NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Changing Trials for Changing Times: *Essentials of Embedded Pragmatic Clinical Trials Workshop*

Participant Guide

Health Care Systems Research Network 2023 Annual Conference

February 20, 2023

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Changing Trials for Changing Times: Essentials of Embedded Pragmatic Clinical Trials Workshop

HCSRN 2023 Annual Conference
Sheraton Downtown Denver, Denver, Colorado
February 20, 2023
8 a.m.-4:45 p.m. MT
Join workshop by Zoom: https://duke.zoom.us/j/93859922865?pwd=elR4SUZTWW1yRWtWTUxmODJFTWRvdz09
Meeting ID: 938 5992 2865; Passcode: 12345

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
8:00-8:50 a.m.	**What are Embedded Pragmatic Clinical Trials (ePCTs)?**	Wendy Weber	• Welcome and introduction of agenda, objectives, and Living Textbook • Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials • Learn about the advantages and disadvantages of ePCTs, when a pragmatic approach can be used to answer the research question. • Q & A with attendees
8:50-9:30 a.m.	**Engaging Stakeholders & Aligning with Health System Partners**	Emily O'Brien	• Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study • Identify skills needed for a strong study team and consider the diversity of the team, including inclusive practices • Understand the real-world priorities and perspectives of healthcare system leaders and how to obtain their support • Identify engagement practices to obtain patient and community perspectives • Highlight challenges of partnering with diverse healthcare systems • Q & A with attendees

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
9:30-10:00 a.m.	**Objectives and Trial Design: An Overview of Hybrid Designs**	Patrick Heagerty	• Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs • Q & A with attendees
10:00-10:30 a.m.	**Measuring Outcomes**	Emily O'Brien	• Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) • Discuss the integration of a health equity lens in evaluating outcomes • Q & A with attendees
10:30-10:45 a.m.	**Break**		• Networking among attendees and presenters
10:45-11:55 a.m.	**ePCT Design and Analysis**	Patrick Heagerty	• Learn about cluster randomized and stepped-wedge study designs • Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what principal investigators (PIs) need to know • Q & A with attendees
11:55 a.m.- 12:55 p.m.	**ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Kevin Weinfurt **Panel:** Arne Beck (GGC4H) Michael Ho (Nudge) Miguel Vazquez (ICD-Pieces)	• Introduce PIs of 3 ongoing ePCTs to reflect on the morning topics and discuss challenges, solutions, lessons learned, and how they leveraged networks and resources to support trial success • Q & A with attendees
12:55-1:40 p.m.	**Lunch**		• Networking among attendees and presenters
1:40-2:10 p.m.	**Pilot & Feasibility Testing**	Wendy Weber	• Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions • Q & A with attendees
2:10-2:40 p.m.	**Ethical & Regulatory Oversight Considerations**	Stephanie Morain	• Learn about the regulatory and ethical challenges of conducting ePCTs • Discuss unique needs of historically underrepresented and mistreated groups • Q & A with attendees

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
2:40-2:55 p.m.	**Break**		• Networking among attendees and presenters
2:55-3:35 p.m.	**Writing a Compelling Grant Application**	Beda Jean-Francois	• Learn how to develop a compelling ePCT application • Tips from Collaboratory PIs • Q & A with attendees
3:35-4:35 p.m.	**ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Kevin Weinfurt **Panel:** Arne Beck (GGC4H) Michael Ho (Nudge) Miguel Vazquez (ICD-Pieces)	• Hear our 3 PI panelists reflect on the afternoon topics and discuss challenges, solutions, lessons learned, and how they leveraged networks and resources to support trial success • Q & A with attendees
4:35-4:45 p.m.	**Next Steps**	Kevin Weinfurt	• Final thoughts from the panelists • Final Q & A • Wrap-up including identifying sources for further learning

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Speaker Biographies

Arne Beck, PhD
Kaiser Permanente Colorado Institute for Health Research
University of Colorado Denver
Arne.Beck@kp.org

Dr. Beck is a health psychologist, Senior Investigator at Kaiser Permanente Colorado's Institute for Health Research, and Associate Professor of Family Medicine at the University of Colorado Denver Health Sciences Center. He serves as the Kaiser Permanente Colorado site lead for the Mental Health Research Network. His research interests include perinatal mental health, suicide prevention, feedback informed care for depression, health risk prevention programs for parents of early adolescents, and integrating behavioral health and medical care for patients with multiple chronic conditions.

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

Dr. 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.

Beda Jean-Francois, PhD
National Center for Complementary and Integrative Health (NCCIH)
beda.jean-francois@nih.gov

Dr. Jean-Francois is a program director in the Clinical Research Branch in the Division of Extramural Research of the NCCIH. She oversees a portfolio of clinical research, including health disparities, pediatric research on mental and emotional well-being, maternal morbidity and mortality, and pragmatic clinical trials. Additionally, she contributes to the Mental, Emotional, and Behavioral (MEB) initiatives as well as the NIH Pragmatic Trials Collaboratory, the NIH HEAL Initiative, and the Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) program. Dr. Jean-Francois is especially passionate about reducing children's health disparities. Other research interests include life-course perspective on health and disease, behavioral health prevention services, health information technology, reproductive health equity, and childhood obesity. Before joining NCCIH, Dr. Jean-Francois served as an NIH health scientist administrator at the National Institute on Minority Health and Health Disparities (NIMHD) since 2017. While at NIMHD, she served as a co-lead for the data coordinating center for the trans-NIH Rapid Acceleration of Diagnostics for Underserved Populations (RADxUP), which is a consortium of more than 85 multidisciplinary grantees working to target disparities in COVID-19 morbidity and mortality. She developed multiple funding opportunities, including Effectiveness of School-Based Health Centers to Advance Health Equity, Addressing Racial Disparities in Maternal Mortality and Morbidity, and Leveraging Health Information Technology to Address Health Disparities. Additionally, she served as project scientist for Center of Excellence research grants to promote research in health disparities and the training of a diverse scientific workforce.

Stephanie Morain, PhD
Johns Hopkins University
smorain1@jhu.edu

Dr. Morain is an Assistant Professor at Johns Hopkins in the Department of Health Policy & Management in the Bloomberg School of Public Health and the Berman Institute of Bioethics. She conducts both empirical and normative research into issues at the intersection of ethics, law, and health policy.

Her work examines ethical and policy challenges presented by the integration of research and care, particularly issues pertaining to learning health care systems and pragmatic clinical trials. Other research interests include the ethics and politics of disease control and injury prevention, and women's reproductive health.

Stephanie received her AB from Lafayette College with a dual major in Biology and History, Government, and Law, her MPH from Columbia University's Mailman School of Public Health, and her PhD from Harvard University's Interfaculty Initiative in Health Policy. She completed her postdoctoral training at the Berman Institute for Bioethics at Johns Hopkins University. From 2016-2021, she was a faculty member in the Center of Medical Ethics & Health Policy at Baylor College of Medicine.

Emily O'Brien, PhD
Duke Clinical Research Institute
Duke University School of Medicine
emily.obrien@duke.edu

Dr. O'Brien is an associate professor in the Departments of Population Health Sciences at the Duke University School of Medicine. An epidemiologist by training, Dr. O'Brien's research focuses on comparative effectiveness, patient-centered outcomes, and pragmatic health services research in chronic disease. Dr. O'Brien's expertise is in systematic assessment of medical therapies in real-world settings, including long-term safety and effectiveness assessment. She is the principal investigator for projects focusing on the linkage and use of secondary data, including administrative claims, clinical registries, and electronic health record data. Dr. O'Brien is the principal investigator for the HERO Registry, a national study of the impact of COVID-19 on healthcare workers in the US. She is an affiliated faculty member in the Duke Clinical Research Institute and the Duke Margolis Center for Health Policy, a fellow of the American Heart Association, and an editorial board member for *Stroke* and the *American Heart Journal*.

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

Miguel A. Vazquez, MD, 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.

Wendy Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH)
wendy.weber@nih.gov

Dr. Weber is the Branch Chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH) at NIH. She joined NCCIH as a program director in 2009. The Clinical Research Branch is responsible for the oversight of all NCCIH-supported clinical trials. Dr. Weber is coordinator for NCCIH's Clinical Trial Specific Funding Opportunity Announcements (FOAs) and point-of-contact for natural product-related clinical trial FOAs. She is a member of the NIH Common Fund-supported Health Care Systems Research Collaboratory and the program officer for the Coordinating Center. Dr. Weber is also a member of the planning and oversight team for the NIH-DoD-VA Nonpharmacologic Approaches to Pain Management Collaboratory and project scientist for its Coordinating Center.

At NCCIH, Dr. Weber oversees a portfolio of pragmatic clinical trials, natural product clinical trials, studies of complementary medicine to promote healthy behavior, and complex complementary/integrative medicine intervention research. Her interests include the use of complementary medicine interventions for common pediatric conditions, mental health conditions, promoting healthy behaviors, and health services research.

Kevin Weinfurt, PhD
Duke Clinical Research Institute
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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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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.

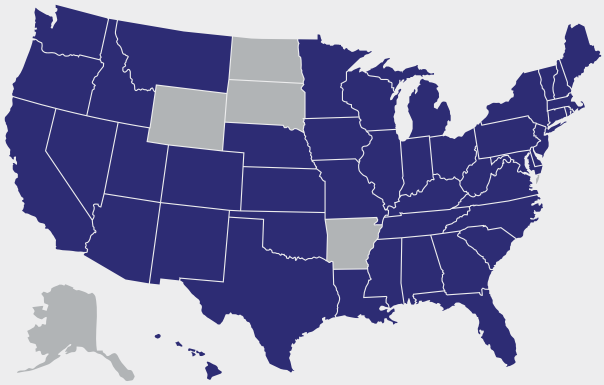
PROGRAM

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

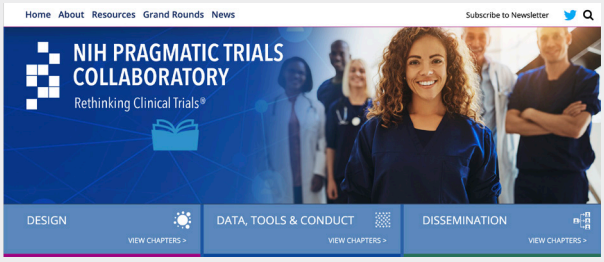
22 DEMONSTRATION PROJECTS

- 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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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

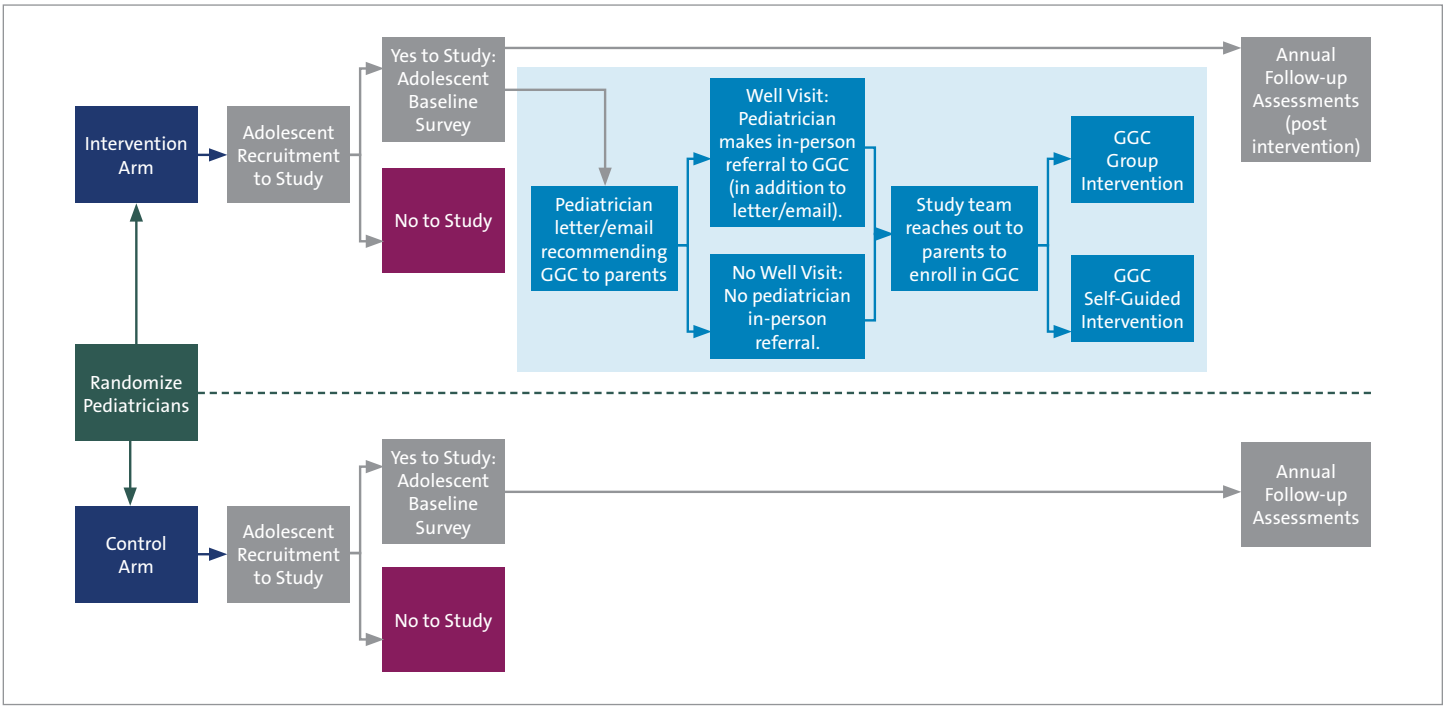
ABSTRACT

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

GGC4H: Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare Systems

Arne L. Beck, PhD
Senior Investigator
Institute for Health Research
Kaiser Permanente

GUIDING GOOD CHOICES

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1

Objectives

- Overview: Guiding Good Choice and opportunities for parent-focused prevention in primary care
- Challenges and opportunities (or…the only constant in life is change…)
  - Engaging stakeholders: Balancing pragmatic implementation and rigorous design
  - Measurement: Could we harness EHR data to address key study questions?
  - Feasibility: Implementation during the pandemic

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Guiding Good Choices (GGC)

- **6 virtual sessions**
  - Specific parenting skills
  - Strategies to promote bonding
- **2 RCTs → GGC reduced**
  - Alcohol, marijuana, cigarette use
  - Symptoms of depression
  - Antisocial behavior
  - For 4-6 years (Grades 10-12)
- **GGC also strengthened families:**
  - Better communication, closer relationships, less family conflict

→ Would implementation in pediatric primary care increase uptake and achieve impact among diverse families?

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Study design

- Randomly assigned 75 pediatricians within 3 healthcare systems and 10 clinics
- Recruited ~1975 adolescents to the study – 2 cohorts
- Offered GGC to 512 enrolled parents in intervention arm
- RE-AIM* measurement framework
  - Implementation: Reach, adoption, implementation fidelity, participant engagement and skills
  - Effectiveness: Evaluate GGC's impact on adolescent health

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Barriers/challenges

- Pragmatic implementation → Challenges for valid statistical inference
- Viability of EHR as a data source
- Impacts of the COVID-19 pandemic

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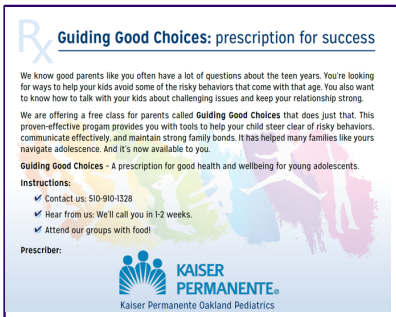
Pragmatic implementation: Key leader support

- All clinics, pediatricians chose to participate…and were retained
- Universal recommendation → no risk assessment
- Low-burden workflow: Minimal ask of pediatricians, flexible tools

Pediatrician 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."

"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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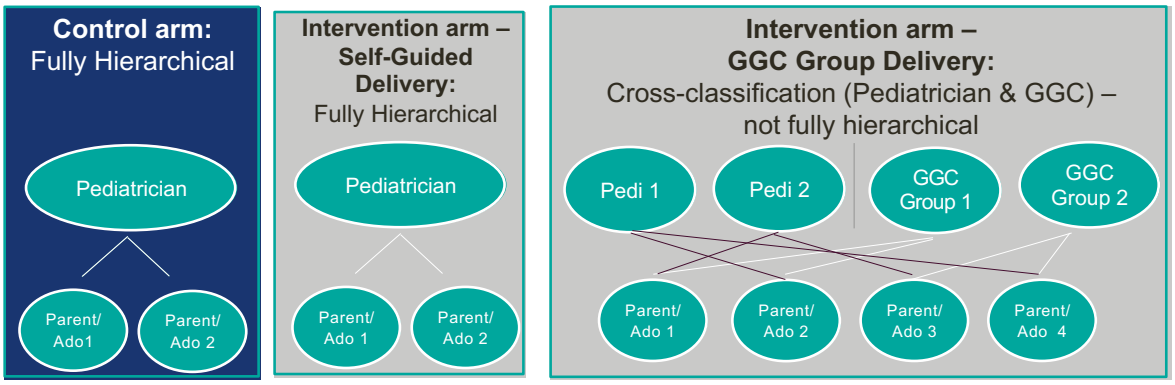
Pragmatic implementation: study design



- Cluster randomized trial with partial cross-classification in intervention arm
- If not modelled appropriately: threats to inference (bias), increased type I error
- Quesenberry adapted Luo et al (2015); Sofrygin simulation showed adequate power, coverage

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EHR did not have the outcomes data GGC4H needed.
We developed a Youth Behavioral Health Survey instead:

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

- 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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COVID-19 → Virtual GGC.

