



Applying implementation science to clinical trial improvement

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Health Research Board: Trial Methodology Research Network Webinar

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Personal context

- Urologic oncologist at the University of Michigan, USA
- Clinical practice: mostly cancer surgery
- Research interests/training:
 - health services research
 - implementation science
 - clinical trials



Disclosures

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Outline

- Introduction
- Clinical trials as a complex, evidence-based practice
- Trials and tribulations: struggling with trial conduct
- A (very brief) intro to implementation science
- Applying implementation science to clinical trials
- Next steps in clinical trials implementation science

Highlighting Clinical Trialists

- Clinical trials are a huge amount of work
- Appreciation and respect to all involved in trials
- Aim of talking about trial “failure” is to focus on future improvement



Clinical trials as evidence-based practice



Why care about trials

- Trials advance science, lead to new treatments, benefit patients
- Trials benefit individual participants regardless of arm
- Trial participation can be considered standard of care



National Comprehensive
Cancer Network®

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial.

Participation in clinical trials is especially encouraged.

Why care about trial *conduct*

- Trials are a huge source of both costs and revenue
 - \$50 billion a year invested in trials worldwide
 - \$millions from individual centers invested in trial support alone
 - \$4,000 - 20,000 paid per patient enrolled on a trial

Grand View Research Clinical Trials Market Size, July 2021
May, *Nature Medicine*, March 2019



Trials' Tribulations



Trials often fail



Adult Cancer Clinical Trials That Fail to Complete: An Epidemic?

Kristian D. Stensland, Russell B. McBride, Asma Latif, Juan Wisnivesky, Ryan Hendricks, Nitin Roper, Paolo Boffetta, Simon J. Hall, William K. Oh, Matthew D. Galsky

Estimating the rate and reasons of clinical trial failure in urologic oncology

Kristian D Stensland, MD, MPH^{a,b,*}, Krystal DePorto, MD^c, James Ryan, BA^c, Samuel Kaffenberger, MD^a, Lael S. Reinstatler, MD, MPH^d, Matthew Galsky, MD^e, David Canes, MD^b, Ted A. Skolarus, MD, MPH^a, Alireza Moinzadeh, MD, MHL^b

- **1 in 5 cancer clinical trials fails**
- Most trials fail due to low enrollment
- Thousands of patients are enrolled on trials that fail

Trial enrollment is low and slow

- 2-8% of eligible cancer patients enroll on trials
- This suggests a majority of patients may not be receiving the best possible care for their cancer
- Few trials complete enrollment in the planned timeframe

Murthy et al., *JAMA* 2004

Fleury et al., *JAMA Onc.* 2021

Strujo et al., *Clinical Trials* 2020

Shadbolt, *JAMA Netw. Open* 2023

Underpowered trials?

JCO® Clinical
Cancer
Informatics

Assessing Genitourinary Cancer Clinical Trial Accrual Sufficiency Using Archived Trial Data

Kristian Stensland, MD, MPH¹; Samuel Kaffenberger, MD²; David Canes, MD¹; Matthew Galsky, MD³; Ted Skolarus, MD, MPH²;
Alireza Moinzadeh, MD, MHL¹

- Half of all trials failed to meet 85% of goal enrollment
- **A third of *completed* trials failed to meet 85% of goal enrollment**

Summing so far

- Trials have huge benefits and can be considered an evidence-based practice
- Trial enrollment remains low, perhaps reflecting poor implementation

Clinical trials are complex evidence-based practices often suffering from poor implementation.

Stensland et al., *Cancer* 2022



Trials implementation framing



The imp sci approach

- How do we get people to do good things more, and better?
- If clinical trials are so good, why aren't more people enrolling?
- How do we close this evidence to practice gap?

Implementation framing

- Vaccines: exceptionally efficacious in clinical trials
- Real world: suboptimal uptake of vaccines
- This reflects poor *implementation* of an evidence-based intervention
- Real world impact = efficacy * implementation

Implementation made (too) easy

- Ultimate goal: increase and improve real world use of things
- Measure how well we're doing the things
- Develop targeted strategies to improve how we do things
- Evaluate context so we can adapt and target the strategies
- Essentially: problem solving with scientific frameworks

Curran, *Imp Sci Comm*, 2020

Our trials problem: enrollment

- How do we improve trial enrollment?

