NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Innovations in Embedded Pragmatic Clinical Trials:

Preconference Workshop

Participant Guide

Society for Clinical Trials 47th Annual Meeting

May 17, 2026

NIH PRAGMATIC TRIALS COLLABORATORY

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Innovations in Embedded Pragmatic Clinical Trials

Society for Clinical Trials 47th Annual Meeting
"Advancing Public Health: Clinical Trials in an Era of Cutting-Edge Information Capabilities"

Arizona Grand Resort & Spa, Phoenix, Arizona
May 17, 2026

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
1:00-1:05 pm	**Welcome**	Emily O'Brien	• Review agenda, objectives, and the Living Textbook
1:05-1:30 pm	**Opportunities for Embedded Pragmatic Clinical Trials (ePCTs)**	Wendy Weber	• Identify key considerations in the design and conduct of ePCTs and describe how they differ from traditional clinical trials • Discuss advantages and disadvantages of ePCTs, and when they can be used to answer research questions • Introduce the intersection between ePCTs and innovative information capabilities • Q & A with attendees
1:30-2:00 pm	**Engaging and Aligning With Partners**	Emily O'Brien	• Consider the breadth of individuals to engage as partners and approaches for engaging them throughout the study • Discuss the importance of working with partners to plan for posttrial activities • Identify infrastructure and expertise needs for cutting-edge information capabilities in ePCTs • Q & A with attendees
2:00-2:45 pm	**ePCT Design**	Patrick Heagerty	• Identify common experimental designs and randomization schemes in ePCTs • Discuss design considerations to ensure delivery of actionable evidence, including why ePCTs are well-suited to evaluating implications of innovative technologies for clinical care delivery • Provide an overview of effectiveness-implementation hybrid trial designs • Q & A with attendees
2:45-2:55 pm	**Break**		

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
2:55-3:40 pm	**Innovative Methods in ePCTs**	Angelo Volandes	• Describe methods for measuring outcomes using sources such as electronic health records and patient-reported outcomes • Discuss how the latest information capabilities, such as AI, can enhance ePCTs • Identify considerations for the use of new data technologies in ePCTs, including ethical issues • Q & A with attendees
3:40-3:50 pm	**Overview of NIH Collaboratory Trials** • Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients with Chronic Pain (AIM-CP) • Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors (Chat 4 Heart Health)	Sebastian Tong Michael Ho	• Hear brief descriptions of the NIH Collaboratory Trials serving as case studies for the small group activity
3:50-4:15 pm	**ePCTs in Context Part 1: Small Group Work**	Emily O'Brien	• Work in small groups to problem-solve challenges faced by ePCTs • Report out the top 1 or 2 ideas from each group
4:15-4:55 pm	**ePCTs in Context Part 2: Panel Discussion with NIH Collaboratory Trial PIs**	**Moderators**: Emily O'Brien Nana Martinson **Panelists**: Sebastian Tong Michael Ho	• Hear from NIH Collaboratory Trial PIs about how they addressed the challenges from attendees' discussions, the workshop topics, and lessons learned • Q & A with attendees
4:55-5:00 pm	**Closing Remarks**	Emily O'Brien Wendy Weber	• Wrap-up, including identifying resources for further learning

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Speaker Biographies

Patrick Heagerty, PhD
University of Washington
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Dr. Patrick Heagerty is professor and former chair of the Department of Biostatistics at the University of Washington. He received a PhD from Johns Hopkins University and a BS from Cornell University. He has extensive experience as an educator, independent and collaborative scientist, and administrator. Dr. Heagerty 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 healthcare delivery systems. Dr. Heagerty coauthored 2 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. The CBS has previously conducted high-impact multisite randomized trials, as well. Dr. Heagerty is cochair of the Biostatistics and Study Design Core for the NIH Pragmatic Trials Collaboratory, coleader of the Scientific Analysis Unit of the Methods Core 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
Kaiser Permanente Colorado
p.michael.x-ho@kp.org

P. Michael Ho, MD, PhD, is the medical director of Innovative Methods Promoting Operational Value and Efficiency (IMPROVE) at Kaiser Permanente Colorado and a senior clinician investigator at the Kaiser Permanente Institute for Health Research. His research focuses on finding ways to optimize delivery of safe, effective, patient-centered, timely, efficient, and equitable care.

Dr. Ho received his medical training at the Tulane University School of Medicine in New Orleans, Louisiana, and completed an internship, residency, and cardiology fellowship at the University of Colorado School of Medicine.

He also received a PhD in clinical science from the University of Colorado Health Sciences Center. His research teams are working to leveraging mHealth technologies to engage patients in self-management and improve cardiovascular risk factors such as high blood pressure, diabetes, and high cholesterol, as well as medication adherence.

Dr. Ho is a practicing clinical physician in cardiology with the Colorado Permanente Medical Group at Kaiser Permanente Colorado. He is also a professor of medicine at the University of University of Colorado School of Medicine in the Division of Cardiology. Dr. Ho is the deputy editor of the journal *Circulation: Cardiovascular Quality and Outcomes*, an active Endorsement and Maintenance (E&M) committee member of the Partnership for Quality Measurement and fellow at the American College of Cardiology and the American Heart Association.

Nana Martinson, MPH
National Center for Complementary and Integrative Health (NCCIH)
nana.martinson@nih.gov

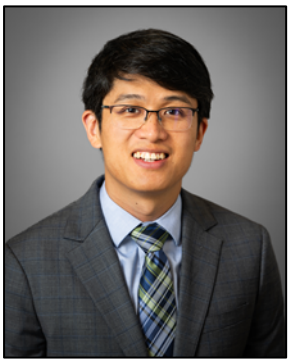
Nana Martinson is a program analyst in the Clinical Research Branch at NIH/NCCIH, where she supports clinical research operations, study performance monitoring, and strategic planning. She also serves as a project scientist on multiple pragmatic clinical trials, contributing to the rigor and consistency of study design and conduct.

Prior to NIH, she managed a portfolio of clinical and infrastructure projects at the Patient-Centered Outcomes Research Institute (PCORI)/PCORnet, supporting comparative effectiveness research. Her work emphasized patient-centered approaches and stakeholder engagement, with a focus on addressing enrollment, feasibility, and implementation challenges in real-world research settings. She also contributed to national health data interoperability efforts at the Office of the National Coordinator for Health IT (ONC), supporting the Trusted Exchange Framework and Common Agreement (TEFCA) through regulatory and policy activities, helping enable researchers to access standardized health data across healthcare systems.

Martinson holds a BS in biology and an MPH from A.T. Still University. Her experience across federal agencies, research networks, and health IT policy provides a strong foundation for advancing pragmatic clinical trials in real-world healthcare settings.

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

Dr. Emily O'Brien is an associate professor in population health sciences and an associate professor in neurology at Duke University, a core faculty member at Duke-Margolis Center for Health Policy, and codirector of Population Health Sciences at the Duke Clinical Research Institute. Her research focuses on comparative effectiveness, patient-centered outcomes, and pragmatic health systems research in cardiovascular and pulmonary disease. Her areas of expertise include epidemiology, pragmatic clinical trials, and clinical decision sciences.
Dr. O'Brien received her PhD in epidemiology from the University of North Carolina at Chapel Hill. As principal investigator for projects funded by the FDA, NIH, and PCORI, she has extensive experience working with diverse data sources including registries, epidemiologic cohorts, electronic health records, and administrative claims data. Dr. O'Brien teaches analytic methods in the Department of Population Health Sciences PhD program and has coauthored over 200 manuscripts in peer-reviewed journals on topics ranging from epidemiologic methods, to comparative effectiveness to pragmatic clinical trials. She is an associate editor for *Circulation: Cardiovascular Quality and Outcomes,* chair of the AHA QCOR Scientific & Clinical Education Lifelong Learning Committee, social media editor for *the Journal of the American Heart Association*, and a fellow of the American Heart Association.



Sebastian Tong, MD, MPH
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Sebastian Tong is a practicing family physician and addiction medicine specialist. He is an associate professor of family medicine at the University of Washington in Seattle where he also serves as the associate director of the Washington, Wyoming, Alaska, Montana and Idaho region Practice and Research Network. He practices outpatient family medicine and addiction medicine at the Harborview Family Medicine Clinic. He conducts research in practice-based research, substance use, loneliness, and chronic pain and has received funding from the National Institute on Drug Abuse, the National Institute of Nursing Research, and the Agency for Healthcare Research and Quality. He is one of the National Academy of Medicine's 2023-2025 James C. Puffer/American Board of Family Medicine Fellows. He completed medical school at Boston University School of Medicine, received a master of public health degree from the Harvard School of Public Health, and finished his residency training in family medicine at the Greater Lawrence Family Health Center.

Angelo Volandes, MD, MPH
Dartmouth Health
Geisel School of Medicine at Dartmouth
Angelo.E.Volandes@dartmouth.edu

Angelo Volandes, MD, MPH, is the Anna Gundlach Huber Professor in Medicine at the Geisel School of Medicine at Dartmouth, a clinician–investigator at Dartmouth Health, and vice chair for research in the Department of Medicine at Dartmouth Hitchcock Medical Center. His work centers on patient-centered decision-making, particularly conversations around serious illness, aging, and end-of-life care, and on the use of video decision support tools to inform patients and families. He leads large, multisite embedded pragmatic clinical trials, including ACP PEACE within the NIH Pragmatic Trials Collaboratory; his prior pragmatic trial work includes the PROVEN cluster randomized trial in US nursing homes.

He is cofounder and president of ACP Decisions, a nonprofit that develops evidence-based video tools to support shared decision-making, and he is the author of *The Conversation: A Revolutionary Plan for End-of-Life Care*. Previously, Dr. Volandes served on the faculty at Harvard Medical School and Massachusetts General Hospital for 20 years. A Brooklyn native and proud graduate of the New York City public schools, he earned an AB in philosophy from Harvard, an MD from Yale, and an MPH from the Harvard T.H. Chan School of Public Health. He trained in internal medicine at the Hospital of the University of Pennsylvania and was an Edmond J. Safra Faculty Fellow at Harvard's Center for Ethics.

Wendy Weber, ND, PhD, MPH
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Wendy J. Weber, ND, PhD, MPH, is the acting deputy director of the National Center for Complementary and Integrative Health (NCCIH). She served as the branch chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at NCCIH until 2025. 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 Opportunities and point-of-contact for all natural product–related clinical trial funding opportunities. She is a member of the NIH Pragmatic Trials Collaboratory and a former program officer for the Coordinating Center. Dr. Weber is also a member of the planning and oversight team for the NIH–Department of Defense–Department of Veterans Affairs Pain Management Collaboratory and served as project scientist for its Coordinating Center.

Dr. Weber's interests include the use of complementary medicine interventions for common pediatric conditions, mental health conditions, promoting healthy behaviors, and health services research.

Dr. Weber earned a doctor of philosophy in epidemiology and a master of public health from the University of Washington. She earned a doctor of naturopathic medicine (ND) from Bastyr University. Prior to joining NCCIH, she was a research associate professor at Bastyr University, where her research included the study of herbal treatments for pediatric conditions. Her clinical practice focused on the treatment of children and adolescents with mental health conditions, abdominal pain, headaches, and allergies.

