NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

# *Essentials of Embedded Pragmatic Clinical Trials Workshop*

## Participant Guide

**Health Care Systems Research Network**
**Annual Conference**
**April 11, 2022**

NIH PRAGMATIC TRIALS COLLABORATORY

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# *Essentials of Embedded Pragmatic Clinical Trials Workshop*

## Table of Contents

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***Essentials of Embedded Pragmatic Clinical Trials Workshop***

**HCSRN Annual Conference – Pasadena CA**

**April 11, 2022**

**Agenda**

| April 11, 2022 | | | |
|---|---|---|---|
| **DURATION** | **TOPIC** | **SPEAKERS** | **GOALS** |
| 1:00 – 1:05 p.m. | **Welcome** | Kevin Weinfurt | • Meeting goals and expectations<br>• Introductions |
| 1:05 – 1:30 p.m.<br>25 mins | **What Are Embedded PCTs (ePCTs)?** | Kevin Weinfurt | • Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials<br>• Learn why a critical element in the success of an ePCT is engaging health system partners at all levels and through all phases of the study<br>• Understand the real-world priorities and perspectives of health system leaders and how to obtain their support<br>• Identify challenges of partnering across diverse health systems |
| 1:30 – 1:45 p.m.<br>15 mins | **Objectives and Trial Design:** ***An Overview of Hybrid Designs*** | Devon Check | • Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs |
| 1:45 – 2:15 p.m.<br>30 mins | **Measuring Outcomes** | Devon Check | • Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) |
| 2:15 – 2:45 p.m.<br>30 mins | **ePCT Experimental Design & Analysis** | Patrick Heagerty | • Learn about cluster-randomized and stepped-wedge study designs<br>• Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know<br><br>**Includes Q&A with attendees |
| 2:45 – 3:00 p.m. | **Break** | | |

| April 11, 2022 | | | |
|---|---|---|---|
| **DURATION** | **TOPIC** | **SPEAKERS** | **GOALS** |
| 3:00 – 3:30 p.m.<br>30 mins | **Pilot & Feasibility Testing** | Miguel Vazquez | • Identify why it's important to do a pilot study to maximize acceptability, maintain affordability, and consider scalability of the ePCT intervention<br>• Learn key approaches to evaluating the capabilities of the partner health system and testing key elements of the intervention |
| 3:30 – 3:45 p.m.<br>15 mins | **Ethical & Regulatory Oversight Considerations** | Kevin Weinfurt | • Learn about the regulatory and ethical challenges of conducting ePCTs |
| 3:45 – 4:00 p.m.<br>15 mins | **Writing a Compelling Grant Application** | Michael Ho | • Identify elements of a compelling ePCT application<br>• Tips on NIH matchmaking |
| 4:00 -4:45 p.m.<br>45 mins | **ePCTs in Context: Panel Discussion** | **Moderator**<br>Kevin Weinfurt<br><br>**Panel**<br>Michael Ho<br>Miguel Vazquez<br>Stacy Sterling | • Presentation of case studies from three Collaboratory Demonstration Projects: Nudge, ICD-Pieces and GGC4H<br><br>**Includes moderated Q&A with attendees |
| 4:45 – 5:00 p.m.<br>15 mins | **Next Steps** | Kevin Weinfurt | • Final Q&A<br>• Wrap up, including identifying sources for further learning. |

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***Essentials of Embedded Pragmatic Clinical Trials Workshop***

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***April 11, 2022***

## Speaker Biographies

**Devon K. Check, PhD**
**Duke University School of Medicine**
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Devon Check, PhD is a health services and implementation researcher. She is an Assistant Professor in the Department of Population Health Sciences at Duke and a member of the Duke Cancer Institute. Her primary research interests are quality of care and implementation of evidence-based practices in oncology. Dr. Check's work combines quantitative and qualitative methods to understand and address barriers to the delivery of high-quality, equitable care during and after cancer treatment. She is a Co-Investigator for the NIH Health Care Systems Research Collaboratory Coordinating Center and leads the implementation science resource efforts for Collaboratory demonstration projects.

**Patrick Heagerty, PhD**
**University of Washington**
heagerty@uw.edu

Dr. Patrick Heagerty is Professor and former Chair of the Department of Biostatistics at the University of Washington. He received a PhD from the Johns Hopkins University, and a BS from Cornell University. He has extensive experience as an educator, independent and collaborative scientist, and administrator. He has developed fundamental methods for longitudinal studies with a focus on prognostic model evaluation and structural longitudinal models, and he has detailed rigorous methods for the design, analysis, and interpretation of cluster-randomized trials conducted within health care delivery systems. Dr. Heagerty has co-authored two leading texts (Analysis of Longitudinal Data, Oxford 2002; Biostatistics: A Methodology for the Health Sciences, Wiley 2004). He is an elected Fellow of the American Statistical Association and has twice been honored by professional societies for specific research contributions (in 2000 as the Snedecor Award winner; and in 2005 by the International Biometrics Society for the best paper published in the society's flagship journal, Biometrics). Dr. Heagerty directs the Center for Biomedical Statistics (CBS), a core partially funded by the NIH Clinical and Translational Science Award (CTSA) with responsibility for coordination of biostatistical collaboration in Seattle and the greater Northwest region (Wyoming, Alaska, Idaho, Montana). The CBS

houses the data coordinating centers for several U01 and R01 funded projects including GARNET (Genomics and Randomized Trials), BOLD (Backpain Outcomes using Longitudinal Data), UH3 funded pragmatic trials including LIRE (Lumbar Imaging Reporting with Epidemiology), and PCORI funded trials evaluating surgical interventions and psychiatric treatment strategies. The CBS has previously conducted high-impact multi-site randomized trials including INVEST (Investigational Vertebroplasty Safety and Efficacy Trial, NEJM 2009), the Carpal Tunnel Surgical Trial (Lancet 2009), and LESS (Lumbar Epidural Steroid Injections for Spinal Stenosis, NEJM 2014). Dr. Heagerty is the Director of the Biostatistics and Research Design Core for the NIH Health Care Systems Research Collaboratory, for the NIH Mental Health Research Network, and a member of the Executive Committee for the FDA Sentinel Innovation Center. Dr. Heagerty is also a licensed teacher (NY State: Mathematics, Biology, and Chemistry) and has taught from middle school to graduate school (UW SPH Outstanding Teacher Award, 2009).

**Michael Ho, MD**
University of Colorado School of Medicine
MICHAEL.HO@CUANSCHUTZ.EDU

Dr. Ho is a Staff Cardiologist at the VA Eastern Colorado Health Care System and Professor at University of Colorado School of Medicine**.** He is also the Co-Director of the Data Science to Patient Value Program and Vice Chair of Quality for the Department of Medicine. His research over the past 15 years has focused on understanding the quality and outcomes of cardiovascular care, including the prevalence of medication non-adherence in cardiovascular diseases, the adverse consequences of medication non-adherence, and testing different interventions to improve medication adherence.

**Stacy Sterling, DrPH, MSW, MPH,**
**Kaiser Permanente Division of Research**
Stacy.A.Sterling@kp.org

Stacy Sterling, DrPH, MSW, MPH, is with the Drug and Alcohol Research Team (DART) and the Behavioral Health Research Initiative. She received her doctoral training at the University of North Carolina Gillings School of Global Public Health, and her Master's degrees in Public Health and Social Welfare at the University of California, Berkeley. Her research interests include developing systems for implementing evidence-based, integrated, behavioral health services into primary care, adolescent behavioral health prevention and early intervention, and alcohol and drug and mental health treatment outcomes and access. She is the Principal Investigator of a study funded by the Conrad N. Hilton Foundation to develop predictive models for adolescent substance use problem development; the Kaiser Permanente Principal Investigator on a trial funded by the Hilton Foundation of single vs. multisession screening, brief intervention and referral to treatment (SBIRT) for adolescents and parents in pediatric primary care; the Kaiser Permanente Principal Investigator of an National Institutes of Health National Institute of Alcohol Abuse and Addiction adolescent SBIRT trial in pediatric primary care and of an NIH/NIAAA survey of pediatrician attitudes toward and practices of adolescent behavioral-health risk screening and intervention; and of studies funded by the Robert Wood Johnson Foundation and Center for Substance Abuse Treatment of adolescents in drug and alcohol treatment in Kaiser Permanente. She has overseen the implementation of region-wide alcohol SBIRT in Kaiser Permanente Northern California adult primary care.

**Miguel Vazquez, MD**
**UT Southwestern Medical Center**
Miguel.Vazquez@UTSouthwestern.edu

Miguel A. Vazquez, M.D., is Professor of Internal Medicine at UT Southwestern Medical Center in Dallas and the Clinical Chief of the Nephrology Division at UT Southwestern and Nephrology Chief of Service at Parkland Hospital in Dallas. His patient care specialties include chronic kidney disease, end stage kidney disease and kidney transplantation. He attended medical school at the University of Puerto Rico in San Juan, and moved to UT Southwestern for his internship and residency in internal medicine. He also completed his fellowship in nephrology and research in immunology and transplantation at UT Southwestern.

Dr. Vazquez is active in patient-oriented research. His current research efforts are focused on improving care for patients with chronic kidney disease and coexistent diabetes and hypertension as part of the pragmatic clinical trial ICD-Pieces. His research efforts also include the Kidney Precision Medicine Project and studies related to dialysis vascular access. Dr. Vazquez is board certified in internal medicine and nephrology by the American Board of Internal Medicine. He is a Fellow of the American College of Physicians and was named a Fellow by the American Society of Nephrology in 2011.

**Kevin Weinfurt, PhD**
**Duke University School of Medicine**
kevin.weinfurt@duke.edu

Dr. Weinfurt is Professor and Vice Chair for Research in the Department of Population Health Sciences in the Duke University School of Medicine. Dr. Weinfurt is also a Professor in the Duke departments of Psychiatry and Behavioral Science, Biostatistics and Bioinformatics, and Psychology and Neuroscience. He is a faculty member of the Duke Clinical Research Institute and Faculty Associate of the Trent Center for the Study of Medical Humanities and Bioethics. Dr. Weinfurt conducts research on measuring patient-reported outcomes, medical decision making, and bioethics.

Dr. Weinfurt was a principal investigator in the NIH PROMIS Network, where he led the development of the SexFS to measure male and female sexual function and satisfaction. Currently, he is co-chair of the coordinating center for the NIH Health Systems Research Collaboratory and served as the former President of the PROMIS Health Organization. As an educator, Dr. Weinfurt co-directs Duke's masters-level Clinical Research Training Program and has taught graduate courses in patient-reported outcomes research and multivariate statistics along with undergraduate courses in introductory psychology, judgment and decision making, and the psychology of medical decision making.

Dr. Weinfurt received his PhD in psychology at Georgetown University and did graduate work in the history of science and philosophy of mind at Linacre College, Oxford.

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# NIH Pragmatic Trials Collaboratory

## GOAL

Strengthen the national capacity to implement cost-effective, large-scale research studies that engage healthcare delivery organizations as research partners

## WHAT ARE EMBEDDED PRAGMATIC CLINICAL TRIALS (EPCTS)?

Trials conducted within healthcare systems that use streamlined procedures and existing infrastructure to answer important medical questions. These trials have the potential to inform policy and practice with high-quality evidence at a reduced cost and increased efficiency compared with traditional clinical trials.

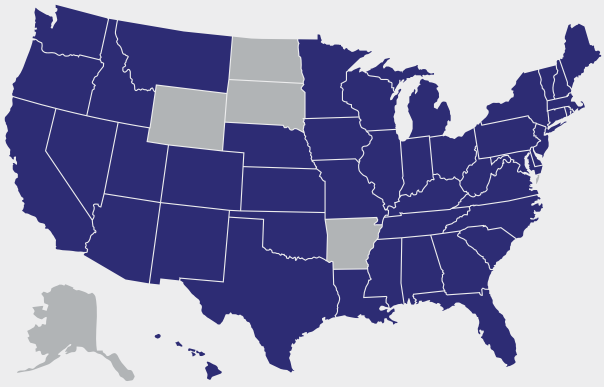
## PROGRAM

**DEMONSTRATION PROJECTS:** ePCTs that address questions of major public health importance and provide proof of concept for innovative pragmatic research designs

**CORES:** Working groups that support the conduct of Demonstration Projects and generate guidance addressing implementation challenges

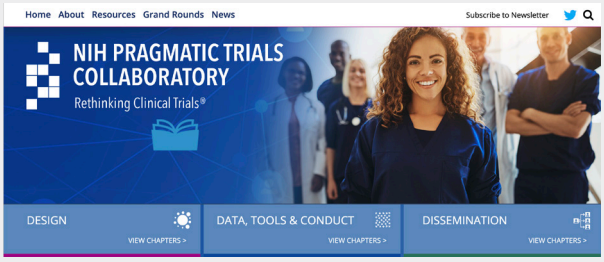
## 22 DEMONSTRATION PROJECTS

- Conducted in partnership with healthcare systems
- Studying diverse clinical areas spanning 12 NIH Institutes and Centers
- >1100 clinical sites across 90% of United States; >940,000 active subjects



## RESOURCES

*Living Textbook of Pragmatic Clinical Trials*
Comprehensive resource expanding on lessons from the Demonstration Projects and Cores




**DESIGN** describes how to plan the trial, including randomization schemes, endpoints and outcomes, analysis, informed consent, using electronic health record data, designing with implementation in mind, and feasibility studies

**DATA, TOOLS & CONDUCT** describes considerations for study startup and participant recruitment

**DISSEMINATION** describes data sharing and embedded research and dissemination and implementation approaches

Plus:

- Grand Rounds webinars and podcasts on ePCT topics
- Monthly NIH Collaboratory newsletter

**Visit the Living Textbook:**
**www.rethinkingclinicaltrials.org**

## HOW IS A CLINICAL TRIAL CONSIDERED PRAGMATIC?

An **EXPLANATORY** approach answers the question, "Can this intervention work under ideal conditions?"
A **PRAGMATIC** approach answers the question, "Does this intervention work under usual conditions?"

A trial's degree of pragmatism will vary along this spectrum:


Source: The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147. PMID:25956159. doi:10.1136/bmj.h2147.

**Visit the Living Textbook:**
**www.rethinkingclinicaltrials.org**

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# Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications (Nudge)


**Principal Investigators**
Michael Ho, MD, PhD, and Sheana Bull, PhD, MPH

**Sponsoring Institution**
University of Colorado

**Collaborators**
- UCHealth
- Denver Health
- VA Eastern Colorado Health Care System

**NIH Institute Providing Oversight**
National Heart, Lung, and Blood Institute (NHLBI)

**Program Official**
Holly Nicastro (NHLBI)

**Project Scientist**
Nicole Redmond (NHLBI)



**ClinicalTrials.gov Identifier**
NCT03973931

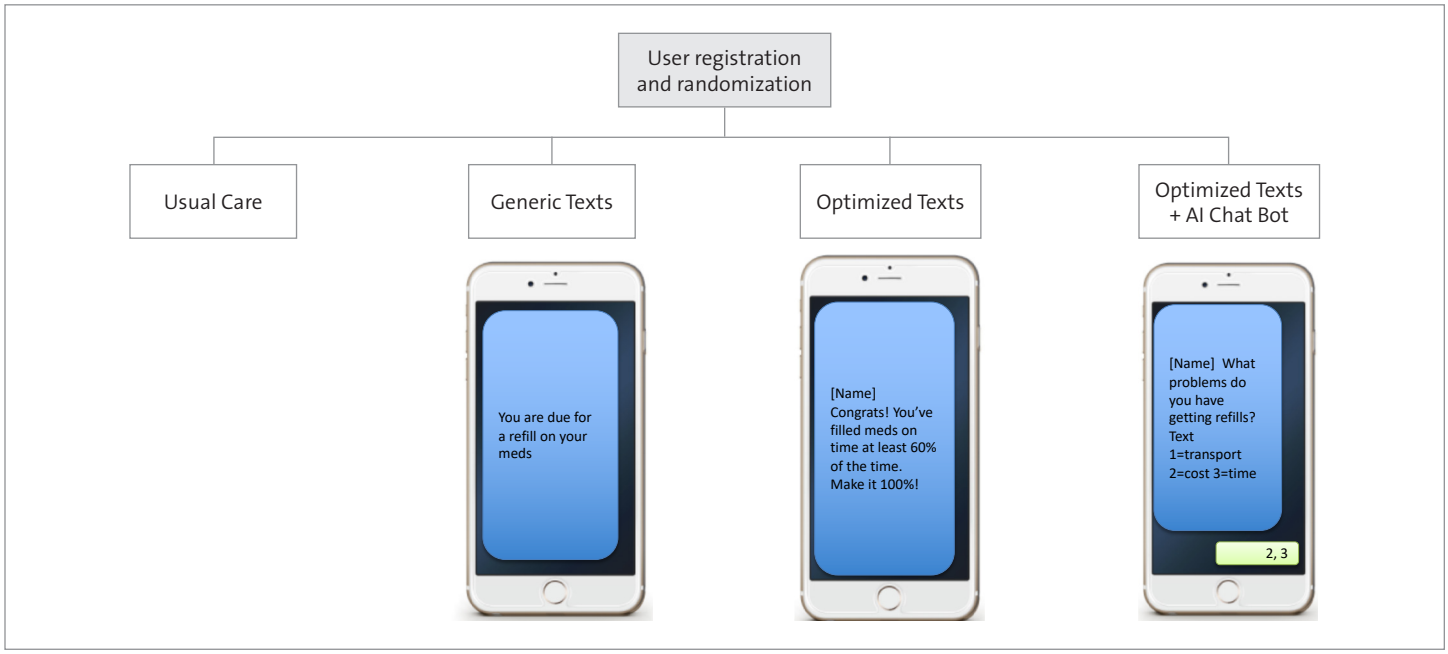


## ABSTRACT

Nearly half of patients do not take their cardiovascular medications as prescribed, resulting in increased morbidity, mortality, and healthcare costs. Interventions to improve adherence—such as patient education, reminders, pharmacist support, and financial incentives—have produced inconsistent results due to limited study designs. Mobile and digital technologies for health promotion and disease self-management offer an opportunity to adapt behavioral "nudges" using ubiquitous mobile phone technology to facilitate medication adherence.

The Nudge Demonstration Project will use population-level pharmacy data to deliver nudges via mobile phone text messaging and an artificial intelligent (AI) interactive chat bot with the goal of improving medication adherence and patient outcomes in 3 integrated healthcare delivery systems. During the planning phase, the Nudge study team developed and piloted a technology-based nudge message library and a chat bot library of optimized interactive content for a range of diverse patients. Patients of interest are those with chronic cardiovascular conditions who take medications to treat hypertension, atrial fibrillation, coronary artery disease, diabetes, or hyperlipidemia. Episodes of nonadherence to prescribed medications are identified through gaps in medication refills. Participants are randomized to one of 4 study arms: usual care (no intervention), generic nudge (text reminder), optimized nudge, and optimized nudge plus intereactive AI chat bot.