Would virtual GGC be delivered with fidelity, satisfying to parents?

- High-fidelity – interventionist ratings across 44 implemented groups
  - Dosage: 86% of planned sessions
  - Adherence: 99% objectives, 96% activities
  - Parent engagement: 4.0 out of 5
  - Overall quality: 4.7 out of 5
  - Independent observers confirmed
- How satisfied were you with the following aspects of the session?
  - Overall Session
  - Video Segments
  - Activities/ Exercises
  - Family Guide
  - Workshop process

3.6 out of 4 – very satisfied
(*n* = 254 parents)

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Solutions/lessons learned

1) Universal/primary prevention programs can be attractive to pediatricians and feasible to deliver within the healthcare system.
2) Challenges to consistent collection and storage of behavioral health outcomes and their precursors remains a challenge – even in healthcare systems participating in the VDW.
3) Parents and caregivers were satisfied with virtual GGC, which can strengthen the business case for GGC because of economies of scale.

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ICD-Pieces: Improving Chronic Disease Management with Pieces™

Principal Investigators
Miguel Vazquez, MD

Sponsoring Institution
University of Texas Southwestern Medical Center

Collaborators
- Parkland health and Hospital System
- Texas Health Resources
- ProHealth
- VA North Texas

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

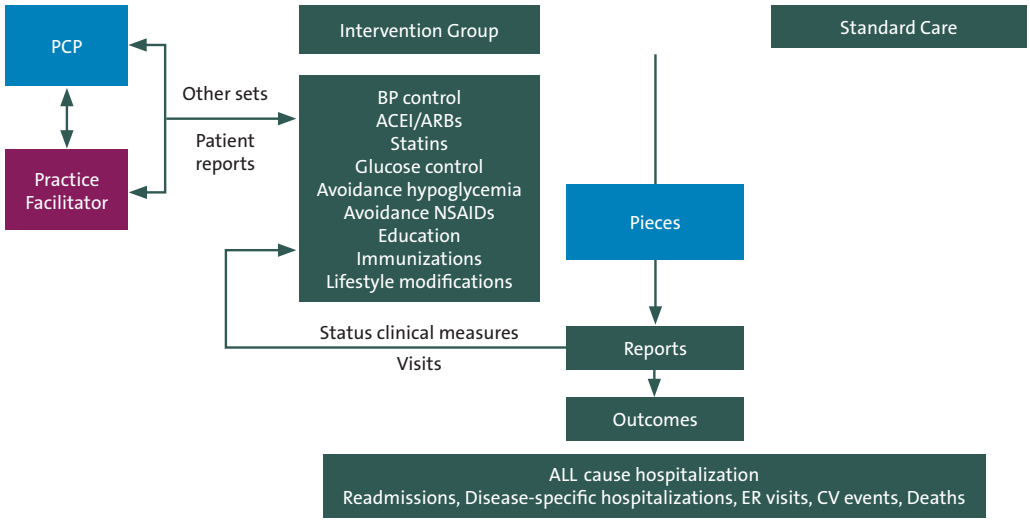
ClinicalTrials.gov Identifier
NCT02587936

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 identifcation of effective treatments for CKD, diabetes, and hypertension has been made, but there is a signifcant 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.

ICD-Pieces Patient Care Work Flow



WHAT WE'VE LEARNED SO FAR

Current Barriers	Solution				
	1	2	3	4	5
Enrollment and engagement of patients/subjects			X		
Engagement of clinicians and health systems				X	
Data collection and merging datasets			X		
Regulatory issues (IRBs and consent)	X				
Stability of control intervention		X			
Implementing/delivering intervention across healthcare organizations			X		

1=litte difficulty; 5=extreme difficulty

Challenge	Solution
Management of multiple chronic conditions varies across different healthcare systems.	Study facilitators developed different workfows to accommodate the variations in resources at every site. These were roles in the healthcare systems and required more multidisciplinary review of the proposed workfows.
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 redefned from individual practitioners to practice sites. The team queried EHR systems with the new cluster defnition 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

ICD-Pieces: Improving Chronic Disease Management With Pieces

Miguel Vazquez, MD
Professor of Internal Medicine
Clinical Director, Division of Nephrology
University of Texas Southwestern Medical Center

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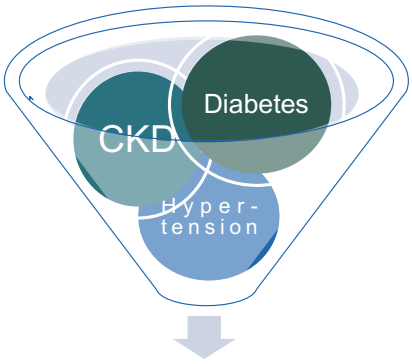
Multiple chronic conditions

->Common
->Serious Complications



->Under-recognized
->Treatable

Opportunity to Advance Care

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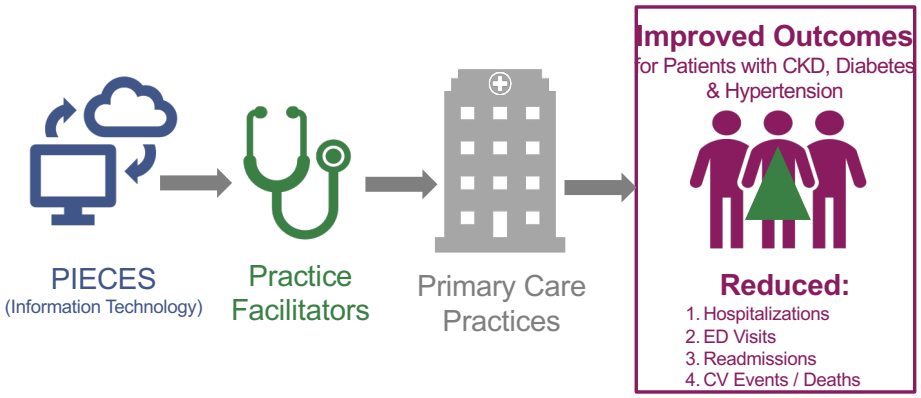
Hypothesis



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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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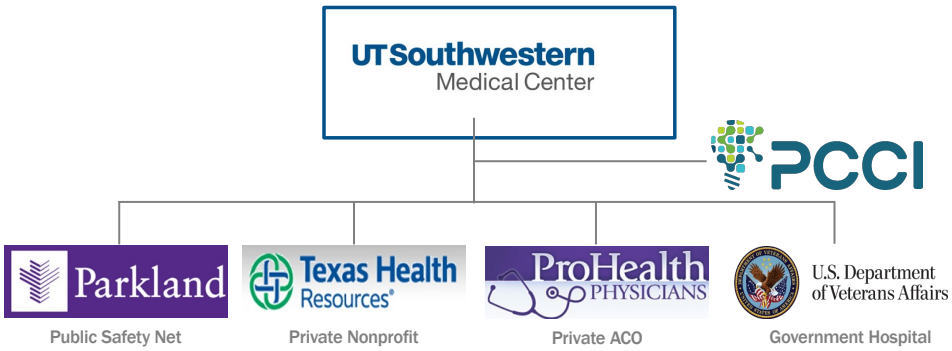
Participating healthcare systems



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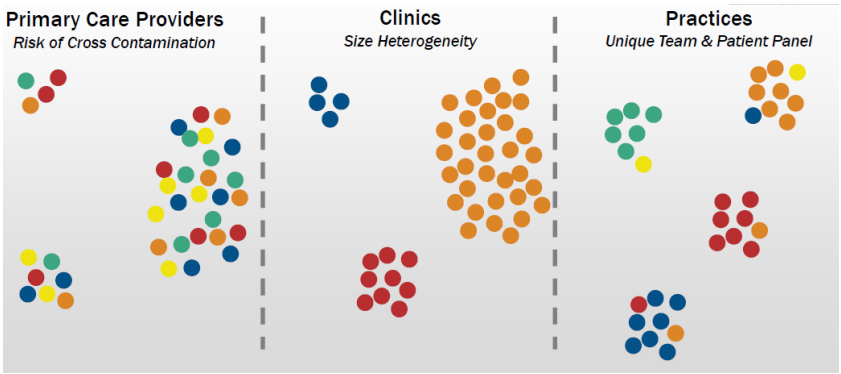
Study design: cluster randomization



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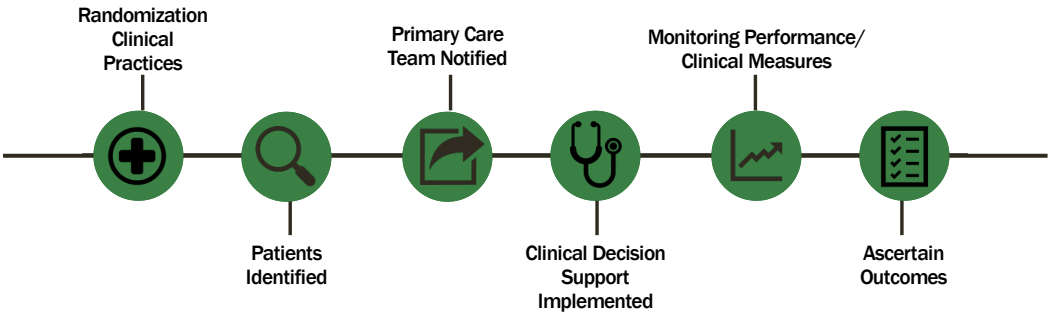
Study conduct



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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 • Plan together • Develop trust • Staffing	• Minimize disruption • Provide tools • Adapt • Create value	• Dissemination / Implementation • Sustainability • Future Projects

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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)

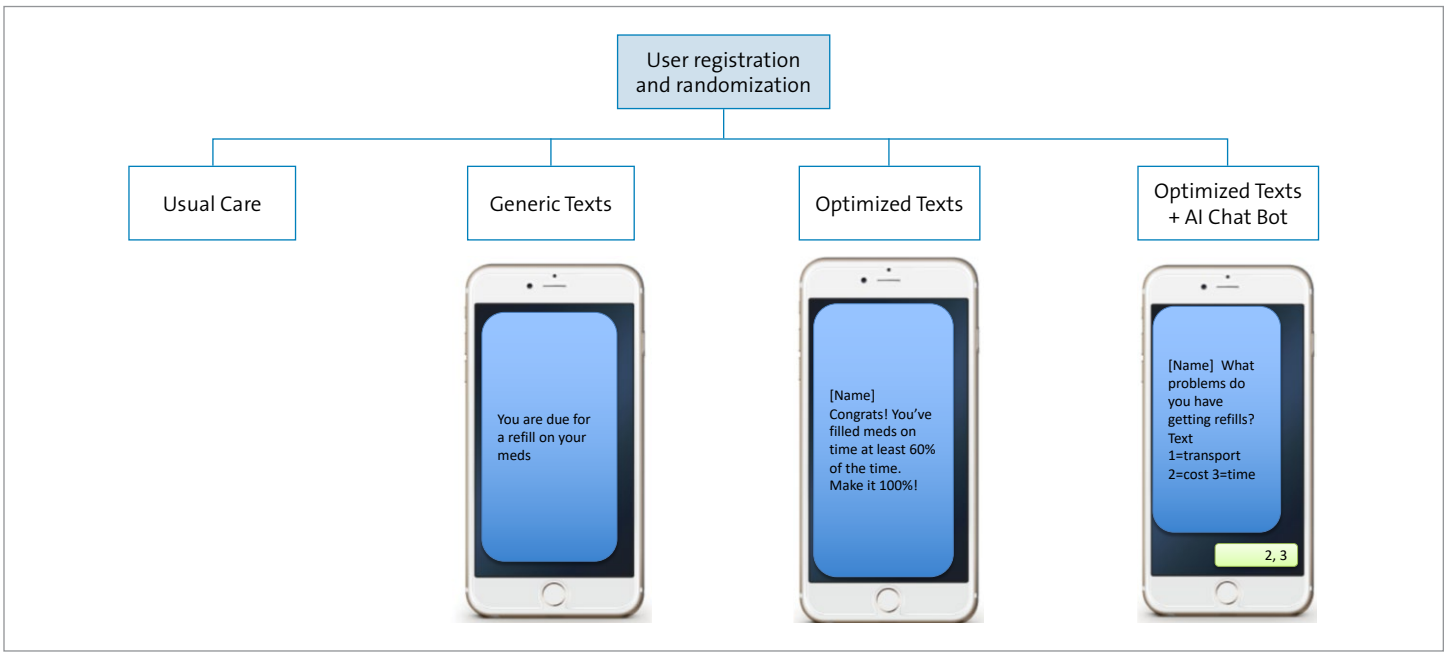
ClinicalTrials.gov Identifier
NCT03973931

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

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

Nudge

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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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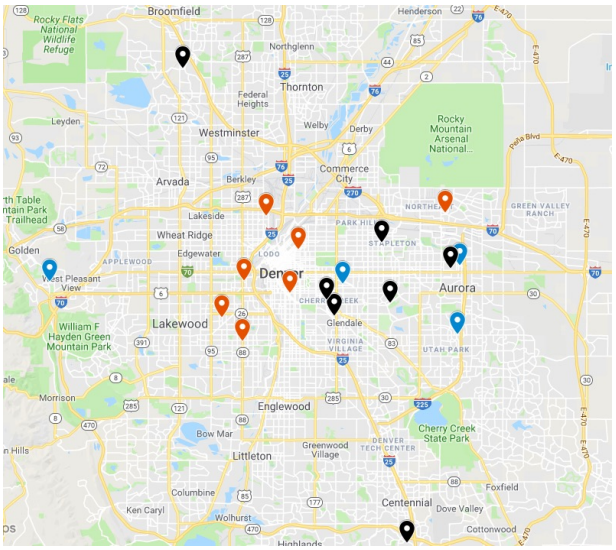
Study setting

- 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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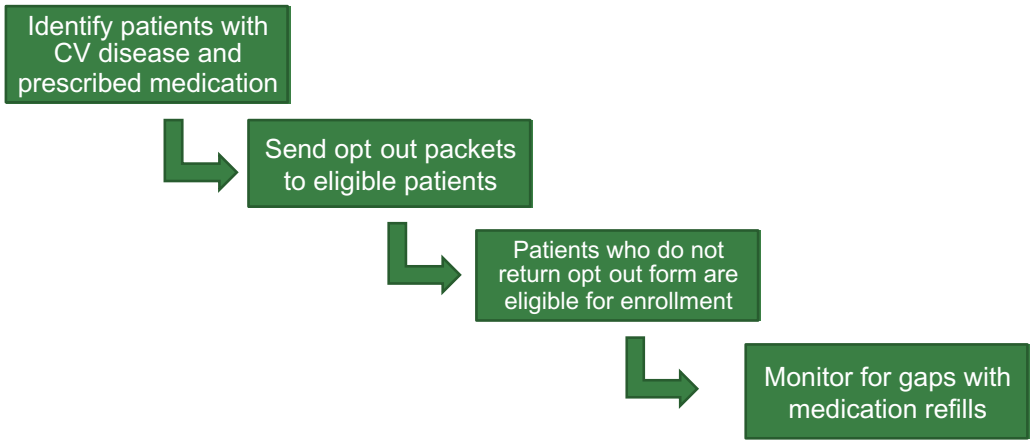
Opt-out study design



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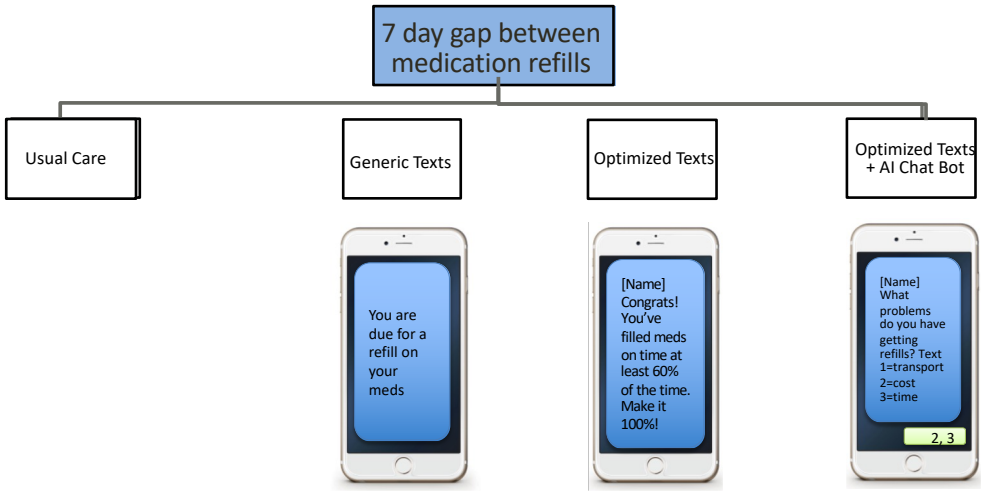
Intervention arms