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About

Since 2012, the NIH Pragmatic Trials Collaboratory has helped rigorous trials be successful in real-world settings, creating standards for more efficient, large-scale clinical research.

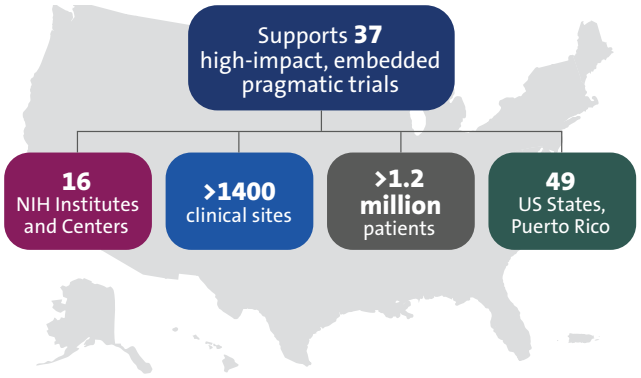
What Are Embedded Pragmatic Clinical Trials?

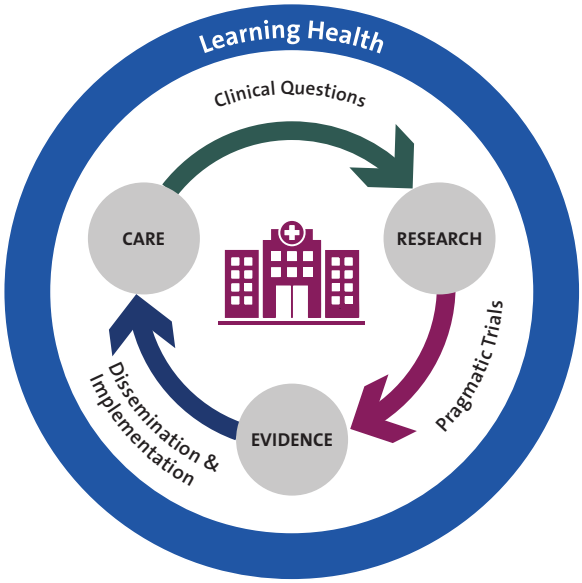
- Conducted in healthcare systems
- Use existing infrastructure and streamlined procedures
- Provide high-quality evidence
- More efficient and cost effective than traditional trials

Our Role

Pragmatic trials are foundational to the learning health model where ongoing evidence generation improves care. The NIH Pragmatic Trials Collaboratory is the nation's leading resource on how to conduct randomized trials embedded in healthcare delivery.

Our Reach





NIH Partners, Past and Present

NCCIH NCI NCMRR NHLBI NIA NIAID
NIAMS NICHD NIDA NIDDK NIMH
NIMHD NINR NINDS OBSSR ODP

Bold denotes current partners (Grant U24AT009676)

Our Impact

We learn and share knowledge from each trial we support to advance pragmatic research methods.

- **>385** publications*
- Work cited **>13,000** times
- **>250** trial consultations
- **>600** Grand Rounds webinars
- **>100,000** website visitors annually
- **30+** Living Textbook chapters

Wide Influence

The success of the NIH Pragmatic Trials Collaboratory and its extensive resources have informed subsequent NIH initiatives for pain management, dementia care, and primary care, as well as research programs in Canada and Japan.

*LAST UPDATED JANUARY 19, 2026

Our Support

As a Resource Coordinating Center, we provide comprehensive expertise and technical assistance to researchers conducting pragmatic trials.

Consult and provide guidance on:

- Study design and analysis
- Regulatory issues and consent practices
- Use of real-word data sources
- Translating results into practice

Offer strategies to:

- Contribute to healthier communities
- Engage health system partners

Assist with:

- Defining study endpoints
- Measuring patient-centered outcomes
- Assessing feasibility of clinical workflows
- Addressing challenges that arise

Why Do an Embedded Pragmatic Clinical Trial? The 5 Rs

Relevant Question

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

Real-World Setting

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

Representative Population

Ability to enroll participants who reflect the real-world population with the disease or condition.

Routinely Collected Data

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

Rigorous Methods

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

About NIH Collaboratory Trials

SETTINGS

- Academic health centers
- Community clinics
- Federally qualified health centers
- For-profit health systems
- Hospitals
- Managed care organizations
- Primary care
- Specialty care

CHARACTERISTICS

- Trials in multiple therapeutic areas
- Each works across multiple health systems
- Use electronic health records, administrative, and claims data
- Strong partnerships with health systems
- Committed to sharing lessons and data

How We Learn and Share

Pragmatic research poses unique challenges that the NIH Pragmatic Trials Collaboratory has a wealth of experience navigating. Through the program's Core Working Groups, research teams are part of a community of scientists with a shared mission to help each other be successful and create generalizable knowledge about the design, conduct, and dissemination of pragmatic research.

DISSEMINATION

Grand Rounds
Weekly webinar with >94,000 all-time attendees and >50 podcast episodes with >24,000 total plays

Living Textbook
Free online textbook, continually updated and expanded, with 30+ chapters, >1800 pages, and >120 contributors

Resources and Tools
Publications, guidance documents, Quick Start Guides, checklists, etc—over 140 study tools available

Education
Provided >90 hours of presenter-led training at 14 workshops, plus video modules, self-paced learning, fellowships, and more

This work was supported within the NIH Pragmatic Trials Collaboratory under award number U24AT009676 from multiple NIH Institutes, Centers, and Offices. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Case Studies

AIM-CP: Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients With Chronic Pain

Chat 4 Heart Health: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors

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Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients With Chronic Pain (AIM-CP)

Principal Investigators
Sebastian T. Tong, MD, MPH
Kushang V. Patel, PhD, MPH

Sponsoring Institution
University of Washington

Collaborators
- WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region Practice and Research Network
- Mecklenburg Area Partnership for Primary Care Research in rural North Carolina

NIH Institutes Providing Funding or Oversight
National Institute of Nursing Research (NINR)

Program Official
Karen Kehl, PhD, RN, FPCN (NINR)

Project Scientist
Alexis Bakos, PhD, MPH, RN (National Institute on Aging [NIA])

ClinicalTrials.gov Identifier
NCT06407115

ABSTRACT

People living in rural communities experience higher rates of chronic pain and poorer health outcomes because of pain. The 46 million Americans who live in rural areas frequently lack access to evidence-based, nonpharmacologic treatments for chronic pain. A critical need exists to implement effective, comprehensive programs for pain management that include nonpharmacologic treatment options. Nurse care management (NCM) has been used successfully to enhance care for individuals with other chronic conditions or at high risk of complications. Using a type 1 hybrid effectiveness-implementation design, the AIM-CP study team will adapt, pilot, and implement an NCM model that includes care coordination, cognitive behavioral therapy (CBT), and referral to a remotely delivered exercise program for rural patients with chronic pain. Each partnering healthcare system will identify appropriate healthcare professionals to be trained as care managers. For the CBT component, care managers will be trained to engage patients in a remotely delivered CBT program. For exercise, the study will offer the remotely delivered Enhance Fitness program, an evidence-based, 16-week program that includes aerobic and strength training exercise. In the planning phase, the study team will engage patients, clinicians, and care managers from 2 healthcare systems serving rural patients in a learning collaborative to pilot the NCM model. The study team will also adapt infrastructure and workflows to implement the intervention and engage the partnering healthcare systems in developing relationships with community partners and identifying care managers. In the implementation phase, the study team will conduct a randomized controlled trial of the adapted NCM model vs usual care for rural-dwelling patients with chronic pain. The research partners include 6 healthcare systems from 2 practice-based research networks: the WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region Practice and Research Network and the Mecklenburg Area Partnership for Primary Care Research in rural North Carolina. The primary outcome is pain interference as measured by the Pain, Enjoyment of Life and General Activity (PEG) scale. Secondary outcomes include physical function, sleep, pain catastrophizing, depression, anxiety, treatment satisfaction, substance use disorder, pain medication use/dosage including opioids, and healthcare utilization. The study team will explore whether disparities exist by examining heterogeneity in treatment effect via subgroup analyses by age, gender, race/ethnicity, and health insurance. They will use the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework to assess implementation outcomes and qualitative interviews conducted with a subset of patients to evaluate experiences with the intervention. If successful, AIM-CP will have a transformative effect on chronic pain management in rural areas by expanding access to evidence-based, nonpharmacologic treatments through an innovative NCM model.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Shortage of nurses in rural areas	Flexibility in working with local primary care systems, allowing them to select which healthcare providers will deliver the intervention
Lack of access to evidence-based exercise programs in rural areas	Helping rural healthcare systems connect to exercise providers in nonrural areas, and engaging a variety of exercise providers to develop referral pathways

"The biggest advice I have for investigators planning a pragmatic trial is to listen to and talk with people at the ground level. Talk with practices, talk with community organizations, talk with patients from the very beginning. Be flexible and think about what core elements you want to retain in your intervention and what things you can change to adapt to the needs of the community." — Dr. Sebastian Tong

SELECTED PUBLICATIONS & PRESENTATIONS

- Video Interview: NIH HEAL Initiative Turns Attention to Pragmatic Trials in Rural Communities (2024)
- Presentation: Presentation to the NIH Collaboratory Steering Committee (2023)

See the complete set of AIM-CP resources.

AIM-CP: Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients With Chronic Pain

Sebastian Tong, MD, MPH
Associate Professor of Family Medicine
University of Washington

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Objective

- To adapt and test a nurse care management model to provide comprehensive coordinated care for patients with chronic pain in rural communities
- Long-term: Reduce geographic disparities in pain-related outcomes through dissemination of this comprehensive approach to chronic pain management

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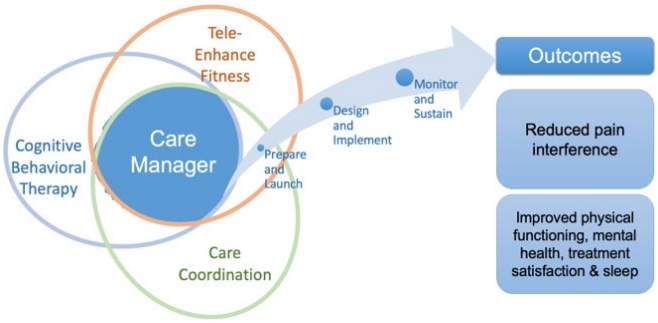
Care management model

- Care coordination
- Cognitive behavioral therapy
- Remotely delivered Enhance Fitness exercise program



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Study population and setting

- Study population
  - Rural-dwelling adults with chronic pain
- Study settings
  - WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region Practice and Research Network
  - Mecklenburg Area Partnership for Primary Care Research (North Carolina)

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Study design

- Individually randomized controlled trial (N = 450)
- Eligibility: Adults living or working in a rural area; chronic pain diagnosis; PEG score 4+
- Intervention for 6 months
- Care manager from each healthcare system provided with training to provide intervention
- Healthcare systems paid for care manager time, part of administrative support staff's time and other study activities