### Intervention arms for the pragmatic trial




## WHAT WE'VE LEARNED SO FAR

| Challenge | Solution |
|---|---|
| Some health systems did not consistently record cell phone numbers in the appropriate place, resulting in cell phone numbers not being imported in the research database. | Study team worked with an EPIC analyst to import cell phone numbers into the research database. |
| There were challenges in comparing definitions (eg, hospitalization) and nuances in how data are captured (eg, inpatient versus outpatient labs). | A team of analysts identified limitations across each system and worked with clinicians on the study team to create variable definitions compatible at each health system. |
| Due to a contractual issue, the study team was not able to obtain pharmacy data at one participating health system. | Team decided to delay enrollment of patients for at least 1 year at that health system and re-assess whether enrollment will be possible at the health system after they obtain more data. They will increase enrollment at the other 2 systems. |

*"Ideally, if people are doing a better job of refilling their meds, they can stay more adherent to their medications, and ultimately, have better health outcomes."*

## SELECTED PUBLICATIONS & PRESENTATIONS

- July 2019: Interview with Nudge PIs in *Living Textbook*
- January 2019: PCT Grand Rounds webinar

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# ICD-Pieces: Improving Chronic Disease Management with Pieces™

## Study Snapshot

**Principal Investigator:** Miguel Vazquez, MD

**Sponsoring Institution:** University of Texas Southwestern Medical Center

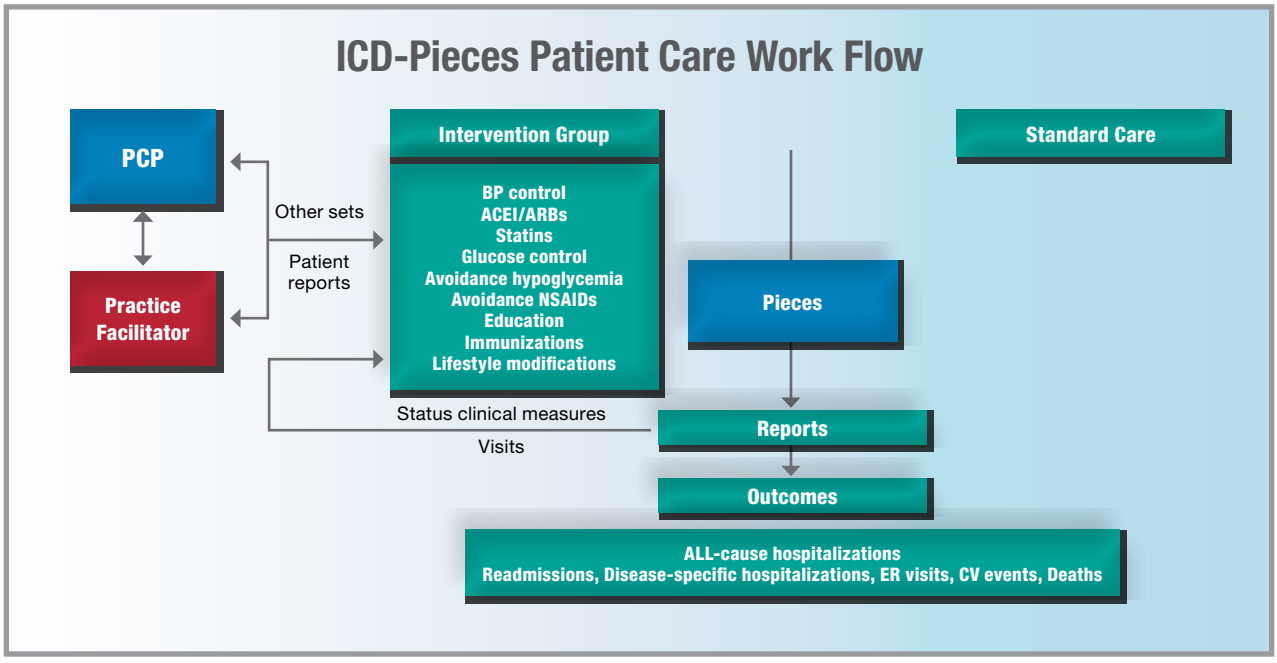
**ClinicalTrials.gov:** NCT02587936

**Collaborating Healthcare Systems:** Parkland health and Hospital System, Texas Health Resources, ProHealth, VA North Texas

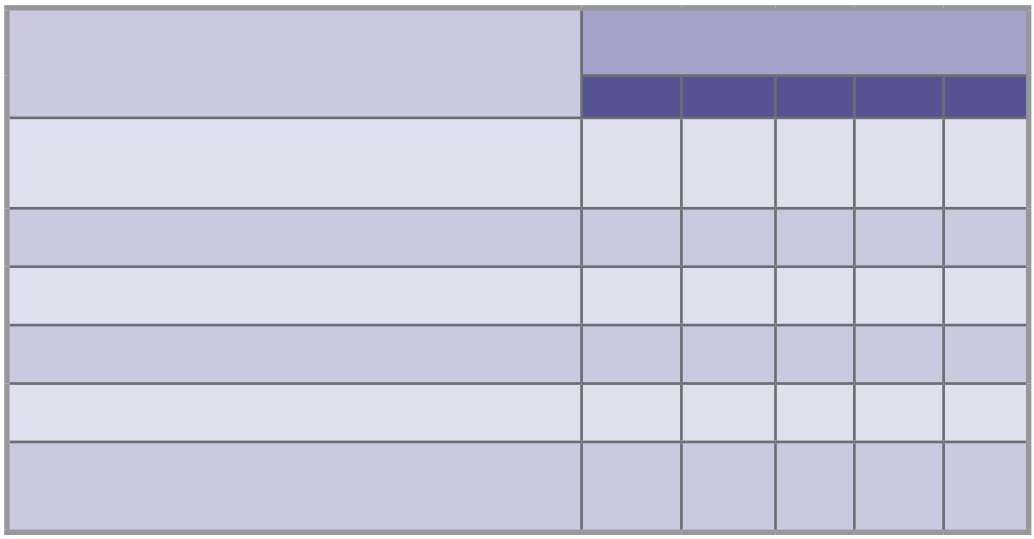
**NIH Institute Oversight:** National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)

**Abstract:** Chronic kidney disease (CKD), diabetes, and hypertension are common medical conditions that are often present together and cause many complications. Among adults in the United States, the prevalence of CKD has increased from 10% to 14% over the last 2 decades, and diabetes and hypertension are the 2 leading causes of CKD and end-stage renal disease. Important progress in identification of effective treatments for CKD, diabetes, and hypertension has been made, but there is a significant gap in translating these treatments to clinical practice.

The goal of ICD-Pieces is to help primary care physicians treat patients with coexisting CKD, diabetes, and hypertension in more effective ways. The main hypothesis is that patients receiving care using a collaborative model of primary care-subspecialty care, enhanced by novel information technology and practice facilitators, will have fewer hospitalizations, readmissions, cardiovascular events, and deaths than patients receiving standard medical care. This study is implementing a novel technology platform (Pieces) supported by practice facilitators across 4 participating large healthcare systems to improve care within primary care practices.



# What We've Learned So Far



1 = little difficulty
5 = extreme difficulty

| Challenge | Solution |
|---|---|
| Management of multiple chronic conditions varies across different healthcare systems. | Study facilitators developed different workflows to accommodate the variations in resources at every site. These were roles in the healthcare systems and required more multidisciplinary review of the proposed workflows. |
| The study team initially planned for structured, step-wise electronic tools that were time-consuming to use but would provide a detailed therapy plan. | After discussing the tool with medical directors and physicians, the team developed more user-friendly, less burdensome tools. |
| The initial sample size was based on broad estimates of the prevalence of multiple chronic conditions across the healthcare systems and was limited by lack of cluster-level detailed information. | In the planning phase, the cluster units were redefined from individual practitioners to practice sites. The team queried EHR systems with the new cluster definition and collaborated with statisticians at the NIH to establish an appropriate sample size. |

| Selected Publications & Presentations | |
|---|---|
| May 2017 | NIH Workshop on Pragmatic Clinical Trials—Unique Opportunities for Disseminating, Implementing, and Sustaining Evidence-Based Practices into Clinical Care: Panel 2—Health System Engagement: Partnership, Relationships, and Transparency |
| September 2016 | PCT Grand Rounds Presentation: Improving Chronic Disease Management with Pieces |

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# Guiding Good Choices for Health (GGC4H)


**Principal Investigators**
Richard Catalano, PhD, Margaret Kuklinski, PhD, Stacy Sterling, DrPH, MSW

**Sponsoring Institution**
University of Washington

**Collaborators**
- Kaiser Permanente Northern California
- Kaiser Permanente Colorado
- Henry Ford Health System

**NIH Institute Providing Oversight**
National Center for Complementary and Integrative Health (NCCIH)

**Program Official**
Robin Boineau (NCCIH)

**Project Scientist**
Jacqueline Lloyd (National Institute on Drug Abuse [NIDA])



**ClinicalTrials.gov Identifier**
NCT04040153



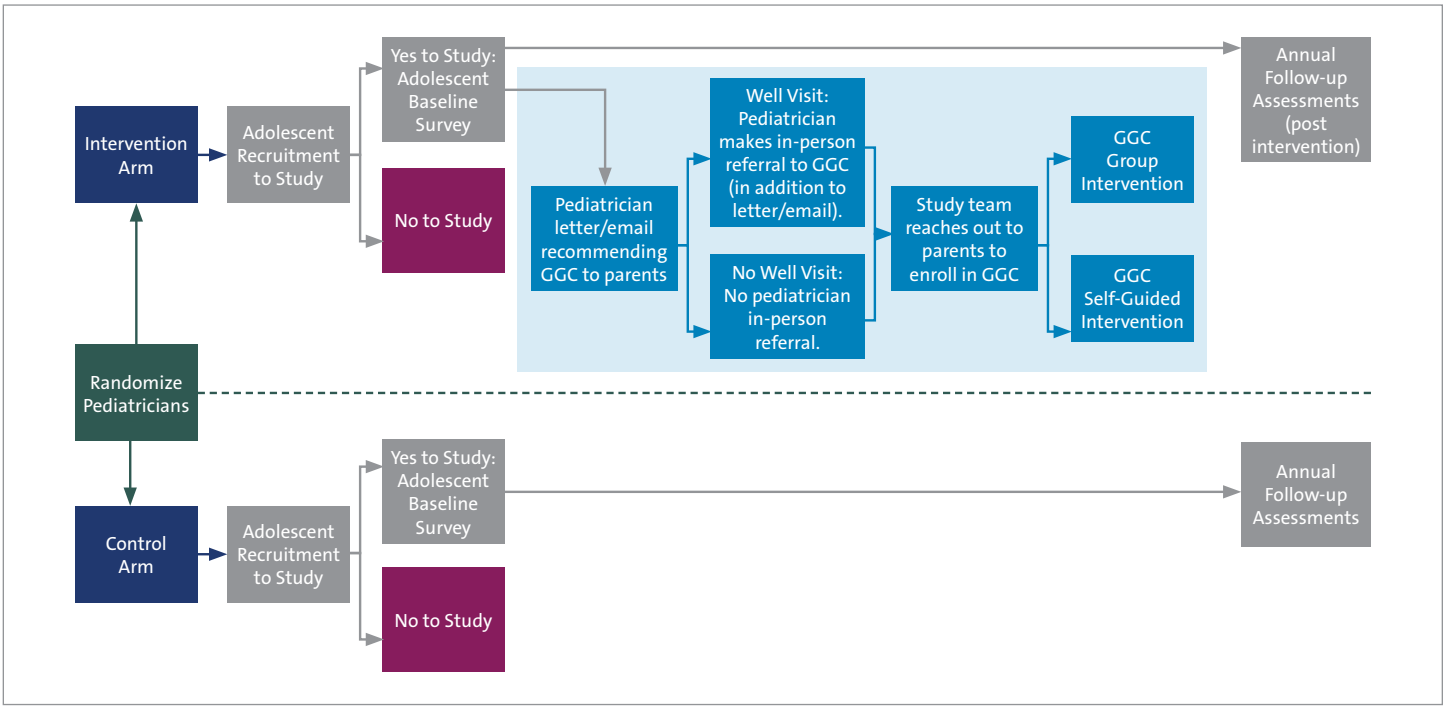
## ABSTRACT

Fifty percent of all adolescents will use some form of illicit drugs before the end of high school, and 20% to 25% will meet criteria for depression, while many others will engage in health-compromising behaviors like delinquency and violence—with consequences for their long-term health. Evidence-based parenting interventions shown to prevent these behavioral health concerns could improve adolescent health trajectories if implemented widely in pediatric primary care. The American Academy of Pediatrics' Bright Futures recommends that pediatricians offer developmentally tailored anticipatory guidance to all parents to support their children's healthy development, but programs providing guidance are not offered universally.

The Guiding Good Choices for Health (GGC4H) Demonstration Project is a cluster-randomized trial that will use the RE-AIM framework to test the feasibility and effectiveness of implementing Guiding Good Choices (GGC)—a universal evidence-based anticipatory guidance curriculum for parents of early adolescents—in three large, integrated healthcare systems serving socioeconomically diverse families. In prior community trials, GGC has been shown to prevent adolescent substance use (alcohol, tobacco, and marijuana), depressive symptoms, and delinquent behavior. This study offers an opportunity to test GGC effectiveness with respect to improving adolescent behavioral health outcomes when implemented at scale in pediatric primary care within a pragmatic trial.


| GUIDING GOOD CHOICES SESSIONS | |
|---|---|
| Session 1 | Getting Started: **How to Prevent Drug Use in Your Family** |
| Session 2 | Setting Guidelines: **How to Develop Healthy Beliefs and Clear Standards** |
| Session 3 | Avoiding Trouble: **How to Say No to Drugs** (with children in attendance) |
| Session 4 | Managing Conflict: **How to Control and Express Your Anger Constructively** |
| Session 5 | Involving Everyone: **How to Strengthen Family Bonds** |

### GGC4H Effectiveness Design




## WHAT WE'VE LEARNED SO FAR

| Challenge | Solution |
|---|---|
| The original plan was to include adolescents who had well visits, but 25% of teens do not have such visits at some pediatric clinics. | The study team revised the study design to include all adolescents who receive care at the pediatric clinic. Although some study participants will not engage with the intervention, results will be more generalizable. |
| The pragmatic GGC implementation plan results in partial cross-nesting of intervention participants, which threatens valid statistical inference. | The study's biostatisticians came up with a modelling approach that resolved statistical concerns and, in a simulation study, showed strong power, nominal alpha levels, and adequate coverage. |
| The study design needs to address the study's two important goals: whether pediatrician recommendation to enroll in GGC increases uptake over historical levels found in community settings, and whether GGC can achieve practice-wide reductions in adolescent substance use initiation. | The study's cluster-randomized trial addresses questions of GGC efficacy. GGC will be offered to all parents in the intervention arm, regardless of whether their adolescents are study participants, to provide important information about GGC uptake among parents outside of the artificial context of a research study, as well as among those who consented to the study. |

*"We have complementary strengths across our site leaders and a collegial team. These features have helped us hit the ground running in this fast-paced trial."*

## SELECTED PUBLICATIONS & PRESENTATIONS

- June 2019: Interview with GGC4H PIs in *Living Textbook*
- December 2018: PCT Grand Rounds webinar

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# *Welcome*

## Speaker

**Kevin Weinfurt, PhD**
**Professor and Vice Chair of Research**
**Department of Population Health Sciences**
**Duke University School of Medicine**

# Welcome

Kevin Weinfurt, PhD
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

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# Workshop learning objectives

- Clarify the definition of ePCTs and explain their utility.
- Introduce attendees to the unique characteristics and challenges of designing, conducting, and implementing ePCTs within diverse health care systems
- Increase the capacity of health service researchers to address important clinical questions with ePCTs.

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# Workshop sessions

- What Are Embedded PCTs (ePCTs)?
  - Kevin Weinfurt
- Objectives and Trial Design: *An Overview of Hybrid Designs*
  - Devon Check
- Measuring Outcomes
  - Devon Check
- ePCT Design & Analysis
  - Patrick Heagerty
- Break (2:45 – 3:00pm)

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# Workshop sessions continued

- Pilot & Feasibility Testing
  - Miguel Vazquez
- Ethical & Regulatory Oversight Considerations
  - Kevin Weinfurt
- Writing a Compelling Grant Application
  - Michael Ho
- ePCTs in Context: Panel Discussions
  - Moderator: Kevin Weinfurt
  - Panel: Michael Ho, Miguel Vazquez, Stacy Sterling

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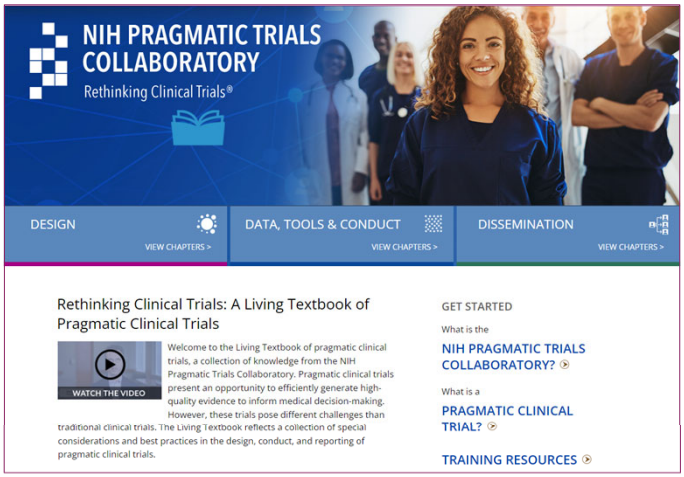
# Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*

**www.rethinkingclinicaltrials.org**

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# *What Are Embedded PCTs?*

## Speaker

**Kevin Weinfurt, PhD**
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

# What Are Embedded PCTs?

Kevin Weinfurt, PhD
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

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## Learning goals

- Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials
- Learn why a critical element in the success of an ePCT is engaging health system partners at all levels and through all phases of the study
- Understand the real-world priorities and perspectives of health system leaders and how to obtain their support
- Identify challenges of partnering across diverse health systems

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## Important things to know

- ePCTs are designed to answer important, real-world clinical questions
- Broad stakeholder engagement and support are essential from beginning to end
- Tradeoffs in flexibility, adherence, and generalizability are inevitable

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## Why conduct ePCTs?

ePCTs have the potential to inform policy and practice with high-quality evidence at reduced cost and increased efficiency compared with traditional clinical trials

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# ePCT characteristics

- Conducted within healthcare systems
- Use streamlined procedures and existing infrastructure
- Answer important medical questions

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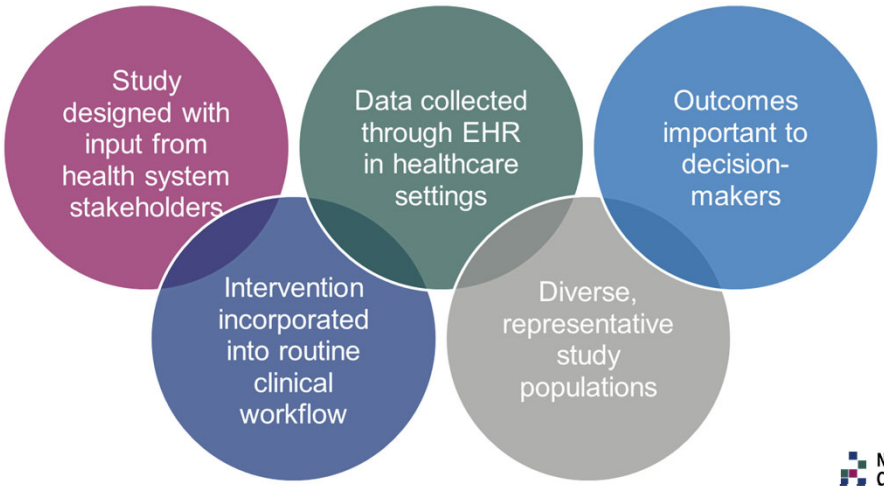
# ePCTs bridge clinical care into research

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# Who are your stakeholders?



Potential stakeholders have varied priorities, values, work cultures, and expectations:

- Healthcare delivery organization leaders
- Clinicians
- Operational personnel
- Patients, caregivers, patient advocacy groups
- Product manufacturers
- Payers, purchasers
- Policymakers, regulators
- Research funders
- Researchers
- Product manufacturers

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# Listen to the frontline

The purpose of the healthcare system is not to do research, but to provide good healthcare. Researchers often have a tail-wagging-the-dog problem. We assume if we think something is a good idea, the healthcare system will too … We need to remember that we're the tail and the healthcare system is the dog.