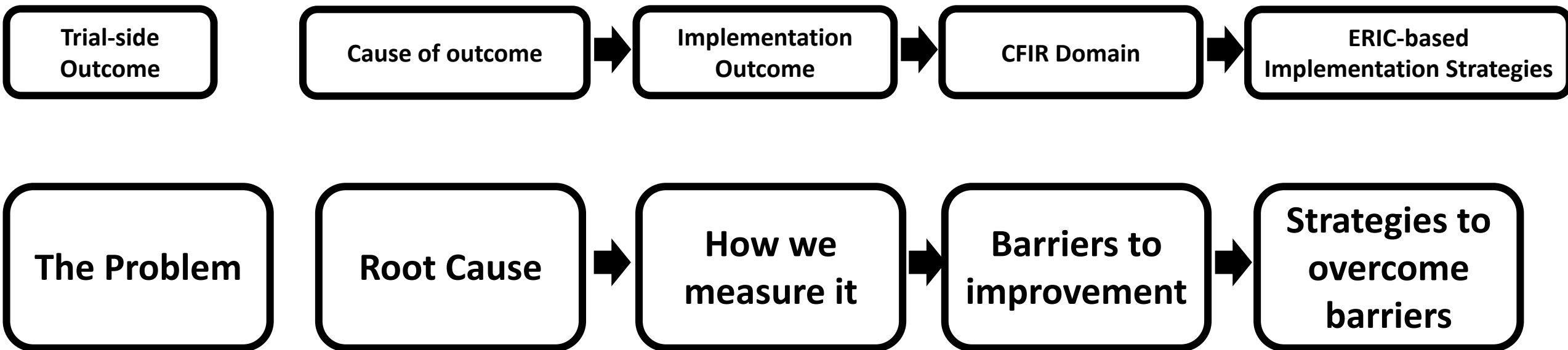


Strategies to improve recruitment to randomised trials (Review)

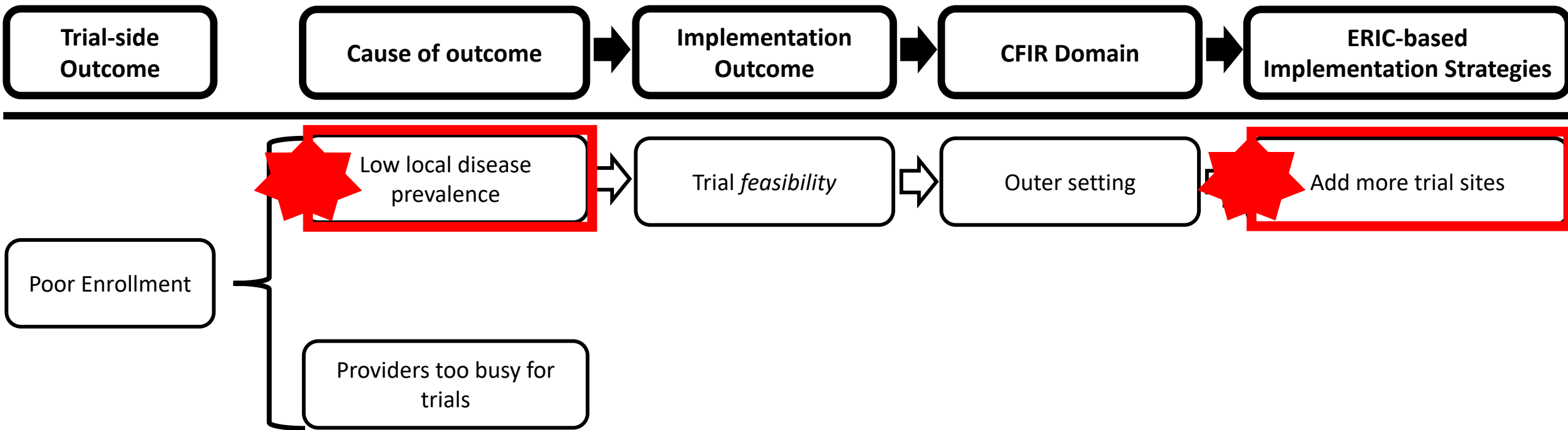
Treweek S, Pitkethly M, Cook J, Fraser C, Mitchell E, Sullivan F, Jackson C, Taskila TK, Gardner H