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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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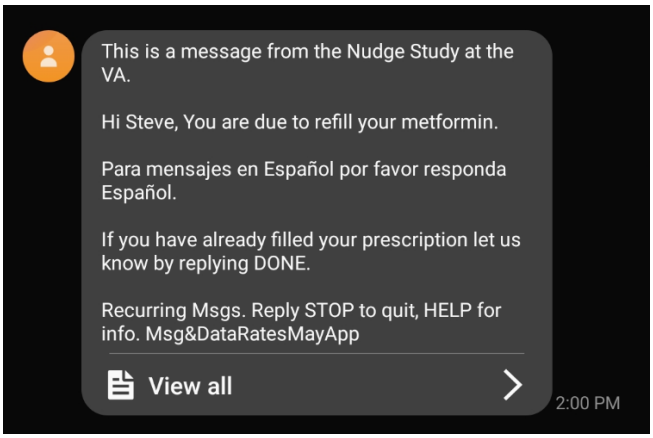
Sample generic message



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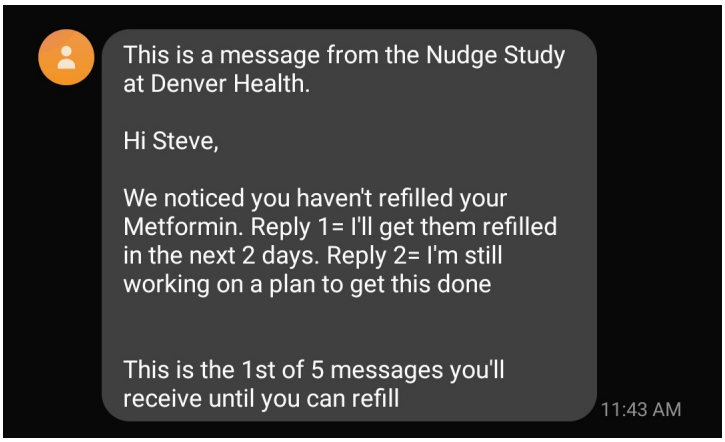
Sample optimized message



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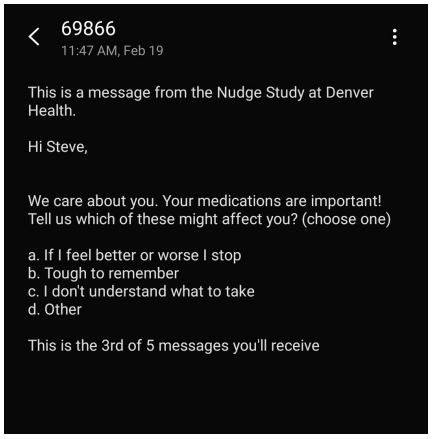
Sample optimized + AI chatbot message



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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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Welcome

Speaker

Wendy J. Weber, ND, PhD, MPH

Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

Welcome

Wendy J. Weber, ND, PhD, MPH
Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

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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 in diverse healthcare systems
- Increase the capacity of health services researchers to address important clinical questions with ePCTs

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Workshop sessions

- What Are Embedded Pragmatic Clinical Trials? (Wendy Weber)
- Engaging Stakeholders & Aligning With Health System Partners (Emily O'Brien)
- Objectives and Trial Design: An Overview of Hybrid Designs (Patrick Heagerty)

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Workshop sessions (continued)

- Measuring Outcomes (Emily O'Brien)
- ePCT Design and Analysis (Patrick Heagerty)
- ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs
- Pilot & Feasibility Testing (Wendy Weber)

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Workshop sessions (continued)

- Ethical & Regulatory Oversight (Stephanie Morain)
- Writing a Compelling Grant Application (Beda Jean-Francois)
- ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs
- Next Steps (Kevin Weinfurt)

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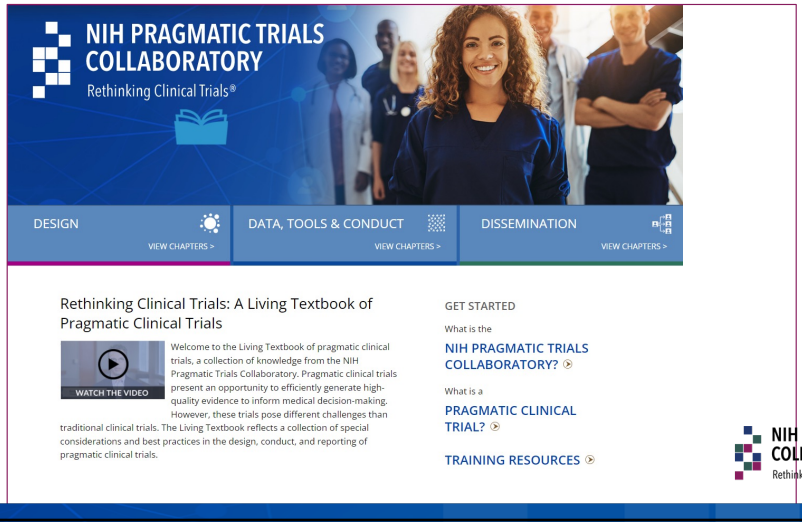
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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What Are Embedded PCTs?

Speaker

Wendy J. Weber, ND, PhD, MPH

Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

What Are Embedded PCTs?

Wendy J. Weber, ND, PhD, MPH
Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

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Learning goals

- Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials
- Learn about the advantages and disadvantages of ePCTs, when a pragmatic approach can be used to answer the research questions
- Q & A with attendees

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

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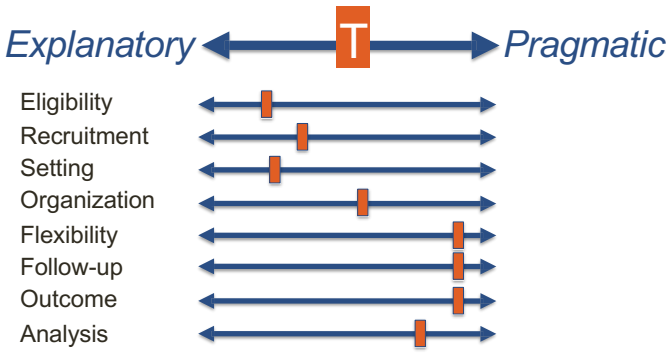
Trials vary across a spectrum of explanatory and pragmatic elements

Different trial elements are, by design, more or less explanatory/pragmatic



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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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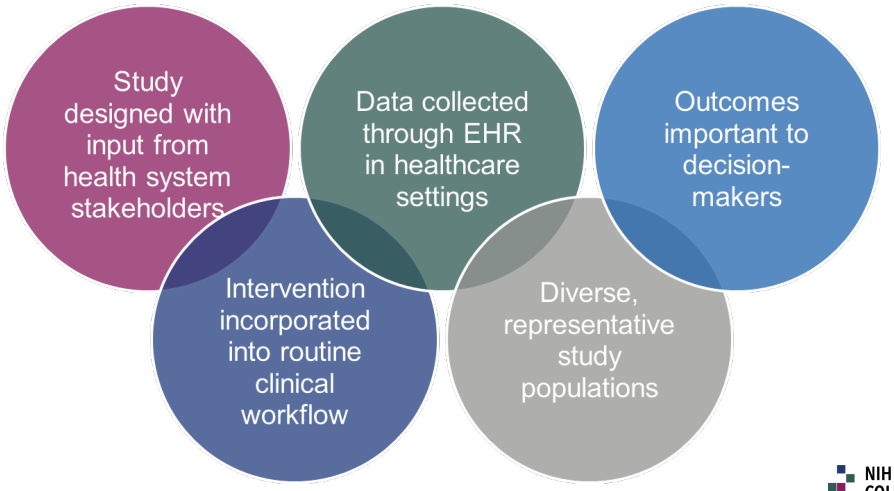
ePCTs bridge clinical care into research



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Who are your stakeholders?

Potential stakeholders have a variety of priorities, values, work cultures, and expectations:

- Healthcare delivery organization leaders
- Clinicians
- Operational personnel
- Patients, caregivers, patient advocacy groups
- Payers, purchasers
- Policy makers, 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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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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Engaging With Stakeholders & Aligning With Health System Partners

Speaker

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

Engaging With Stakeholders & Aligning With Health System Partners

Emily C. O'Brien, PhD
Associate Professor of Population Health Sciences
Duke University

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Learning goals

- Identify skills needed for a strong study team and consider the diversity of the team, including inclusive practices
- Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study
- Understand the real-world priorities and perspectives of healthcare system leaders and how to obtain their support
- Identify engagement practices to obtain patient and community perspectives
- Highlight challenges of partnering across diverse health systems
- Q & A with attendees

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Important things to know

- ePCTs are a team sport
- Necessary expertise depends on the study aims and how the intervention will be implemented
- Plan for ongoing training—Clinical, IT, or other staff turnover may be high
- Plan for sustainability—If the intervention will be turned on at all sites at end of study, what are the plans to maintain or turn off intervention?

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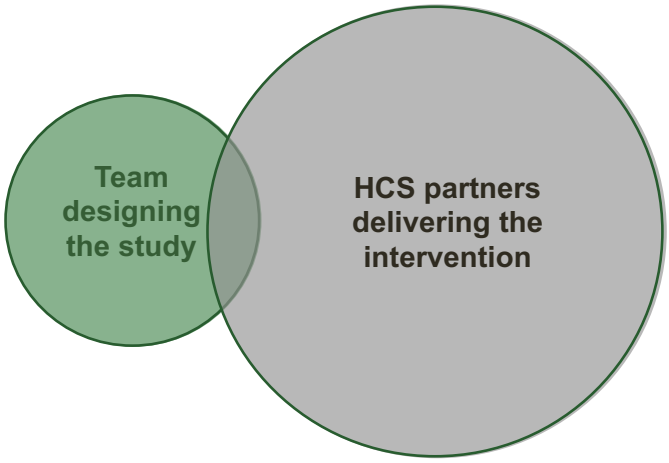
Who is involved?



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Potential team members

- Principal investigator, co-investigator
- Health system leader or executive
- Biostatistician
- Lead clinician (eg, pediatrician, behavioral specialist, radiologist, pharmacist, physical therapist)
- Clinical staff (eg, nurse, operations manager, business manager)
- IT specialist for EHR data extraction or clinical decision support tool design
- Implementation science researcher
- Site champion/liaison
- Practice facilitator
- Research assistant
- Project coordinator
- Research participant, patient, or patient advocate
- Society leadership

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Important things to do

- Identify the skills that are needed during the planning phase
- Recruit team members during the planning phase and engage them throughout for the duration of the trial
- Plan for staff turnover, especially clinical and IT
- Plan for dissemination, implementation, de-implementation at the start

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What skills will be needed?

- Best skill set depends on the study aims and how the intervention will be embedded in the healthcare system workflow
- Questions to ask:
  - What clinical specialties will be needed to carry out the intervention?
  - What roles will support clinic operations?
  - Who will be the liaison between HCS 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?

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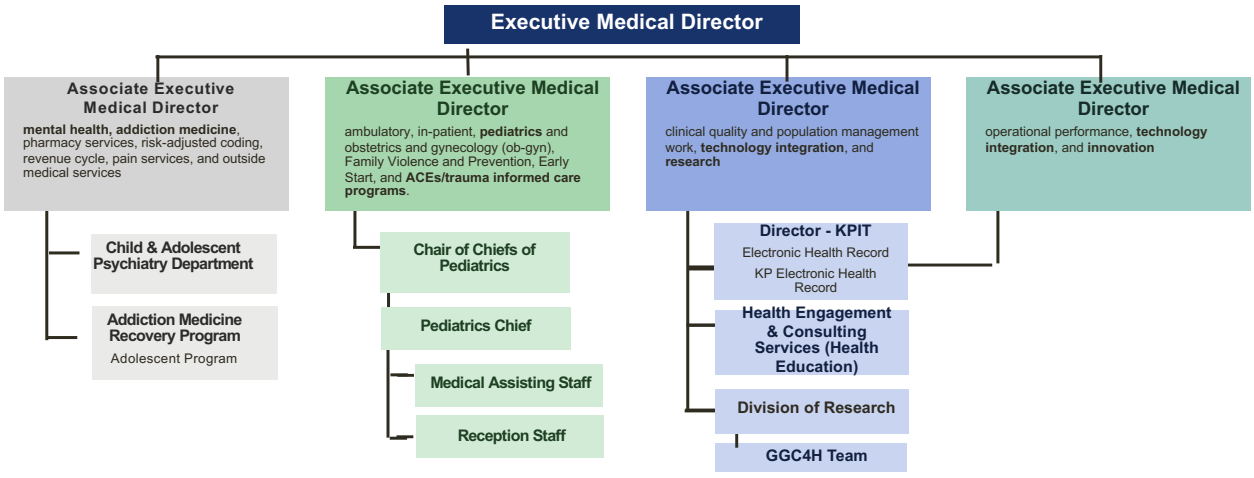
Kaiser Permanente Northern California



<u>Guiding Good Choices for Health:</u> The study team engaged with all of these aspects of The Permanente Medical Group at Kaiser Permanente Northern California. These stakeholders represent a small fraction of the many relevant stakeholders in large, complex healthcare systems. Most systems are comprised of several different entities – e.g., medical group, health plan, hospitals/facilities, etc. + labor partners

8

Considerations for Training Front-Line Staff and Clinicians on Pragmatic Clinical Trial Procedures

EPCT QUICK START GUIDE FOR RESEARCHER AND HEALTHCARE SYSTEMS LEADER PARTNERSHIPS

This Quick Start Guide is designed to help clinical investigators successfully partner with healthcare system leaders to support the successful conduct of an embedded pragmatic clinical trial (ePCT) within their healthcare system. It provides advice from the Collaboratory and serves as an annotated Table of Contents, pointing readers to essential content in the *Living Textbook* regarding partnering to conduct an ePCT.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Contents lists available at ScienceDirect

Healthcare

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

Perspectives

Trials without tribulations: Minimizing the burden of pragmatic research on healthcare systems

Eric B. Larson[a], Chris Tachibana[a], Ella Thompson[a], Gloria D. Coronado[b], Lynn DeBar[b], Laura M. Dember[c], Stacey Honda[d], Susan S. Huang[e], Jeffrey G. Jarvik[f], Christine Nelson[g], Edward Septimus[h], Greg Simon[a], Karin E. Johnson[a,*]

journal

Review article

Pragmatic clinical trials offer unique opportunities for disseminating, implementing, and sustaining evidence-based practices into clinical care: Proceedings of a workshop

Leah Tuzzio*, Eric B. Larson, David A. Chambers, Gloria D. Coronado, Lesley H. Curtis, Wendy J. Weber, Douglas F. Zatzick, Catherine M. Meyers

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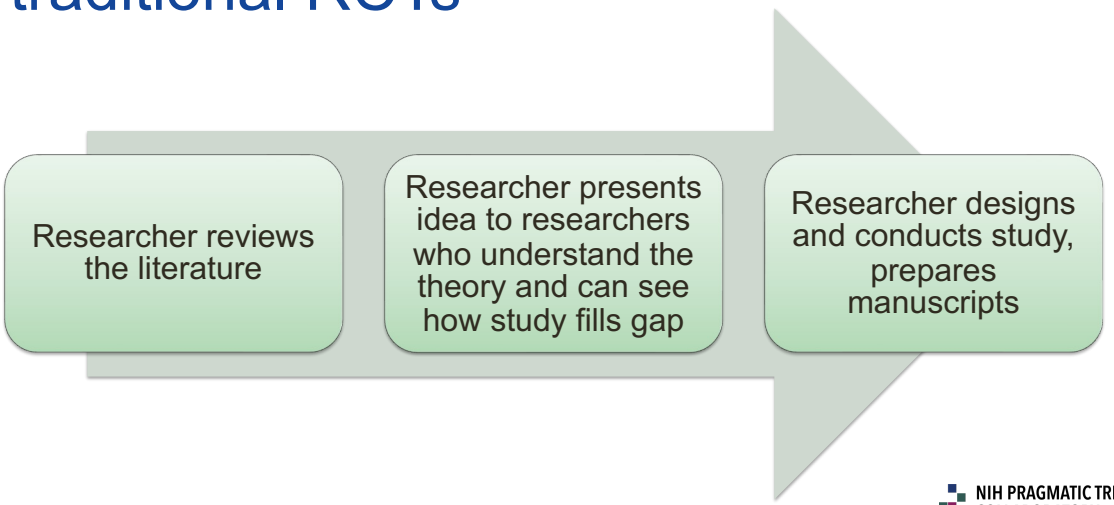
How researchers approach stakeholders in traditional RCTs



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Researchers partner with stakeholders in ePCTs differently.

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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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Important things to know

- **Start engagement early**, even before you have a research question or study design
- Be patient: Relationships take time to build and nurture
- Consider whether your intervention will add value
- Expect changes and disruptions
- Engage stakeholders continuously

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Who will be impacted? Who are the decision makers?

Potential stakeholders have a variety of priorities, values, work cultures, and expectations:

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

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Roles of stakeholders

1. Designing the trial
2. Successfully conducting the research
3. Disseminating the results

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Roles of stakeholders

1. **Designing the trial**
2. Successfully conducting the research
3. Disseminating the results

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Choosing a salient question

We want to know what you need.
What research should we be doing?