– Greg Simon, MD, MPH (SPOT)

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# 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)

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# It's a balancing act

Achieving both relevance and efficiency is a goal of pragmatic trials, yet high relevance to real-world decision-making may come at the expense of trial efficiency

*For example, a trial measuring outcomes that matter most to patients and health systems may not be able to rely exclusively on information from the EHR, and instead need to assess patient-reported outcomes, which is more expensive and less efficient*

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# 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 lifecycle of your ePCT
- Show appreciation and celebrate accomplishments early and often to have sustained partnerships

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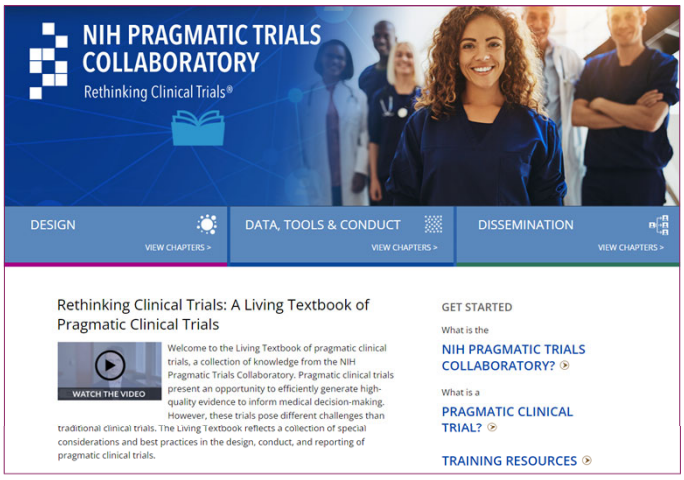
## Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*

**www.rethinkingclinicaltrials.org**

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## Resources:

## What Are Embedded PCTs (ePCTs)?

*Living Textbook* readings

- Why are We Talking About Pragmatic Clinical Trials?
- Elements: An Introduction to PRECIS-2

Collaboratory Grand Rounds webinar recordings & slides

- Introduction to Pragmatic Clinical Trials Embedded Pragmatic Clinical Trials
- Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory

Key journal articles

- Weinfurt et al., 2017. Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory
- Johnson et al., 2016. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory
- Loudon et al., 2015. PRECIS-2 tool: designing trials that are fit for purpose
- Califf et al., 2014. Exploring the ethical and regulatory issues in pragmatic clinical trials

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# *Objectives and Trial Design: An Overview of Hybrid Designs*

## Speaker

**Devon Check, PhD**
Assistant Professor
Department of Population Health Sciences
Duke University School of Medicine

# Trial Objectives and Design:
## *An Overview of Hybrid Designs*

Devon Check, PhD
Assistant Professor
Department of Population Health Sciences
Duke University School of Medicine

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## Learning goals

- Review 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs

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# Hybrid trial design

- Trials with a focus on both clinical (i.e., patient) and implementation outcomes

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# 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 levels of adoption and fidelity?
  - How will we know this without data from both sides?

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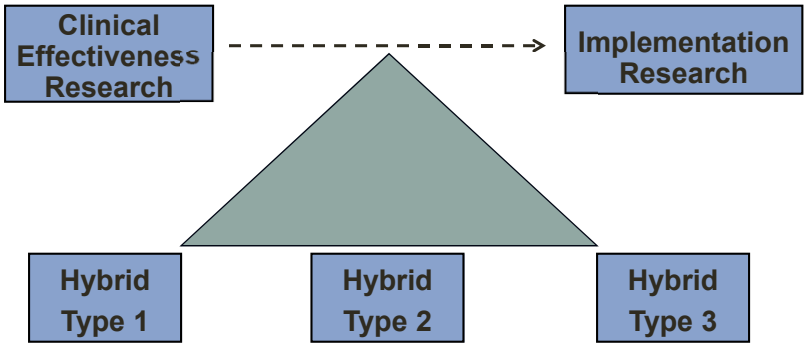
# Types of hybrids




**Hybrid Type 1**: test a clinical intervention, observe/gather information on implementation

**Hybrid Type 2**: test a clinical intervention, test/study an implementation strategy

**Hybrid Type 3**: test an implementation strategy, observe/ gather information on intervention's effectiveness

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# Type 1

- Clinical Trial PLUS
  - Implementation-focused process evaluation
  - Usually mixed method study of what worked/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…)

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# Type 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

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# Type 3

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

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# Concluding points

- 1 This was a VERY brief summary!

- 2 ePCTs would usually be type 1 or 2, depending on
  - How ready you are to test an implementation strategy or strategies on summative implementation outcomes
    - Just want to describe implementation during the trial and prepare for more work later on real-world implementation strategies = 1
    - Ready to test the impact of real-world strategies on implementation outcomes like adoption or fidelity = 2

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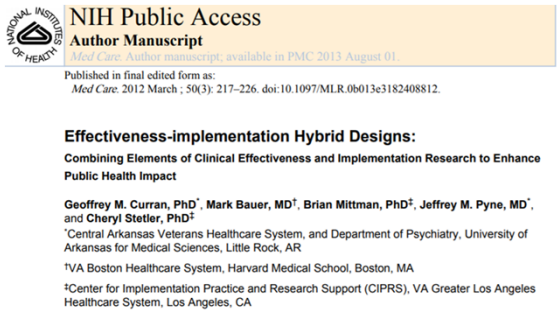
# Concluding points

- 3 If you want to learn more…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**Effectiveness-implementation Hybrid Designs:**
**Combining Elements of Clinical Effectiveness and Implementation Research to Enhance Public Health Impact**

**Geoffrey M. Curran, PhD**[*], **Mark Bauer, MD**[†], **Brian Mittman, PhD**[‡], **Jeffrey M. Pyne, MD**[*], and **Cheryl Stetler, PhD**[‡]
[*]Central Arkansas Veterans Healthcare System, and Department of Psychiatry, University of Arkansas for Medical Sciences, Little Rock, AR
[†]VA Boston Healthcare System, Harvard Medical School, Boston, MA
[‡]Center for Implementation Practice and Research Support (CIPRS), VA Greater Los Angeles Healthcare System, Los Angeles, CA


Contents lists available at ScienceDirect
Psychiatry Research
journal homepage: www.elsevier.com/locate/psychres

An introduction to effectiveness-implementation hybrid designs

Sara J. Landes[a,b,c,*], Sacha A. McBain[b,c], Geoffrey M. Curran[b,c,d]
[a] The Department of Veterans Affairs Quality Enhancement Research Initiative (QUERI) for Team-Based Behavioral Health, 2200 Fort Roots Drive, North Little Rock, AR 72114, USA
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[c] University of Arkansas for Medical Sciences, Department of Psychiatry, 4301 W. Markham St, Little Rock, AR 72205, USA
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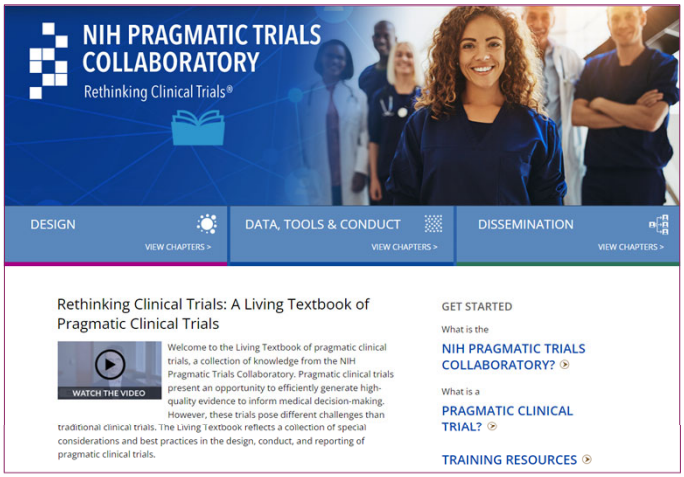


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## Resources:

## Objectives and Trial Design: An Overview of Hybrid Designs

*Living Textbook* readings

- Hybrid Design

Key journal articles

- Curran et al., 2012. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact.

- Landes, McBain, Curran. 2019. An introduction to effectiveness-implementation hybrid designs.

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# *Measuring Outcomes*

## Speaker

**Devon Check, PhD**
Assistant Professor
Department of Population Health Sciences
Duke University School of Medicine

# Measuring Outcomes

Devon Check, PhD
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## Learning goals

- Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)

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## Endpoints and outcomes

- An endpoint usually refers to an analyzed parameter (eg, change from baseline at 6 weeks in mean PROMIS Fatigue score)
- An outcome usually refers to a measured variable (eg, peak volume of oxygen or PROMIS Fatigue score)

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## Important things to know

- Endpoints and outcomes should be meaningful to providers and patients
- Endpoints and outcomes should be relatively easy to collect (ie, pragmatic)
- Researchers do not control the design or data collected in EHR systems

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# Choosing and specifying endpoints in ePCTs

Endpoints and outcomes need to be available as part of routine care


- Acute MI
- Broken bone
- Hospitalization


- Suicide attempts
- Gout flares
- Silent MI
- Early miscarriage

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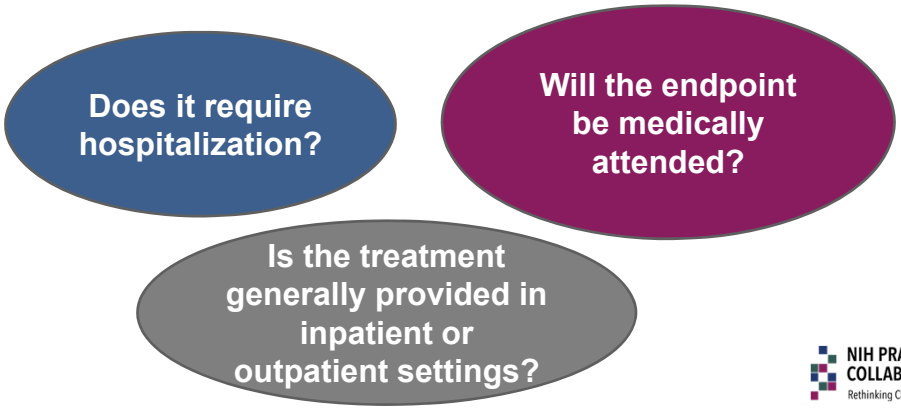
# Key questions for choosing endpoints

Is the outcome medically significant such that a patient would seek care?

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# Data sources for endpoints in ePCTs

"The first challenge in using big biomedical data effectively is to identify what the potential sources of health care information are and to determine the value of linking these together."

Weber GM et al. JAMA. 2014;311(24):2479-2480.

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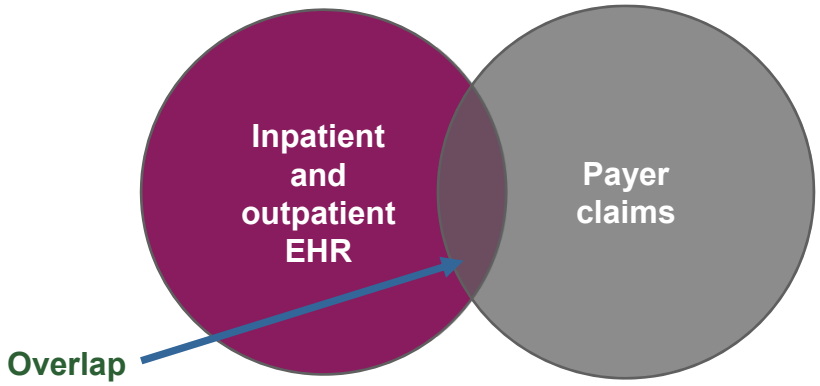
# Where is the signal?

- EHR (laboratory values, treatments, etc)
- Claims data (does the event generate a bill?)

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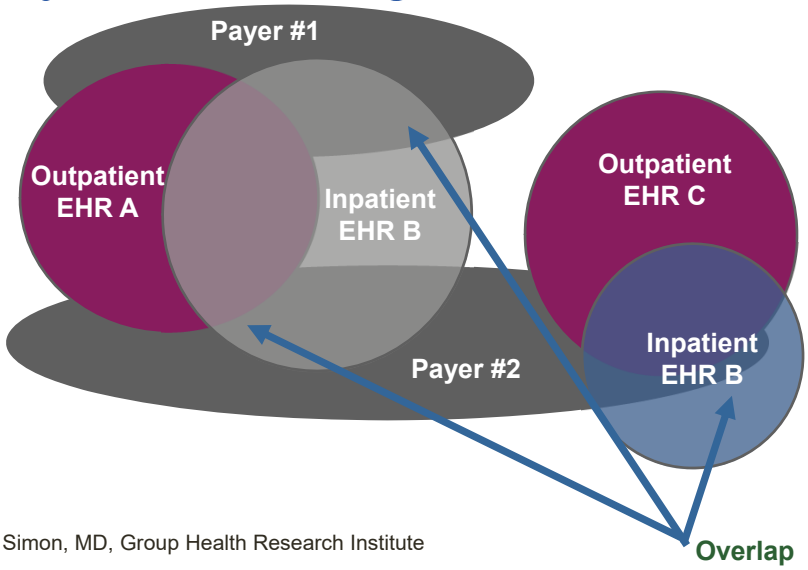
# Reality is not straightforward




Source: Greg Simon, MD, Group Health Research Institute

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# Longitudinal data linkage

- To fully capture all care—complete longitudinal data—linking research & insurance claims data is often necessary
- Without explicit consent, getting longitudinal data from an insurance carrier can be an insurmountable hurdle, both technically and legally

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# Data sources for endpoints in ePCTs

- EHR or ancillary health information systems
- Patient report
- Patient measurement

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# It's a balancing act

High relevance to real-world decision-making may come at the expense of efficiency

*For example, a trial measuring outcomes that matter most to patients and health systems may not be able to rely exclusively on information from the EHR, and instead need to assess patient-reported outcomes, which is more expensive and less efficient*

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# Outcomes measured via direct patient report

- Patient-reported outcomes (PROs) are often the best way to measure quality of life
- Challenges
  - Not routinely or consistently used in clinical care
  - Not regularly recorded in EHR
- Need a mechanism to collect PROs

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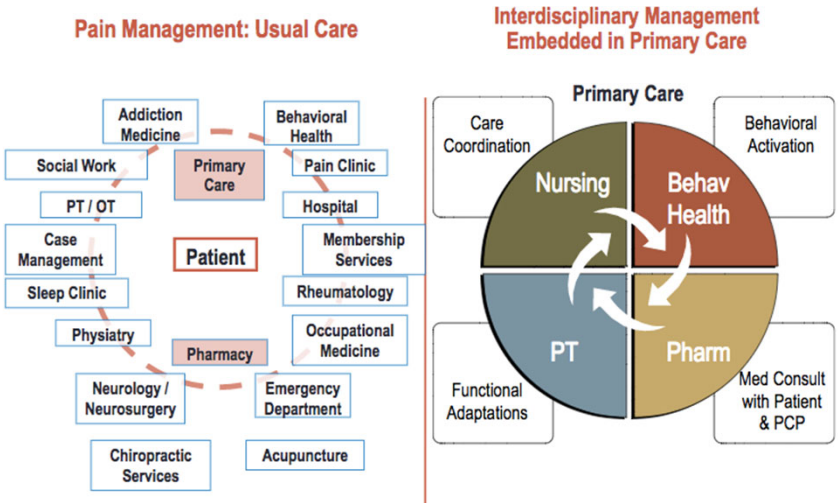
# Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)




Source: Lynn DeBar, PhD, MPH, Kaiser Permanente Washington Health Research Institute

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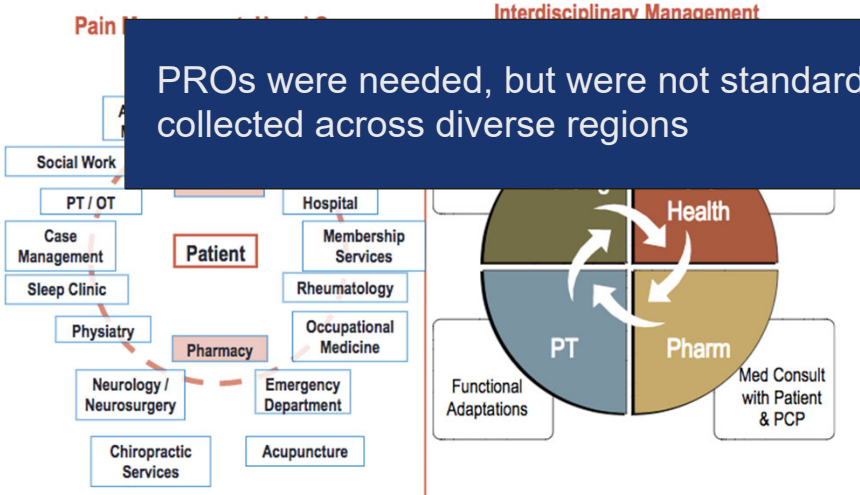
# Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)




PROs were needed, but were not standardly collected across diverse regions

Source: Lynn DeBar, PhD, MPH, Kaiser Permanente Washington Health Research Institute

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# Case example: PPACT

- Project leadership worked with national Kaiser to create buy-in for a common instrument
- Local IT built it within each region
- A multi-tiered approach supplemented the clinically collected PRO data at 3, 6, 9, 12 months
- A follow-up phone call by research staff was necessary to maximize data collection at each time point

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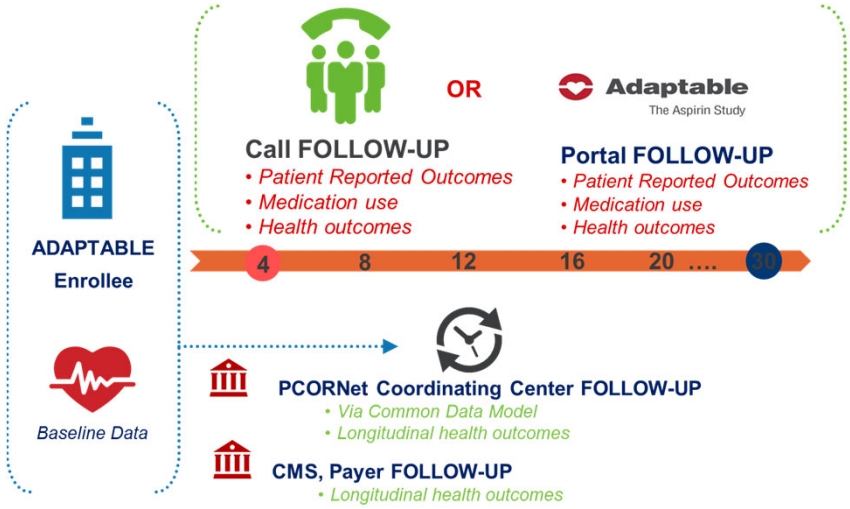
# Enabling pragmatic research: e-screening, e-enrollment & e-follow-up

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# Mobile devices for outcome measurement

- Smartphones, tablet computers, and portable, implantable, or wearable medical devices (mHealth)
  - Some mHealth devices transmit data to a data warehouse every night
  - Largely considered imperfect measures
- Patient-facing mobile phone apps can be used in ePCTs for passive or active surveillance

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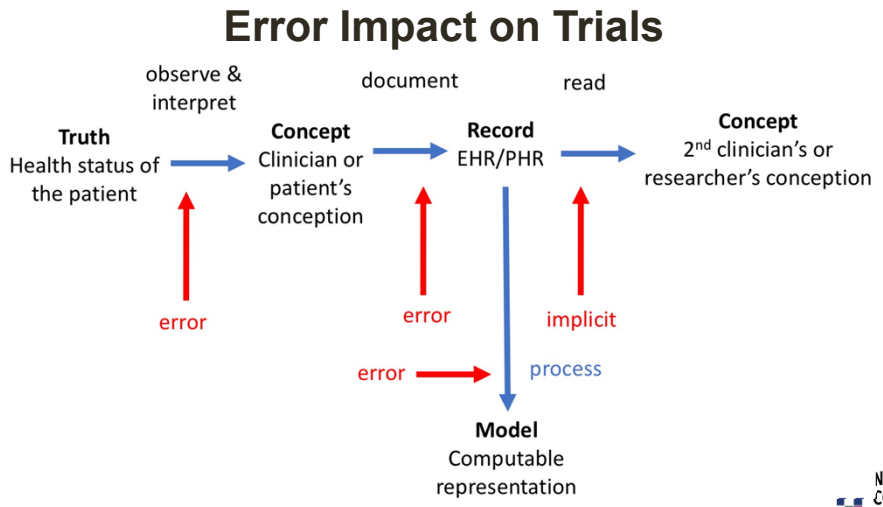
# Data is a surrogate for clinical phenomena




Adapted from Hripcsak et al. 2009

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# Data quality assessment

- Identify variation between populations at different sites or study groups
- Recommend formal assessment of accuracy, completeness, and consistency for key data
- Data quality should be described, reported, and informed by workflows

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## Important things to do

- Ask questions that the data will support and design trials to minimize new data collection
- Engage EHR and data experts when defining endpoints and outcomes
- Budget for data and systems experts at each site (… and then double it)
- Develop a robust data quality assessment plan to improve value of data and to detect and address data issues

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## Concluding points

- Data available from the EHR may be convenient and pragmatic, but might not actually drive clinical practice or policy if used as endpoints
- Need to make sure that conveniently available endpoint will also be accepted as influential for stakeholders when the ePCT results are disseminated
- Plan with implementation in mind

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# Resource: The Living Textbook

## Choosing and Specifying Endpoints and Outcomes

SECTIONS

1. Introduction
2. Meaningful Endpoints
3. Outcomes Measured via the Electronic Health Record
4. Using Death as an Endpoint
5. Inpatient Endpoints in Pragmatic Clinical Trials
6. Outcomes Measured via Direct Patient Report
7. Outcomes Measured via Mobile Devices
8. Additional Resources
9. FAQ


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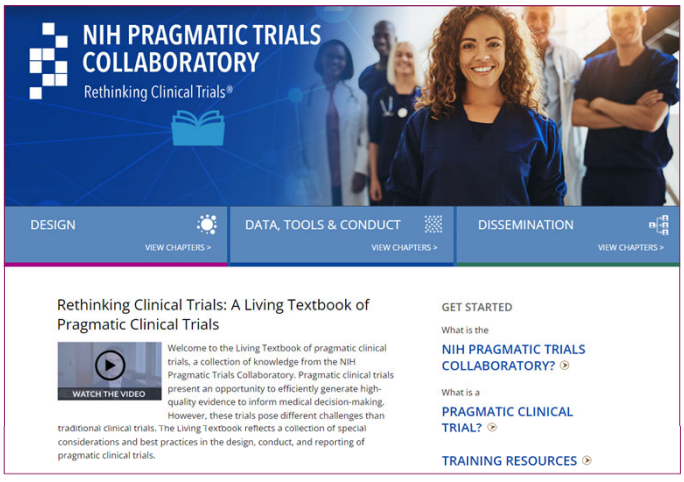


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# Resources:

## Measuring Outcomes

*Living Textbook* readings

- Electronic Health Records Core
- Patient-Reported Outcomes Core
- Choosing and Specifying Endpoints
- Using Electronic Health Record Data in Pragmatic Clinical Trials
- Assessing Data Quality for Healthcare Systems Data Used in Clinical Research
- PCT Reporting Template

Collaboratory Grand Rounds webinar recordings & slides

- Approaches to Patient Follow-Up for Clinical Trials: What's the Right Choice for Your Study?
- Thoughts from the Phenotypes, Data Standards & Data Quality Core
- Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-OUTCOMES EHR Ancillary Study
- Update from the Phenotypes, Data Standards, and Data Quality Core
- Enhancing EHR Data for Research and Learning Healthcare

Key journal articles

- Richesson et al., 2017. Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory Bradley et al., 2010. Health Services Research and Data Linkages: Issues, Methods, and Directions for the Future
- Weber et al., 2014. Finding the Missing Link for Big Biomedical Data
- Hersh et al., Caveats for the use of operational electronic health record data in comparative effectiveness research
- Richesson et al., A comparison of phenotype definitions for diabetes mellitus

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# *ePCT Experimental Design and Analysis*

## Speaker

**Patrick Heagerty, PhD**
University of Washington

# ePCT Experimental Design and Analysis

Patrick Heagerty, PhD
Professor, Biostatistics
University of Washington
School of Public Health

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## Learning goals

- Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know -- highlighting design and analysis considerations and key decision points.

