longer effective
- Massive investment in innovations has not translated to expected gains in population health
- Clear performance gaps—innovations are not reaching all intended recipients
- Innovations are also not reaching recipients equitably
- Funders see implementation as important for the “last mile” delivery of innovations

3 types of implementation scientists



Why hybrid trial designs?

- Let's go faster!
 - Sequential looks at effectiveness and implementation are slower
- Don't wait for perfect effectiveness data before moving to implementation research
- We can backfill effectiveness data while we test/evaluate implementation strategies
- How do clinical outcomes relate to adoption and fidelity?
 - How will we know this without data from both sides?

Important things to know about hybrid trials



Hybrid trial designs focus on both clinical effectiveness and implementation outcomes

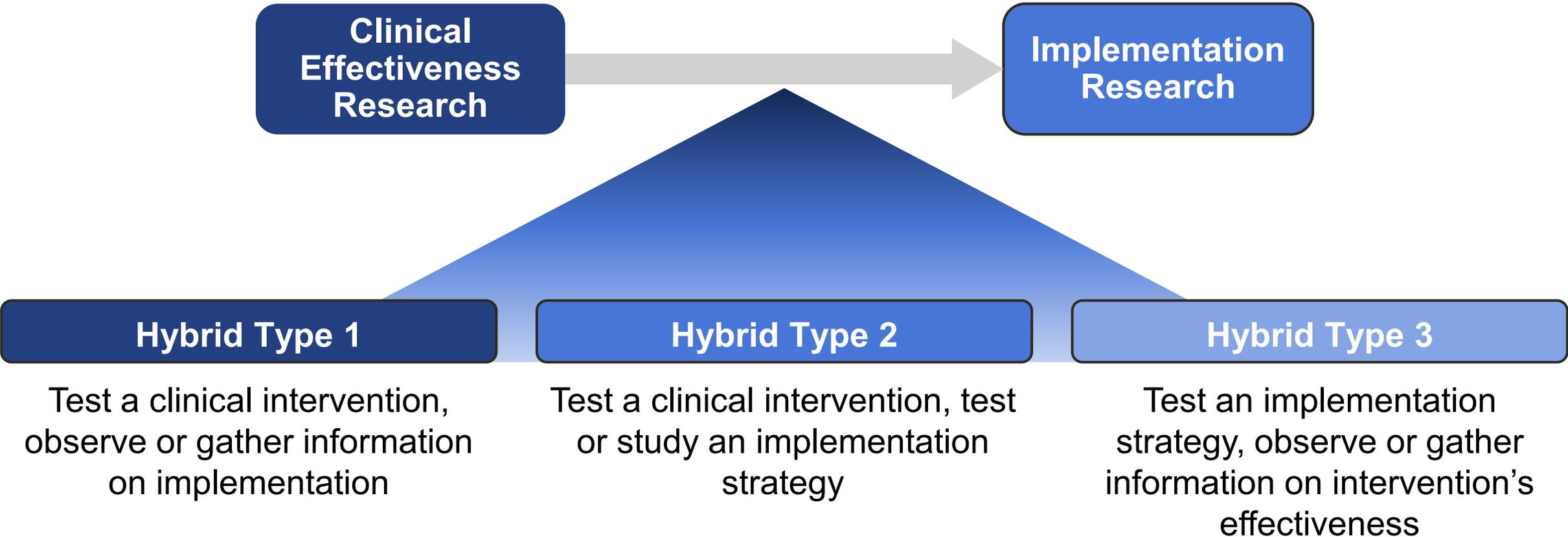


ePCTs are usually type 1 or type 2 hybrid trials



Choosing the right design balances understanding effectiveness and optimizing implementation strategies

Types of hybrid designs



Hybrid type 1

1

- Clinical trial PLUS
 - Implementation-focused process evaluation
 - Usually a mixed-methods study of what worked or didn't
 - Revise intervention? Implementation strategies needed?
- Indications
 - Clinical effectiveness data remain limited, so “too early” for intensive focus on implementation, but...
 - Ideal opportunity to explore implementation issues, learn what's needed for future focus on implementation (study or do...)