Source: Greg Simon, MD, MPH

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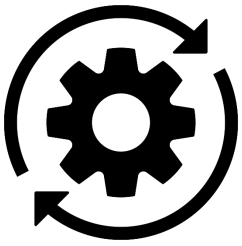
Designing the intervention for sustainment



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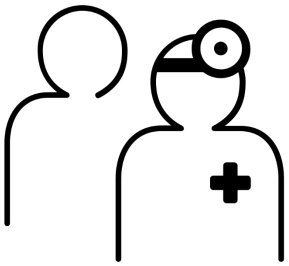
Designing the intervention to minimize burden for patients and clinicians



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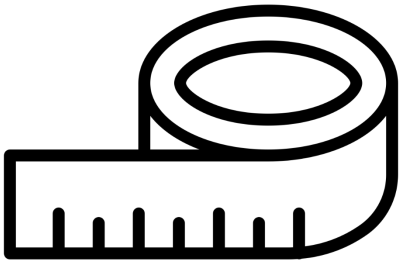
Selecting outcome measures



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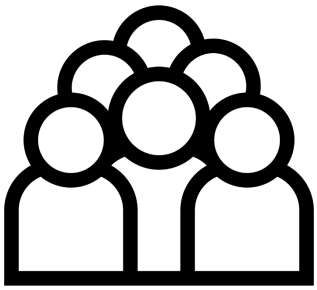
Determining inclusion and exclusion criteria



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Roles of stakeholders

1. Designing the trial
2. **Successfully conducting the research**
3. Disseminating the results

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Develop recruitment strategies

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Serve as study champions

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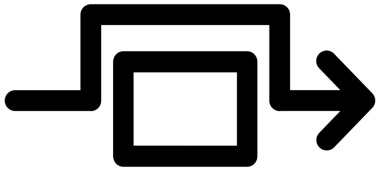
Track challenges and adaptations



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Interpret study results

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Roles of stakeholders

1. Designing the trial
2. Successfully conducting the research
3. **Disseminating the results**

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Determine key messages for different stakeholder groups and identify avenues for dissemination

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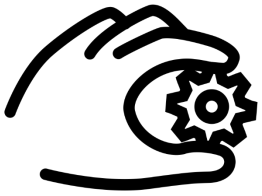
Support implementation or de-implementation



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Consider changes to policies and guidelines

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Roles of stakeholders

1. Designing the trial
2. Successfully conducting the research
3. Disseminating the results

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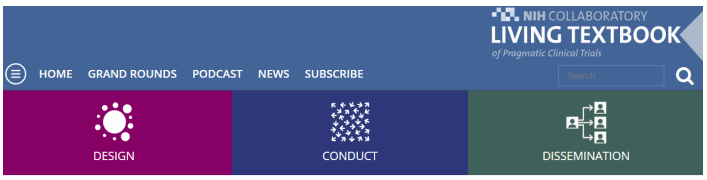
Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

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



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Resources: Journal articles

- Concannon TW et al. Practical guidance for involving stakeholders in health research. *J Gen Intern Med*. 2019 Mar;34(3):458-463.
- Whicher DM et al. Gatekeepers for pragmatic clinical trials. *Clin Trials*. 2015 Oct;12(5):442-448.
- Johnson KE et al. A guide to research partnerships for pragmatic clinical trials. *BMJ*. 2014 Dec 1;349:g6826.

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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

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Questions?

Stakeholder roles in:

Design	Conduct	Dissemination
• Question	• Recruitment	• Messaging
• Intervention	• Advocacy	• Venues
• Outcomes	• Challenges	• Implementation
• Population	• Interpretation	• Guidelines

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Ancillary slides

- Additional slides with ancillary content

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How to engage stakeholders

If the goal of ePCTs is to provide health systems with effective, evidence-based, practical ways to improve healthcare, how should researchers engage stakeholders to achieve this goal?

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Identify and form collaborations

- Network at conferences, attend webinars, and use a snowball approach
- Meet regularly by phone, e-mail, video chat, in-person, consider establishing an advisory board
- Understand the frameworks the stakeholders use for quality improvement (QI) initiatives. Adapt research language using a framework that speaks to health system needs and the language they more readily understand
- Set expectations to work collaboratively and build trust from the beginning

Source: Bev Green, MD, MPH, and Lynn DeBar, PhD

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Get to know each other

- Learn about each other's goals, needs, priorities, motivations for implementing a trial, and what or who influences decisions
- Learn about ideal "wins" and potential conflicts and competing priorities
- Understand workflows and work together to make study-related activities feasible and least burdensome

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Pilot and assess stakeholders' capacity and capabilities

- Are sufficient patient numbers and data available for the analysis?
- Can data be collected at a few or all clinical sites?
- How do the sites vary in services and capabilities?
- Can the system's regulatory and administrative infrastructure support approval and oversight by ethics committees and review boards?
- Will the intervention add long-term value to the system?

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Resources:

Engaging All Stakeholders & Aligning With Healthcare System Partners

Living Textbook readings

- Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial
- Delineating the Roles of All Stakeholders to Determine Training Needs
- Establishing Close Partnerships With Participating Healthcare System Leaders and Staff
- Health Care Systems Interaction Core

Collaboratory Grand Rounds webinar recordings & slides

- Integrating Research Into Health Care Systems: Executives' Views
- PCTs and Learning Health Care Systems: Strategies to Facilitate Implementation of Results into Clinical Care

Key journal articles

- Concannon et al., 2019. Multi-Group Stakeholder Engagement
- Whicher et al., 2015. Gatekeepers for pragmatic clinical trials
- Larson et al., 2016. Trials without tribulations: Minimizing the burden of pragmatic research on healthcare systems
- Johnson et al., 2014. A guide to research partnerships for pragmatic clinical trials

Other

- Health Care Services Research Network website

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Trial Objectives and Design: An Overview of Hybrid Designs

Speaker

Patrick J. Heagerty, PhD

Professor, Biostatistics
University of Washington

Trial Objectives and Design: An Overview of Hybrid Designs

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University of Washington

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Learning goals

- Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs
- Q & A with attendees

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Hybrid trial designs

- Trials with a focus on both clinical (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 adoption and fidelity?
  - How will we know this without data from both sides?

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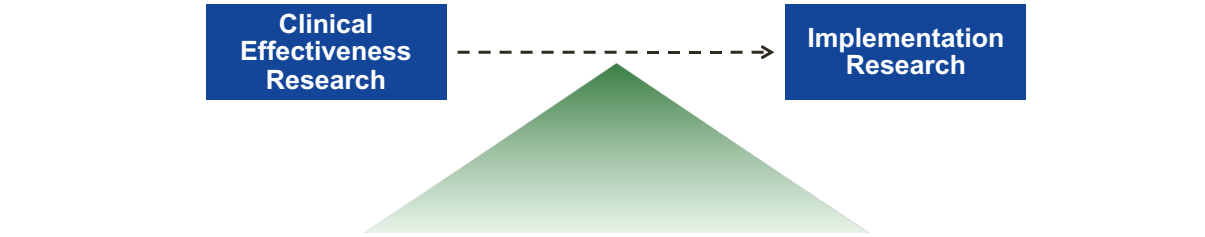
Types of hybrids



Hybrid Type 1	Hybrid Type 2	Hybrid Type 3
Test a clinical intervention, observe or gather information on implementation	Test a clinical intervention, test or study an implementation strategy	Test an implementation strategy, observe or gather information on intervention's effectiveness

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Type 1

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

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Type 1 example: PPACT

Contemporary Clinical Trials 67 (2018) 91–99

Contents lists available at ScienceDirect

Contemporary Clinical Trials

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

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

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

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Type 1 example: PPACT

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

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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 2 example: STOP CRC

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

Implementation Science

METHODOLOGY Open Access

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

Beverly B. Green[1*], Gloria D. Coronado[2], Malaika Schwartz[3], Jen Coury[4] and Laura-Mae Baldwin[3]

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Type 2 example: STOP CRC

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

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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 rollouts or implementation studies of interventions without strong effectiveness data
  - Interested in exploring how clinical effectiveness might vary by extent and/or quality of implementation?

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Type 3 example: ENABLE

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

Implementation Science

STUDY PROTOCOL Open Access

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

Lisa Zubkoff[1,2*], Kathleen Doyle Lyons[3,4], J. Nicholas Dionne-Odom[5,6,7], Gregory Hagley[3], Maria Pisu[1,7], Andres Azuero[1,5,6], Marie Flannery[8], Richard Taylor[5,6], Elizabeth Carpenter-Song[9], Supriya Mohile[8†] and Marie Anne Bakitas[5,6,7†]

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Concluding points

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

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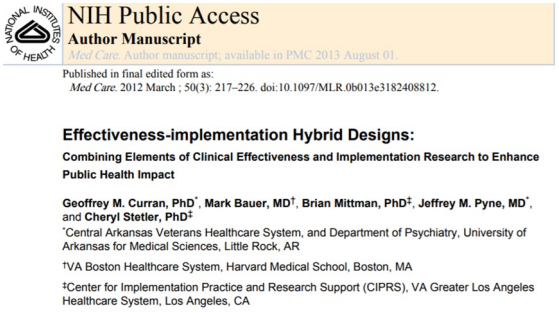
Concluding points

- 3 If you want to learn more…



NIH Public Access
Author Manuscript
Med Care. Author manuscript; available in PMC 2013 August 01.

Published in final edited form as:
Med Care. 2012 March ; 50(3): 217–226. doi:10.1097/MLR.0b013e3182408812.

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**[‡]

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[†]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*
[b] *South Central Mental Illness Research Education and Clinical Center (MIRECC), Central Arkansas Veterans Healthcare System, 2200 Fort Roots Drive, North Little Rock, AR 72114, USA*
[c] *University of Arkansas for Medical Sciences, Department of Psychiatry, 4301 W. Markham St, Little Rock, AR 72205, USA*
[d] *University of Arkansas for Medical Sciences, Department of Pharmacy Practice, 4301 W. Markham St, Little Rock, AR 72205, USA*

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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

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

Measuring Outcomes

Emily C. O'Brien, PhD
Associate Professor of Population Health Sciences
Duke University

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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)
- Discuss the integration of a health equity lens in evaluating outcomes
- Q & A with attendees

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Endpoints and outcomes

- An endpoint usually refers to an analyzed parameter (such as change from baseline at 6 weeks in mean PROMIS Fatigue score)
- An outcome usually refers to a measured variable (such as 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 ePCT endpoints

Endpoints and outcomes should 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?

Does it require hospitalization?

Will the endpoint be medically attended?

Is the treatment generally provided in inpatient or outpatient settings?

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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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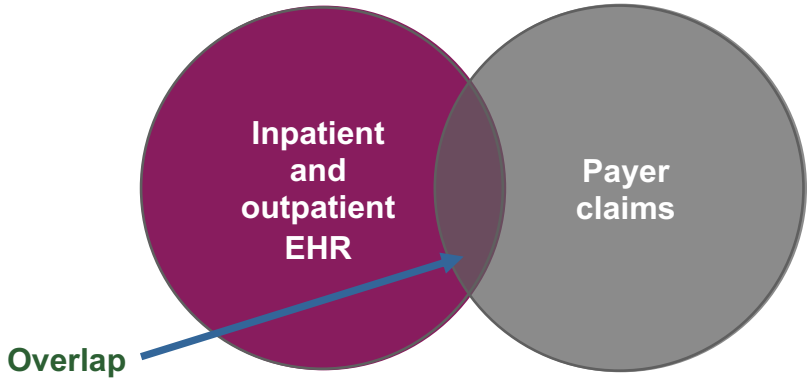
Where is the signal?

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



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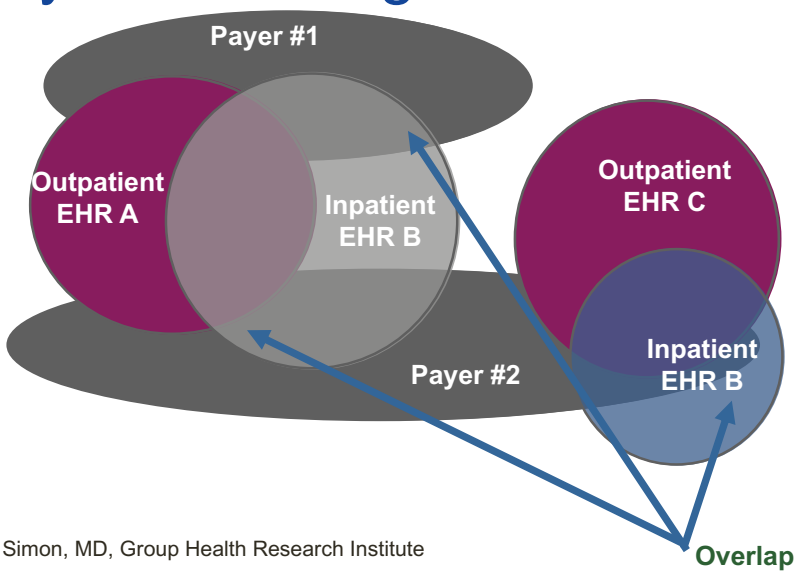
Reality is not straightforward



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 and 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

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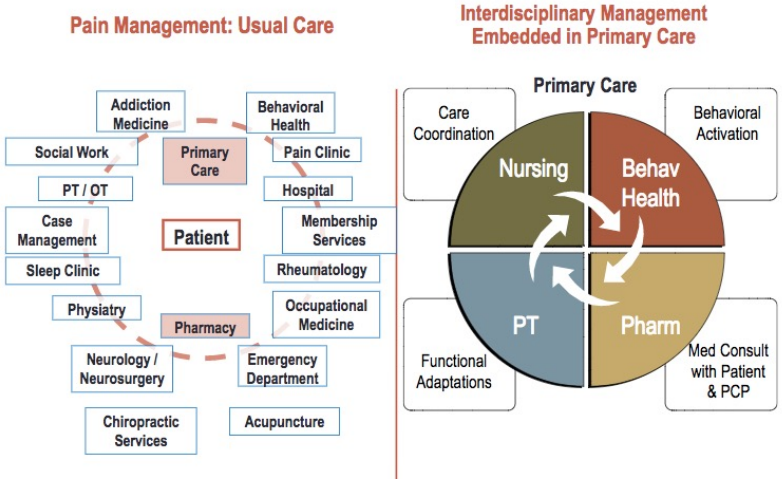
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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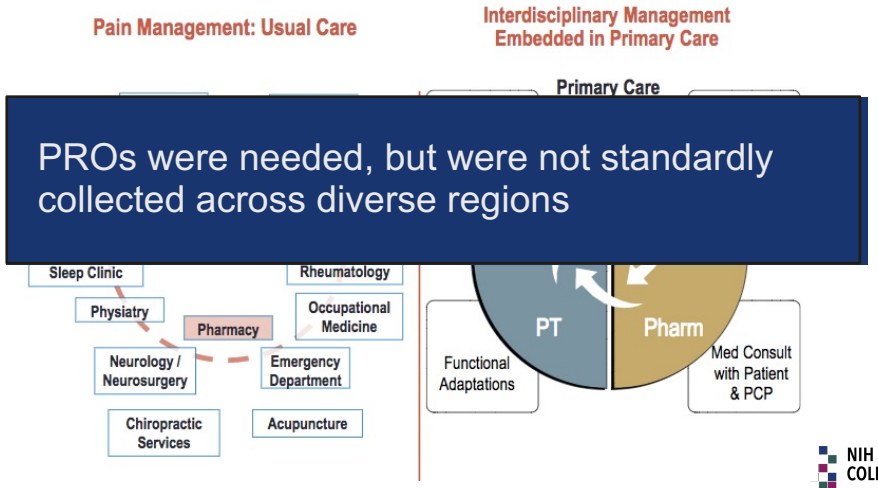
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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 multitiered approach supplemented the clinically collected PRO data at 3, 6, 9, and 12 months
- A follow-up phone call by research staff was necessary to maximize data collection at each time point

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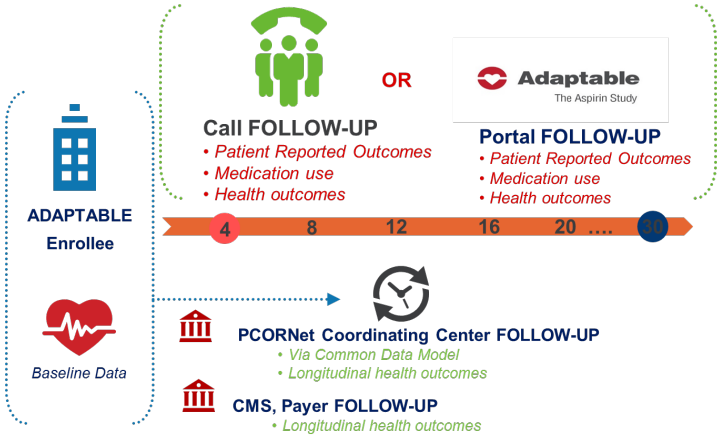
Enabling pragmatic research: e-screening, e-enrollment & e-follow-up



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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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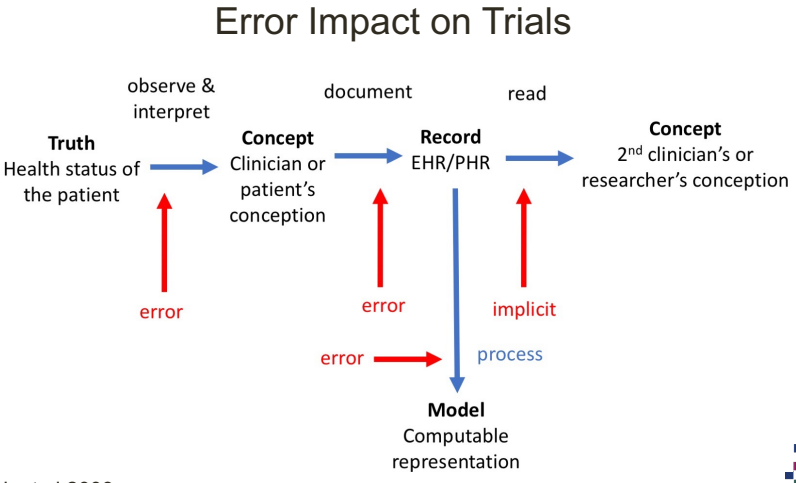
Data is a surrogate for clinical phenomena