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# Important things to know

- Studies that randomize groups or deliver interventions to groups face special analytic challenges not found in traditional individually randomized trials
- Failure to address these challenges will result in an underpowered study and/or an inflated type 1 error rate
- We won't advance the science by using inappropriate methods

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# NIH Collaboratory ePCT: STOP CRC

stop screen to prevent colon cancer

- Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations (STOP CRC)
- 40,000+ patients across 26 clinical sites
- Intervention
  - Health system–based program to improve CRC screening rates
  - Applied to clinical site → cluster randomization
- Unit of randomization: clinical site
- Two-arm cluster randomized trial (CRT)
  - Also referred to as a group-randomized or community randomized trial

Coronado GD et al. *Contemp Clin Trials*. 2014;38(2):344-349.

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# Reasons to randomize clusters instead of individuals

- Intervention targets health care units rather than individuals
  - STOP CRC: clinic-based intervention to improve screening
- Intervention targeted at individual risks "contamination"
  - Intervention spills over to members of control arm
  - For example, physicians randomized to new educational program may share knowledge with control-arm physicians in their practice
  - Contamination reduces the observed treatment effect
- Logistically easier to implement intervention by cluster

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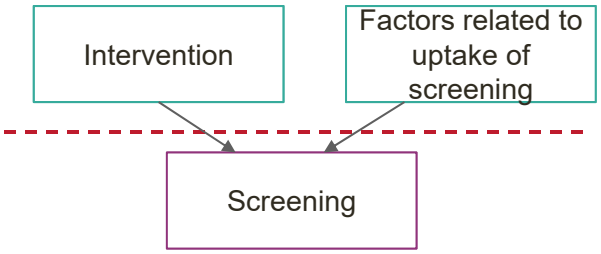
# STOP CRC cluster randomization

**Level 2**: Randomization at the level of the clinic (ie, cluster)




**Level 1**: Individual-level outcomes nested within clinics

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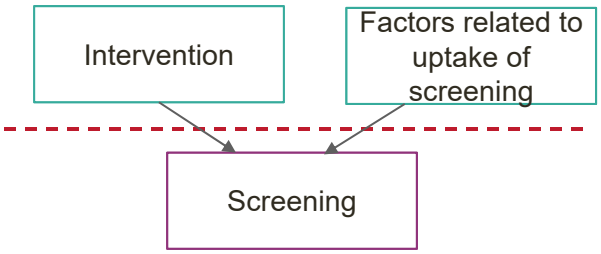
# STOP CRC cluster randomization




**Level 1**: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (ie, to *cluster*)

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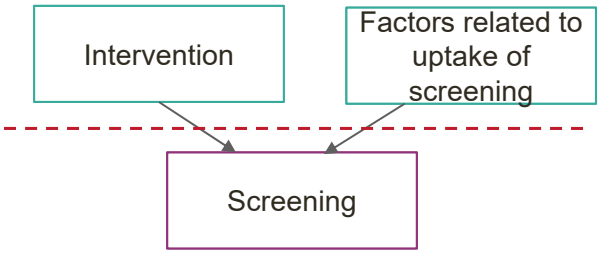
# STOP CRC cluster randomization




**Level 1**: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (ie, to *cluster*)

- Reduces power to detect treatment effect if same sample size used as under individual randomization

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# Understanding outcome clustering

- Consider 10 control-arm clinics (ie, clusters)
- Each with 5 age-eligible patients: ie, who are not up to date with colorectal cancer (CRC) screening
- Binary outcome: refused screening (Y/N)

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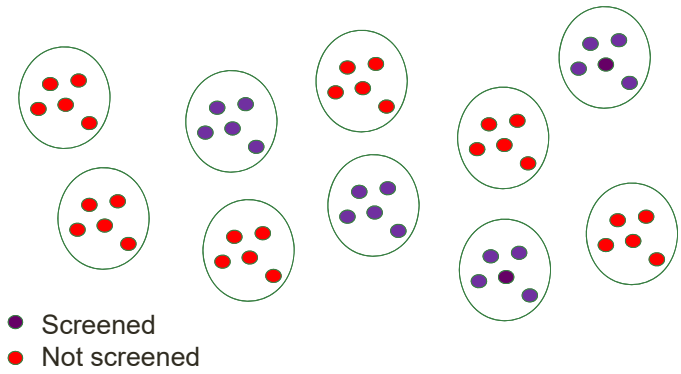
# Understanding outcome clustering: complete clustering

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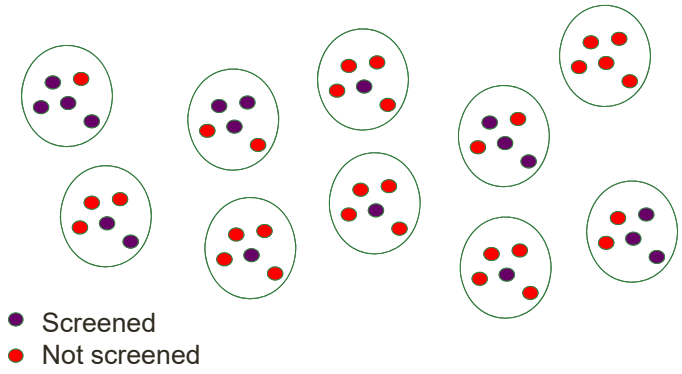
# Understanding outcome clustering: some clustering

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# Methods for pragmatic trials

- Pragmatic trials do not require a completely different set of research designs, measures, analytic methods, etc.
- As always, the choice of methods depends on the research question.
- The research question dictates
  - the intervention, target population, and variables of interest,
  - which dictate the setting, research design, measures, and analytic methods.
- Randomized trials will provide the strongest evidence.
  - What kind of randomized trial depends on the research question and how the intervention will be delivered.
- Alternatives to randomized trials are available, but not included in this presentation.

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# Summary of design issues

- All the design features common to RCTs are available to GRTs with the added complication of an extra level of nesting:
  - Cohort and cross-sectional designs;
  - Post only, pre-post, and extended designs;
  - Single-factor designs and factorial designs;
  - A priori matching or stratification;
  - Constrained randomization
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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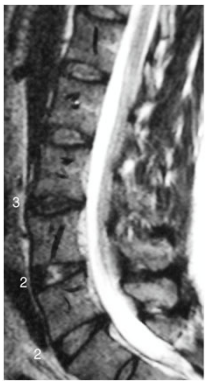
# NIH Collaboratory ePCT: LIRE



- Lumbar Imaging with Reporting of Epidemiology (LIRE)
- Goal: reduce unnecessary spine interventions by providing info on prevalence of normal findings
- Patients of 1700 PCPs across 100 clinics
- Clinic-level intervention → cluster randomization
- Unit of randomization: clinic
- Pragmatic trial
  - All clinics will eventually receive intervention
  - Stepped-wedge CRT

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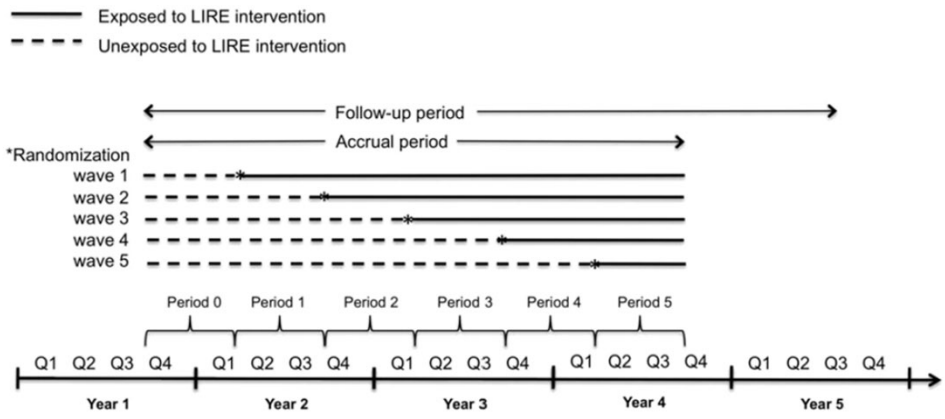
Jarvik JG et al. *Contemp Clin Trials*. 2015;45(Pt B):157-163.

# NIH Collaboratory ePCT: LIRE

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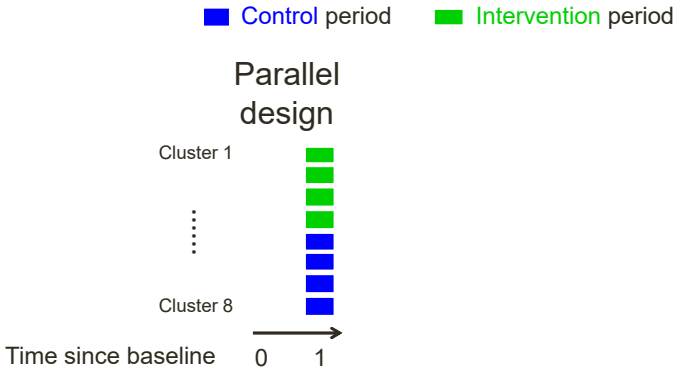
Source: Jarvik JG et al. *Contemp Clin Trials*. 2015;45(Pt B):157-163.

# Types of CRT designs

Examples with 8 clusters: 1-year intervention




Based on: Hemming K, Lilford R, Girling AJ. 2015. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Stat Med. 34:181-196. doi:10.1002/sim.6325. PMID: 25346484

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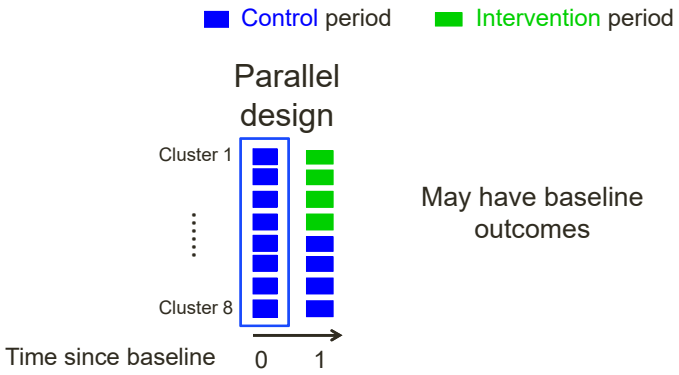
# Types of CRT designs

Examples with 8 clusters: 1-year intervention

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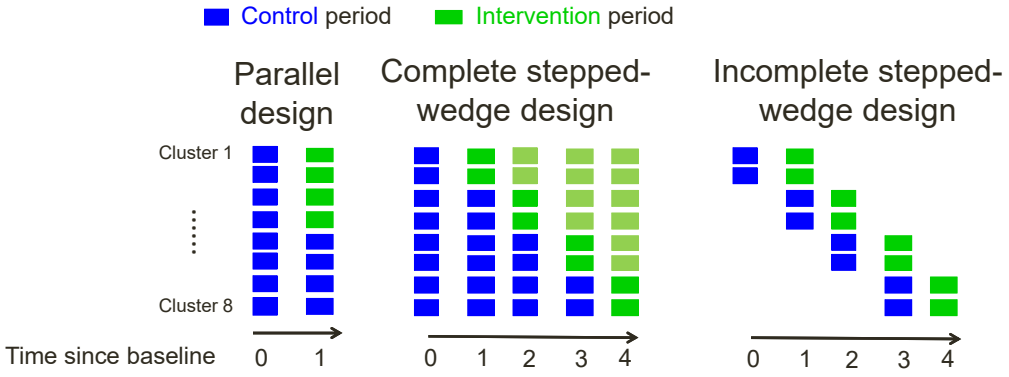
# Types of CRT designs

Examples with 8 clusters: 1-year intervention

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# Summary of design issues

- Many of the design features common to RCTs are available to SW-GRTs:
  - Cohort and cross-sectional designs;
  - Single-factor designs and factorial designs;
  - A priori matching, stratification, or constrained randomization to create comparable sequences.
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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# Challenges of pragmatic study design

- Trade-offs in flexibility, adherence, and generalizability are inevitable
- Implementation by healthcare system staff, not research staff
- New staff workflow and responsibility acknowledged
- Triage or case selection by healthcare system staff using existing structures with some modification

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# NIH Collaboratory: examples of analytic challenges and trade-offs

- Stepped wedge designs "roll out" over time and are more susceptible to disruption!
- Parallel group randomized designs are simple and powerful, but still need to address "clustering" for design and analysis.

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# It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

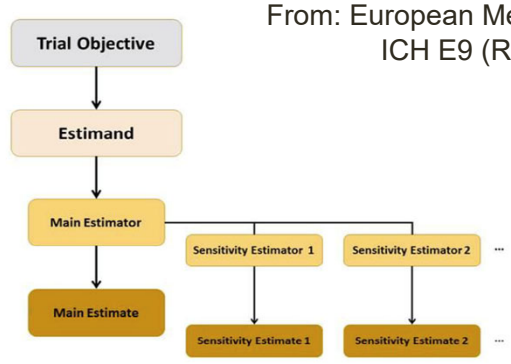


**Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective**

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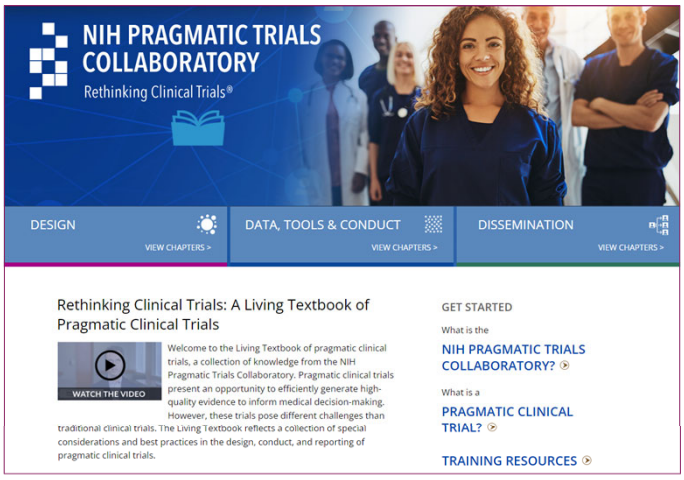
## Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*
**www.rethinkingclinicaltrials.org**

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# NIH resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  - https://prevention.nih.gov/grt
  - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
  - https://prevention.nih.gov/education-training/methods-mind-gap
    - SW-GRTs for Disease Prevention Research (Monica Taljaard, July 11, 2018)
    - Design and Analysis of IRGTs in Public Health (Sherri Pals, April 24, 2017)
    - Research Methods Resources for Clinical Trials Involving Groups or Clusters (David Murray, December 13, 2017)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs and IRGTs and a sample size calculator for GRTs

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# Resources

- Recommended reading:
  - Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of recent methodological developments in group-randomized trials: Part 1-design. Am J Public Health. 2017;107:907-915.
  - Turner EL, Prague M, Gallis JA, Li F, Murray DM. Review of recent methodological developments in group-randomized trials: Part 2-analysis. Am J Public Health. 2017;107:1078-1086.
  - Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
  - Murray DM, Pals SL, George SM, et al. Design and analysis of group-randomized trials in cancer: A review of current practices. Prev Med. 2018;111: 241-247.

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# Resources:

# ePCT Experimental Design & Analysis

## *Living Textbook* readings

- Biostatistics and Study Design Core
- DESIGN: Experimental Designs & Randomization Schemes
- DESIGN: Analysis Plan
- Key Issues in Extracting Usable Data from Electronic Health Records for Pragmatic Clinical Trials
- The Intraclass Correlation Coefficient
- Unequal Cluster Sizes in Cluster-Randomized Clinical Trials
- Pair-Matching vs Stratification in Cluster-Randomized Trials
- Frailty Models in Cluster-Randomized Trials
- Small-Sample Robust Variance Correction for Generalized Estimating Equations for Use in Cluster-Randomized Trials

## NIH Research Methods

- Group- or Cluster-Randomized Trials (GRTs)
- Individually Randomized Group-Treatment Trials (IRGTs)
- 7-part online webinar on Pragmatic and Group-Randomized Trials in Public Health and Medicine
- Mind the Gap webinars
- Research Methods Resources

## Collaboratory Grand Rounds webinar recordings & slides

- Lessons Learned from the NIH Collaboratory Biostatistics and Design Core

## Key journal articles


- Turner EL, Li F, Gallis JA, Prague M, Murray DM. 2017. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1-Design. Am J Public Health 107: 907-15
- Turner EL, Prague M, Gallis JA, Li F, Murray DM. 2017. Review of Recent Methodological Developments in Group-Randomized Trials: Part 2-Analysis. Am J Public Health 107: 1078-86
- Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, et al. 2018. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ 363: k1614
- Murray DM, Pals SL, George SM, Kuzmichev A, Lai GY, et al. 2018. Design and analysis of group-randomized trials in cancer: A review of current practices. Prev Med 111: 241-47


Additional resources


- Murray DM. Design and Analysis of Group-Randomized Trials. New York, NY: Oxford University Press; 1998.
- Pragmatic Trials: A Workshop Handbook
- Statistical lessons learned for designing cluster randomize pragmatic clinical trials from the NIH Healthcare Systems Collaboratory Biostatistic and Design Core

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# *Pilot and Feasibility Testing*

## Speaker

**Miguel Vazquez, MD**
University of Texas
Southwestern Medical Center

# Pilot and Feasibility Testing

Miguel Vazquez, MD
UT Southwestern Medical Center

Wendy Web, ND, Ph.D, MPH
National Center for Complementary and Integrative Health (NCCIH)

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## Learning goals

- Identify why it's important to do a pilot study to maximize acceptability, maintain affordability, and consider scalability of the ePCT intervention
- Learn key approaches to evaluating the capabilities of the partner health system and testing key elements of the intervention

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## Important things to know

- Pilot testing the ePCT methods increases likelihood of completing the trial and can prevent silly mistakes
- You need a biostatistician in the pilot/feasibility stage
- “Process issues” can derail the ePCT
- Use the pilot study to maximize acceptability, maintain affordability, and consider scalability of your intervention

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## ePCTs are not efficacy trials

- ePCTs bridge research into clinical care
- Intervention is integrated into real-world healthcare settings

- Involves streamlined data collection
- Pragmatic does not always mean low cost

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# During the pilot phase

- Establish close partnerships with healthcare system personnel
- Test and validate EHR data collection and extraction
- Evaluate whether generalizable patient population can be identified and enrolled with available healthcare systems
- Assess how well the intervention can be integrated into the clinical workflow
- Identify multiple local champions at each study site

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# Build partnerships

- Is the intervention aligned with the priorities of the partner healthcare system?
- How ready is the partner?
  - Are extra resources needed to support the intervention, identify participants, and extract necessary data?
  - How many sites are available to fully participate?
  - How much provider training will be needed, and can training use existing healthcare system infrastructure?
- If the intervention proves successful, what adaptations would be needed to implement it in other healthcare settings?