- Few reproducible studies of enrollment improvement
 - Only 3 of 72 studies in review with high GRADE evidence
- If we try something and it works, will it work everywhere?
- We need a structured approach to improving enrollment

Structuring the approach

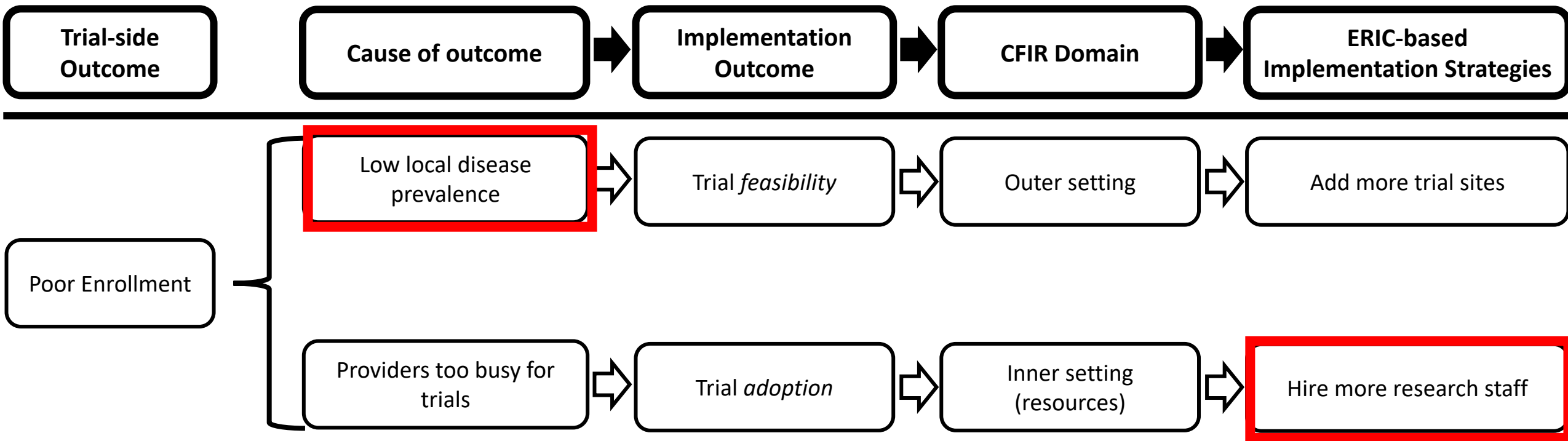


Poor enrollment is complex



Stensland et al., *Implementation Science Communications* 2022

Poor enrollment is complex



Stensland et al., *Implementation Science Communications* 2022



Trials implementation science



Implementation Science

- Tries to improve the delivery of evidence-based care
- Assesses context so tailored interventions can be designed
 - *determinant frameworks*
 - *implementation outcome frameworks*
 - *implementation strategies*

How to decide what works where?

- Context assessment
- Multiple levels of context: patient, provider/group, organization, market/policy
- Some obvious, some subtle

How can we structure context assessment?

- Looking for barriers and facilitators of successful implementation
 - aka *determinants*
 - What is helping or hurting trial enrollment?
- Use a *determinant framework*
 - Consolidated Framework for Implementation Research (CFIR)
 - Theoretical Domains Framework (TDF)
 - Tailored Implementation in Chronic Disease (TICD)

The CFIR

- Framework for identifying determinants (aka barriers and facilitators)
- 5 domains containing 37 constructs
- Used extensively in implementation research
- Has key links to other implementation science frameworks

The CFIR: adapted for trials

- Intervention Characteristics
- Outer setting
- Inner setting
- Characteristics of individuals
- Process