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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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 J. Heagerty, PhD

Professor, Biostatistics
University of Washington

ePCT Experimental Design and Analysis

Patrick J. Heagerty, PhD
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University of Washington

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Learning goals

- Learn about cluster randomized and stepped-wedge study designs
- 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
- Q & A with attendees

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Design Considerations

Embedded Pragmatic Clinical Trials

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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 invalid inference (confidence interval too small; 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

- 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
  - Applied to clinical site → cluster randomization
- Unit of randomization: clinical site
- Two-arm cluster randomized trial (CRT)
  - Also referred to as a group-randomized trial

stop screen to prevent colon cancer

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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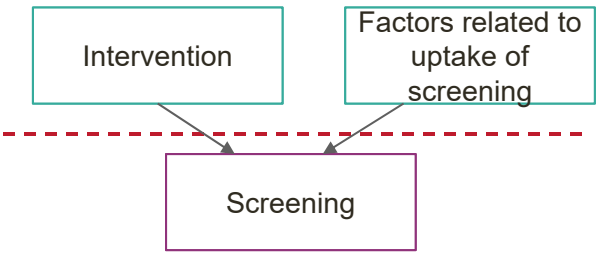
STOP CRC cluster randomization

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



Level 1: Individual-level outcomes nested within clinics

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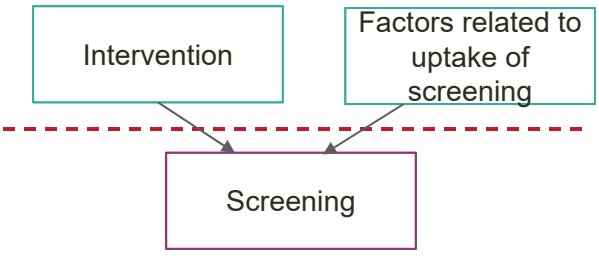
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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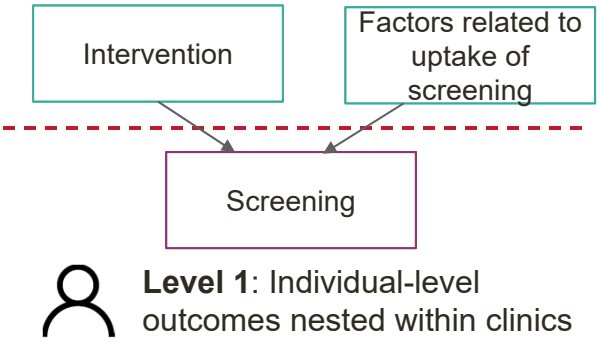
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (i.e., 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 (i.e., clusters)
- Each with 5 age-eligible patients: ie, who are not up to date with colorectal cancer (CRC) screening
- Binary outcome: not screened (Y/N)

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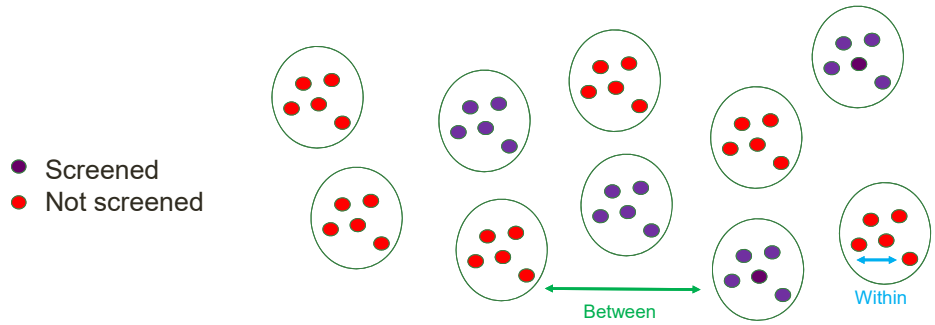
Understanding outcome clustering: complete clustering (ICC =1)



Intracluster correlation coefficient (ICC) = $\frac{\sigma_B^2}{\sigma_{\text{Total}}^2} = \frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2} = \frac{\sigma_B^2}{\sigma_B^2} = 1$, because σ_W^2 =0

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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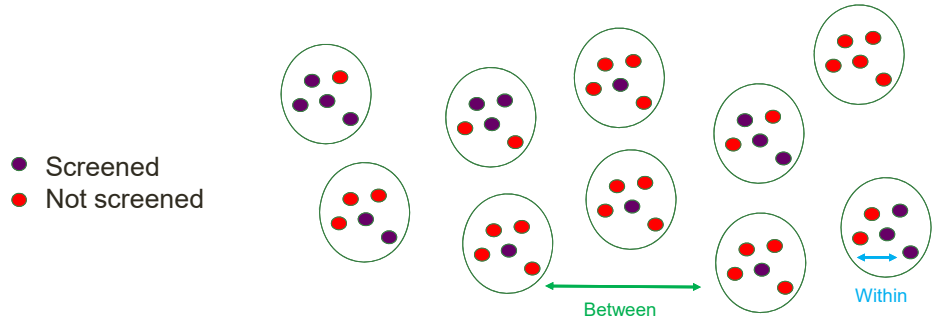
Understanding outcome clustering: some clustering (0 < ICC < 1)



ICC = $\frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2}$; 0 < ICC < 1, because 0< σ_W^2 <1 & 0< σ_B^2 <1

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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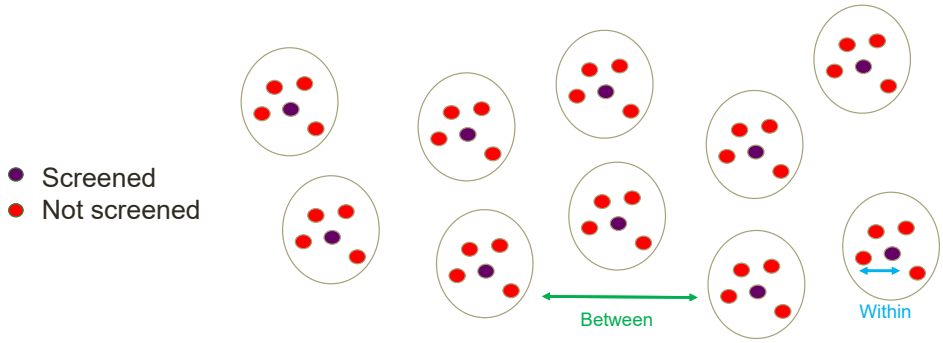
Understanding outcome clustering: no clustering (ICC=0)



ICC = $\frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2}$; ICC =0 because σ_B^2 =0 & σ_W^2 >0

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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Summary of design issues for CRTs

- All the design features common to RCTs are available to CRTs with the added complication of an extra level of nesting:
  - Cohort and cross-sectional designs
  - Post only, pre-post, and extended designs
  - Single-comparison 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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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.

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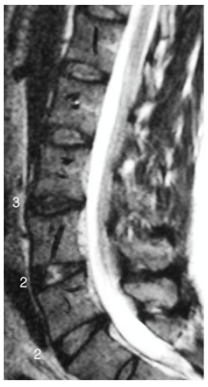
NIH Collaboratory ePCT: LIRE



- 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 (SW-CRT)

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

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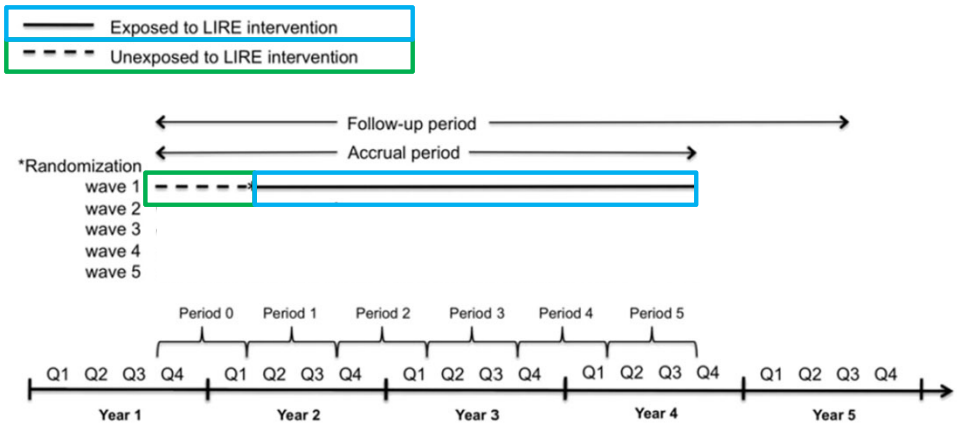
NIH Collaboratory ePCT: LIRE



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

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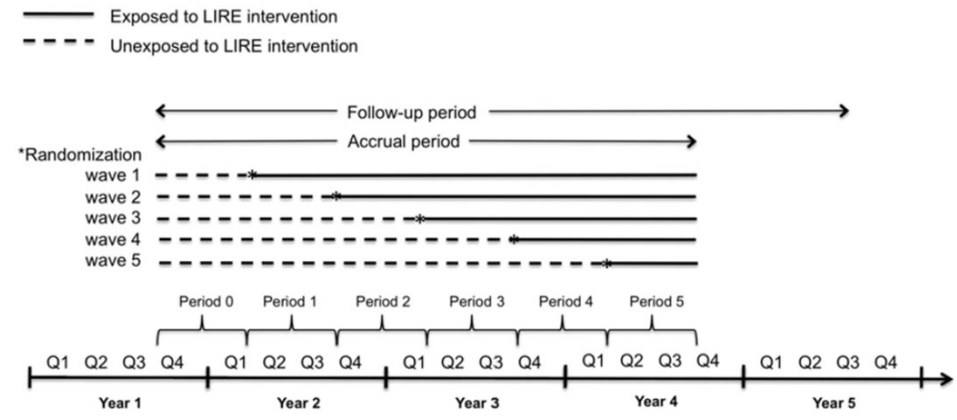
NIH Collaboratory ePCT: LIRE



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

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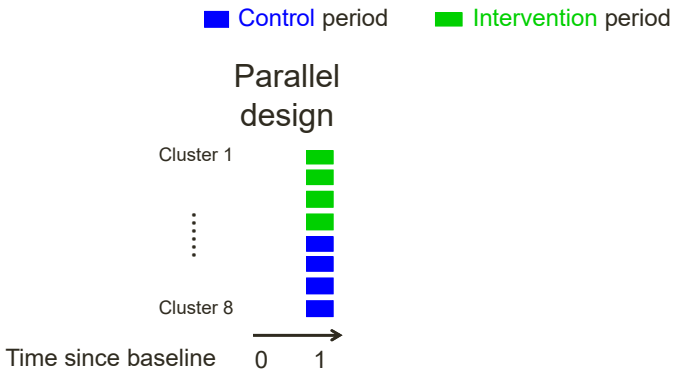
Types of CRT designs

Examples with 8 clusters: 1-year intervention



Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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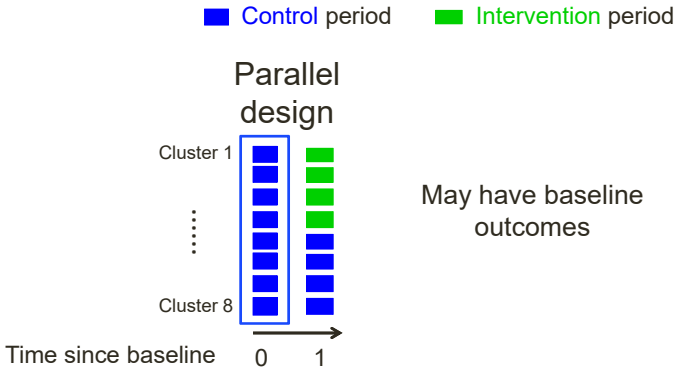
Types of CRT designs

Examples with 8 clusters: 1-year intervention



May have baseline outcomes

Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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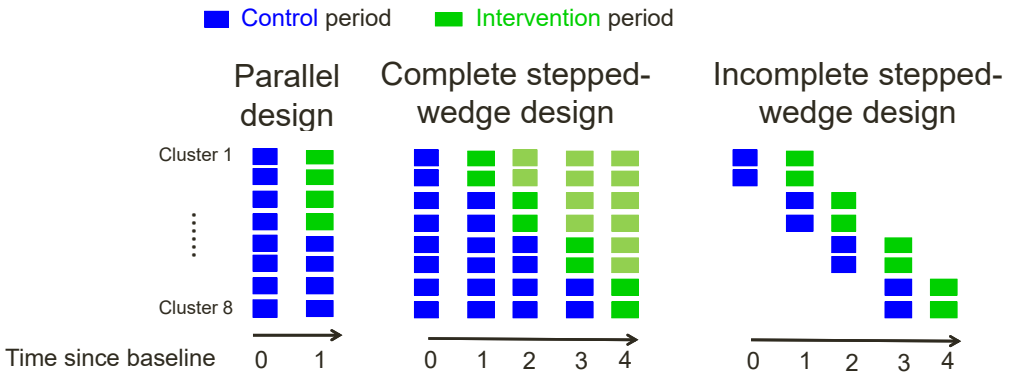
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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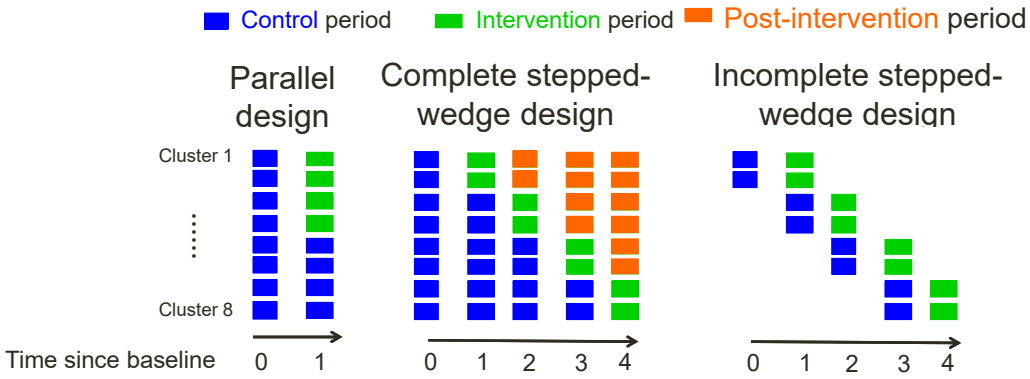
Types of CRT designs

Examples with 8 clusters: 1-year intervention



Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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Summary of design issues

- Many design features common to RCTs are available to SW-CRTs:
  - Cohort and cross-sectional designs
  - Single-comparison 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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NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

- Optimizing Pain Treatment In Medical settings Using Mindfulness (OPTIMUM)
- Goal: to reduce pain and pharmacologic medications via a group-based mindfulness-based stress reduction (MBSR) program
- Study population: individuals with chronic lower back pain
- Group-based online intervention → groups must be formed by study team
- Unit of randomization: individual → individually-randomized group treatment (IRGT) trial
- Pragmatic trial
  - Diverse settings: Safety-net hospital, FQHCs & academic hospital
  - Healthcare utilization data via EMR

Greco CM et al. *Contemp Clin Trials*. 2021;109:106545.

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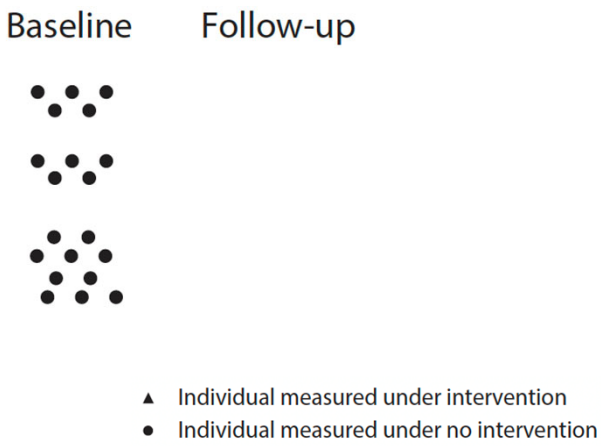
NIH Collaboratory ePCT: OPTIMUM



Extracted from Figure 1 in Turner et al. *Am J Public Health*. 2017;107(6).

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Summary of design issues

- Many design features common to RCTs are available to IRGTTs:
  - Cohort, but not easy to conceive of a cross-sectional design;
  - Single-comparison designs and factorial designs
  - A priori stratification, or other restricted randomization procedures such as minimization to create comparable treatment arms
- 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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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

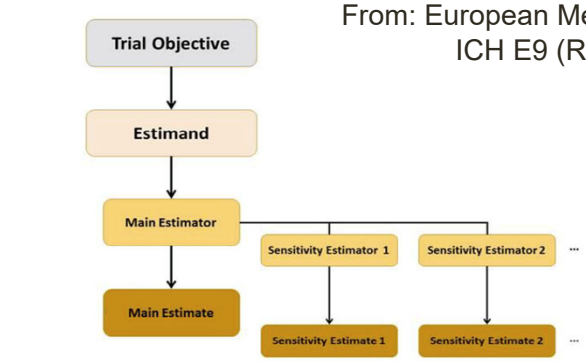

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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How to choose the right design?

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How to choose the right design?