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Outcomes

Outcome	Measure	Data Source
Pain interference	PEG	Patient report
Pain intensity	PEG	Patient report
Physical function	PROMIS Physical Functioning Short Form 6b	Patient report
Sleep	PROMIS Sleep Disturbance	Patient report
Pain catastrophizing	Pain Catastrophizing Scale	Patient report
Depression	PHQ-9	Patient report
Anxiety	GAD-7	Patient report
Global satisfaction with treatment	Patients' Global Impression of Change scale	Patient report
Substance use disorder	TAPS-1	Patient report
Pharmacologic treatments	Medication name, dose and, if opioid, morphine milligram equivalent	EHR and/or patient report
Healthcare utilization	Hospital admissions; ED, urgent care, primary care visits	EHR and/or patient report

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Chat for Heart Health

Using AI Text Messaging to Improve the American Heart Association's Life's Essential 8 Health Behaviors (Chat 4 Heart Health)

Principal Investigators
Michael Ho, MD, PhD; Sheana Bull, PhD, MPH

Sponsoring Institution
University of Colorado Denver

Collaborators
- Denver Health and Hospital Authority
- Salud Family Health Centers
- STRIDE Community Health Center

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

Program Official
Eric Shiroma, ScD, MEd (NHLBI)

Project Scientist
Nicole Redmond, MD, PhD, MPH (NHLBI)

ClinicalTrials.gov Identifier
NCT06324981

ABSTRACT

The goal of Chat 4 Heart Health is to improve control of risk factors for cardiovascular disease using a multilevel intervention that leverages mobile phone–based text messaging integrated within healthcare systems to improve adherence to the American Heart Association's Life's Essential 8 (LE8). The LE8 health factors are eating better, being more active, quitting tobacco, getting healthy sleep, managing weight, controlling cholesterol, managing blood sugar, and managing blood pressure. When unmanaged, these lifestyle factors lead to common coexisting chronic conditions like hypertension and diabetes, as well as greater morbidity, mortality, and healthcare costs. Populations that experience health disparities (including minoritized ethnic groups, patients with limited English proficiency, and patients with lower income) are disproportionately affected by cardiovascular disease, have worse disease control, and experience greater sequelae. Self-management of chronic disease by patients has strong evidence of benefit. It includes self-care, lifestyle changes, taking medications as prescribed, and managing exacerbations of chronic conditions. Text messaging interventions have improved health behaviors, including physical activity and medication adherence. Incorporating a behavioral "nudge," a small change in choice architecture that alters behavior, into text messages may further augment its impact. However, text messaging interventions have typically not been delivered to large samples, have not focused on populations that experience health disparities, and have not leveraged healthcare systems' electronic health record (EHR) data to personalize content and maximize the scale, reach, and impact of the intervention. Using a pragmatic trial with patient-level randomization, Chat 4 Heart Health is testing the comparative effectiveness of 3 text messaging delivery strategies: (1) generic text messages; (2) interactive artificial intelligence (AI)–based chatbot text messaging that uses evidenced-based communication strategies with attention to patient context and sociocultural factors that influence self-management; and (3) interactive AI-based chatbot text messaging plus proactive pharmacist management. Chat 4 Heart Health will enroll approximately 2200 patients from clinics in 3 healthcare systems that care for large populations that experience health disparities: Denver Health and Hospital Authority, Salud Family Health Centers, and STRIDE Community Health Center. The study team will use EHR data from the partnering healthcare systems to identify eligible patients, deliver the intervention, and assess patient-centered outcomes. The study's findings will provide evidence regarding the best population-based strategy for universal delivery to engage all patient populations experiencing health disparities in self-management to improve LE8 adherence. The intervention will be delivered in real-world settings to augment routine clinical care and improve access to care. The study team will incorporate lessons learned from one of the partnering healthcare systems into adaptations for the other healthcare systems in the study.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Impacts of a new rule from the Federal Communications Commission on the planned implementation of the trial's text messaging strategy, including additional barriers to participant enrollment	Consulted with the Biostatistics and Study Design Core to consider the analytic implications of a smaller sample size; and consulted with the Health Equity Core to develop strategies for ensuring all participants can trust the text messaging process
Partnership with 2 new healthcare delivery systems brought challenges associated with accessing and using their EHR systems to identify eligible patients	Worked closely with healthcare system partners to set up security measures and establish protocols to address concerns about data sharing; and used information from the Coordinating Center about onboarding new healthcare system partners and ensuring compliance with HIPAA and data sharing requirements

"Our hope is that one of these arms will improve cardiovascular health. Given the ubiquity of text messaging in everyday life, our hope is that one of these study arms will improve cardiovascular health and can be a generalizable intervention that's low cost and can be widely disseminated." — Dr. Michael Ho

"Being part of the NIH Collaboratory is very helpful for us, primarily because of the network of people who are using similar designs and facing similar challenges. The biggest lesson we've had this year is, try not to take on too much. We have a lot of questions we can explore, but we're focusing on what is the most critical question we can try to answer." — Dr. Ed Vasilevskis

SELECTED PUBLICATIONS & PRESENTATIONS

- Presentation: NIH Pragmatic Trials Collaboratory Onboarding Meeting (2023)
- Video Interview: Chat 4 Heart Health Transitions to Implementation Phase (2024)
- PCT Grand Rounds Presentation: Texting for Behavior Change: Lessons Learned Across 2 Interventions to Improve Chronic Care Management (2025)

See the complete set of Chat 4 Heart Health resources.

Chat 4 Heart Health: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors

P. Michael Ho, MD, PhD
Medical Director of IMPROVE and Senior Clinician Investigator
Kaiser Permanente Institute for Health Research

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Objective

- Use an artificially intelligent chatbot to deliver text messages and interact with patients to help them improve their control of AHA's Life's Essential 8 (LE8) lifestyle factors: blood glucose, cholesterol, blood pressure, physical activity, weight, diet, sleep, and smoking

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Study population and setting

- Clinics in 3 healthcare systems that care for large populations that experience health disparities: Denver Health and Hospital Authority, Salud Family Health Centers, and STRIDE Community Health Center
- English/Spanish-speaking primary care patients with:
  - Diagnosis of >1 of the following cardiovascular risk factors: hypertension, diabetes, hyperlipidemia
  - Risk factor poor or intermediate as defined by LE8 (eg, BP > 140/90 mm Hg)

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Study design

- Pragmatic clinical trial with patient-level randomization testing the comparative effectiveness of 3 text messaging delivery strategies:
  - Generic text messages
  - Interactive AI-based chatbot text messaging that uses evidenced-based communication strategies with attention to patient context and sociocultural factors that influence self-management
  - Interactive AI-based chatbot text messaging plus proactive pharmacist management

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Generic text group

- Eating well is one of the best ways to manage diabetes, hypertension and high cholesterol.
- Consider including a variety of colorful fruits and vegetables in your meals, opting for whole grains, and choosing lean proteins.
- Your health is a long-term investment, and making nutritious food choices is a great way to ensure a healthier, happier future.

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Interactive chatbot text groups

- People who live to be 100 eat a healthy diet, including whole grains, beans, fruits, and vegetables. They also eat less meat and cheese overall. Here is a good starter list of the healthiest food to eat: https://www.ucsfhealth.org/education/top-ten-foods-for-health. (This links to the website with the list of healthy foods)
- If you find it expensive to buy healthy food, you are not alone. 1 in 3 people in Colorado struggle to afford food. Hunger Free Colorado is a great resource for information on local food pantries & for info on help to pay for food & programs to bring meals to you. (This links to Hunger Free CO)
- You're making great choices with foods lower in calories, fat & sugar, but high in fiber & protein are great. Like this chicken fajita recipe for example: https://www.mayoclinic.org/healthy-lifestyle/recipes/chicken-fajitas/rcp-20049943. Chicken breasts are low fat & high protein; recipes with vegetables are low calorie & high fiber.

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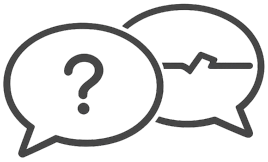
Misunderstood and off-topic patient messages

- "I don't have a family here just me"
- "Is the survey sent to my email?"
- "Is someone going to call me about this study?"
- "Who's this?"
- "Is this chat monitored by a human?"
- "Who are you?"
- "How can I slow down cod?"
- Chatbot often struggled to respond to prompts like these



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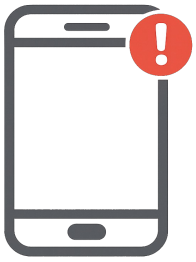
In case of emergency

- Patient: "Just curious—are you a real person or an AI?"
- Chatbot response: "I am a chatbot (not a real person). For help from our team, please call (303) 436-6000 between 8 and 5 during the week. Call 911 if you have a medical emergency."



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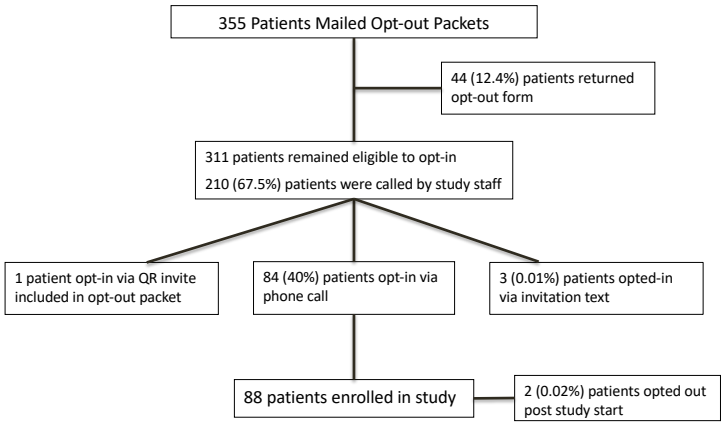
Enrollment process

- Patients mailed study info packet, including study information, opt-out form, opt-in form with QR code, and study phone number
- If patient does not opt out of study, need to get opt-in to study text messages
  - EHR invitation message
  - Study staff calls patients
  - EHR-enabled text message

Enrollment experience from UG3 pilot



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Outcomes

- Primary outcome:
  - Change in LE8 measure at 7 and 12 months
- Secondary outcomes
  - Individual components of the LE8
  - Patient self-efficacy
  - Clinical events
- Anticipated sample size
  - 2097 patients

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Welcome

SPEAKER

Emily O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Welcome

Emily O'Brien, PhD
Associate Professor in Population Health Sciences
Duke University

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Learning objectives

Clarify	Describe the **characteristics and utility** of embedded pragmatic clinical trials (ePCTs)
Demystify	Introduce the unique **opportunities and challenges** of designing, conducting, and implementing ePCTs within healthcare systems
Innovate	Explore how the latest **information capabilities** can be employed in ePCTs to address important public health questions

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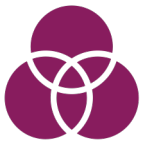
Workshop sessions: Part 1



Opportunities for Embedded Pragmatic Clinical Trials (ePCTs)