Intervention Characteristics

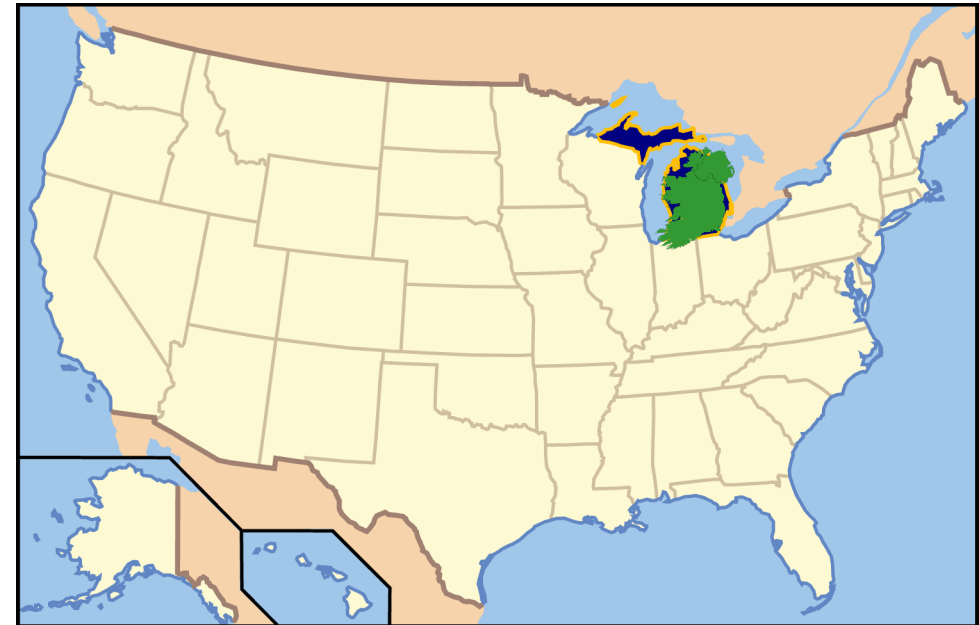
- What is being tested in the trial?
 - Few other treatments: high *relative advantage* of trial
 - Lots of existing data: high *evidence strength*
 - Can you stop the intervention? (trialability)
- Consider:
 - Drug trial for previously untreatable cancer
 - Phase 3 drug trial for drug effective in other settings
 - Trial for surgical removal of an organ

Outer setting

- Does a trial reflect local needs?
- How connected is a trial site to other organizations?
- How much *peer pressure* do providers feel to enroll to trials?
- What *external policy and incentives* exists for trials?

Outer setting: importance of context!

- Where a trial is set will hugely impact how it's implemented
- Health policy WAY different in Ireland than in USA
 - Reimbursement?
 - Trial incentives?
- Geographic considerations



Inner setting

- What is the *culture* of trials within an institution?
- Are there *organizational incentives* for trial participation?
- How much is organizational leadership involved in trials?

Characteristics of individuals

- What are providers' and patients' *beliefs* about clinical trials?
- What are providers' beliefs about the trialed intervention?
- Is the head trial investigator from the enrollment site?

Process

- How much *planning* for trial implementation occurred?
- Is there a strong trial site *champion*?
- Is there evaluation (e.g., audit and feedback) in place?

Determinant summary

- Multiple levels of barriers and facilitators to success
- For trials, this can range from intervention up to international policy
- Using a determinant framework for trials can organize these factors

How do we know if it's working?

- Implementation outcomes:
 - indicate implementation success
 - proximal indicators of implementation processes
 - key intermediate outcomes
- Implementation outcome frameworks:
 - Proctor's outcomes (IOF)
 - RE-AIM

Proctor's Outcomes

- 8 outcomes meant to measure implementation success
- Consolidates some terms
- Allows for some granularity in outcomes vs. other frameworks
 - e.g., “acceptability” and “appropriateness”

Trial enrollment outcomes

- Adoption: proportion of providers offering clinical trials to patients
- Penetration: proportion of eligible patients being offered a trial
 - *low adoption, high penetration:*
 - a few engaged providers enrolling well
 - consider advertising better
 - *high adoption, low penetration*
 - lots of provider buy-in, few patients enrolled
 - consider admin support, identifying eligible patients

Trial / intervention outcomes

- Acceptability

- perceived equipoise between arms
- reasonable participant logistics (e.g., distance to trial site)
- reasonable provider clinical burden

- Appropriateness

- question is amenable to a clinical trial
- trial design is appropriate for the trial question

“Appropriate” but not acceptable: antibiotic vs. placebo for sepsis

Acceptable but not appropriate: underpowered trial

Trial process outcomes

- Feasibility
 - possible to meet enrollment goals
 - can perform all parts of trial
- Implementation cost
 - cost of trial administration
 - cost of additional trial staff, materials
- Sustainability
 - maintenance of enrollment rates after trial opens
 - continued provision of intervention after trial concludes