Is there a strong rationale for randomizing groups rather than individuals to study conditions?

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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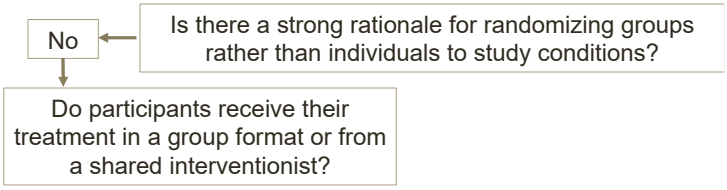
How to choose the right design?



Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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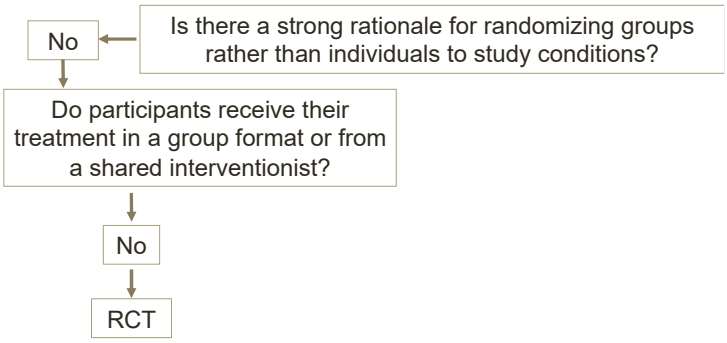

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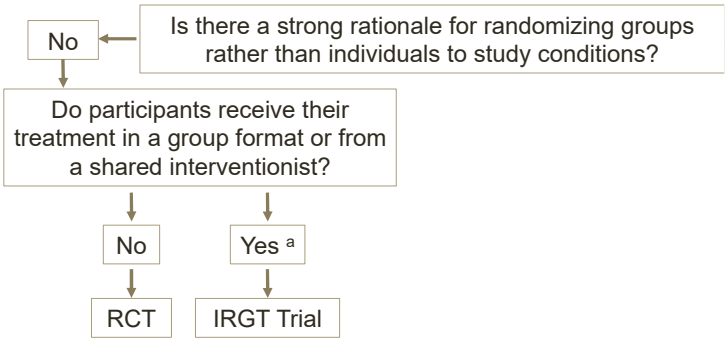

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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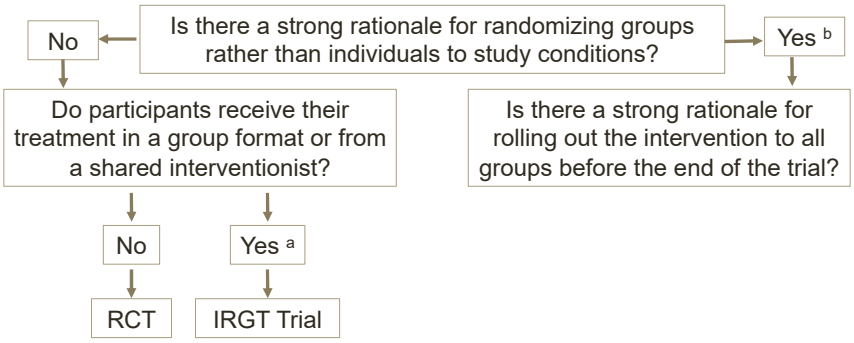
How to choose the right design?



[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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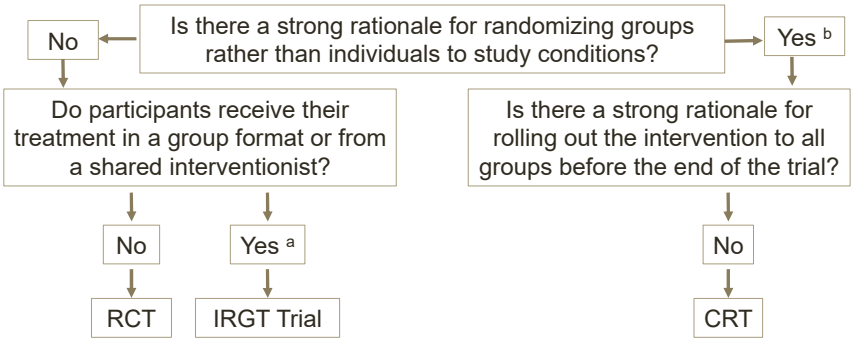
How to choose the right design?



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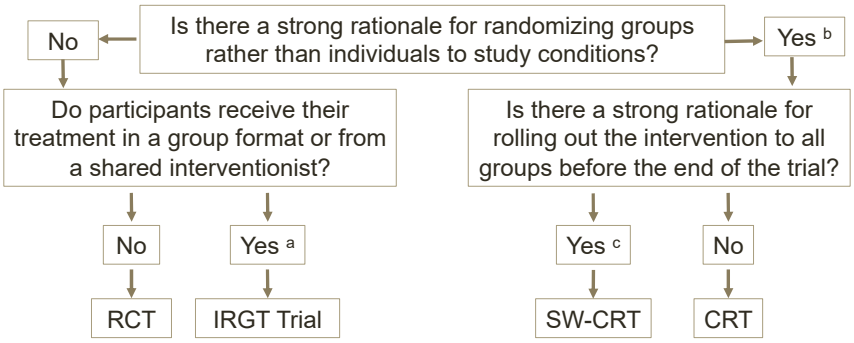

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

[c] There may be legitimate political or logistical reasons to roll out the intervention to all clusters.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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Implications of design choice

- Randomized controlled trials
  - Randomization usually distribute potential confounders evenly, as most RCTS have N>100
  - If well executed, confounding is usually not a concern
- Individually randomized group treatment (IRGT) trials
  - There may be less opportunity for randomization to distribute potential confounders evenly, as many IRGT Trials have N<100

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Implications of design choice

- Parallel cluster randomized trials (CRTs)
  - Most CRTs are “small”, ie, total # clusters (C) <50
  - Randomization may not evenly distribute potential confounders.
  - Confounding may be a concern in CRTs if C<50
  - Can use restricted randomization, eg, constrained randomization
- Stepped wedge CRTs
  - Clusters crossed with study condition, which minimizes confounding except, intervention effects confounded with time
  - SW-CRTs more complicated than parallel CRTs
    - Only choose when a parallel CRT not appropriate.

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The need for these designs

- An RCT is the best comparative design whenever…
  - Individual randomization possible without post-randomization interaction of participants
- An IRGT trial is the best comparative design whenever...
  - Individual randomization is possible but there are reasons to allow post-randomization interaction of participants.
- A CRT is the best comparative design whenever the investigator wants to evaluate an intervention that…
  - Cannot be delivered to individuals without risk of contamination
- An SW-CRT is an alternative to a parallel CRT if…
  - Intervention is being rolled out to all groups as part of system-wide implementation
  - Cannot implement intervention in many groups at same time
  - External events are unlikely to affect the outcomes (disruption!)

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Clustering: Impact on power

- Power and sample size
  - Account for anticipated clustering in CRTs (inc. SW-CRTs) & IRGTTs
  - Inflate RCT sample size
  - Work with statistician to do this correctly
- Use ICC for outcome
  - ICC often 0.01-0.05 in CRTs, larger in IRGT Trials
  - STOP CRC: ICC = 0.03 for primary outcome
  - OPTIMUM: ICC = 0.053 for primary outcome
  - Depends on outcome & study characteristics
  - Different outcome = different ICC, even in same CRT or IRGT Trial
  - **More than 1 ICC in longitudinal study like SW-CRT!**

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Clustering: Impact on power in STOP CRC

- "Assumed equal numbers of subjects per clinic and equal numbers of clinics (n = 13) per [arm]. In practice, the clinic sizes will not be equal, but since almost all clinics have at least **450** active age-eligible patients, we conservatively use this figure for all sites.

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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Clustering: Impact on power in STOP CRC

- We based our calculations on the simple paradigm of comparing two binomial proportions with a type I error rate of 5%, and **adjusted both for intraclass correlation (ICC) and the reduced degrees-of-freedom (n = 24) for the critical values**. […] we expect the ICC to be about .03.

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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Clustering: Impact on power in STOP CRC

- "Using this figure, we will have **very good power (>91%) to detect absolute differences as small as 10 percentage points** even if the FIT [fecal immunochemical testing] completion rate in the **UC arm is as high as 15%** (fecal testing rates for 2013 for usual care clinics was 10%)."

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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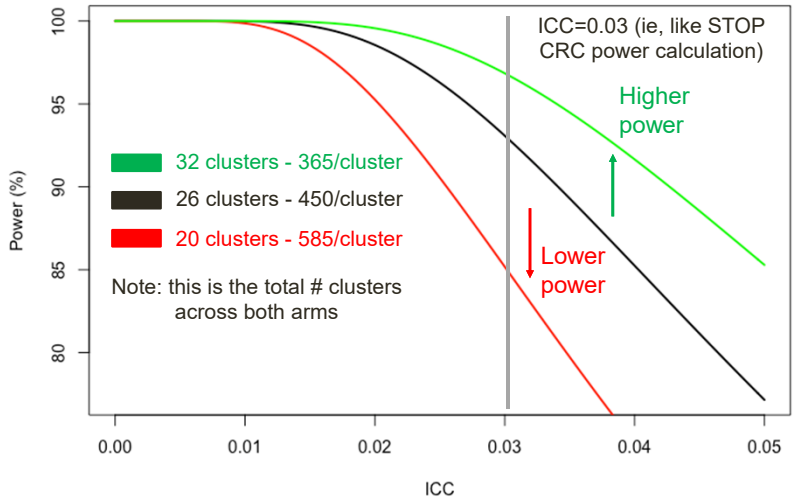
Clustering: Impact on power in STOP CRC



Power for parallel-arm CRT to compare two proportions of 15% vs 25% at two-tailed 5% significance (alpha) for an **overall sample of 11,700** (ie, like STOP CRC CRT)

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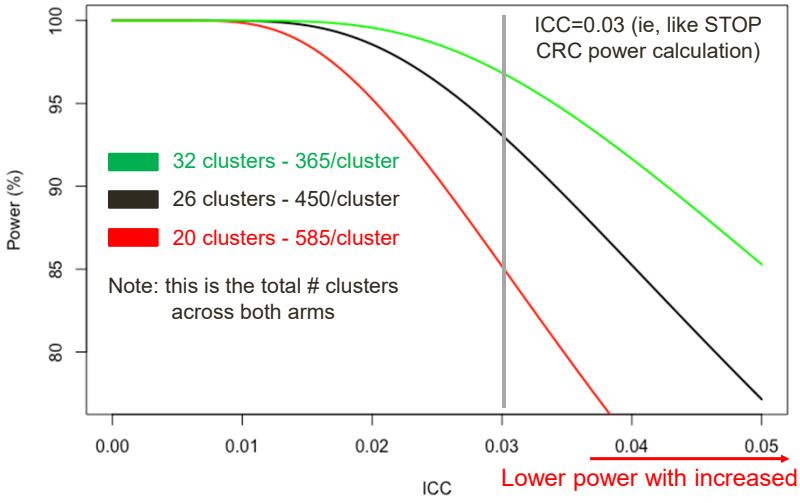
Clustering: Impact on power in STOP CRC



Power for parallel-arm CRT to compare two proportions of 15% vs 25% at two-tailed 5% significance (alpha) for an **overall sample of 11,700** (ie, like STOP CRC CRT)

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Summary: 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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Analysis Considerations

Embedded Pragmatic Clinical Trials

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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 invalid inference (confidence interval too small; an inflated type 1 error rate)
- We won't advance the science by using inappropriate methods

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Two example CRTs inspired by STOP CRC

- 10 clinics/CRT
  - 5 intervention (I) clinics & 5 control (C) clinics
  - 100 patients/clinic
- 1000 patients per trial
  - 500 intervention vs. 500 control
- Binary outcome: “No screening within year of enrollment”

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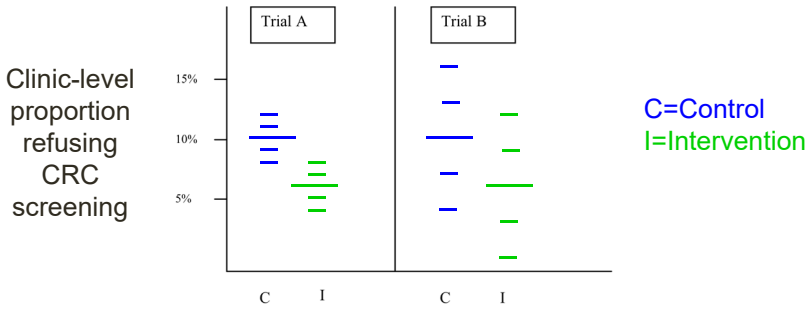
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

- 5 clinics each randomized to control and intervention
- 100 eligible participants per clinic measured

Overall screening refusal proportion in both trials: 10% vs 6%
Question: is intervention effective?

Adapted from Hayes & Moulton (2009)

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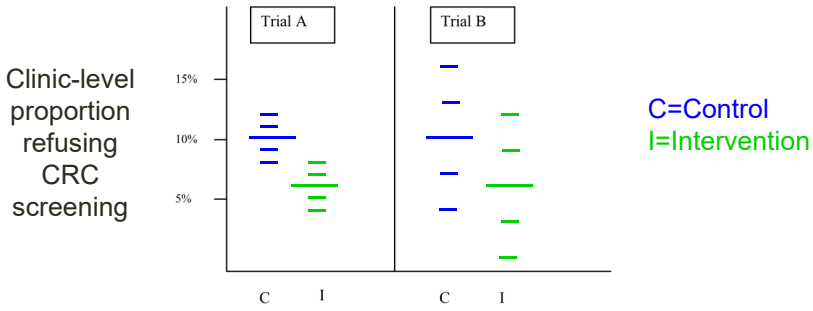
Clustering in CRTs: Implications for analysis



Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

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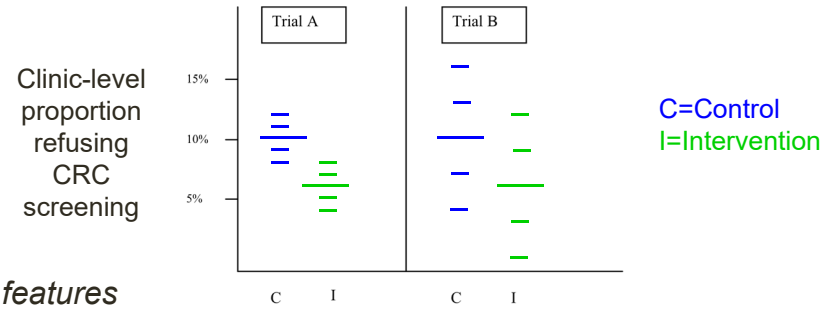
Clustering in CRTs: Implications for analysis



Study features

- Trial A:
  - Lower between-clinic variability (ie, less clustering)
  - Little overlap of I & C clinic-level proportions
- Trial B: overlap of intervention (I) & control (C) clinic-level proportions

Adapted from Hayes & Moulton (2009)

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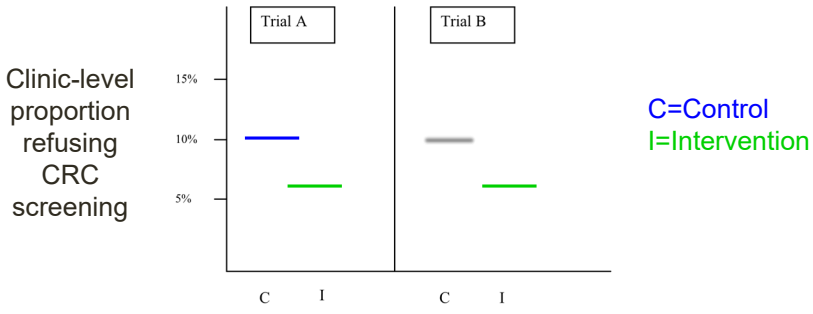
Clustering in CRTs: Implications for analysis



- If ignore clustering: p-value = **0.02** for both trials
- Comparison of 10% (50/500) vs 6% (30/500) by chi-sq. test

Adapted from Hayes & Moulton (2009)

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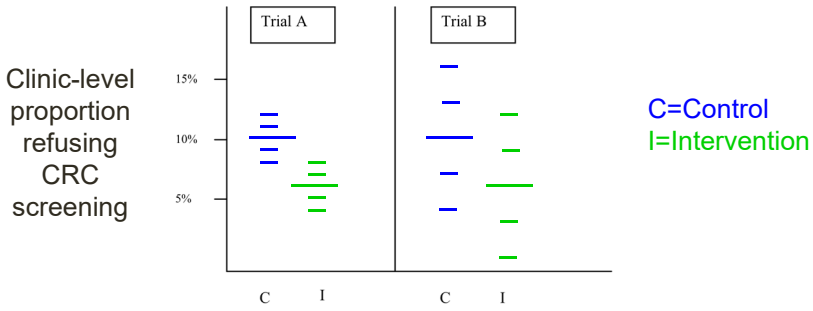
Clustering in CRTs: Implications for analysis