Wendy Weber

Engaging and Aligning With Partners

Emily O'Brien

ePCT Design

Patrick Heagerty

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Workshop sessions: Part 2

Innovative Methods in ePCTS

Angelo Volandes

ePCTs in Context

Sebastian Tong, Michael Ho

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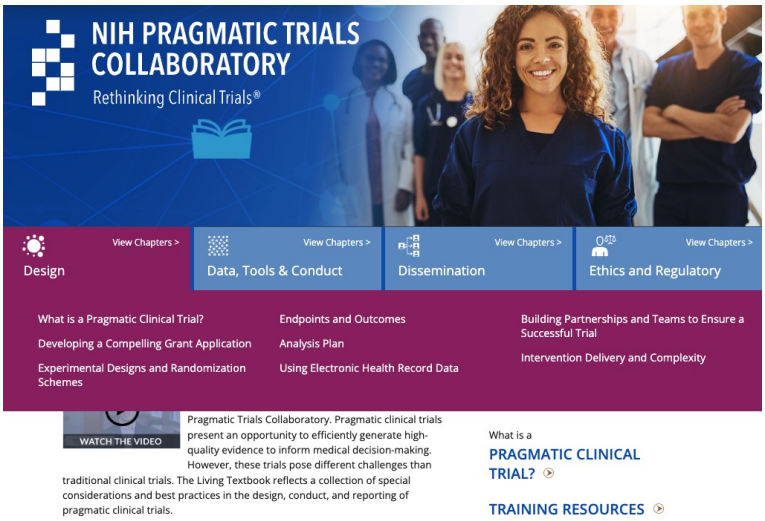
Resource: Living Textbook of Pragmatic Clinical Trials

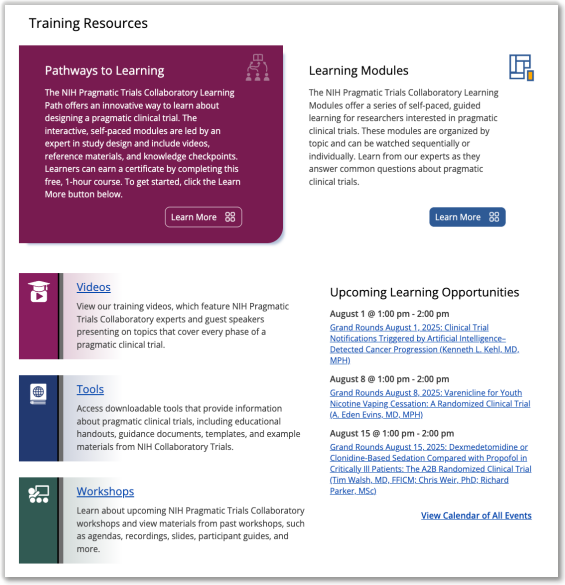


Visit
rethinkingclinicaltrials.org

ePCT Training Resources

rethinkingclinicaltrials.org/training-resource/

- Learning pathways
- Learning modules
- Video library
- Tools (handouts, checklists, guides, etc.)
- Workshop materials (slides, recordings, etc.)
- Upcoming opportunities



Rethinking Clinical Trials® Grand Rounds

- Weekly webinars
  - **Fridays, 1:00-2:00 pm ET**
  - Open to public
  - >570 held to date
  - >150 attendees/session
  - Timely, high-interest topics
  - Feature NIH Collaboratory work and beyond

Learn more:

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https://impactcollaboratory.org

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About you

- **What best matches your professional position?**
  - Academic faculty
  - Clinician or healthcare system leadership
  - Research support staff
  - Student or trainee
  - Other

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About you

- **Where are you in your career track?**
  - Student
  - Postdoctoral fellow
  - New faculty (K award, early-stage investigator, etc)
  - Established faculty (associate or full professor)
  - Other

About you

- **What is experience conducting pragmatic trials in healthcare systems?**
  - Curious about pragmatic trials, but have not conducted one yet
  - Planning a pragmatic trial now
  - Conducting my first pragmatic trial now
  - Have conducted many pragmatic trials
  - What is a pragmatic trial?

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Opportunities for Embedded Pragmatic Clinical Trials (ePCTs)

SPEAKER

Wendy Weber, ND, PhD, MPH

Acting Deputy Director
National Center for Complementary and Integrative Health

Opportunities for Embedded Pragmatic Clinical Trials (ePCTs)

Wendy Weber, ND, PhD, MPH
Acting Deputy Director
National Center for Complementary and Integrative Health

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Disclosures

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Learning goals

- Identify key considerations in design and conduct of ePCTs and how they differ from explanatory trials
- Learn about the advantages and disadvantages of ePCTs and when they can be used to answer research questions
- Introduce the intersection between ePCTs and innovative information capabilities

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Important things to know

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

Broad engagement and support are essential from beginning to end

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

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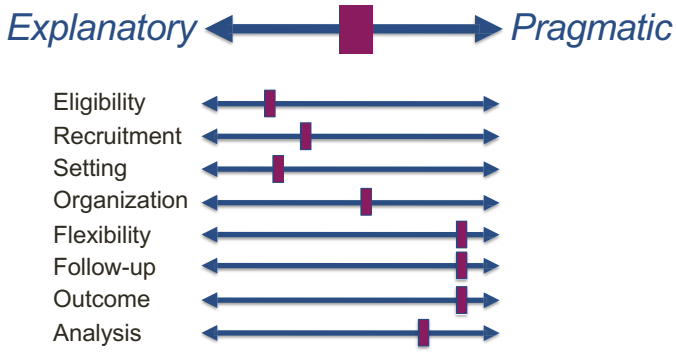
Trials elements vary across a spectrum



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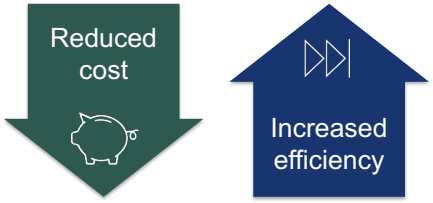
Why conduct ePCTs?

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



vs traditional trials

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ePCT characteristics

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

Why Do an ePCT? The 5 Rs

Relevant Question	Real-World Setting	Representative Population	Routinely Collected Data	Rigorous Methods
The question is pressing, and healthcare system leaders, patients, and front-line clinicians care about the answer.	Desire to test in diverse healthcare delivery settings with the hope of implementing findings widely.	Ability to recruit a population reflective of patients with the condition, including those from minoritized communities.	Can use data collected as part of healthcare delivery to answer the question, supplemented by data from other sources.	Randomized research is needed to answer the question and inform changes in care, policy, or reimbursement.

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

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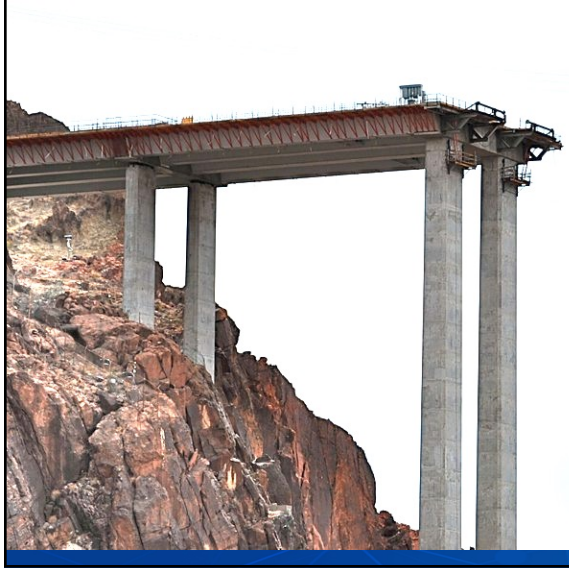
Problems



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

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

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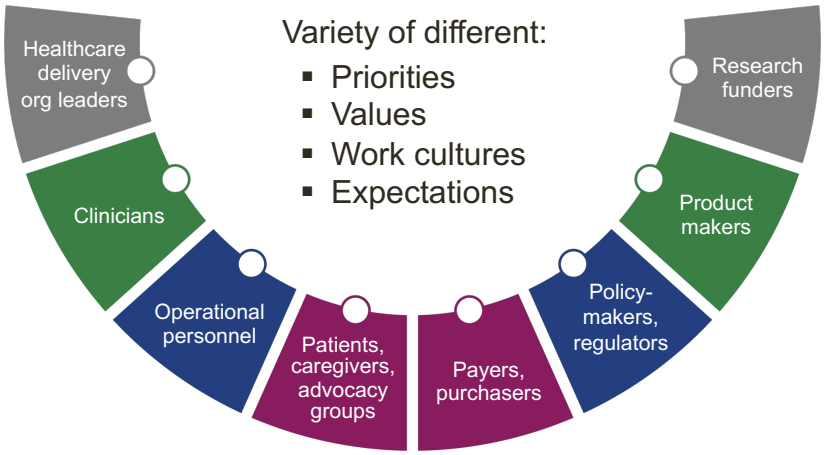
Who is interested and involved?



Variety of different:

- Priorities
- Values
- Work cultures
- Expectations

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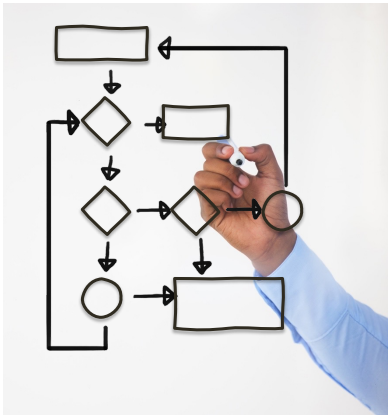
Use existing workflows



> *"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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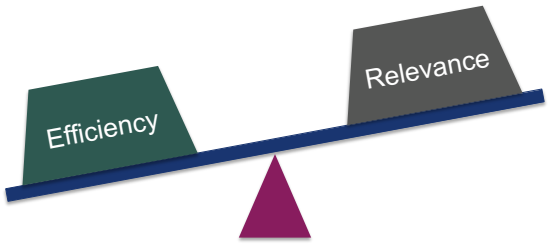
It's a balancing act



ePCTs want to achieve both

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

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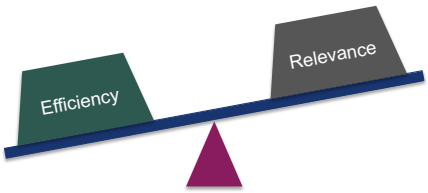
Example



Trial seeks to measure outcomes that matter most to patients and health systems + Information needed not available from the EHR = Must assess patient-reported outcomes, which are more expensive and less efficient

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ePCTs and innovative information capabilities

- Plan for infrastructure and expertise needs when incorporating innovative technologies and information capabilities into a trial
- Understand the ways ePCTs are well-suited for evaluating implications of innovative technologies for clinical care delivery
- Consider how the latest information capabilities, such as AI, can enhance ePCTs, and think through the ethical considerations

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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 life cycle of your ePCT
- Show appreciation and celebrate accomplishments early and often to have sustained partnerships

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Question & Answer

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Resources

Opportunities for Embedded Pragmatic Clinical Trials (ePCTs)

Living Textbook Readings

- What Is a Pragmatic Clinical Trial?
- Incorporating Implementation Research Into PCTs

Rethinking Clinical Trials Grand Rounds Webinars

- Pragmatic and Explanatory Attitudes to RCTs: Using the PRECIS-2 Tool to Describe the Design of the MyTEMP Trial (Ahmed Al-Jaishi, PhD; Amit Garg, MD, PhD, Merrick Zwarenstein, MBBCh, MSc, PhD)
- FDA Draft Guidance on Real-World Evidence (John Concato, MD, MS, MPH)
- Pragmatic and Explanatory Attitudes to RCTs: Using the PRECIS-2 Tool to Describe the Design of the MyTEMP Trial (Ahmed Al-Jaishi, PhD; Amit Garg, MD, PhD, Merrick Zwarenstein, MBBCh, MSc, PhD)

Key Journal Articles

- Gordon KS, Peduzzi P, Kerns RD. Designing trials with purpose: Pragmatic clinical trials of nonpharmacological approaches for pain management. *Pain Med*. 2020 Dec 12;21(Suppl 2):S7-S12. PMID: 33313727.
- Johnson KE, Neta G, Dember LM, et al. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. *Trials*. 2016 Jan 16;17:32. PMID: 26772801.
- Weinfurt KP, Hernandez AF, Coronado GD, et al. Pragmatic clinical trials embedded in healthcare systems: Generalizable lessons from the NIH Collaboratory. *BMC Med Res Methodol*. 2017 Sep 18;17(1):144. PMID: 28923013.