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# Aspects of feasibility that can be piloted

| | | |
|---|---|---|
| Verify that target population can be identified via the EHR | Test phenotypes needed for sample identification | Validate data quality, collection, extraction methods & accuracy |
| Evaluate if generalizable patient population is available | Coordinate processes with local champions | Test the training materials for frontline providers & staff |
| Test appropriateness & usability of study toolkits or other materials | Evaluate informed consent materials | Evaluate whether fidelity/adherence measures can be achieved to justify the full-scale ePCT |

***Use what you learn to design the ePCT***

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# Evaluate power calculations

If cluster randomization is involved, collect data to confirm estimate of the intraclass correlation coefficient (ICC) for power calculations

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# Quantify feasibility for pilot study aims

- Eligibility
- Recruitment
- Randomization
- Adverse events
- Retention
- Missing data
- Intervention fidelity

***Keep in mind realistic targets for the study's patient population***

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# Quantifying example 1



Demonstrate effective recruitment and retention, which we define as the ability to

- Recruit an average of 10 patients per month per site
- Retain 80% of participants for final data collection at 6 months

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# Quantifying example 2

Determine whether the intervention can be delivered with reasonable feasibility, which we define as 70% of the enrolled participants engaging in the intervention

Determine whether the smoking cessation intervention can be delivered with reasonable feasibility, which we define as 20% of the approached participants engaging in the intervention

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# Quantifying example 3

Demonstrate ability to collect primary outcomes and minimize missing data to less than 5% of primary outcome measures

Demonstrate ability to collect primary outcome of depression symptoms (patient-reported) and minimize missing data to less than 10% of primary outcome measures

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# Ensuring trial readiness

- Troubleshooting and iterative testing
- Flexibility to accommodate local conditions and changes over time
- Continuous engagement with healthcare system
- Readiness tasks
  - Recruitment plans are finalized with backup plans available
  - Ethical/regulatory aspects are addressed
  - Intervention is fully developed and finalized
  - Data collection methods are adequately tested
  - Budget and timeline are realistic and feasible

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# Readiness checklist

| Milestone | Completed |
|---|---|
| *Recruitment plans are finalized* | |
| All sites identified (documentation of site commitment) | |
| Methods for accurately identifying participants validated | |
| All agreements for necessary subcontracts in place | |
| *Ethical/regulatory aspects are addressed* | |
| Coordinated IRB oversight in place | |
| Finalized plans for informed consent or waiver of informed consent | |
| Finalized data and safety monitoring plan | |
| *Intervention is fully developed and finalized* | |
| Finalized intervention (including materials and training at sites) ready for site implementation | |
| Finalized protocol is IRB approved (informed consent and data collection forms, if applicable) | |
| *Data collection methods are adequately tested* | |
| Validated methods for the electronic health record information | |
| Validated study surveys, interviews, or other data collection modes | |
| Demonstrated quality assurance and harmonization of data elements across healthcare systems/sites | |
| Statistical and data analysis methods have been adequately developed | |
| *Budget is realistic, feasible, and accounts for potential changes* | |

Implementation Readiness Checklist available on the Living Textbook

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# In the end, good planning will help

- Avoid silly mistakes
- Maximize acceptability
- Maintain affordability
- Remember scalability

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# Important things to do

- Conduct a pilot or feasibility study of the intervention to inform the final design of the ePCT
- Work with a great biostatistician and an informatician (if needed)
- Develop a partnership approach to working with your healthcare systems
- Identify multiple local champions for all your sites
- Anticipate, identify, and make a plan to address changes in the healthcare system

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# Resources

- Healthcare system partnerships: Establishing Close Partnerships with Healthcare System Leaders and Staff
- Trial readiness criteria: Implementation Readiness Checklist
- Pilot and feasibility testing: Assessing Feasibility: Pilot Testing and Feasibility Assessment Scenarios from the Collaboratory's Demonstration Projects

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

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# Resource: The Living Textbook

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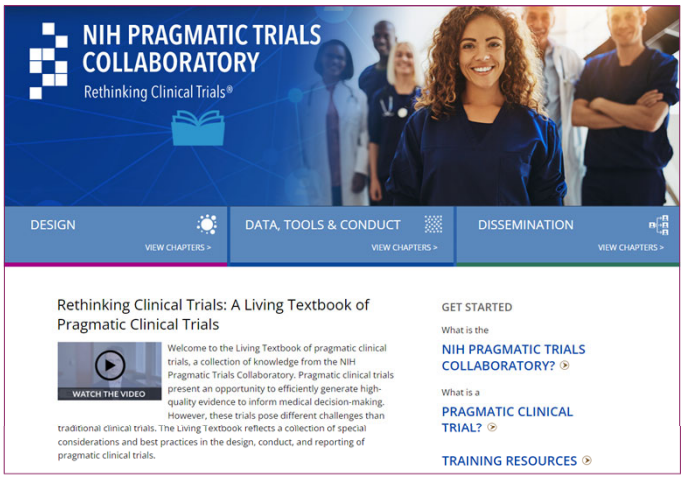


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# Resources:

# Pilot and Feasibility Testing

## *Living Textbook* readings

- Establishing Close Partnerships with Healthcare System Leaders and Staff
- Assessing Feasibility: Pilot Testing
- Feasibility Assessment Scenarios from the Collaboratory's Demonstration Projects
- Spotlight on Four Demonstration Projects
- Implementation Readiness Checklist

## Collaboratory Grand Rounds webinar recordings & slides

- Embedded Pragmatic Clinical Trials: Triumphs and Tribulations
- ICD-Pieces: From Planning to Performance
- Who to Include in a Pragmatic Trial? It Depends

## Key journal articles

- Weinfurt et al., 2017. Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory
- Hubbard et al., 2016. The feasibility and acceptability of trial procedures for a pragmatic randomised controlled trial of a structured physical activity intervention for people diagnosed with colorectal cancer
- Leon et al., 2011. The role and interpretation of pilot studies in clinical research

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# *Ethical and Regulatory Oversight Considerations*

## Speaker

**Kevin Weinfurt, PhD**
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

# Ethical and Regulatory Oversight Considerations

Kevin Weinfurt, PhD
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

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## Learning goals

- Learn about the regulatory and ethical challenges associated with ePCTs
- Understand considerations for distinguishing quality improvement versus research

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# Important things to know

- Ethical analysis for ePCTs is a work in progress
- Federal and local policies and/or their operationalization regarding the oversight of ePCTs are in flux
- There is often confusion and misunderstanding about ePCTs on the part of patients, providers, IRBs, and DSMBs

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# ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions

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# Evolving understanding of unique ethical/regulatory issues for ePCTs

- Informed consent
- Data monitoring
- Defining minimal risk
- Research/quality improvement distinction
- Vulnerable subjects
- IRB harmonization
- Data sharing
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
- Management of collateral findings

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Article

CLINICAL TRIALS

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ctj.sagepub.com

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**Exploring the ethical and regulatory issues in pragmatic clinical trials**

**Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]**

**Abstract**

The need for high-quality evidence to support decision making about health and health care by patients, physicians, care providers, and policy-makers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials that use novel techniques including emerging information and communication technologies to explore important research questions rapidly and at a fraction of the cost incurred by more "traditional" research methods promise to help close this gap. Nevertheless, while pragmatic clinical trials can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges. In this article, the authors briefly survey the current state of evidence that is available to inform clinical care and other health-related decisions and discuss the potential for pragmatic clinical trials to improve this state of affairs. They then propose a new working definition for pragmatic research that centers upon fitness for informing decisions about health and health care. Finally, they introduce a project, jointly undertaken by the National Institutes of Health Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), which addresses 11 key aspects of current systems for regulatory and ethical oversight of clinical research that pose challenges to conducting pragmatic clinical trials. In the series of articles commissioned on this topic published in this issue of *Clinical Trials*, each of these aspects is addressed in a dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research aimed at informing "real-world" choices about health and health care.

**Keyword**

Clinical trials, cluster-randomized trial, ethics, evidence-based medicine, learning health-care system, patient-centered outcomes research, pragmatic clinical trial

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# Current ethics/regulatory in flux


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# Determining if the Common Rule applies

- ✓ The activity is conducted or supported by HHS
- ✓ The activity is non-exempt human subjects research

To determine whether the activity is non-exempt human subjects research, **ask these questions:**

1) Does the activity involve **research**?
2) Does the research involve **human subjects**?
3) Is the human subjects research **exempt**?

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# Does the ePCT involve a research intervention?

**Definition of research:**

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

Common Rule: 45 CFR 46.102(l)

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# Distinguishing QI versus research

- Quality improvement activities
  - Are not subject to the Common Rule
  - Are intended to improve the quality of a healthcare delivery locally
  - Are not intended to contribute to generalizable knowledge

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# Regulatory perspective:
## *Who are the subjects in ePCTs?*

**Definition of human subject:**

Human subject means a living individual about whom an investigator conducting research:

- obtains **information or biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

Common Rule: 45 CFR 46.102(e)(1)

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# Regulatory perspective:
## *Who are the subjects in ePCTs?*

- **Test Case:**
  - Nursing homes randomized to receive a training intervention for staff
  - Post-training, investigators use data from medical records to assess patient health outcomes and staff behaviors

Largent et al. Ethical & Regulatory Issues for Embedded Pragmatic Trials Involving People Living with Dementia. JGAS 2020.

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# Regulatory & ethical challenges of ePCTs

**Ethical, not regulatory, question:**

*Whose rights and welfare need to be protected?*

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# Types of participants in an ePCT

Direct Indirect

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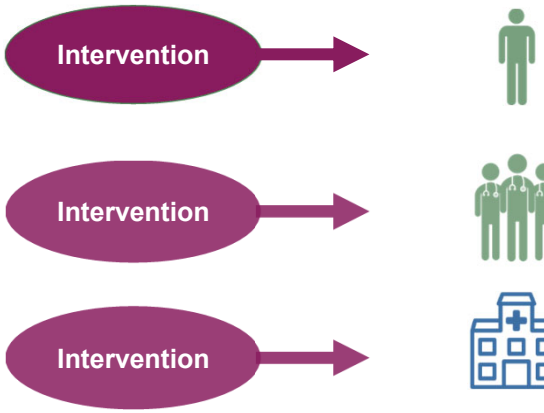
# Direct participants

Immediate or mediated targets of the intervention

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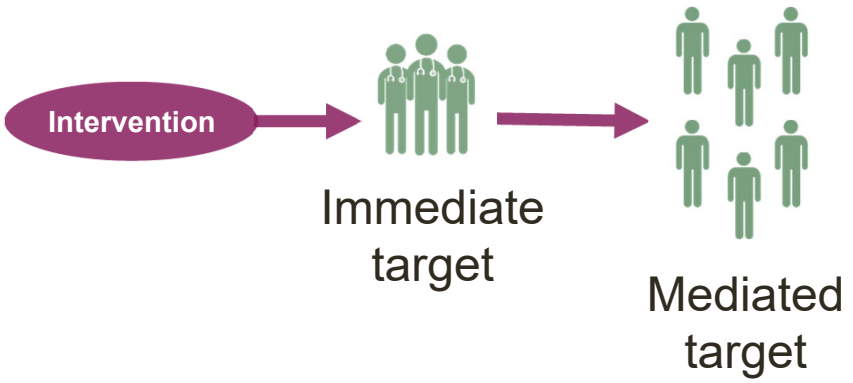
# Direct participant

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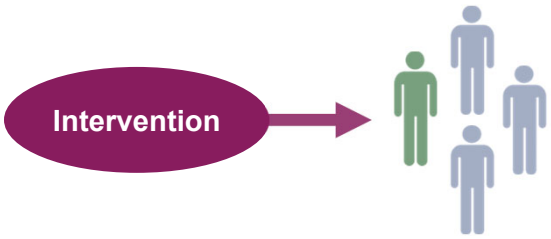
# Indirect participants

People affected by routine exposure to the environment (e.g., family/caregivers)

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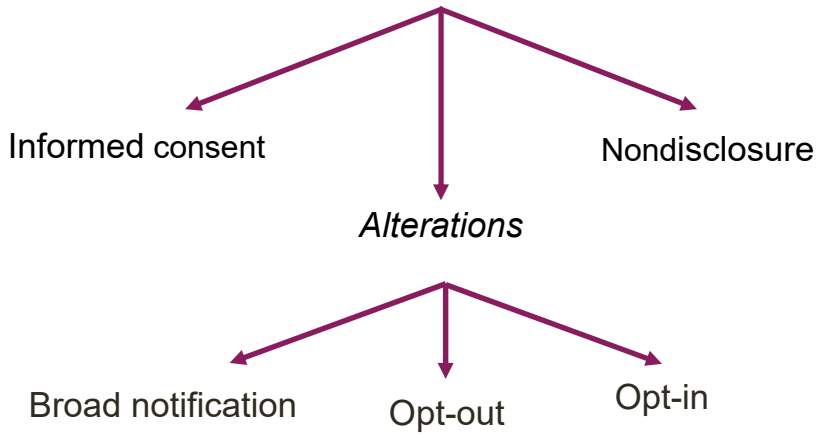
# Approaches to notification & authorization

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# Criteria for waiver/alteration of informed consent

- The research involves no more than minimal risk
- The research could not be carried out practicably without the waiver or alteration
- The waiver or alteration will not adversely affect the rights & welfare of the subject, and
- Where appropriate, the subjects will be provided with additional information about their participation

Common Rule: 45 CFR 46.116(f)

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# Working with human subjects oversight bodies

- Institutional review boards (IRBs)
- Data monitoring committees (DMCs) or data and safety monitoring boards (DSMBs)

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# Requirement for single IRB review

- Applicability
  - US institutions engaged in cooperative research for the portion of the research conducted in the United States
- Does not apply:
  - When more than single IRB review is required by law (including tribal law)
  - Whenever any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context

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# Data monitoring committee

Group of experts that review the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial

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# Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct
- Differential data collection/contact by study arm
- Level of data needed to change practice, especially when studying treatments in wide use?
- Are interim analyses actionable?

Adapted from Greg Simon, PCT Grand Rounds, December 8, 2017

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# Important things to do

- Designate someone to track local and federal regulatory developments and serve as liaison with regulatory/oversight bodies
- You can contact OHRP for guidance
- Budget sufficient time for proactive education and negotiations with relevant regulatory/oversight bodies
- Identify all parties who might be affected by the study and its findings; consider protections

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# Resource: OHRP contacts and resources

- Submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Bookmark this page for quick reference to OHRP resources on the revised Common Rule: www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html

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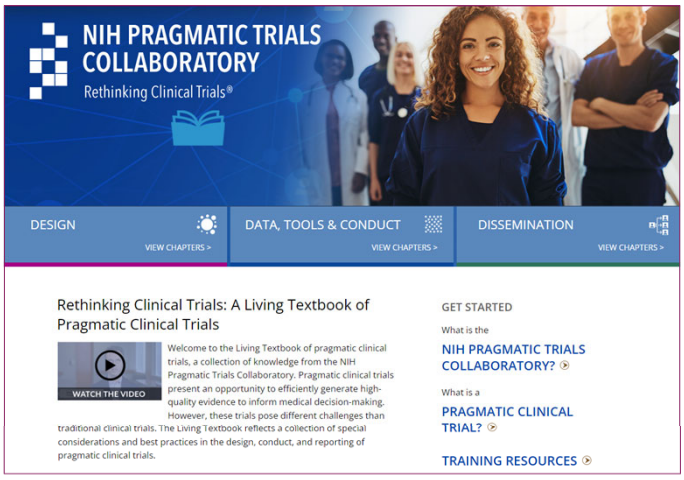
## Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*

**www.rethinkingclinicaltrials.org**

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## Resources:

# Ethical and Regulatory Considerations

*Living Textbook* readings

- Consent, Disclosure, and Non-disclosure
- Data & Safety Monitoring
- Ethics and Regulatory Core
- Collaboratory Demonstration Projects: Ethics and Regulatory Documentation

Collaboratory Grand Rounds webinar recordings & slides

- Data and Safety Monitoring in Pragmatic Clinical Trials
- The DSMB Role in Pragmatic Trials: NIMH Progress and Challenges
- A Tentative Introduction to the Revised Common Rule for the Protection of Human Subjects
- Comparison of Different Approaches for Notification and Authorization in Pragmatic Clinical Research Evaluating Commonly Used Medical Practices
- Recommendations from the Clinical Trials Transformation Initiative's Data Monitoring Committee Project
- Research on Medical Practices
- Privacy and Confidentiality in Pragmatic Clinical Trials
- FDA and Pragmatic Clinical Trials of Marketed Medical Products
- Oversight on the Borderline
- Altered Informed Consent in Pragmatic Clinical Trials
- Considerations in the Evaluation and Determination of Minimal Risk in Research Studies
- Ethical Responsibilities Toward Indirect and Collateral Participants in Pragmatic Clinical Trials (PCTs)

## Key journal articles

- Sugarman et al., 2014. Ethics and regulatory complexities for pragmatic clinical trials
- Weinfurt et al., 2017. Comparison of approaches for notification and authorization in pragmatic clinical research evaluating commonly used medical practices
- Topazian et al., 2016. Physicians' perspectives regarding pragmatic clinical trials
- Sugarman, 2016. Ethics of research in usual care settings: data on point
- Weinfurt et al., 2015. Patients' views regarding research on medical practices: implications for consent
- Mentz et al., 2016. Good clinical practice guidelines and pragmatic clinical trials: balancing the best of both worlds

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# *Writing a Compelling Grant Application*

## Speaker

**Michael Ho, MD, PhD**
University of Colorado Anschutz Medical Campus

# Writing a Compelling ePCT Grant Application

Michael Ho, MD, PhD
University of Colorado Anschutz Medical Campus

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## Learning goals

- Provide tips on NIH matchmaking
- Identify elements of a compelling ePCT application

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# Definitions:

- **Embedded pragmatic clinical trials** are conducted within the health care delivery setting and are "primarily designed to determine the effects of an intervention under the usual conditions in which it will be applied", which is in contrast with explanatory trials that "are primarily designed to determine the effects of an intervention under ideal circumstances" (http://www.bmj.com/content/350/bmj.h2147). "
- There are "three key attributes of pragmatic clinical trials (PCTs):
  - (1) an intent to inform decision-makers (patients, clinicians, administrators, and policy-makers), as opposed to elucidating a biological or social mechanism;
  - (2) an intent to enroll a population relevant to the decision in practice and representative of the patients or populations and clinical settings for whom the decision is relevant; and
  - (3) either an intent to (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or (b) measure a broad range of outcomes

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# Pragmatic or Implementation Trials RFA-AT-22-001

- Milestone-driven phased cooperative agreements for efficient, large-scale pragmatic or implementation trials
- Single application
  - One year planning phase - UG3, direct cost cap $500K
  - 2-4 year study conduct phase - UH3, direct cost cap $1M/yr
- At least 3 partnering HCS must be identified in the project, unless a strong justification for fewer HCS is provided in the application
- Include a diverse patient population that approximates the US population of patients with the condition being studied

**https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-22-001.html**

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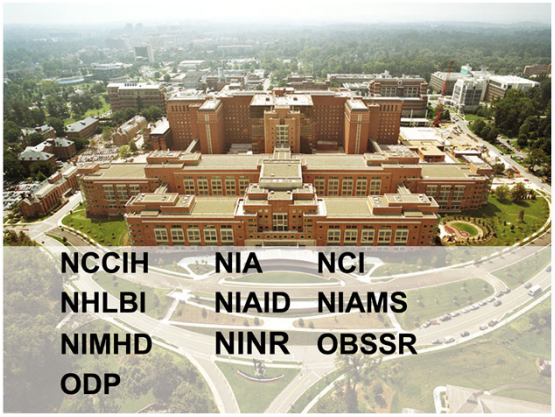
# Pragmatic or Implementation Trials RFA-AT-22-001

## Current participating Institutes, Centers and Offices




## New Areas of Focus

- Implementation Science trials study strategies for implementing evidence-based interventions into healthcare delivery.
- Trials to address health disparities in health care delivery
- Engaging health care systems with less historical involvement in research studies

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# NCCIH Areas of Interest

Applications should include a complementary or integrative interventions with **strong evidence of efficacy to warrant their inclusion in health care delivery:**

- Management of chronic pain conditions
- Promotion of whole person health, health restoration, emotional well-being, or resilience
- Prevention or treatment of symptoms including sleep disorders or disturbances, depression, anxiety, post-traumatic stress (disorder), and obesity
- Enhancement of adherence to medications or prescribed behavioral approaches
- Reduction of inappropriate use of medications or substances
- Improving minority health and eliminating disparities in the above conditions

Contact:
Wendy Weber, N.D., Ph.D., M.P.H.
weberwj@mail.nih.gov

NCCIH expects to support 1-2 projects

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# NIA Areas of Interest

NIH National Institute on Aging

**Include but are not limited to:**

- Compare effectiveness of treatment strategies for comorbid conditions that occur frequently in combination with Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD).
- Evaluation of beneficial and adverse outcomes from differing management strategies for multiple chronic conditions, testing an intervention, or coordinating several interventions.
- Evaluation of benefits and harms of screening for cognitive impairment in community-dwelling older adults in primary care–relevant settings, and effect on decision-making, patient, family or caregiver, and/or societal outcomes.
- Evaluation of benefits and harms of interventions for mild cognitive impairment or mild to moderate dementia in older adults in terms of decision-making, patient, family or caregiver, and/or societal outcomes.