- Trial B p-value accounting for clustered design = **?**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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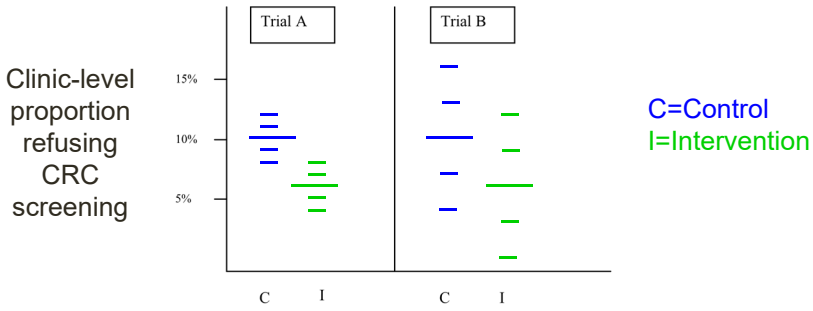
Clustering in CRTs: Implications for analysis



- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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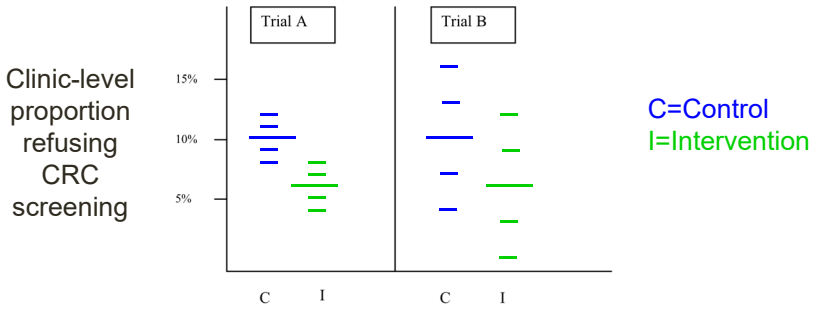
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design = **?**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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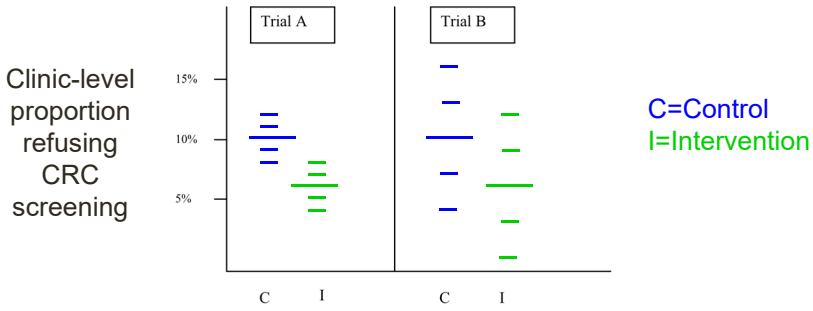
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design = **0.01**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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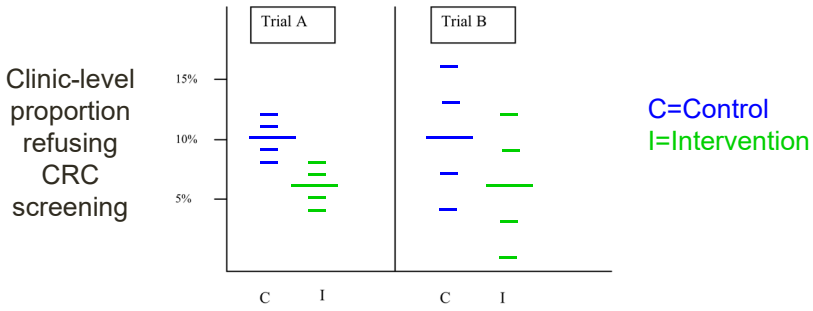
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

*By using a cluster-level analysis where the 10 cluster-level proportions (5 per arm) are treated as continuous variables and analyzed with Wilcoxon rank sum test

Adapted from Hayes & Moulton (2009)

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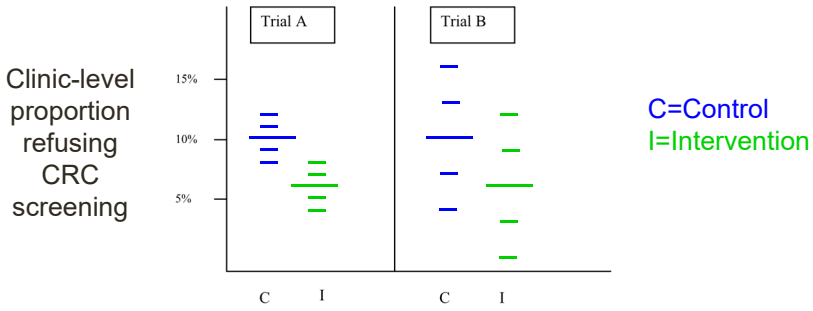
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design* = **0.004**
- Trial B p-value accounting for clustered design* = **0.22**

*Alternative cluster-level analysis using t-test, which has stronger assumptions (ie, normality of cluster-specific prevalence) than the Wilcoxon rank sum test

Adapted from Hayes & Moulton (2009)

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Summary: Analysis of two example CRTs

- Two example trials
  - Analyzed with cluster-level analysis
  - Overall sample size (# clinics/trial) =10
  - Both trials had same signal (10% vs 6%)
  - Totally different hypothesis testing (and confidence intervals) from each trial
  - Between-cluster variability (& clustering) in Trial A < Trial B
  - P-value Trial A < P-value Trial B
  - Important: if incorrectly ignore clustered design, could claim 'significant' when not (eg, Trial B)

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Analysis of CRTs, including SW-CRTs

- Regression analysis more common than cluster-level analysis
- Analyze individual-level data
  - eg, data from 1000 participants/trial not only one proportion/clinic
- Methods to account for clustering
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
- If SW-CRT, **must** account for time
- Work with statistician to ensure properly account for clustering

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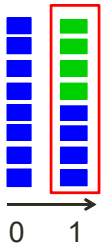
Analysis of CRTs, including SW-CRTs

Parallel design

Estimated (primarily) using between-cluster ie, **vertical** information

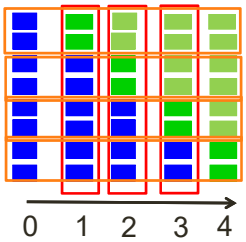


Time since baseline

0 1

Complete SW design

Estimated using both **vertical** & **horizontal** (ie, within-cluster) information



0 1 2 3 4

Control period Intervention period

Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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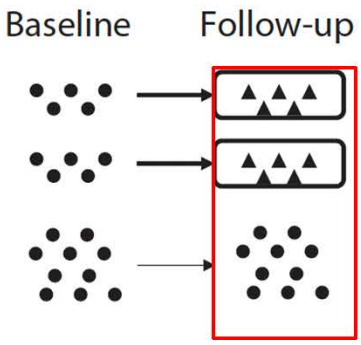
Analysis of IRGT trials



Parallel design

Estimated (primarily) using between-individual ie, **vertical** information

▲ Individual measured under intervention
● Individual measured under no intervention

Extracted from Figure 1 in Turner et al. *Am J Public Health*. 2017;107(6).

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Analysis of IRGT trials

- Analyze individual-level data accounting for clustering
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
- Considerations on clustering
  - Clustering in both arms: if both conditions group-based & may need different degree of clustering in two arms
  - Clustering in intervention arm only: if intervention group-based but control condition not
- Work with statistician to ensure properly account for clustering

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Analysis of CRTs, SW-CRTs, and IRGTTs

- Clustering must be accounted for in analysis
- Challenges in “small” trials (# clusters < 50)
  - Limited degrees of freedom (df) for testing intervention as df driven by # clusters (i.e. groups)
  - Use t-test not Z-test & calculate correct df
  - Intervention effect SE may be under-estimated
    - Can correct e.g. finite-sample bias corrections for GEE
  - Ignore either penalty (df & SEs) leads to inflated Type I error
    - Type I error rate may be 30-50% in a CRT, even with small ICC
    - Type I error rate may be 15-25% in an IRGTT, even with small ICC
- Work with statistician to ensure properly account for clustering

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Analysis of CRTs, SW-CRTs, and IRGTTs

- May need to account for complex clustering structures
  - Different clustering (ICC) in two conditions
  - Repeated measures on same individuals, if cohort
  - Decay/change in pairwise correlations over time (eg, SW-CRT)
- Other considerations
  - May need non-constant intervention effect if multiple follow-up time points (eg, like in SW-CRT)

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Strategies to protect the analysis

Avoid model misspecification

- Plan analysis
  - To reflect the study design
  - Around the primary endpoints
- Anticipate
  - All sources of random variation
  - Patterns of over-time correlation
  - Pattern of the intervention effect over time
    - Important with repeated measures designs, e.g. SW-CRTs
  - Potential confounding & effect modification

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Strategies to protect the analysis

Avoid low power

- Use strong interventions with good reach
- Maintain reliability of intervention implementation
- Use more & smaller groups not few large groups
- For SW-CRTs, use more steps
- Use regression adjustment
  - For covariates to reduce variance & intraclass correlation
  - In SW-CRTs, to adjust for calendar time

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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 cluster randomized designs are simple and powerful, but still need to address “clustering” for design and analysis.
- Individually randomized group treatment trial designs have benefits of individual-level randomization, 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)

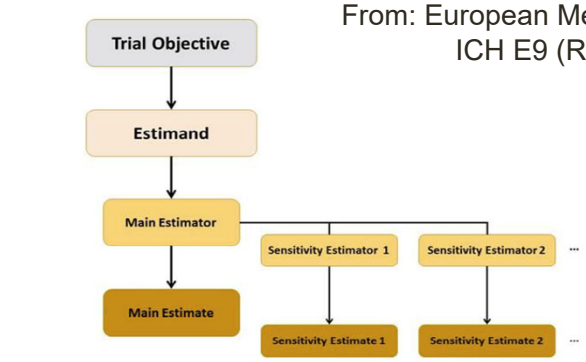

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Summary: 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 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
    - Toward Causal Inference in Cluster Randomized Trials: Estimands and Reflection on Current Practice (Fan Li, November 3, 2022)
    - An Introduction to Cross-classified, Multiple Membership, and Dynamic Group Multilevel Models (Don Hedeker, October 20, 2022)
    - Robust Inference for Stepped Wedge Designs (Jim Hughes, May 17, 2022)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs, IRGTs, SWGRTs and a sample size calculator for each

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Recommended reading

- Murray DM et al. Essential ingredients and innovations in the design and analysis of group-randomized trials. Ann Rev Public Health. 2020;41:1-19
- Kenny A et al. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. Stat Med. 2022. PMID: 35774016.
- Kahan BC et al. Estimands in cluster-randomized trials: choosing analyses that answer the right question. Int J Epidemiol. 2022. PMID: 35834775.
- Brown CH et al. Accounting for Context in Randomized Trials after Assignment. Prevention science : the official journal of the Society for Prevention Research. 2022. PMID: 36083435.

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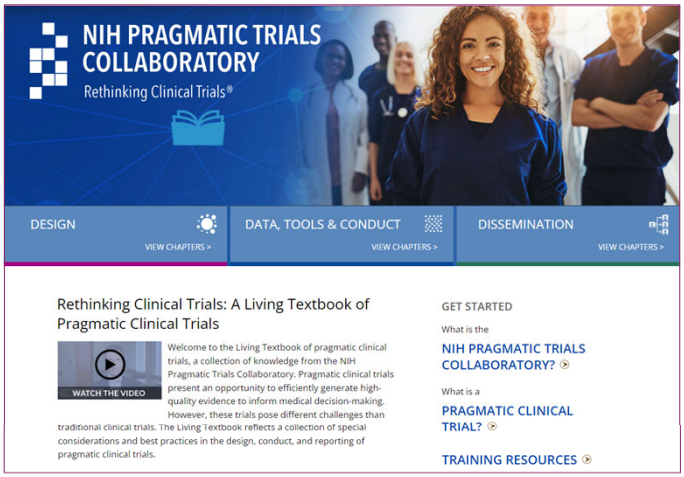
Resource: The Living Textbook

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



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Resources:

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

- Murray DM, Taljaard M, Turner EL, George SM. Essential ingredients and innovations in the design and analysis of group-randomized trials. *Annu Rev Public Health*. 2020 Apr 2;41:1-19. PMID: 31869281.
- Kenny A, Voldal EC, Xia F, Heagerty PJ, Hughes JP. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. *Stat Med*. 2022 Sep 30;41(22):4311-4339. PMID: 35774016.
- Kahan BC, Li F, Copas AJ, Harhay MO. Estimands in cluster-randomized trials: choosing analyses that answer the right question. *Int J Epidemiol*. 2023 Feb 8;52(1):107-118. doi: 10.1093/ije/dyac131. PMID: 35834775.
- Brown CH, Hedeker D, Gibbons RD, et al. Accounting for context in randomized trials after assignment. *Prev Sci*. 2022 Nov;23(8):1321-1332. PMID: 36083435.

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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ePCTs in Context

Speaker

Kevin P. Weinfurt, PhD

James B. Duke Distinguished Professor
and Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

ePCTs in Context

Panel Discussion With Demonstration Project Investigators

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

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Challenges, solutions & lessons learned

- Morning topics
  - Engaging stakeholders and aligning with healthcare system partners
  - Selecting and measuring outcomes
  - Design and analysis

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ePCT examples

- **GGC4H** (Arne Beck, PhD)
- **ICD-Pieces** (Miguel Vazquez, MD)
- **Nudge** (Michael Ho, MD, PhD)

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Pilot & Feasibility Testing

Speaker

Wendy J. Weber, ND, PhD, MPH

Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

Pilot & Feasibility Testing

Wendy J. Weber, ND, PhD, MPH
Branch Chief, Clinical Research in Complementary and Integrative Health Branch
Division of Extramural Research
National Center for Complementary and Integrative Health

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Learning goals

- Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions
- Q & A with attendees

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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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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 & Regulatory Oversight Considerations

Speaker

Stephanie Morain, PhD, MPH

Assistant Professor
Johns Hopkins Bloomberg School of Public Health and Berman Institute of Bioethics

Ethical & Regulatory Oversight Considerations

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Assistant Professor
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and Berman Institute of Bioethics

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Learning goals

- Learn about the regulatory and ethical challenges of conducting ePCTs (and resources for addressing them!)
- Discuss unique needs of historically underrepresented and mistreated groups
- Q & A with attendees

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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 patient-subjects, 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 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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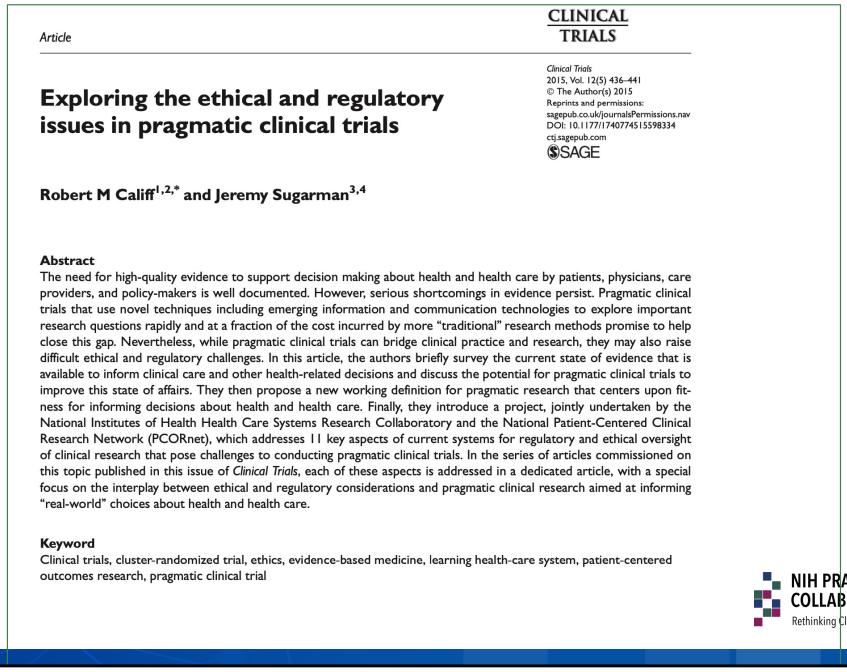

Article

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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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Evolving understanding of 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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Informed Consent, Waivers, and Alterations

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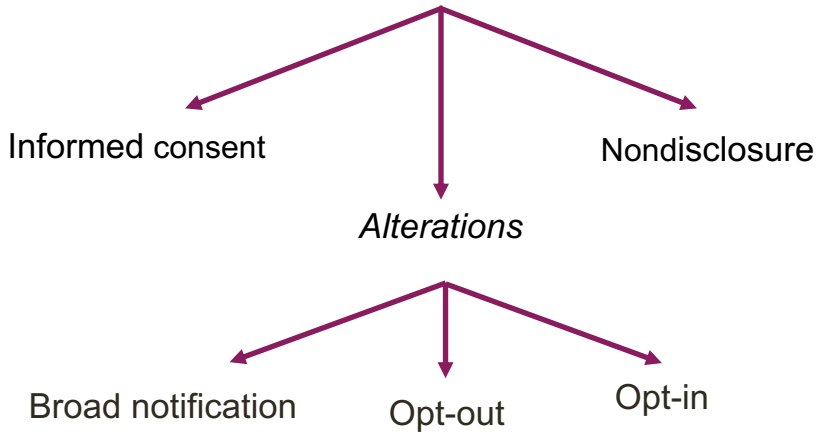
Approaches to notification & authorization



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Criteria for waiver/alteration of consent

- Research involves no more than minimal risk
- Research could not practicably be carried out without the waiver or alteration
- If research involves using identifiable private information or identifiable biospecimens, it could not practicably be carried out without using such information or biospecimens in an identifiable format
- Waiver or alteration will not adversely affect the rights and welfare of the subject
- Where appropriate, subjects will be provided with additional information about their participation