Hybrid type 1 example: PPACT

1

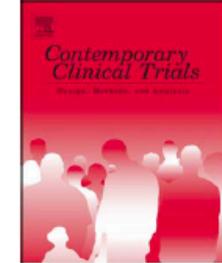
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journal homepage: www.elsevier.com/locate/conclintrial



Interdisciplinary team-based care for patients with chronic pain on long-term opioid treatment in primary care (PPACT) – Protocol for a pragmatic cluster randomized trial



Lynn DeBar^{a,*,1}, Lindsay Benes^{a,b}, Allison Bonifay^a, Richard A. Deyo^c, Charles R. Elder^a, Francis J. Keefe^d, Michael C. Leo^a, Carmit McMullen^a, Meghan Mayhew^a, Ashli Owen-Smith^{e,f}, David H. Smith^a, Connie M. Trinacty^g, William M. Vollmer^a

Hybrid type 1 example: PPACT

1

- Effectiveness aim: Determine effectiveness of team-based intervention for reducing pain impact
- Implementation aim: Conduct an implementation-focused process evaluation to assess reach of and fidelity to the intervention, and barriers and facilitators

Hybrid type 2

2

- Clinical trial nested within...
 - Implementation trial of competing strategies
 - Pilot (one-arm) study of single implementation strategy
- Indications
 - Clinical effectiveness data available, though perhaps not for your population or context of interest
 - Have data on barriers and facilitators to implementation
 - “Implementation momentum” within healthcare system

Hybrid type 2 example: STOP CRC

2

Green *et al. Implementation Science* (2019) 14:53
<https://doi.org/10.1186/s13012-019-0903-5>

Implementation Science

METHODOLOGY

Open Access

Using a continuum of hybrid effectiveness-implementation studies to put research-tested colorectal screening interventions into practice



Beverly B. Green^{1*} , Gloria D. Coronado², Malaika Schwartz³, Jen Coury⁴ and Laura-Mae Baldwin³

Hybrid type 2 example: STOP CRC

- Effectiveness aim: Determine effectiveness of mailed outreach for increasing colorectal cancer screening
- Implementation aim: Determine feasibility and potential utility of an implementation strategy (training, technical support, PDSA)

Hybrid type 3

3

- Implementation trial!
 - Primary test is comparing implementation strategies
 - Clinical effectiveness is a secondary analysis
- Indications
 - We sometimes proceed with rollouts or implementation studies of interventions without strong effectiveness data
 - Interested in exploring how clinical effectiveness might vary by extent and/or quality of implementation?

Hybrid type 3 example: ENABLE

3

Zubkoff *et al. Implementation Science* (2021) 16:25
<https://doi.org/10.1186/s13012-021-01086-3>

Implementation Science

STUDY PROTOCOL

Open Access

A cluster randomized controlled trial comparing Virtual Learning Collaborative and Technical Assistance strategies to implement an early palliative care program for patients with advanced cancer and their caregivers: a study protocol



Lisa Zubkoff^{1,2*} , Kathleen Doyle Lyons^{3,4}, J. Nicholas Dionne-Odom^{5,6,7}, Gregory Hagley³, Maria Pisu^{1,7}, Andres Azuero^{1,5,6}, Marie Flannery⁸, Richard Taylor^{5,6}, Elizabeth Carpenter-Song⁹, Supriya Mohile^{8†} and Marie Anne Bakitas^{5,6,7†}

Concluding points

- This was a very brief summary!
- ePCTs are usually type 1 or 2, depending on how ready you are to test an implementation strategy on summative implementation outcomes
 - To describe implementation during the trial and prepare for later work on real-world implementation strategies = 1
 - To test the impact of real-world strategies on implementation outcomes like adoption and fidelity = 2

Learn more

- Curran et al. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. 2012 Mar;50(3):217-26. PMID: 22310560.



- Landes et al. An introduction to effectiveness-implementation hybrid designs. *Psychiatry Res*. 2019 Oct;280:112513. PMID: 31434011.

Question & Answer



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Knowledge Checkpoint



- Which of the following are common design elements of embedded pragmatic clinical trials?
 1. Interventions delivered by clinicians or other providers already in the health care setting
 2. Enrollment criteria for participants are broad to increase generalizability
 3. Data from electronic health records are leveraged for some of the study outcomes
 4. All of the above

Knowledge Checkpoint



- True or False: Researchers know the most important questions to ask in clinical trials and it doesn't matter if the health care system partner thinks the research is unimportant.

Knowledge Checkpoint



- True or False: Implementation science methods and strategies can improve the conduct of embedded pragmatic clinical trials.