- Cocoros NM, Gurwitz JH, Cziraky MJ, et al. Pragmatic guidance for embedding pragmatic clinical trials in health plans: Large simple trials aren't so simple. *Clin Trials*. 2023 Aug;20(4):416-424. PMID: 37322894.
- Green T, Bosworth HB, Coronado GD, et al. Factors affecting post-trial sustainment or de-implementation of study interventions: A narrative review. *J Gen Intern Med*. 2024 May;39(6):1029-1036. PMID: 38216853.
- Fortney JC, Curran GM, Lyon AR, Check DK, Flum DR. Similarities and differences between pragmatic trials and hybrid effectiveness-implementation trials. *J Gen Intern Med*. 2024 Jul;39(9):1735-1743. PMID: 38627320.
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Engaging and Aligning With Partners

SPEAKER

Emily O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Engaging and Aligning With Partners

Emily O'Brien, PhD
Associate Professor in Population Health Sciences
Duke University

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Learning goals

- Consider the breadth of individuals to engage as partners and approaches for engaging them throughout the study
- Discuss the importance of working with partners to plan for posttrial activities
- Identify infrastructure and expertise needs for cutting-edge information capabilities in ePCTs

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Approaching partners in traditional clinical trials

Researcher reviews the literature

↓

Research presents the idea to other researchers who understand the theory and can see how study fills gap

↓

Researcher designs and conducts study, prepares manuscripts

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ePCTs work differently.

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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 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, and engage partners continuously

Be patient: Relationships take time to build and nurture

Expect changes and disruptions

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Who will be affected? Who are the decision-makers?

Potential partners 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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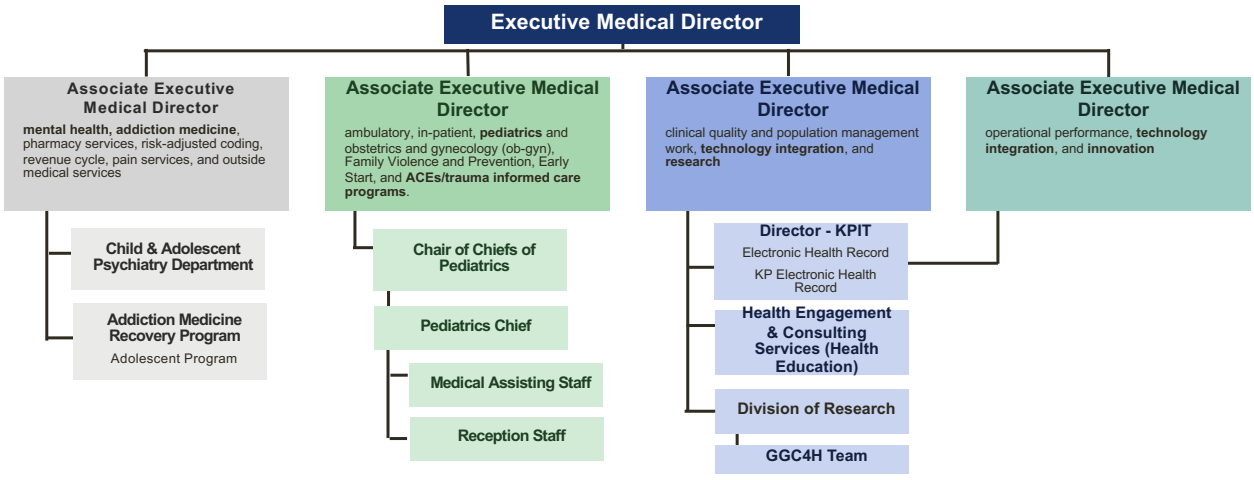
Kaiser Permanente Northern California



<u>Guiding Good Choices for Health:</u> The study team engaged with all of these partners within the The Permanente Medical Group at Kaiser Permanente Northern California. These partners 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

Roles of partners

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

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Roles of partners

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

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Choose 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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Design the intervention for sustainment

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Design the intervention to minimize burden for patients and clinicians

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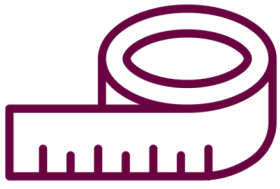
Select outcome measures



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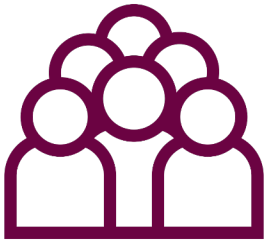
Determine inclusion and exclusion criteria



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Roles of partners

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

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Develop recruitment strategies

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Example: Community advisory board

- Feedback from OPTIMUM's Community Advisory Board
  - Make materials more diverse and visually appealing
  - Include more of "mindfulness" theme in recruitment materials
  - Highlight benefits of participating in study
- Response from study team
  - New posters and updated study website
  - Quarterly newsletter
  - Study animation video

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Example: Patient advisory panel

- Old name
  - LS7 Bot and Backup: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Simple 7 Health Behaviors
- New name suggested by patient
  - Chat 4 Heart Health

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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 partners

- Designing the trial
- Successfully conducting the research
- **Disseminating the results**

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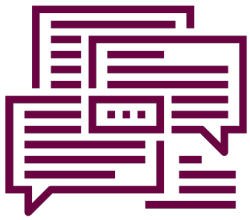
Determine key messages for different groups and identify avenues for dissemination



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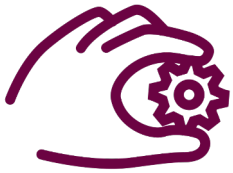
Support implementation or deimplementation



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Consider changes to policies and guidelines

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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 life cycle of your ePCT
- Show appreciation and celebrate accomplishments early and often to have sustained partnerships

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Q&A

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Knowledge checkpoint

- Why is it essential to engage partners early, even before the study design phase?
  1. To meet regulatory requirements
  2. To build relationships and ensure alignment with healthcare system goals
  3. To increase data collection efficiency

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Knowledge checkpoint

- Who are some of the key partners researchers should consider when designing and conducting ePCTs?
  1. Only clinicians
  2. Patients and caregivers, healthcare organization leaders, policymakers
  3. Laboratory staff only

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Knowledge checkpoint

- What is a critical aspect researchers should remember when partnering with healthcare systems for ePCTS?
  1. Researchers should lead all study decisions independently
  2. The healthcare system's primary goal is to provide good healthcare, not conduct research
  3. Engagement is only necessary during study recruitment

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Resources

Engaging and Aligning With Health System and Community Partners

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

- Integrating Research Into Health Care Systems: Executives' Views (Eric Larson MD, MPH; Karin Johnson, PhD)
- Pragmatic Clinical Trials and Learning Health Care Systems: Strategies to Facilitate Implementation of Results Into Clinical Care (Eric B. Larson, MD, MPH; Leah Tuzzio, MPH)
- BeatPain Utah: Partnering With Community Health Centers Within a Socio-Technical Framework (Julie Fritz, PT, PhD, FAPTA; Guilherme Del Fiol, MD, PhD)
- FM-TIPS Community Engagement Methods for Recruitment (Dana Dailey PT, PhD; Heather Schacht Reisinger, PhD)
- Significance in ePCTs: *P* Values vs Decision-Maker Perspectives (Gregory E. Simon, MD, MPH; Susan Huang, MD, MPH; Elizabeth Turner, PhD)

Key Journal Articles

- Johnson KE, Tachibana C, Coronado GD, et al. A guide to research partnerships for pragmatic clinical trials. *BMJ*. 2014 Dec 1;349:g6826. PMID: 25446054.

- Whicher DM, Miller JE, Dunham KM, Joffe S. Gatekeepers for pragmatic clinical trials. Clin Trials. 2015 Oct;12(5):442-8. doi: 10.1177/1740774515597699. PMID: 26374683.
- Larson EB, Tachibana C, Thompson E, et al. Trials without tribulations: Minimizing the burden of pragmatic research on healthcare systems. *Healthc (Amst)*. 2016 Sep;4(3):138-41. PMID: 27637816.
- Concannon TW, Grant S, Welch V, et al. Practical guidance for involving stakeholders in health research. *J Gen Intern Med*. 2019 Mar;34(3):458-463. PMID: 30565151.
- Tuzzio L, Larson EB, Chambers DA, et al. Pragmatic clinical trials offer unique opportunities for disseminating, implementing, and sustaining evidence-based practices into clinical care: Proceedings of a workshop. *Healthc (Amst)*. 2019 Mar;7(1):51-57. PMID: 30594497.
- Tuzzio L, Larson EB. The promise of pragmatic clinical trials embedded in learning health systems. *EGEMS (Wash DC)*. 2019 Apr 3;7(1):10. PMID: 30972359.
- Tuzzio L, Meyers CM, Dember LM, et al. Accounting for quality improvement during the conduct of embedded pragmatic clinical trials within healthcare systems: NIH Collaboratory case studies. *Healthc (Amst)*. 2021 Jun;8 Suppl 1(Suppl 1):100432. PMID: 34175091.