**Contact**
Marcel Salive, M.D., M.P.H.
301-496-5278
Marcel.Salive@nih.gov

NIA expects to support 1-2 projects

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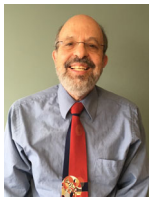
# NHLBI's Perspective (Key criteria)

- If at least two of the three or more participating health care systems are Federal Qualified Health Center (FQHC) networks or similar safety net health care systems.
- Applications that propose embedded pragmatic clinical or implementation trials which focus on improving heart, lung, blood, or sleep (HLBS) disorders in an underserved US patient populations who have suffered a disproportionate disease burden, and which focus on interventions to reduce health disparities are high priority.
- Many examples are listed but they are only illustrative



Lawrence Fine email:
Lawrence.fine@nih.gov

An email with the RFA number and your tentative specific aims are helpful.

If you know a NHLBI program official who is likely to be interested in your topic, reaching out to them directly or cc them is a good idea.

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# NINR Areas of interest

- NINR supports research that builds the scientific foundation for nursing practice and policy across diverse clinical and community settings to advance the prevention, detection, and management of disease and disability across the lifespan.
- NINR encourages research that integrates factors at multiple levels to identify their role in health, health improvement and health inequities with the goal of improving the health of individuals, families, and populations by translating science in order to maximize the impact of findings on practice and policy.
- In the context of this FOA, priority will be given to studies that propose projects that:
  - Study social needs care, integrating services that address health-related social risk factors and social needs within the context of clinical practice and health care delivery
  - Projects that are targeted at the medically underserved, uninsured, and underinsured populations

Contact:
Karen Kehl, R.N., Ph.D., F.P.C.N.
karen.kehl@nih.gov

NINR expects to support one project

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# NIAMS Areas of Interest

Study topics for pragmatic trials of interest to NIAMS include:

- Approaches to improve the management of chronic rheumatic, muscle, bone, joint, and/or skin diseases in adults and children, particularly through testing the use of different regimens to optimize outcomes and reduce known risks.

Contact:
Charles H. Washabaugh, Ph.D.
washabac@mail.nih.gov

NIAMS expects to support 1 project

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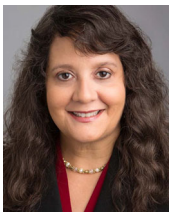
# NIMHD Areas of Interest

- NIMHD is interested in multilevel pragmatic intervention studies within the context of health care systems that serve primarily or a significant number of patients from populations with health disparities:
  - Multi-level interventions focused on reducing unnecessary or preventable emergency care utilization.
  - Multi-level interventions focused on reducing delayed health care system response to needed emergency care especially in remote or low-income settings and for patients for whom English is not their primary language.
  - Interventions testing the incorporation of technology to enhance communication between the patient and the health care system, and promote patient agency and decision making and/or medical adherence.
  - Interventions focused on older adult wellness aimed at reducing polypharmacy and serious or incapacitating medication side effects, and accounting for sociocultural determinants of health.
  - Studies focused on enhancing timely access to services conspicuously delayed for many patients from populations with health disparities.
  - Multi-level interventions on facilitating access and referral to timely palliative and/or end of life care for patients from populations with health disparities.



Contact:
Larissa Aviles-Santa, M.D., M.P.H.
avilessantal@mail.nih.gov

NIMHD expects to support 1 project

NIMHD Research Framework

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# Important things to know

- Online resources are available for the development of pragmatic trial grant applications
- NIH has new policies and forms related to clinical trial grant applications
- Some things, such as milestones and safety monitoring, may be negotiable around the time of an award

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# Tailor the application

*Tailor your application to address all the FOA-specific instructions and review criteria*

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# Common application pitfalls

- Overly ambitious–beyond the life or length of the application
- Missing or inappropriate control groups
- Lack of sufficient expertise or skilled collaborators needed to complete the studies
- Not sufficient publications in the area of proposed studies
- Insufficient statistical power
- Cannot recruit the needed population

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# Application dos

- Justify the research
- Include pilot data
- Address potential overlaps
- Reduce complexity
- Ensure aims are capable of advancing the field
- Choose appropriately expert personnel for a multidisciplinary team
- Link data collection and analysis to aims
- Justify the use of multiple sites and sample size

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# Application dont's

- Skip any steps (eg, literature review)
- Use dense or confusing writing style
- Use appendix inappropriately
- Include untestable aims
- Include non-relevant aims or fishing expeditions
- Assume that prior collaboration is irrelevant

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# Strategies for success

- Pose a clear research question
- Convince the reviewer your study is worth doing
- Sell your research plan–highlight the strengths
- Identify weaknesses and explain how you will deal with them
- Tailor your application to the funding agency
- Obtain feedback from your collaborators, consultants, and others

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# Watch the Technical Assistance Webinar

## https://videocast.nih.gov/watch=45075

**Technical Assistance Videocast for NIH Health Care Systems Research Collaboratory – Pragmatic and Implementation Trials of Embedded Interventions (UG3/UH3) – RFA-AT-22-001**

## Questions after the Conference?

## Email: nccihwebinarq@nih.gov

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# Resource: The Living Textbook

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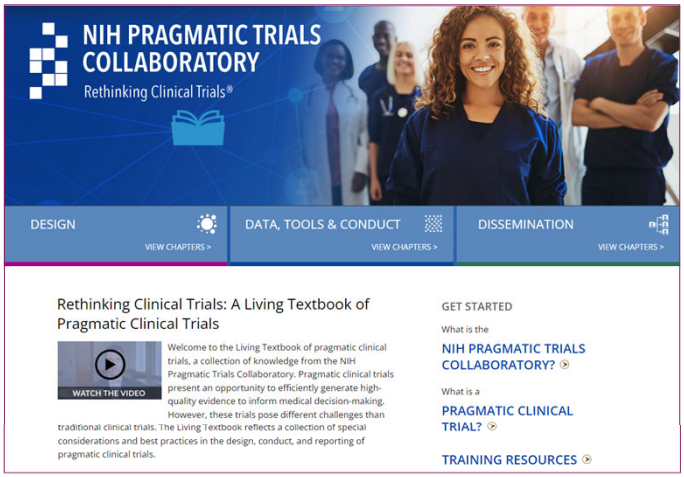


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# Resources:

# Writing a Compelling Grant Application

## *Living Textbook* readings

- *ePCT Team Composition*
- *Developing a Compelling Grant Application*
- *Assessing Feasibility: Developing the Trial Documentation*

## Key journal articles

- *Johnson et al., 2014. A guide to research partnerships for pragmatic clinical trials*
- *Dolor et al., 2014. Guidance for researchers developing and conducting clinical trials in Practice-based Research Networks (PBRNs)*

## Other

- *NIH Reporter (Tool)*
- *National Institute on Aging (NIA) Stage Model for Behavioral Intervention Development*
- *NIA RFA-AG-20-029, Pragmatic Trials of Managing Multimorbidity in Alzheimer's Disease*
- *Health Care Services Research Network website*
- *RFA-RM-16-019: NIH Health Care Systems Research Collaboratory*
- *Clinical Trial-Specific Funding Opportunities*
- *Clinical Trial-Specific Review Criteria*
- *Health Care Systems Research Network*
- *Research Toolkit*

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# *ePCTs in Context: Panel Discussion*

## Moderator

**Kevin Weinfurt, PhD**
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

## Speakers

**Michael Ho, MD, PhD**
University of Colorado Anschutz Medical Campus

**Miguel Vazquez, MD**
University of Texas Southwestern Medical Center

**Stacy Sterling, DrPH, MSW, MPI GGC4H**
Kaiser Permanente Northern California Division of Research

# ePCTs in Context: Panel Discussion

Moderator:
Kevin Weinfurt, PhD
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

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## Panel Speakers

- Michael Ho, MD, PhD
  - Nudge
- Miguel Vazquez, MD
  - ICD-Pieces
- Stacy Sterling
  - GGC4H
- Followed by Q&A

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# Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications (The Nudge Study)

**Michael Ho, MD, PhD**
**University of Colorado Anschutz Medical Campus**

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## Study objectives

- Conduct a pragmatic patient-level randomized intervention across 3 HCS to improve adherence to chronic CV medications.
  - Primary outcome: Medication adherence defined by the proportion of days covered (PDC) using pharmacy refill data.
  - Secondary outcomes:
    - Intermediate clinical measures (e.g., BP control)
    - CV clinical events (e.g., hospitalizations)
    - Healthcare utilization
    - Costs

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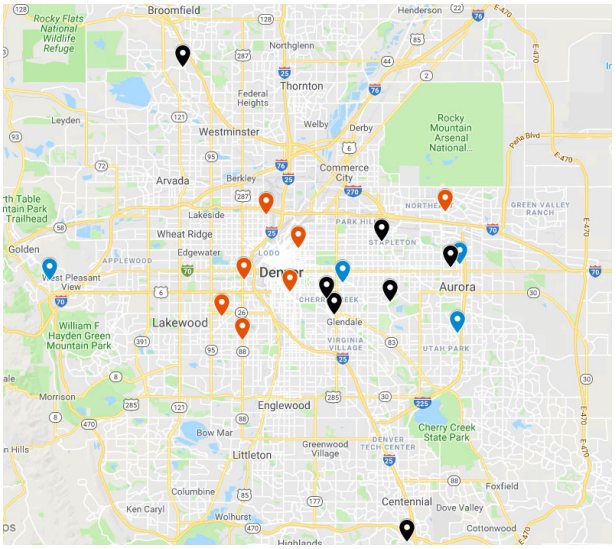
# Study setting

- Denver Health Clinics
- VA Eastern Colorado HCS Clinics
- UCHealth Clinics

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# Patient population

- Adult patients diagnosed with ≥ 1 condition of interest and prescribed ≥ 1 medication of interest

| Condition | Classes of medications |
|---|---|
| Hypertension | Beta-blockers (B-blockers), Calcium Channel Blocker (CCB), Angiotensin converting enzyme inihibitors (ACEi), Angiotensin Receptor Blockers (ARB), Thiazide diuretic |
| Hyperlipidemia | HMG CoA reductase inhibitor (Statins) |
| Diabetes | Alpha-glucosidase inhibitors, Biguanides, DPP-4 inhibitors, Sodium glucose transport inhibitor, Meglitinides, Sulfonylureas, Thiazolidinediones, and statins |
| Coronary artery disease | PGY-2 inhibitor (Clopidogrel, Ticagrelor, Prasugrel, Ticlopidine), B-blockers, ACEi or ARB and statins |
| Atrial fibrillation | Direct oral anticoagulants, B-blockers, CCB |

- English or Spanish-speaking

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# Opt-out study design

Identify patients with CV disease and prescribed medication

→ Send opt-out packets to eligible patients

→ Patients who do not return opt-out form are eligible for enrollment

→ Monitor for gaps with medication refills

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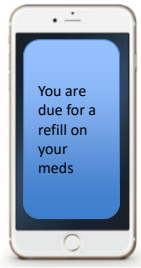
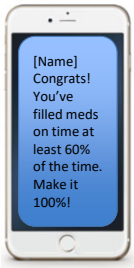
# Intervention arms

7 day gap between medication refills

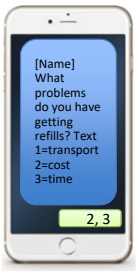
- Usual Care
- Generic Texts




- Optimized Texts




- Optimized Texts + AI Chat Bot

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# Types of nudges employed in this study

- Social Norms: Others like you are performing this behavior
  - Examples—testimonials "*People like Joseph have had success in remembering to pick up his meds by making it a habit to drive by his pharmacy on the way home from work*"
- Behavioral Commitments: Making a stated intention to take action
  - Example--"*Will you mention to a family member your intention to refill your medications today*?"
- Narrative stories: Evoking emotional connection
  - Example—"*Marta has committed to her daughter that she will stay on top of her refills so she'll be around longer for her grandkids!*"

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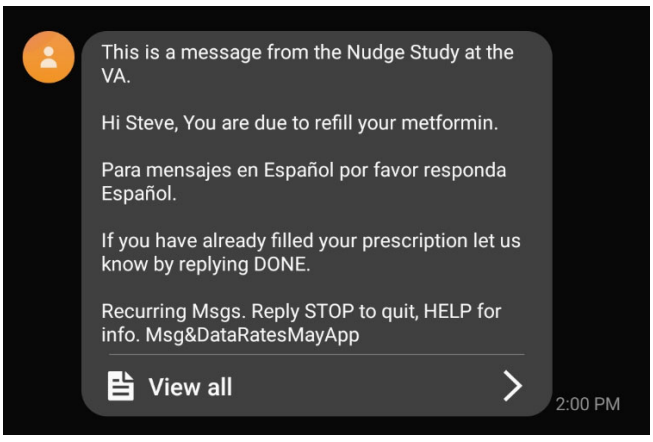
# Sample generic message

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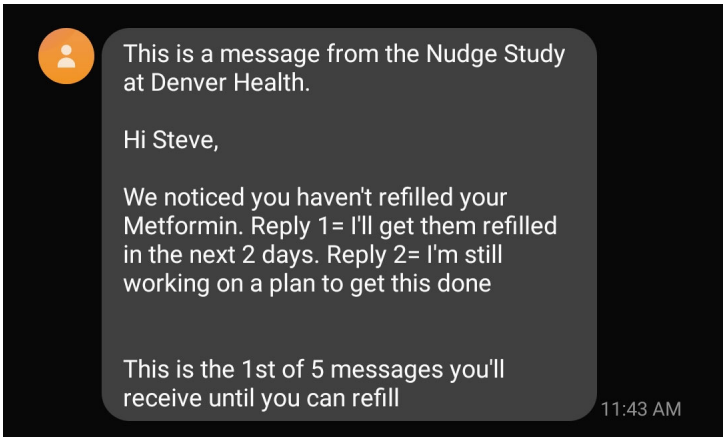
# Sample optimized message

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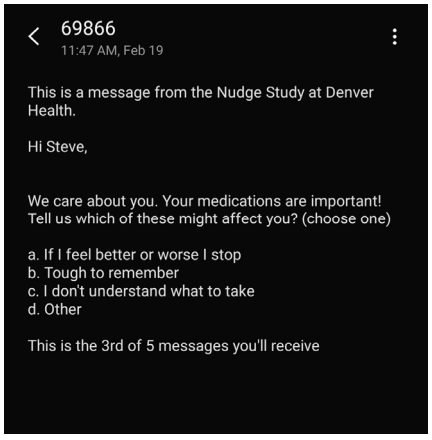
# Sample optimized + AI chatbot message

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# Potential Barriers

- Unable to confirm patient receipt of text messages and/or patient comprehension
- Possibility of switching numbers or losing cell service, particularly at the end of the month
- Growing burden of text messages in general
- Competing hospital/health system priorities
- Data integration (e.g., Surescripts pharmacy data)

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# Lessons Learned

- Stakeholder (i.e., patient, providers and health systems) engagement is critical
- Persistence and adaptability (particularly when COVID occurred) is key
- Creating multi-disciplinary and engaged teams to solve study issues

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# Improving Chronic Disease Management with Pieces (ICD-Pieces)

Miguel Vazquez, MD
University of Texas Southwestern Medical Center

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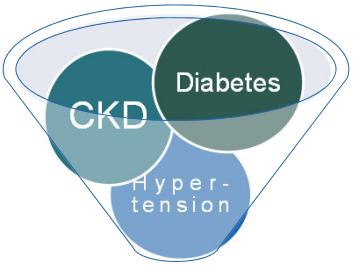
## Multiple chronic conditions

->Common
->Serious Complications




->Under-recognized
->Treatable

Opportunity to Advance Care

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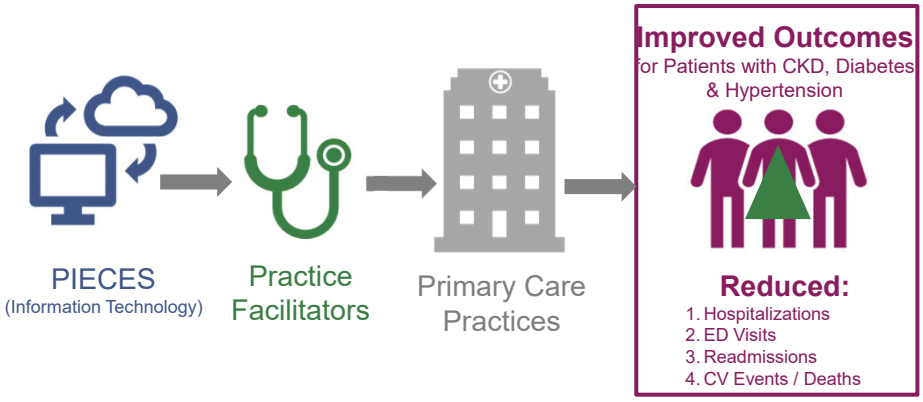
# Hypothesis

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# Study Design

| | |
|---|---|
| Population | Adult primary care patients with CKD, diabetes, and hypertension in 4 major health systems (Parkland, Texas Health Resources, VA North Central Texas and ProHealth CT) |
| Design | Open-label, pragmatic trial randomized by primary care practice (cluster) |
| Intervention | During primary care clinic visit |
| ICD-Pieces | Practice facilitator implemented evidence-based care for secondary prevention of HTN, DM, CKD, and CV complications |
| Control | Standard of Care |
| Waiver of informed consent | (opt-out) |
| Outcome | one-year documented hospitalization (claims / EHR) |

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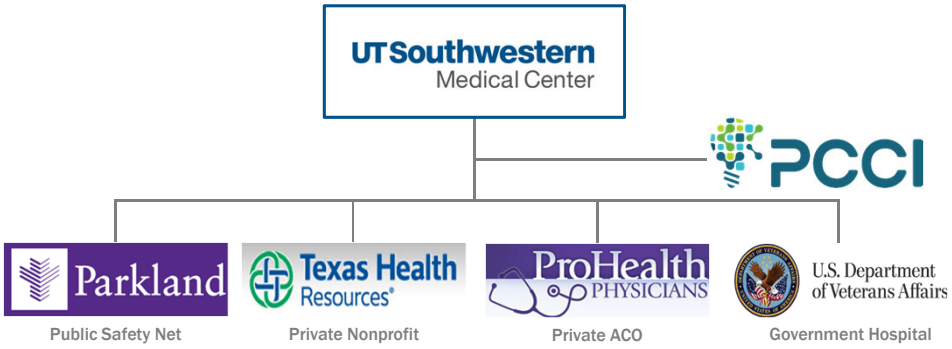
# Participating healthcare systems