Trial implementation outcomes

- Can help evaluate success of interventions
 - can serve as outcomes for SWATs
- Can maybe indicate early success or sustainability of trial interventions
- Can help identify targets for trial improvement



Consolidating the approach



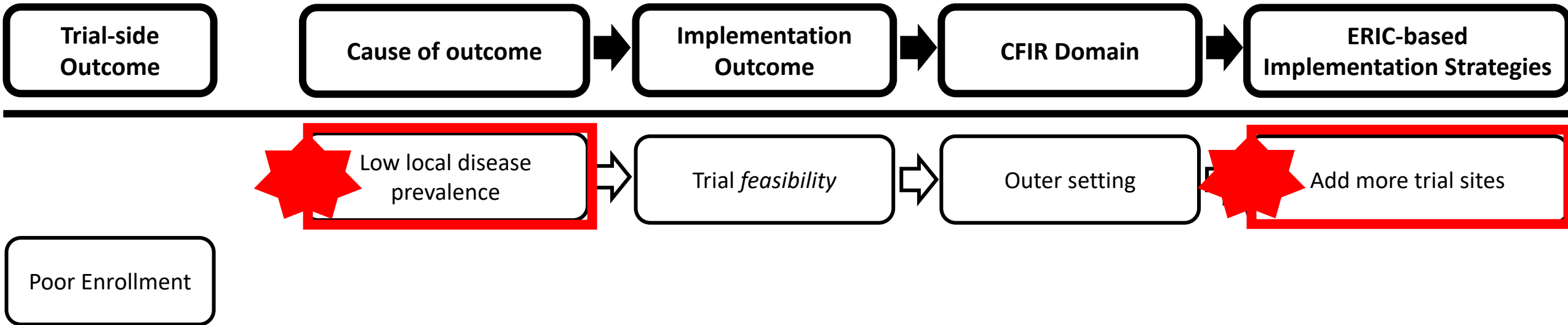
Why do we care about all this?

- Leading us back to developing strategies
- Identify barriers (determinants) to achieving successful implementation (outcomes), then overcome them with strategies

Sample case

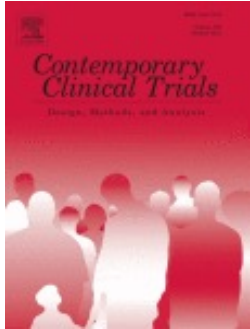
- My prostate cancer clinical trial is under-enrolling
- Trial lead suggests we hire more recruiting staff
- Is this the right call?

Poor enrollment is complex



Stensland et al., *Implementation Science Communications* 2022

But where do we place new sites?



Prostate cancer clinical trial completion: The role of geography

Kristian D. Stensland^{a,b,1}, Samuel D. Kaffenberger^b, Arvin K. George^{b,c}, Todd M. Morgan^b, David C. Miller^{a,b}, Simpa S. Salami^b, Rodney L. Dunn^a, Ganesh S. Palapattu^b, Jeffrey S. Montgomery^b, Brent K. Hollenbeck^{a,b}, Ted A. Skolarus^{a,b,c,*2}

- Merged ClinicalTrials.gov data with incidences from StateCancerProfiles.cancer.gov
- Identified areas with lots of prostate cancer cases, but few clinical trial sites

C. Counties with 0 or 1 trial and >61 annual PCa Cases



On mouseover:





Next Steps in Trials Implementation Science



Applying to real trials

- Applying our adapted framework to existing trials
- Assessing determinants in varied contexts
- Developing strategies to improve trial enrollment

Approaching other problems

- Today we focused on enrollment as a whole
- Can re-focus on other gaps, such as equity
- Representation in clinical trials has been poor historically
 - Implementation lens could provide needed context for ensuring interventions engage, include, and are appropriate for all



Summary



Summary

- Clinical trials are evidence-based interventions currently suffering from poor implementation.
- Applying implementation science to the trials context can build a platform for trial improvement through rigorous science and shared vocabulary.
- We can use implementation science to better structure approaches to addressing critical gaps in clinical trial conduct, such as enrollment and equity.
- Ongoing work is applying these methods to developing scalable approaches to improving clinical trials.

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Interview subjects

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