Other Resources

- ePCT Quick Start Guide for Researcher and Healthcare System Leader Partnerships
- Communicating With Health System Partners During the Lifecycle of a Trial

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ePCT Design

SPEAKER

Patrick Heagerty, PhD

Professor of Biostatistics
University of Washington

ePCT Design

Patrick Heagerty, PhD
Professor of Biostatistics
University of Washington

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Learning goals

- Identify common experimental designs and randomization schemes in ePCTs
- Understand the importance of monitoring adherence and fidelity
- Discuss design considerations to ensure delivery of actionable evidence, including why ePCTs are well-suited to evaluating implications of innovative technologies for clinical care delivery
- Provide an overview of effectiveness-implementation hybrid trial designs

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Design Considerations

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Three kinds of randomized trials

- Traditional randomized controlled trials (RCTs)
- Individual randomized group treatment (IRGT) trials
- Cluster randomized trial (CRTs)
  - Parallel CRT
  - Stepped-wedge CRT

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Methods for pragmatic trials

- As with traditional RCTs:
  - State a hypotheses
  - Prespecify the analyses
  - Calculate the sample size needed for desired power
  - Consider restricted randomization (such as stratified randomization)
  - Determine what data on participant characteristics will be collected
  - Anticipate sources of heterogeneity
- The trial design you choose will depend on the research question and how the intervention will be delivered

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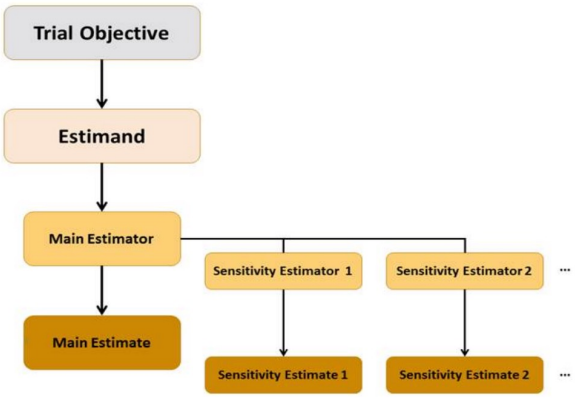
Start with a clear research question

Elements of a research question:

- **P**opulation
- **I**ntervention
- **C**omparisons
- **O**utcomes
- **T**iming
- **S**etting



Source: European Medicines Agency, ICH E9 (R1): Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Important things to know

Studies that randomize groups, or deliver interventions to groups, face special design and analytic challenges

Failure to address challenges of outcome clustering in design and analysis will result in an underpowered study and/or invalid inferences

Appropriate designs and analytic methods are the only way to advance the science

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Three kinds of randomized trials

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OPTIMUM, an NIH Collaboratory Trial

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

Optimizing Pain Treatment In Medical Settings Using Mindfulness (OPTIMUM)

- Intervention: Group-based, mindfulness-based stress reduction to reduce pain and opioid use
- Population: 450 adults with chronic low back pain
- Unit of randomization: individual
- Group-based online intervention; groups must be formed by study team; postrandomization interactions between participants
- **Individually randomized group treatment (IRGT) trial**, because post-randomization groupings potentially induce correlated outcomes

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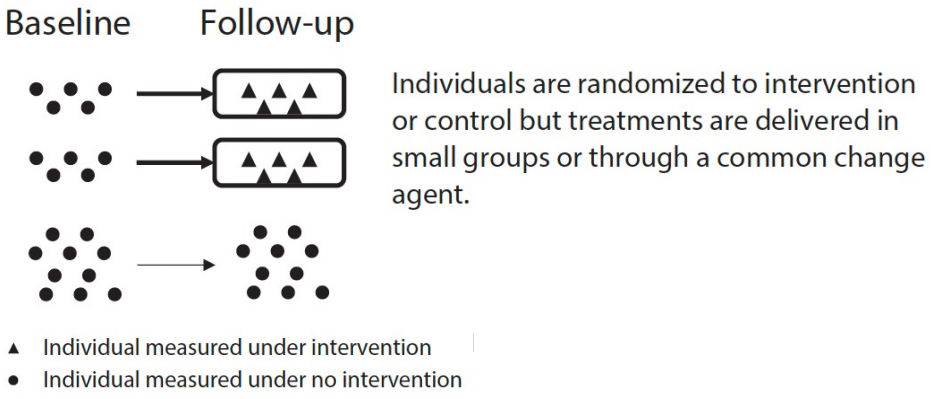
IRGT trial design in OPTIMUM



From Turner et al. *Am J Public Health*. 2017;107(6).

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Three kinds of randomized trials

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  - Parallel CRTs
  - Stepped-wedge CRTs

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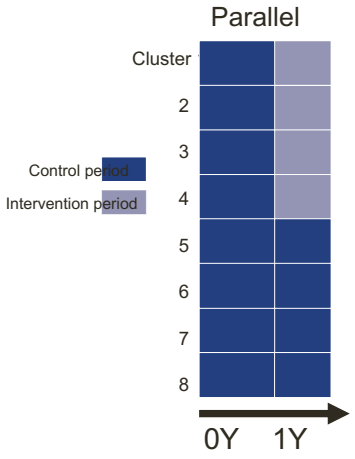
In this example:
- 8 clusters
- 1-year intervention



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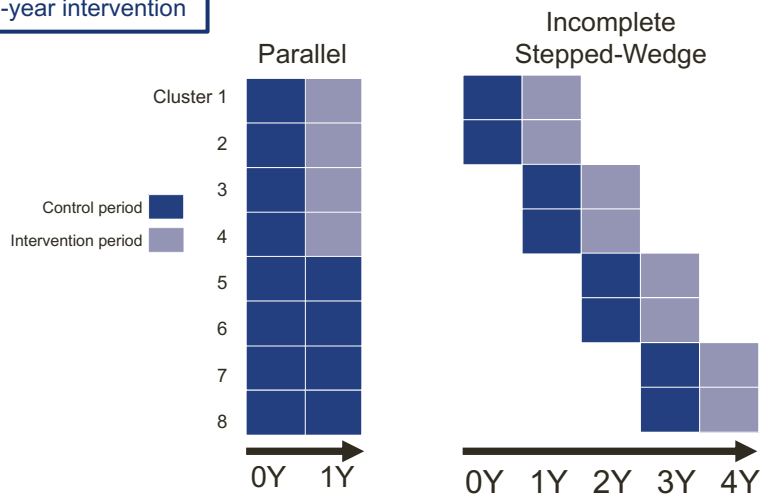

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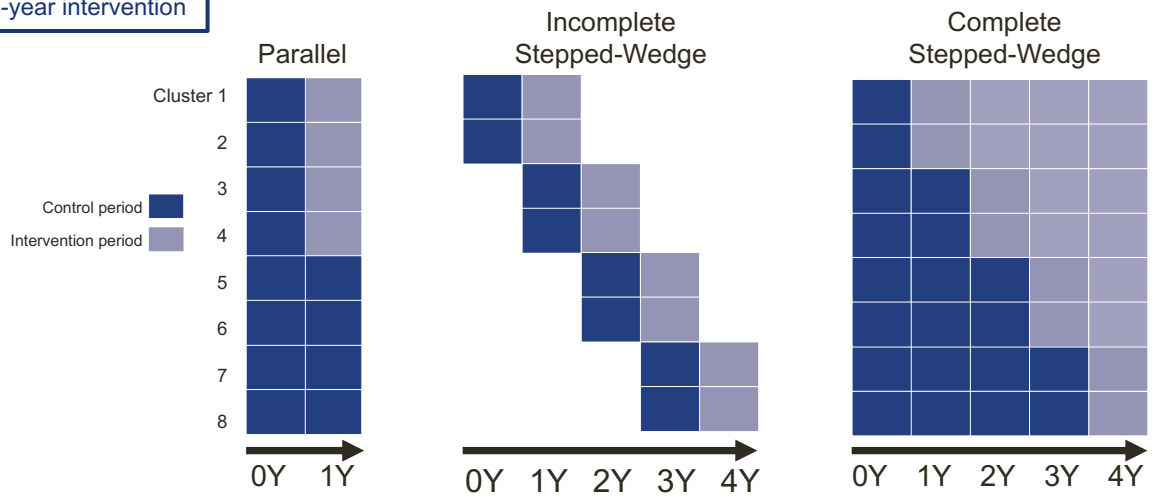
In this example:
- 8 clusters
- 1-year intervention



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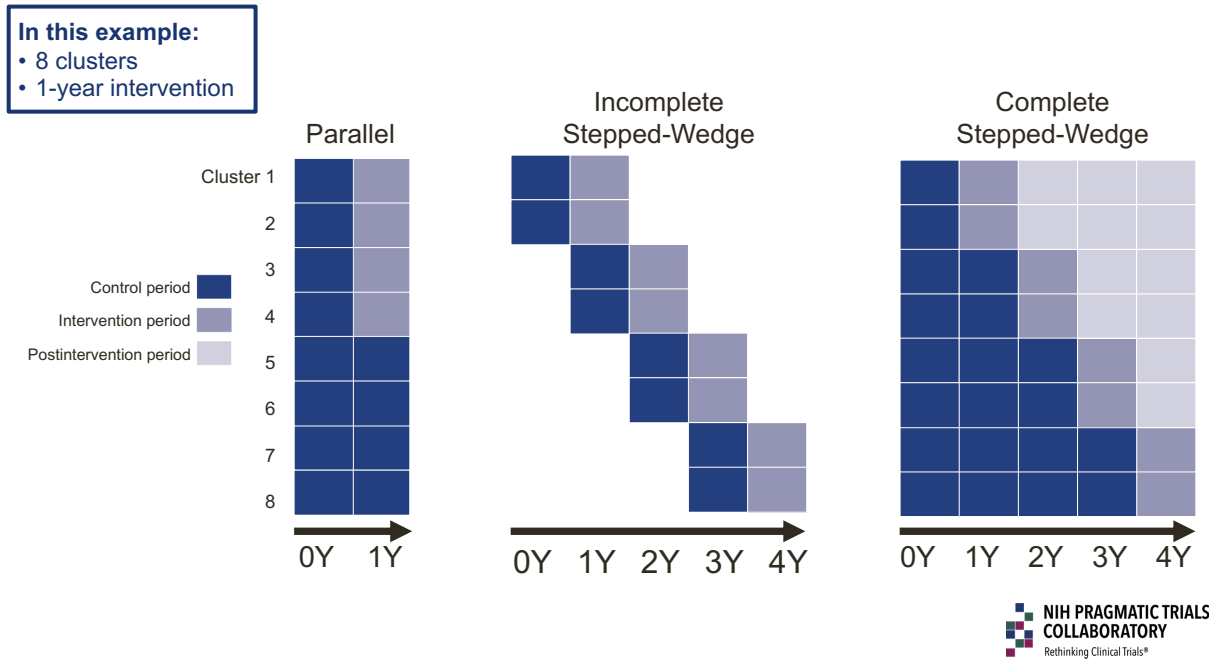

Three kinds of randomized trials

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STOP CRC, an NIH Collaboratory Trial

Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations (STOP CRC)

- Population: More than 40,000 patients at 26 clinical sites
- Intervention: Healthcare system–based program to improve rates of colorectal cancer screening
- Unit of randomization: clinic
- Two-arm **cluster randomized trial (CRT)**

Reasons to randomize clusters instead of individuals

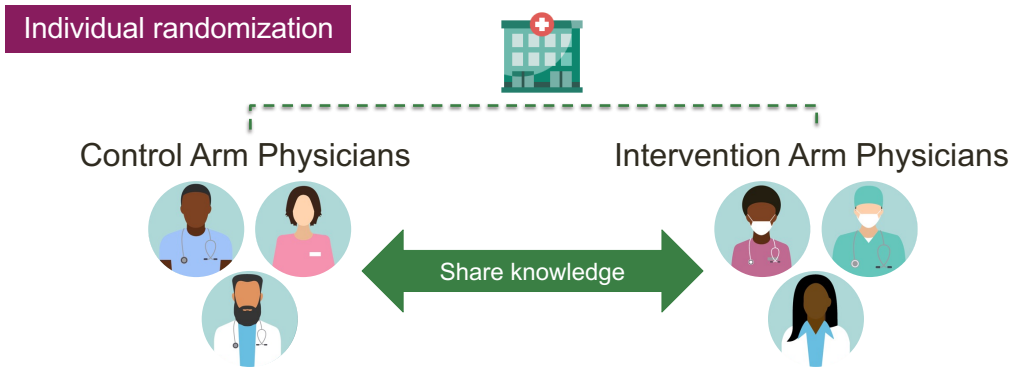
- The intervention targets healthcare units rather than individuals