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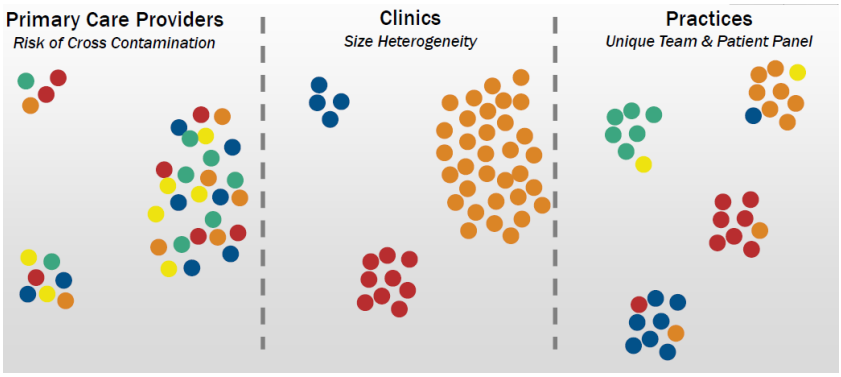
# Study design: cluster randomization

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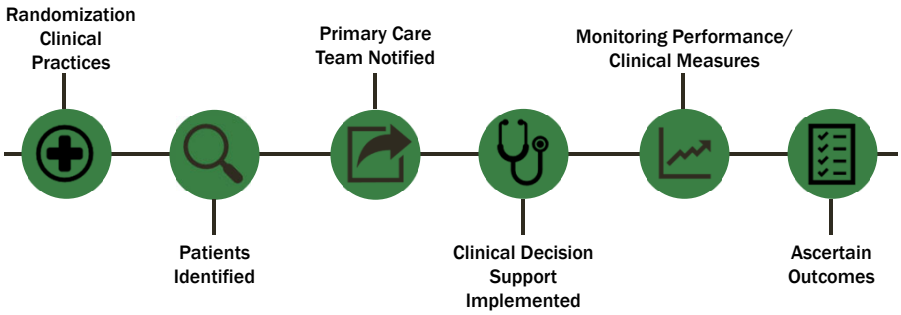
# Study conduct

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# Potential barriers

- Personnel turnover at multiple sites and levels
- Measuring study fidelity
- Data sharing and transmission

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# Lessons learned

| Early Planning | Delivery | Completion |
|---|---|---|
| • Align Goals<br>• Plan together<br>• Develop trust<br>• Staffing | • Minimize disruption<br>• Provide tools<br>• Adapt<br>• Create value | • Dissemination / Implementation<br>• Sustainability<br>• Future Projects |

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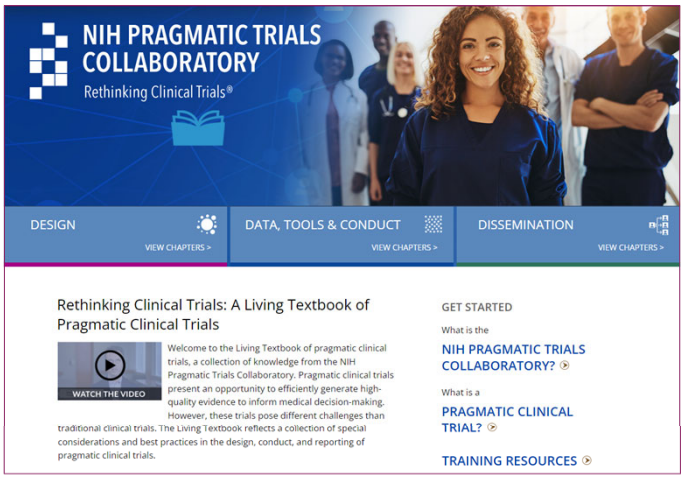
## Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*

**www.rethinkingclinicaltrials.org**

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# Guiding Good Choices for Health (GGC4H): Lessons from a Pragmatic Trial in Three Large Healthcare Systems

Stacy Sterling, DrPH, MPI
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# Objectives

- Overview: Guiding Good Choice for Health (GGC4H)
- Opportunities for Parent-focused Prevention in Primary Care
- Challenges and Opportunities (or… the only constant in life is change…)
  - Balancing pragmatic implementation and rigorous design
  - Could we harness EHR data to address key study questions?
  - Implementation during the pandemic

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# GGC4H Leadership Team & Funders

**Guiding Good Choices for Health (GGC4H)**

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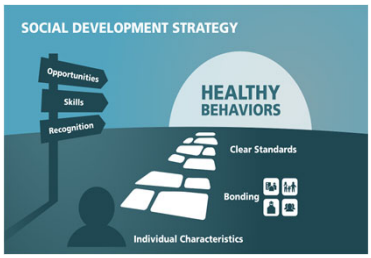
# Guiding Good Choices

- Theoretical foundation: Social Development Strategy
- Five 2-hour sessions teach specific skills*
  - Getting Started: How to Promote Health and Wellbeing During the Teen Years
  - Setting Guidelines: How to Develop Healthy and Clear Standards
  - Managing Conflict: How to Deal with Anger in a Positive Way
  - Avoiding Trouble: How to Say No, Keep Your Friends, and Still Have Fun *(with adolescents)*
  - Involving Everyone: How to Strengthen Family Bonds
- Evidence-based – 2 prior RCTs
  - Reduced alcohol, marijuana, cigarette use; depression symptoms; antisocial behavior -- for 4-6 years after middle-school baseline
  - Strengthened families: Better communication, closer relationships, less family conflict

**Anticipatory guidance curriculum, consistent with AAP guidelines**

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***An Introductory Session is added when GGC is delivered virtually.***

# Guiding Good Choices (GGC)

- 2 prior RCTs:
  - Affects Parenting Behavior regardless of family risk (Spoth et al., 1998)
  - Reduced Growth in Substance Use, Delinquency; Depressive Symptoms (Mason et al., 2003, 2007)
  - Cost-beneficial: Benefit-Cost Ratio: $2.77 (WSIPP, 2018)
- Session goals – Social Development Model
  - Build family bonding
  - Establish and reinforce clear and consistent guidelines; monitor children's behavior
  - Teach children skills to resist peer influence
  - Improve family management practices
  - Reduce family conflict
- GGC is organized around substance use prevention delivered universally, but skills generalize to other parenting concerns.

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## GGC Helps Fill a Service Gap in Pediatric Primary Care

- AAP recommends pediatricians provide anticipatory guidance to parents – but there are barriers to doing this.
- Have pediatricians refer parents to GGC for delivery by embedded behavioral health specialists within each HCS.
  - Pediatricians have high credibility and parents' trust. They are good agents for validating positive parenting practices.
  - Care provided in a pediatric primary care setting is non-stigmatizing.
- *Advantages **may create higher recruitment and retention rates in primary care** compared to community settings.*
  - This pragmatic trial, set in the context of real-world health systems, will allow us to examine recruitment and retention outcomes as well as adolescent behavioral health impacts.

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## Outcomes: RE-AIM Framework

**Effectiveness - Adolescent Health Outcomes**

- Primary – Substance use initiation with 4 indicators
  - Alcohol, Marijuana, e-Cigarette, Tobacco Use
- Secondary – Other impacts from prior trials
  - Depression symptoms, Antisocial behavior
- Exploratory – Available in EHR, not previously evaluated but plausibly linked to GGC
  - Anxiety symptoms, Health service utilization (inpatient, ED)

**Implementation Outcomes**

- Reach, Adoption, Implementation, Maintenance
- Includes health economic evaluation: Cost, cost-effectiveness

**Protocol Paper:** Scheuer, Kuklinski, Sterling, Catalano, et al. (2022, *Contemporary Clinical Trials)*

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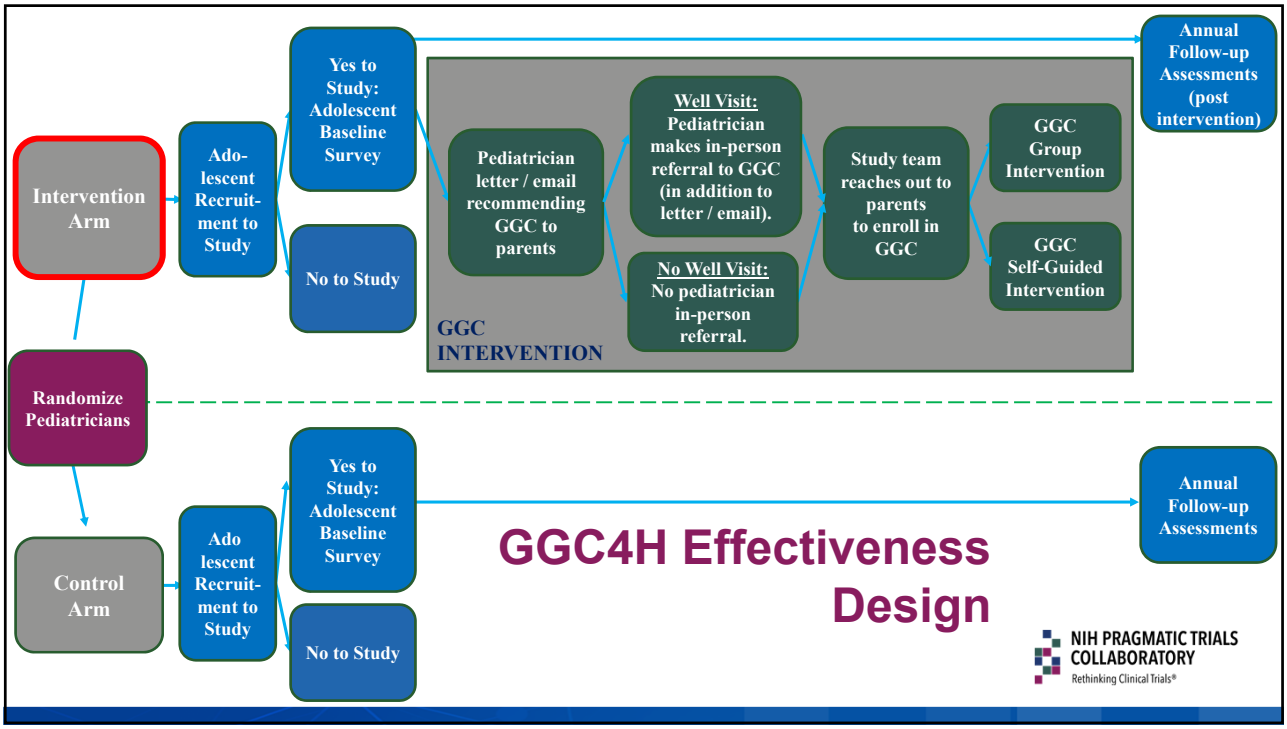
## PRE-COVID 19 TIMELINE

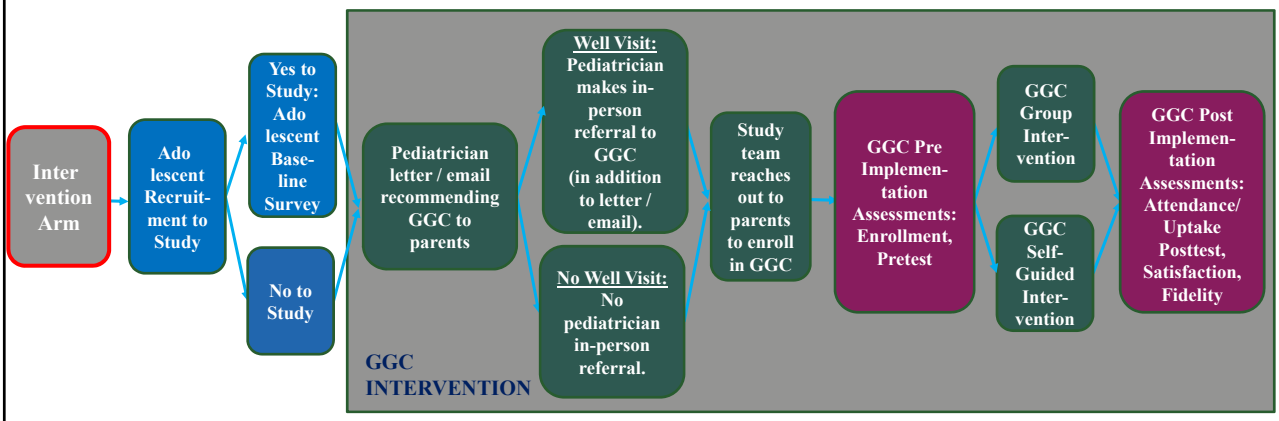
| Year 1<br>May 2018 – Apr 2019 | Year 2<br>May 2019 – Apr 2020 | Year 3<br>May 2020 – Apr 2021 | Year 4<br>May 2021 – Apr 2022 | Year 5<br>May 2022 – Apr 2023 |
|---|---|---|---|---|
| • Milestones-driven planning phase<br>• Pilot study | • Recruit Cohort 1 into study<br>• Implement GGC with Cohort 1 | • Recruit Cohort 2 into study<br>• Implement GGC with Cohort 2<br>• Cohort 1 Follow-up 1 | • Cohort 1 Follow-up 2<br>• Cohort 2 Follow-up 1 | • Cohort 1 Follow-up 3<br>• Cohort 2 Follow-up 2 |

COVID-19

## ACTUAL TIMELINE

| Year 2<br>May 2019 – Apr 2020 | Year 3<br>May 2020 – Apr 2021 | Year 4<br>May 2021 – Apr 2022 | Year 5<br>May 2022 – Apr 2023 | Year 6 NCE<br>May 2023-Apr 2024 |
|---|---|---|---|---|
| • Develop Virtual GGC | • Retrain for Virtual GGC<br>• Cohort 1 Mini-baseline<br>• Implement GGC with Cohort 1 | • Recruit Cohort 2 into study<br>• Implement GGC with Cohort 2<br>• Cohort 1 Follow-up 1 | • Cohort 1 Follow-up 2<br>• Cohort 2 Follow-up 1 | • Cohort 2 Follow-up 2 |






# GGC4H Implementation Design

We realized we could offer intervention to all parents of eligible adolescents empaneled with intervention arm pediatricians.

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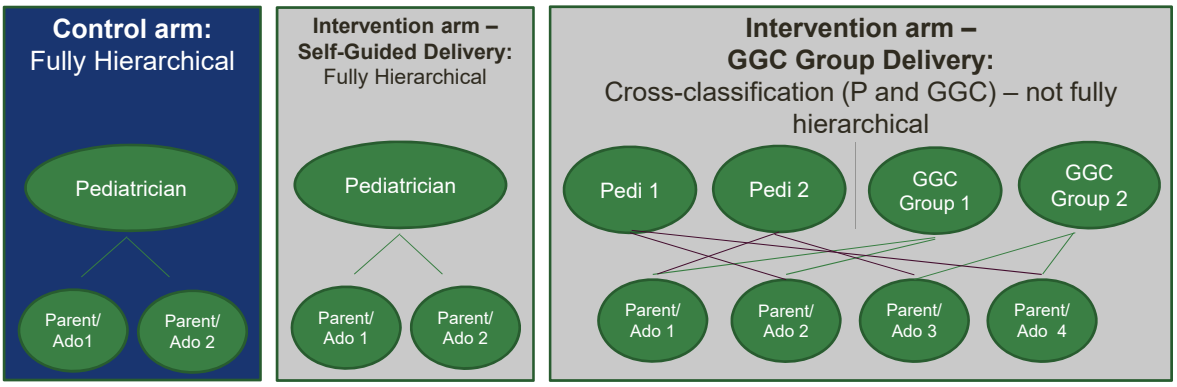
# (1) Design: Could we achieve pragmatic implementation and valid statistical inference? Yes




Cluster-randomized trial with partial cross-classification in intervention arm

If not modelled appropriately: Threats to inference (bias), increased Type I error

Valid statistical inference in the face of a complex but pragmatic implementation approach.

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# Innovative Modelling Approach from Biostatisticians Quesenberry and Sofrygin

- Extend Luo et al.'s (2015) linear model to generalized linear model for binary outcomes (logistic mixed effects regression)
- Appropriately model random effects – with 2 different subsets in intervention arm
  - **Self-guided subset:** Pediatrician is the only random effect, same as in the **control arm**
  - **Group GGC:** Both P and GGC group are random effects
- Fixed parent/adolescent-level and Pediatrician-level covariates, with focus on point and interval estimation of trial arm indicator regression coefficient

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# (2) Data: Could we use EHR data to address key study questions? Yes and No

**Eligibility** ✓
Identification of
Intervention and Control Cohorts
Identification of 12-year old well-child visits
Pediatrician reminders about upcoming well-visits with eligible adolescents

**Adolescent Outcomes** –
Patient data collected during routine clinical care:
- Substance use
- Mental health symptoms, diagnoses
- Medical diagnoses
- Utilization – ED, inpatient, outpatient

**GGC Cost-Effectiveness** ✓–
Cost decision-support systems integrate utilization data and general accounting ledgers
Clinical encounters: Activities-based costing → service unit cost
Services provided at non-HCS facilities but paid for by HCS are also available

**EHR data sources:**

1) **Clarity:** Relational database refreshed in real time or daily, used to identify well-child visits
2) **Virtual Data Warehouse:** Database developed over 20 years to support multisite HCS research
   - Coverage: Enrollment, demographics, encounters, diagnoses, pharmacy, laboratory, PRO, claims
   - Data are harmonized, standardized across member sites, continually updated

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# Would EHR data yield behavioral health outcomes? No!

| GGC4H YOUTH OUTCOMES | | | |
|---|---|---|---|
| **Primary Outcomes** | **Secondary Outcomes** | **Exploratory Outcomes** | **Mechanisms to Impact** |
| **Substance Use**<br>Age of Initiation<br>**Substances Examined**<br>Alcohol, Marijuana, Cigarettes, E-Cigarettes, Inhalants, Opioids, Other Drugs | **Mental Health**<br>Depression (PHQ-9)<br>**Antisocial Behavior**<br>Ever<br>Past-Year<br>**Substance Use**<br>Lifetime Frequency<br>Past-Year, Past 30-day Use<br>Past 30-day Use Amount | **Anxiety (GAD-7)**<br>**Screen & Social Media Time**<br>**Sexting** | **Parent and Family Risk & Protective Factors (RPFs)**<br>**Individual RPFs**<br>**Peer RPFs**<br>**School RPFs** |

- Not measured consistently or documented systematically in EHRs across the 3 HCS
- Developed **Adolescent Behavioral Health Survey** to collect data on behavioral health outcomes; **widely used, validated measures**
- **Administered online or by telephone with trained interviewers**

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# (3) Implementation: Would Pediatrician Referral lead to higher intervention enrollment rates? Yes, but…

- Pragmatic referral process at well child visit
  - Role needs to be brief to fit normal workflow
  - Needs to be flexible to account for different pediatrician styles
  - Provide tools to support the role:
    Flexible scripts and prescription pads
- Trial logistics
  - Naturalistic experiment with two modes of recruitment

| Pediatrician Referral | Enrollment Rate |
|---|---|
| **In-person** | 31% (range: 28%-71%) |
| **Via letter / email** | 25% (range: 18% - 29%) |

- Both modes: Higher enrollment than in community settings
  - Some preliminary evidence that “in-person” pediatrician referral resulted in stronger enrollment

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## Sample Referral Scripts

"We have a new free program called Guiding Good Choices for Health and I'm encouraging all parents of my 11-12 year old patients to attend this free program."

"The reason I'm recommending this class is that there is research showing that it is effective in helping parents talk to their kids about the importance of avoiding risky behaviors, while also supporting strong parent-child relationships."

"We're offering a new free class called Guiding Good Choices. It's for parents of children your son's/daughter's age in my practice, to provide you with tools to help your child avoid risky behaviors during the challenging teen years while keeping your relationship strong."