Common Rule: 45 CFR 46.116(f)

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Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

> "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." §46.102

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Distinguishing research risks

- "Minimal risk" refers only to the additional risk of the research (not the underlying risk of the disease)

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Regulatory permissible ≠ ethically optimal

- Regulatory criteria for waivers and alterations identical…but they are ethically distinct
  - Aim for alterations to consent to be the "minimum necessary"
  - Consider options to demonstrate respect for persons, beyond consent processes

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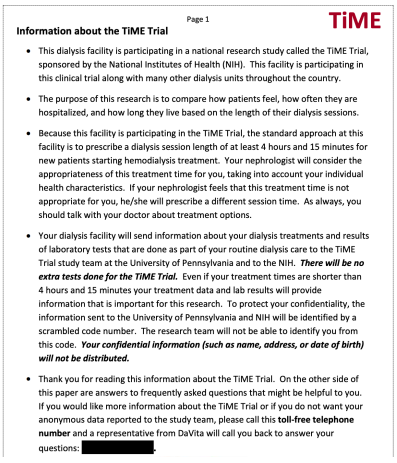
Examples: information sheets or flyers

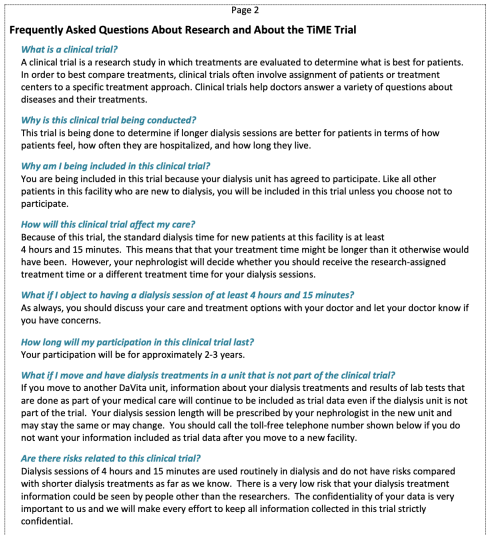


Page 1

Information about the TiME Trial

TiME

- This dialysis facility is participating in a national research study called the TiME Trial, sponsored by the National Institutes of Health (NIH). This facility is participating in this clinical trial along with many other dialysis units throughout the country.
- The purpose of this research is to compare how patients feel, how often they are hospitalized, and how long they live based on the length of their dialysis sessions.
- Because this facility is participating in the TiME Trial, the standard approach at this facility is to prescribe a dialysis session length of at least 4 hours and 15 minutes for new patients starting hemodialysis treatment. Your nephrologist will consider the appropriateness of this treatment time for you, taking into account your individual health characteristics. If your nephrologist feels that this treatment time is not appropriate for you, he/she will prescribe a different session time. As always, you should talk with your doctor about treatment options.
- Your dialysis facility will send information about your dialysis treatments and results of laboratory tests that are done as part of your routine dialysis care to the TiME Trial study team at the University of Pennsylvania and to the NIH. ***There will be no extra tests done for the TiME Trial.*** Even if your treatment times are shorter than 4 hours and 15 minutes your treatment data and lab results will provide information that is important for this research. To protect your confidentiality, the information sent to the University of Pennsylvania and NIH will be identified by a scrambled code number. The research team will not be able to identify you from this code. ***Your confidential information (such as name, address, or date of birth) will not be distributed.***
- Thank you for reading this information about the TiME Trial. On the other side of this paper are answers to frequently asked questions that might be helpful to you. If you would like more information about the TiME Trial or if you do not want your anonymous data reported to the study team, please call this **toll-free telephone number** and a representative from DaVita will call you back to answer your questions: [redacted].



Page 2

Frequently Asked Questions About Research and About the TiME Trial

What is a clinical trial?
A clinical trial is a research study in which treatments are evaluated to determine what is best for patients. In order to best compare treatments, clinical trials often involve assignment of patients or treatment centers to a specific treatment approach. Clinical trials help doctors answer a variety of questions about diseases and their treatments.

Why is this clinical trial being conducted?
This trial is being done to determine if longer dialysis sessions are better for patients in terms of how patients feel, how often they are hospitalized, and how long they live.

Why am I being included in this clinical trial?
You are being included in this trial because your dialysis unit has agreed to participate. Like all other patients in this facility who are new to dialysis, you will be included in this trial unless you choose not to participate.

How will this clinical trial affect my care?
Because of this trial, the standard dialysis time for new patients at this facility is at least 4 hours and 15 minutes. This means that that your treatment time might be longer than it otherwise would have been. However, your nephrologist will decide whether you should receive the research-assigned treatment time or a different treatment time for your dialysis sessions.

What if I object to having a dialysis session of at least 4 hours and 15 minutes?
As always, you should discuss your care and treatment options with your doctor and let your doctor know if you have concerns.

How long will my participation in this clinical trial last?
Your participation will be for approximately 2-3 years.

What if I move and have dialysis treatments in a unit that is not part of the clinical trial?
If you move to another DaVita unit, information about your dialysis treatments and results of lab tests that are done as part of your medical care will continue to be included as trial data even if the dialysis unit is not part of the trial. Your dialysis session length will be prescribed by your nephrologist in the new unit and may stay the same or may change. You should call the toll-free telephone number shown below if you do not want your information included as trial data after you move to a new facility.

Are there risks related to this clinical trial?
Dialysis sessions of 4 hours and 15 minutes are used routinely in dialysis and do not have risks compared with shorter dialysis treatments as far as we know. There is a very low risk that your dialysis treatment information could be seen by people other than the researchers. The confidentiality of your data is very important to us and we will make every effort to keep all information collected in this trial strictly confidential.

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Data and Safety Monitoring

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Why monitor for changes to risk-benefit balance and data integrity?

- Protect the welfare of research participants
- Inform decision making for patients with the same clinical condition outside the trial
- Ensure trial results will be informative

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Data monitoring committee

Group of experts that review the ongoing conduct of a clinical trial to ensure continuing patient-subject 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
- Are interim analyses actionable?
- Differential data collection/contact by study arm

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

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Unique considerations for monitoring ePCTs

- Nature of the study interventions (and evidence base regarding their safety)
- Level of data needed to change practice, especially when studying treatments in wide use?
- Differential obligations for trials using waivers/alterations of consent?

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

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Identifying Direct and Indirect Participants

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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
  - After 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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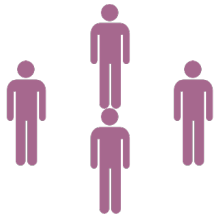
Ethical perspective:
Whose rights and welfare need to be protected?



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

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Types of participants in an ePCT

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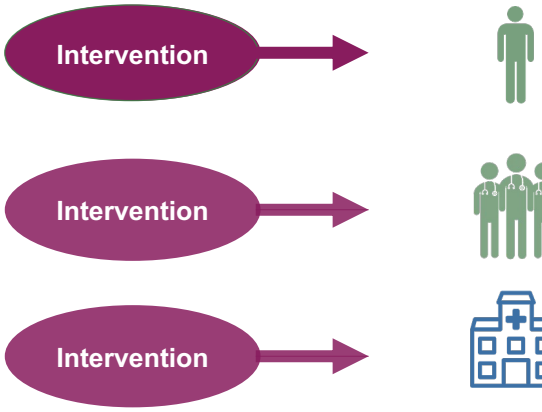
Direct participants

Immediate or mediated targets of the intervention



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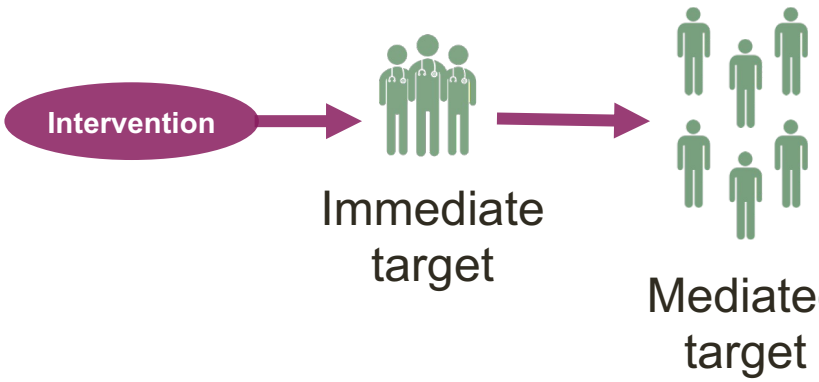
Direct participant



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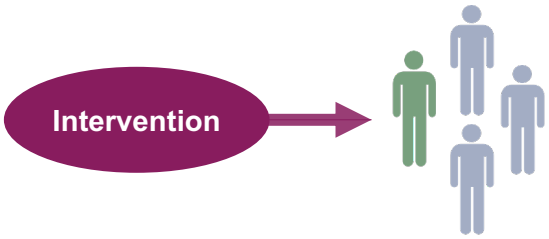
Indirect participants

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



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PCTs and Underrepresented Groups

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PCTs, equity, and underrepresented groups

- Traditional explanatory research often lacks representativeness
- Yet embedded nature of PCTs may similarly reinforce research inequities

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Promoting equity and representativeness

- Selection of health system partners
- Prospective engagement of stakeholders to identify and mitigate barriers to recruitment and implementation

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POLICY ANALYSES

Learning Health Systems

Justice and equity in pragmatic clinical trials: Considerations for pain research within integrated health systems

Joseph Ali[1,2] | Alison F. Davis[3] | Diana J. Burgess[4,5] | Daniel I. Rhon[6] | Robert Vining[7] | Stacey Young-McCaughan[8,9] | Sean Green[3] | Robert D. Kerns[10,11]

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

Special Article | Free Access

Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers

Ana R. Quiñones PhD, Susan L. Mitchell MD, Jonathan D. Jackson PhD, María P. Aranda PhD, Peggye Dilworth-Anderson PhD, Ellen P. McCarthy PhD, Ladson Hinton MD

First published: 26 June 2020 | https://doi.org/10.1111/jgs.16614 | Citations: 4

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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 and processes

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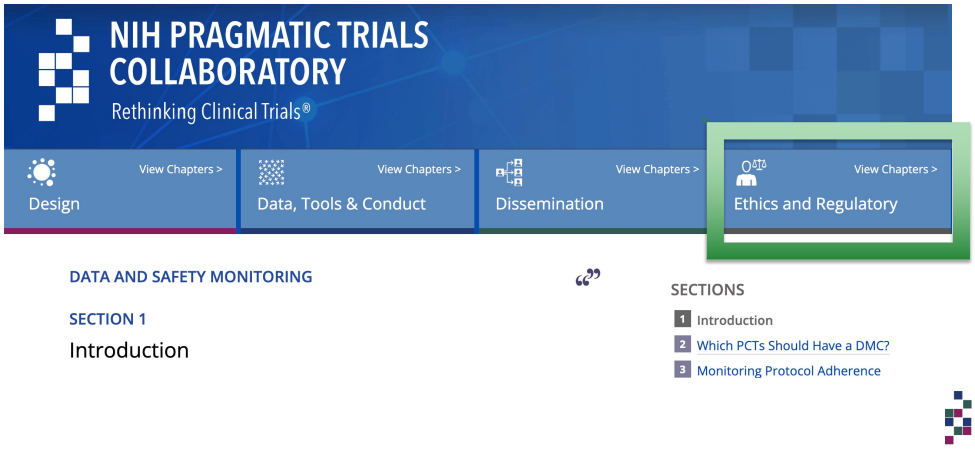
Important things to do

- Make use of existing resources!



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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

Beda Jean-Francois, PhD

Program Director, Clinical Research in Complementary and Integrative Health Branch
National Center for Complementary and Integrative Health (NCCIH)

Writing a Compelling Grant Application

Beda Jean-Francois, PhD
Program Director, Clinical Research in Complementary and Integrative Health Branch
National Center for Complementary and Integrative Health (NCCIH)

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Learning goal

- Learn how to develop a compelling ePCT application
- Tips from Collaboratory PIs
- Q & A with attendees

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Important things to know

- Online resources are available for the development of pragmatic trial grant applications
- NIH continues to update 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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National Institutes of Health

NIH
National Institutes of Health

- NIH is made up of 27 institutes and centers, or ICs
- ICs award >80% of the NIH budget each year for research studies
- Each IC has a budget and a director, and typically their own review for large trials

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Find the right NIH program official

- IC mission and priorities
  - Focus on a specific disease area, organ system, or stage of life
  - Use Matchmaker tool in NIH RePORTER for suggestions
  - Talk to program officials
  - Consult your mentor and colleagues

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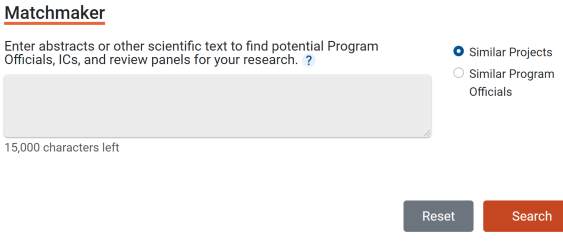
NIH RePORTER matchmaker tool

- Use draft of specific aims
- Email query to program official rather than call (we telework and attend meetings)



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Matchmaker results (example)

- This can help to connect you with the most appropriate PO(s)
- Prepare agenda and questions, to productively interact!
- Program officer can recommend a study section or two

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Find the right FOA

- Request for Application (RFA)
  - For specific areas of science where more research is needed, and applications are encouraged for investigator-initiated research in this specific area of science
- Notice of Special Interest (NOSI) and Program Announcement (PA, PAS, PAR)
  - For an area of scientific interest for one or more ICs where investigator-initiated research is needed

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NIH scientific contacts

NCCIH	Wendy Weber		
NCI	Wynne Norton	**NIDA**	Sarah Duffy
NHLBI	Larry Fine	**NIDCR**	Dena Fischer
NIA	Marcel Salive	**NIDDK**	Susan Medley
NIAAA	Brett Hagman	**NIMH**	Matthew Rudorfer
NIAID	Clayton Huntley	**NINDS**	Rebecca Hommer
NIAMS	Chuck Washabaugh	**NINR**	Karen Kehl
NICHD	Sue Marden	**ODP**	Elizabeth Nielson
NIMHD	Larissa Aviles-Santa		

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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
- Choose sites with access to diverse populations

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Application don’ts

- 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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NIH online resources

https://researchmethodsresources.nih.gov/

- Research methods resources on designing pragmatic and group randomized trials
- NIH Grants Guide: finding FOAs
- NIH Guidance on Biosketches
- NIH Peer Review
- NIH General Application Guide
- NIH Inclusion Policies for research involving human subjects

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Think through team diversity

- Rethinking Clinical Trials Website: Diversity Workshop Video Modules https://rethinkingclinicaltrials.org/training-resources/diversity-workshop-video-modules/
- NCCIH Hot Topic Webinar: Engaging Diverse Communities in Complementary and Integrative Health (recording online)
- NIH UNITE Initiative https://www.nih.gov/ending-structural-racism
- NIH continues to support increased participation of women and minority populations in

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Important things to do

- Read relevant Funding Opportunity Announcement multiple times
- Identify program staff at your target NIH Institute/Center and review your Specific Aims and any questions about them
- Obtain adequate feedback on the Research Plan from the entire study team

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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*

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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ePCTs in Context

Speaker

Kevin P. Weinfurt, PhD

James B. Duke Distinguished Professor and
Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

ePCTs in Context

Panel Discussion With Demonstration Project Investigators

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

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Challenges, solutions & lessons learned

- Afternoon topics
  - Pilot and feasibility testing
  - Ethical and regulatory oversight considerations
  - Writing a grant application

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ePCT examples

- **GGC4H** (Arne Beck, PhD)
- **ICD-Pieces** (Miguel Vazquez, MD)
- **Nudge** (Michael Ho, MD, PhD)

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Next Steps: Embedded Pragmatic Clinical Trials

Speaker

Kevin P. Weinfurt, PhD

James B. Duke Distinguished Professor and
Vice Chair of Research
Department of Population Health Sciences
Duke University School of Medicine

Next Steps: Embedded Pragmatic Clinical Trials

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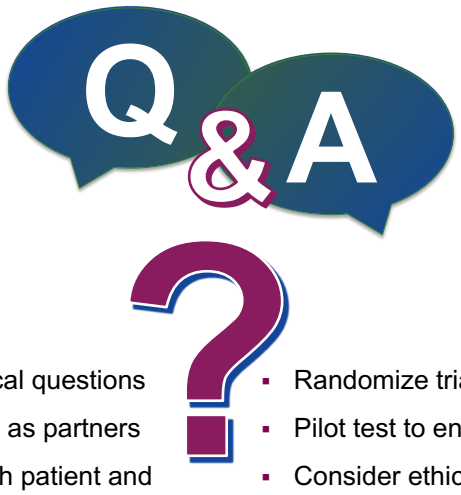

- Answer real-world clinical questions
- Engage health systems as partners
- Design your trial for both patient and implementation outcomes
- Choose meaningful and pragmatic endpoints and outcomes
- Randomize trials for the strongest evidence
- Pilot test to ensure trial readiness
- Consider ethical 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
  - https://rethinkingclinicaltrials.org/training-resources/
- Grand Rounds
  - https://rethinkingclinicaltrials.org/grand-rounds-hub/
- eNewsletter
  - https://rethinkingclinicaltrials.org/newsletter-subscribe/

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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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