Healthcare Units

Individuals

Reasons to randomize clusters instead of individuals

- The intervention targets individuals, but there is risk of contamination



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Reasons to randomize clusters instead of individuals

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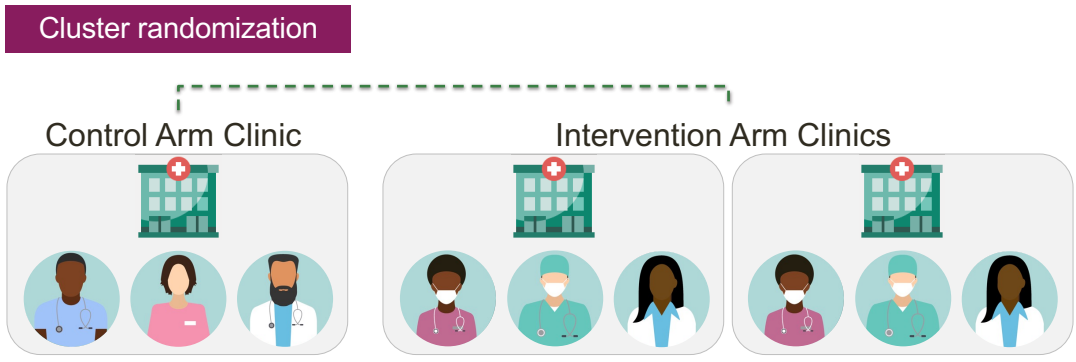

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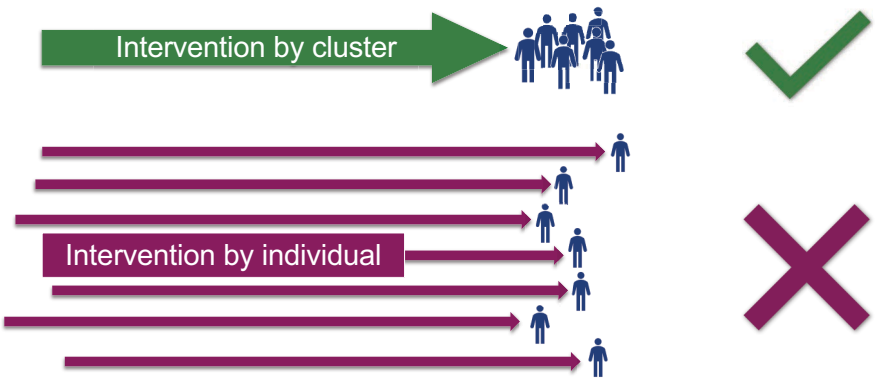
Reasons to randomize clusters instead of individuals

- Logistically easier to implement the intervention by cluster



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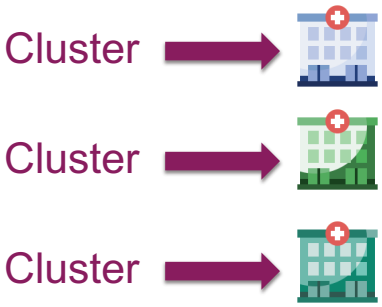
Cluster randomization in the STOP CRC trial

stop screen to prevent colon cancer

Target population	40,000 patients across 26 clinical sites
Intervention	Health system–based program to improve colorectal cancer screening rates



Level 2

Randomize at the level of the clinic

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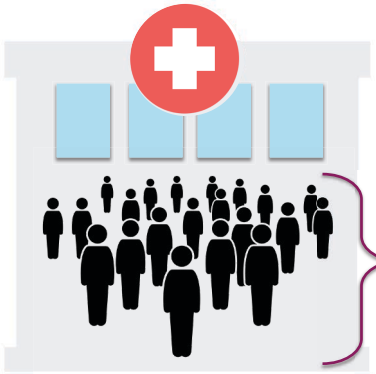
Cluster randomization in the STOP CRC trial

stop screen to prevent colon cancer

Target population	40,000 patients across 26 clinical sites
Intervention	Health system–based program to improve colorectal cancer screening rates



Level 1

Patient-level outcomes are nested within the clinic

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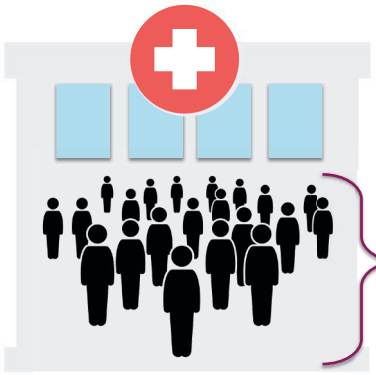
Cluster randomization in the STOP CRC trial

stop screen to prevent colon cancer

Target population	40,000 patients across 26 clinical sites
Intervention	Health system–based program to improve colorectal cancer screening rates



STOP CRC outcomes

Did the patients agree to be screened for colorectal cancer?

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stop screen to prevent colon cancer

Individual outcomes within the same clinic are expected to be correlated

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stop screen to prevent colon cancer

Clustering = Outcome Clustering


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes

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stop screen to prevent colon cancer

STOP CRC outcomes

Did the patient agree to be screened for colorectal cancer?

Binary outcome → Yes No

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  - **Stepped-wedge CRTs**

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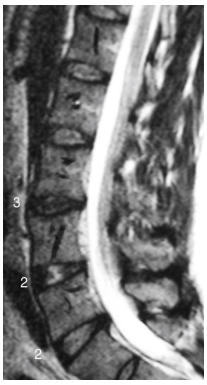
LIRE, an NIH Collaboratory Trial

Lumbar Imaging With Reporting of Epidemiology (LIRE)

- Population: 250,401 patients in 98 primary care clinics in 4 large healthcare systems
- Intervention: Insert benchmark information about common imaging findings in lumbar spine imaging reports to reduce spine-related healthcare utilization
- Unit of randomization: clinic
- All clinics will eventually receive intervention
- **Stepped-wedge CRT**



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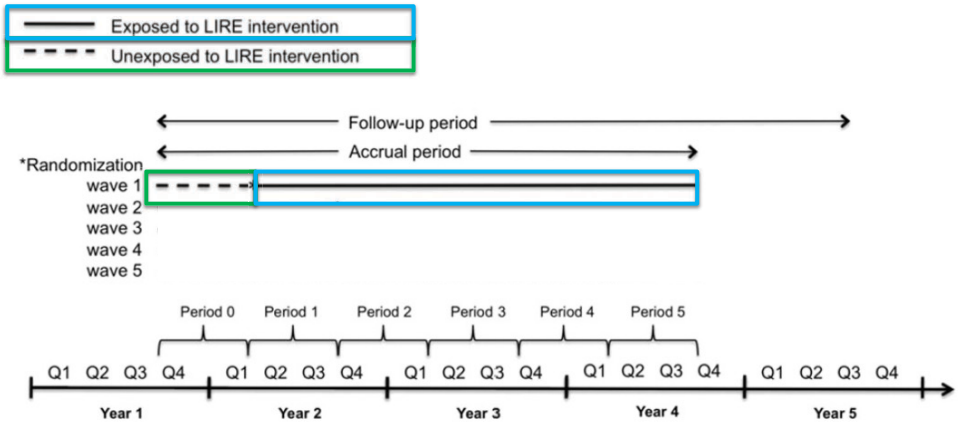
Design of LIRE trial



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

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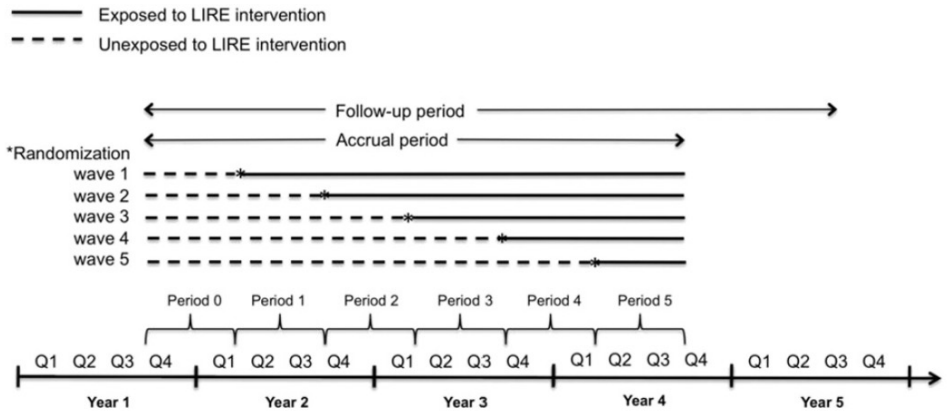
Design of LIRE trial



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

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Important things to know about many pragmatic and implementation trials

Studies that randomize groups, or deliver interventions to groups, face special design and analytic challenges

Failure to address challenges of outcome clustering in design and analysis will result in an underpowered study and/or invalid inferences

Appropriate designs and analytic methods are the only way to advance the science

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Knowledge checkpoint

- Researchers are interested in the effect of participation in support groups vs usual care on weight loss. The intervention involves attending group meetings, while usual care involves no group meetings. Out of 20 enrolled participants, 10 are randomly assigned to the intervention and attend support groups. Two therapists each lead a support group that meets on different weekday nights. Participants' BMI will be measured at baseline (before randomization) and at 3 months.
  - What design is this trial?
  - Researchers powered this study assuming an randomized controlled trial with 20 participants. How is the power likely to change if the IRGT nature of the trial is properly accounted for?
  - What would be better approach to address correlated observations: Increase the caseloads of the 2 therapists, or increase the number of therapists leading support groups?

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Q&A

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Resources

Design and Analysis Considerations

Living Textbook Readings

- Biostatistics and Study Design Core
- Experimental Designs and Randomization Schemes
- Analysis Plan

Rethinking Clinical Trials Grand Rounds Webinars

- Guidelines for Design and Analysis of Stepped-Wedge Trials (James P. Hughes, PhD)
- Linking Design to Analysis of Cluster Randomized Trials: Covariate Balancing Strategies (Fan Li, PhD)
- Lessons Learned from the NIH Collaboratory Biostatistics and Design Core (Andrea J. Cook, PhD)

Key Journal Articles

- Cook AJ, Delong E, Murray DM, Vollmer WM, Heagerty PJ. Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core. *Clin Trials*. 2016 Oct;13(5):504-12. PMID: 27179253.
- 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.
- Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. *Stat Methods Med Res*. 2021 Feb;30(2):612-639. PMID: 32631142.

- Federico CA, Heagerty PJ, Lantos J, et al. Ethical and epistemic issues in the design and conduct of pragmatic stepped-wedge cluster randomized clinical trials. *Contemp Clin Trials*. 2022 Apr;115:106703. PMID: 35176501.
- Wang X, Turner EL, Li F, et al. Two weights make a wrong: Cluster randomized trials with variable cluster sizes and heterogeneous treatment effects. *Contemp Clin Trials*. 2022 Mar;114:106702. PMID: 35123029.
- 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. 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.
- Wang X, Turner EL, Li F. Designing individually randomized group treatment trials with repeated outcome measurements using generalized estimating equations. *Stat Med*. 2024 Jan 30;43(2):358-378. PMID: 38009329.

Other Resources

- Murray DM. *Design and Analysis of Group-Randomized Trials*. New York, NY: Oxford University Press; 1998.