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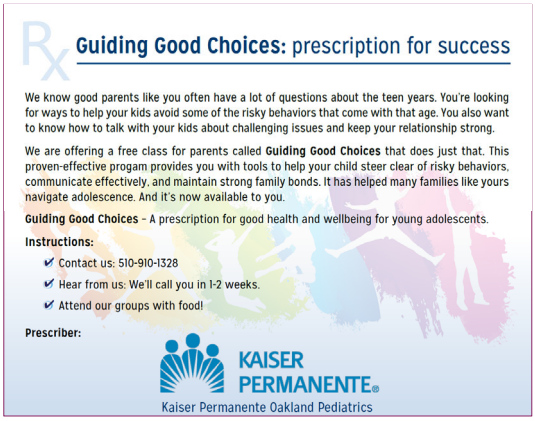
## Prescription pads

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## (3) Implementation: Would Pediatrician Referral lead to higher intervention enrollment rates? Yes, but…


## Virtual GGC – Adaptation, implementation, satisfaction

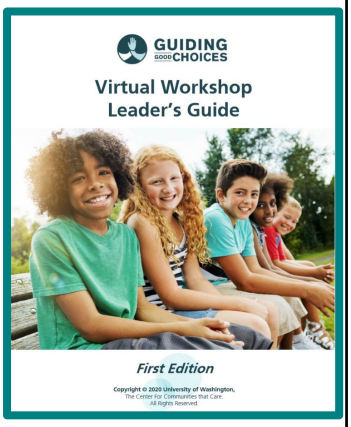
Preliminary step: Focus groups, qualitative interviews with parents – Summer 2020

Goals of developing Virtual GGC

- Maintain fidelity and efficacy
- Engage parents in virtual environment → strong exposure
- Added Introductory session & "Tech Check"
- Adjusted activities to work better in virtual environment

Questions

- Would parents enroll?
- Was adapted GGC feasible, acceptable, satisfying?

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# Preliminary Findings

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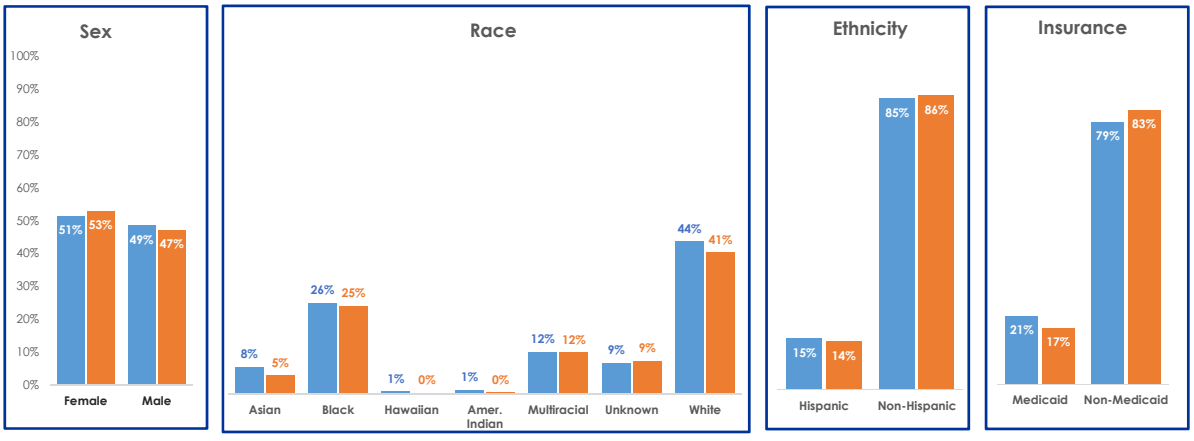
# Cohort 1 Demographics

965 Adolescents, 75 Pediatricians

GGC (*n* = 468) Control (*n* = 497)

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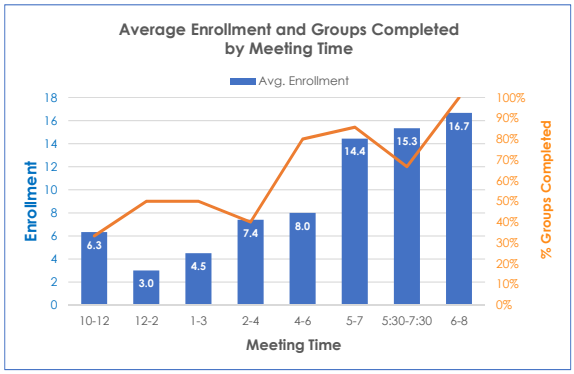
# Cohort 1: Virtual GGC Enrollment

- Offered 5 Cycles of GGC from November 2020 – June 2021
  - Plan: 2 groups/site per cycle → 30 groups total (10 per site)
  - Launched: 26 groups (7-10 per site)
- Enrolled 308 families – 11.8 per group
  - 27% among PAWS families, 16% among broader set of families GGC offered to
  - Evening groups had better enrollment and retention
  - Fall, winter, early spring -- better enrollment than late spring, summer

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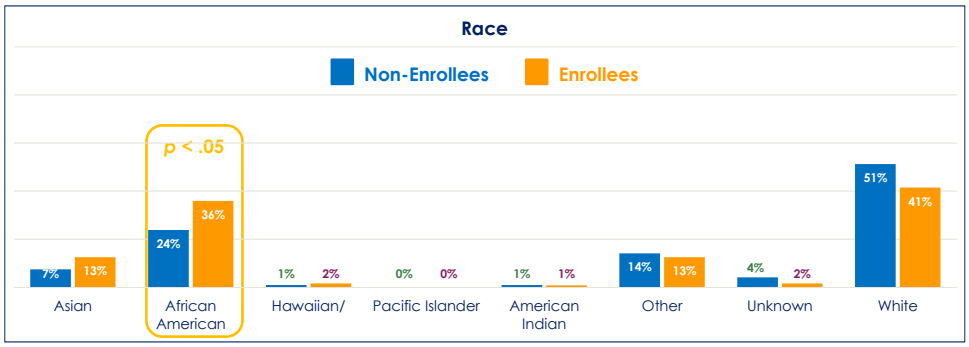
# 27% of study families enrolled in GGC

- **~10% higher than in community settings**
  - Few well visits → few in-person pediatrician recommendations due to COVID
- **Enrollees compared to non-enrollees***
  - Sex, ethnicity, insurance were similar
  - Some differences in race: More African Americans enrolled

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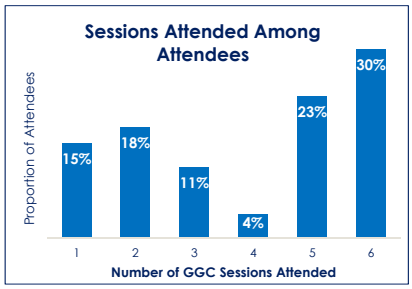
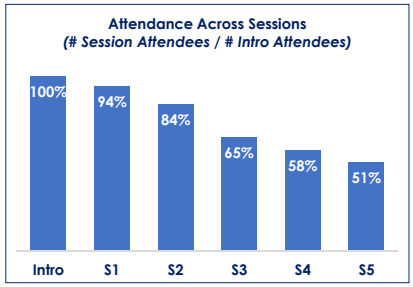
*Adolescent demographics

# Attendance

- 63% of enrollees attended at least one session
- Attendees compared to non-enrollees*
  - Sex, ethnicity were similar
  - More likely to identify as Asian, less likely to be insured through Medicaid
- Among attendees, attendance was strong
  - Over 50% attended 5 or 6 sessions
  - *M* = 3.9 sessions, Median = 5 sessions, Mode = 6 sessions
- Some attrition after sessions – especially Session 2 (Guidelines) to Session 3 (Anger Management)

**Adolescent demographics*

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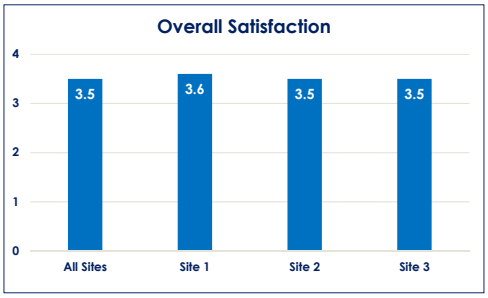
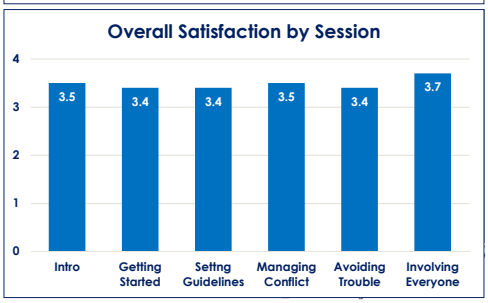
# Satisfaction with Virtual GGC

**How satisfied were you with each of the following aspects of the session?**
*(parent post-session surveys completed voluntarily, n = 120)*

- Overall Session
- Video Segments
- Activities/ Exercises
- Family Guide
- Workshop process

| | |
|---|---|
| 1 | Not Satisfied |
| 2 | Somewhat Satisfied |
| 3 | Satisfied |
| 4 | Very Satisfied |



# What Parents are Saying

"I feel empowered to **better deal with family conflicts** and my own contribution to them. Thank you!"

"The topic of this session [Session 2 - **guidelines, monitoring, consequences] could be the topic of the entire program**. Much of our **children's emotional health is in reaction to the choices made regarding substance abuse** and/or other excessive behaviors."

"The **small group discussions were awesome**. They gave us a chance to **connect with and learn from other parents**."

"I appreciated these sessions and that they **started conversations that can be difficult for parents to have with their children.** This course would be **extremely beneficial to most families."**

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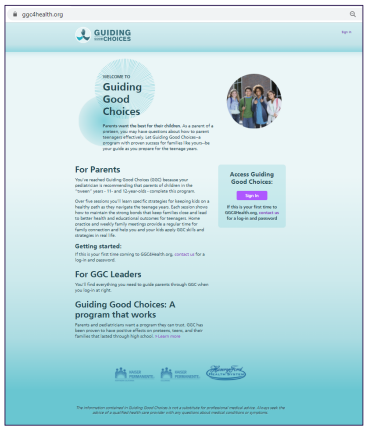
# eGGC – Self-Guided Option

- Little engagement
  - Vast majority of eGGC participants never log in to website!
  - Outreach calls have not boosted engagement
- Hard-to-engage population
  - Declined option to enroll in GGC groups
  - Stopped attending GGC groups
  - Did not respond to enrollment outreach (calls, emails, texts)
- Offer more modest outreach
  - "Nudge" through emails, text messages
  - Offer calls to those who engage
  - Respond to any requests for support

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# Next Steps

- Complete Cohort 2 recruitment and implementation
- Complete stakeholder interviews at each site to understand support for prevention
- Analyze Spanish language implementation (KPNC supplement & TPMG EID supplement)
- Continue analyses
  - Examine baseline levels of risk, protection, outcomes – pre-COVID and during the pandemic
  - Assess implementation fidelity
  - Assess parent knowledge, attitudes, skills prior to GGC
  - Patient Outcomes
- Manuscript Development

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SOCIAL DEVELOPMENT RESEARCH GROUP, University of Washington

KAISER PERMANENTE® Northern California

Henry Ford Health System

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## Thank You!

Stacy.A.Sterling@kp.org

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# Learn more about NIH Pragmatic Trials Collaboratory Demonstration Projects


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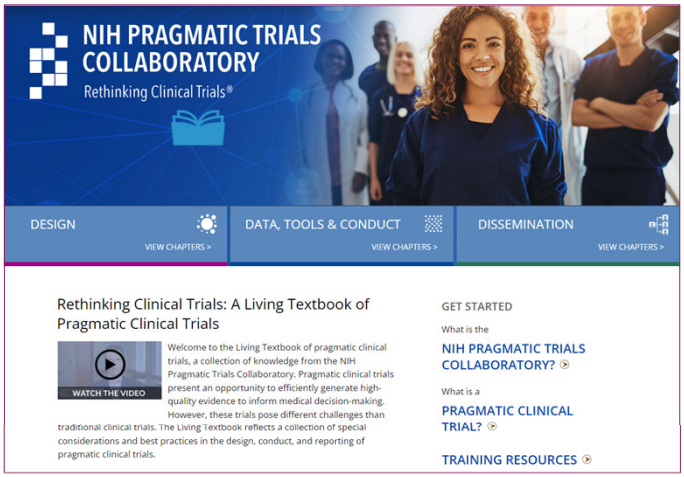
# Resource: The Living Textbook

*Visit the Living Textbook of Pragmatic Clinical Trials at*

**www.rethinkingclinicaltrials.org**

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## Resources:

## ePCTs in Context: Panel Discussion

Nudge

- UH3 Project: Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications (Nudge)

ICD-Pieces

- UH3 Project: Improving Chronic Disease Management with Pieces (ICD-Pieces™)

GGC4H

- UH3 Project: Guiding Good Choices for Health (GGC4H): Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare Systems

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# *Next Steps*

## Speaker

**Kevin Weinfurt, PhD**
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

# Next Steps:
# Embedded Pragmatic Clinical Trials

Kevin Weinfurt, PhD
Professor and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

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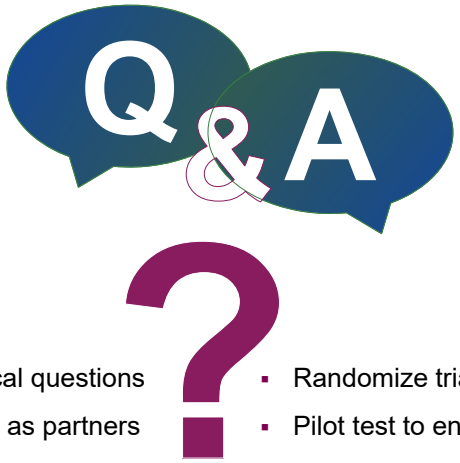


- Answer real-world clinical questions
- Engage health systems as partners
- Design your trial for both patient and implementation outcomes
- Choose meaningful and pragmatic endpoints and outcomes
- Randomize trials for the strongest evidence
- Pilot test to ensure trial readiness
- Consider ethical and regulatory guidelines for all parties who might be affected by the study
- Use NIH resources to find the right funding mechanism for your study

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# Sources for further learning

- Living Textbook video modules
  - https://rethinkingclinicaltrials.org/training-resources/living-textbook-video-modules/
- EHR video modules
  - https://rethinkingclinicaltrials.org/training-resources/ehr-workshop-video-modules/
- Online Training Workshops
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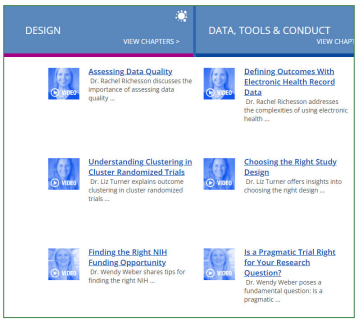


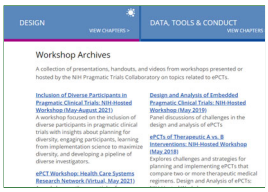


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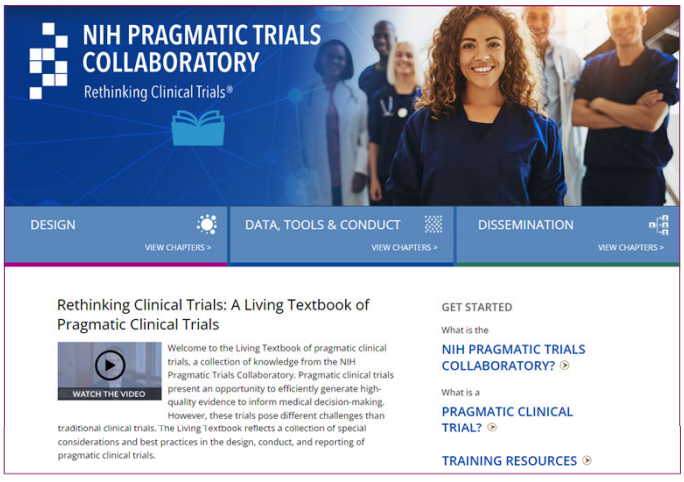


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# Considerations for Planning Your Embedded Pragmatic Clinical Trial

**1. ePCT Aims and Significance**

- What decision is the ePCT intended to inform?
- In what setting?
- Important things to do:
  - For each domain of PRECIS-2, determine the approach along the pragmatic-explanatory continuum that is most appropriate for answering your research question
  - Remember that trials may have some elements that are more pragmatic and some that are more explanatory

**2. Engaging All Stakeholders and Aligning with Healthcare System Partners**

- Who are your stakeholders?
- Does your intervention add long-term value to the health system and its patients?
- Important things to do:
  - Engage stakeholders early and often
  - Set expectations to work collaboratively and build trust from the beginning
  - Use familiar language that stakeholders understand
  - Get to know your stakeholders' 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

**3. Measuring Outcomes**

- Is your research question supported by the data?
- How will your outcomes be ascertained? (eg, passive or active data collection)
- Are your outcomes relevant to stakeholders?

- Important things to do:
    - Ask questions that the data will support and design trials to minimize new data collection
    - Engage EHR and data experts when defining endpoints and outcomes
    - Budget for data and systems experts at each site (… and then double it)
    - Develop a robust data quality assessment plan to improve value of data and to detect and address data issues

**4. ePCT Design and Analysis**

- What is the unit of randomization? (eg, individual patient, provider, clinic)
- What kind of expertise is needed to deliver your intervention?
- Will there be flexibility in how it is delivered and in the degree of adherence?
- If designing a group-randomized trial, will your design involve parallel groups or stepped-wedge?
- What is the estimate of the intraclass correlation coefficient (ICC)?
- Important publications to read:
    - Turner EL, Li F, Gallis JA, Prague M, Murray DM. 2017. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1-Design. Am J Public Health 107: 907-15
    - Turner EL, Prague M, Gallis JA, Li F, Murray DM. 2017. Review of Recent Methodological Developments in Group-Randomized Trials: Part 2-Analysis. Am J Public Health 107: 1078-86
    - Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, et al. 2018. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ 363: k1614
    - Murray DM, Pals SL, George SM, Kuzmichev A, Lai GY, et al. 2018. Design and analysis of group-randomized trials in cancer: A review of current practices. Prev Med 111: 241-47

**6. Pilot and Feasibility Testing**

- Is the intervention aligned with the priorities of the partner healthcare system (HCS)?
- How ready is the partner?
- Are extra resources needed to support the intervention, identify participants, and extract necessary data?
- How many sites are available to fully participate?
- How much provider training will be needed, and can training use existing HCS infrastructure?

- If the intervention proves successful, what adaptations would be needed to implement it in other healthcare settings?
- Important things to do
    - Conduct a pilot or feasibility study of the intervention to inform the final design of the ePCT
    - Work with a great biostatistician and an informatician (if needed)
    - Develop a partnership approach to working with your healthcare system
    - Identify multiple local champions for all your sites
    - Anticipate, identify, and make a plan to address changes in the healthcare system

**7. Ethical and Regulatory Oversight Considerations**

- Who are the participants and how should they be protected?
- Is written informed consent required of any participants?
- Important things to do:
    - Designate someone to track local and federal regulatory developments and serve as liaison with regulatory/oversight bodies
    - You can contact OHRP for guidance
    - Budget sufficient time for proactive education and negotiations with relevant regulatory/oversight bodies
    - Identify all parties who might be affected by the study and its findings; consider protections

**8. Dissemination and Implementation**

- To whom will the results of your trial apply?
- Will there be a demand for the study results or intervention?
- Can your intervention be delivered within the existing structure of the healthcare system?
- Important things to do:
    - Think about designing your study in ways that can facilitate broader dissemination and implementation
    - Involve patients, providers, organizational leaders, and other key stakeholders in the design and conduct of the trial to increase applicability and relevance to other potential end-users
    - Create materials (eg, manuals, resources, training documents) that can be distributed after the study to help disseminate findings

- Use a variety of outlets to share study findings with practitioner communities

**9. Assembling Your ePCT Team**

- What clinical specialties will be needed to carry out the intervention?
- What roles will support clinic operations?
- Who will be the liaison between healthcare system departments for interventions that are multidisciplinary?
- What aspects of the trial will require IT staff expertise?
- Will the trial need training videos, online materials, or toolkits?
- Important things to do:
  - During the planning phase, identify the skill sets that will be needed
  - Recruit team members during the planning phase and engage them for the duration of the trial
  - Plan for staff turnover, especially clinical and IT staff
  - Plan for dissemination/implementation/de-implementation at the start

**10. Writing the Grant Application**

- Important things to do:
  - Use the online resources available for the development of pragmatic trial grant applications
  - Read the relevant Funding Opportunity Announcement multiple times
  - Identify program staff at your target NIH Institute/Center and review your Specific Aims and any questions with them
  - Obtain adequate feedback on the Research Plan from the entire team

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