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Innovative Methods in ePCTS

SPEAKER

Angelo Volandes, MD, MPH

Professor and Vice Chair of Research, Department of Medicine
Dartmouth Health and Geisel School of Medicine at Dartmouth

Innovative Methods in ePCTs

Angelo Volandes, MD, MPH
Professor and Vice Chair of Research, Department of Medicine
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Disclosures

- Dr. Angelo Volandes has a financial interest in ACP Decisions, a nonprofit organization developing advance care planning video decision support tools. Dr. Volandes' interests were reviewed and are managed by Dartmouth in accordance with their conflict-of-interest policies. No other disclosures to report.

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Learning goals

- Describe methods for measuring outcomes using real-world data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
- Discuss how the latest information capabilities, such as AI, can enhance ePCTs
- Identify considerations for the use of new data technologies in ePCTs, including ethical issues

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Outcome, measure, endpoint

- **Outcome** usually refers to a variable of interest or a meaningful aspect of health (such as oxygen volume or fatigue)
- **Measure** usually refers to a specific, standardized process to obtain information on an outcome
  - Includes instructions, administration materials, content, formatting, and scoring rules

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Types of measures

- Patient-reported outcome measure (PROM)
- Observer-reported outcome measure (ObsRO)
- Clinician-reported outcome measure (ClinRO)
- Performance outcome measure (PerfO)

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Outcome, measure, endpoint

- **Endpoint** usually refers to a precisely defined variable that is statistically analyzed to address a particular research question

Examples:

- Change from baseline at 6 weeks in mean PROMIS Fatigue score
- Mean difference in PROMIS Fatigue score between patients in the intervention and usual care groups, after controlling for baseline status

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Important things to know

Outcomes and their related endpoints should be **meaningful** to providers and patients

Outcomes and related measures should be relatively **easy** to collect (ie, pragmatic)

Researchers do not control the design or data collected in EHR systems

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Choosing and specifying endpoints in ePCTs

Outcomes and related endpoints should be available as part of routine care

- Acute myocardial infarction
- Broken bone
- Hospitalization

- Suicide attempts
- Gout flares
- Silent myocardial infarction
- 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?
- Is treatment provided in inpatient or outpatient settings?
- Will the event be medically attended?

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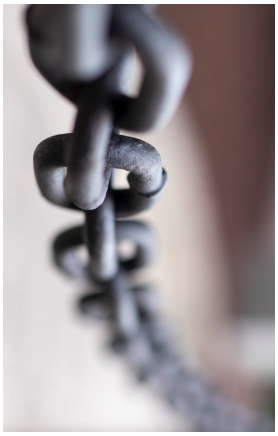
Data sources for endpoints in ePCTs

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



Weber GM, Mandl KD, Kohane IS. Finding the missing link for big biomedical data. *JAMA*. 2014 Jun 25;311(24):2479-80. doi: 10.1001/jama.2014.4228.

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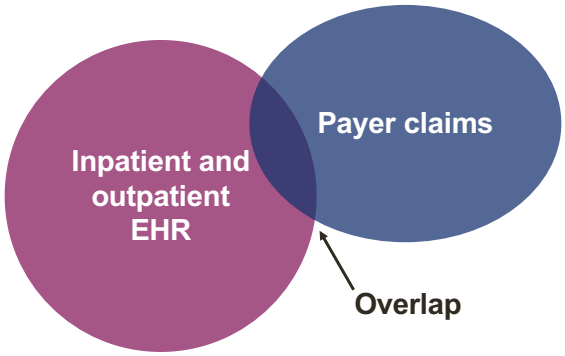
Where is the signal?

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



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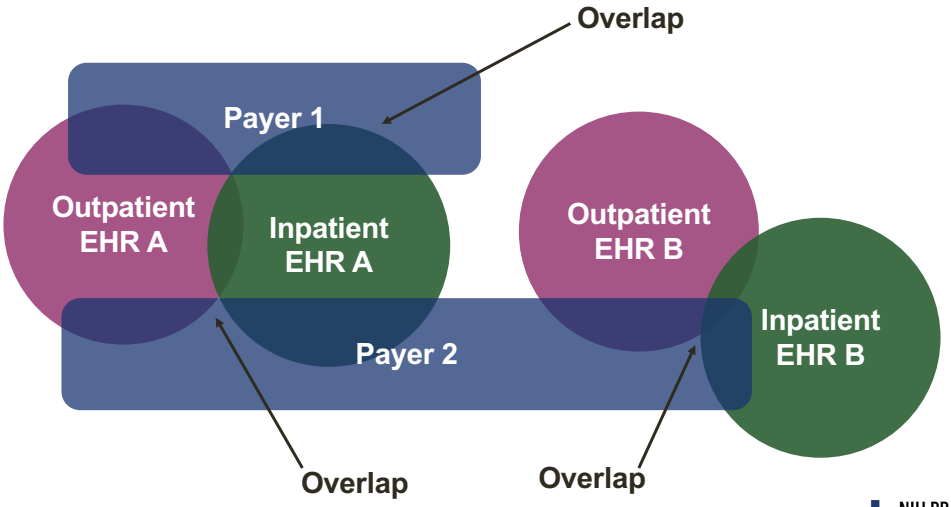
Reality is not straightforward



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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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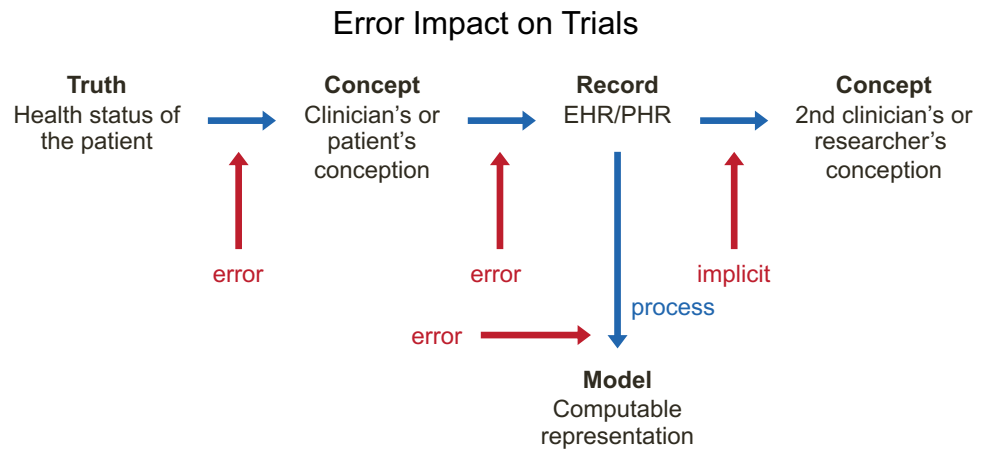
Data is a surrogate for clinical phenomena



Adapted from Hripcsak et al. J Am Med Inform Assoc. 2009 Mar-Apr;16(2):220-7.

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Data sources for endpoints in ePCTs

Traditional

- EHR or ancillary health information systems

Complementary

- Other types of health data not routinely collected outside standard clinical practice, such as PROs

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It's a balancing act

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

A trial measuring outcomes that matter most to patients and healthcare systems may not be able to rely exclusively on information from the EHR, and instead may 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 the best way to measure quality of life and often the best way to measure how patients are feeling and functioning
- Challenges
  - Not routinely or consistently used in clinical care
  - Not regularly recorded in EHR
- Need a mechanism to collect PROs

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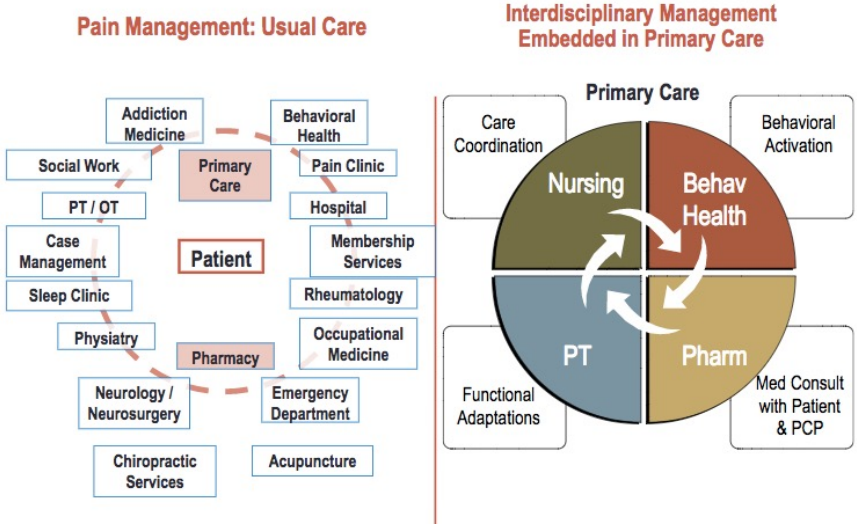
Example: PPACT Trial



Source: Lynn DeBar, Kaiser Permanente Washington Health Research Institute

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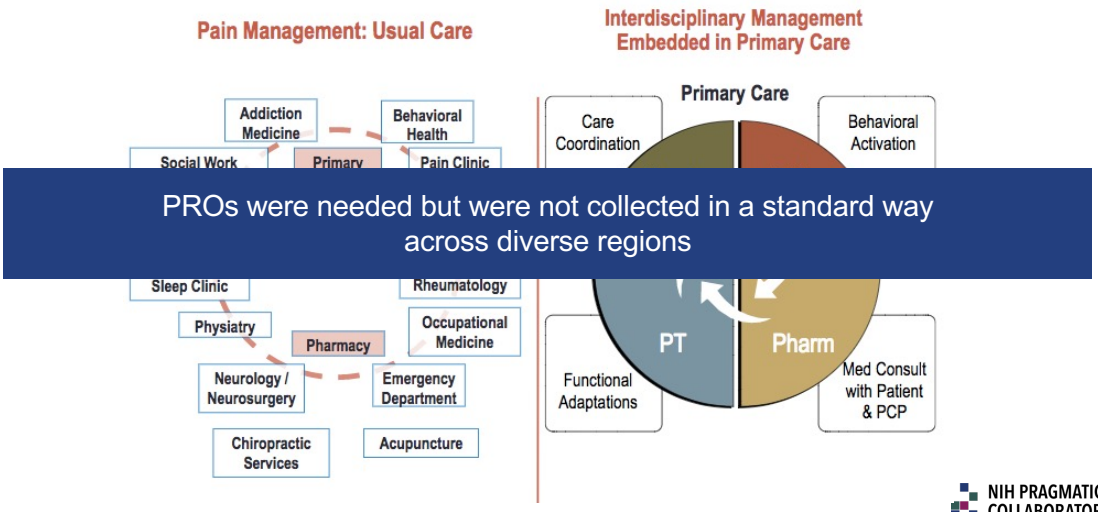
Example: PPACT Trial



PROs were needed but were not collected in a standard way across diverse regions

Source: Lynn DeBar, Kaiser Permanente Washington Health Research Institute

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Example: PPACT Trial

- Project leaders worked with national Kaiser Permanente to create buy-in for a common instrument
- Local IT staff built it within each region
- A multitiered approach supplemented PROM data collected in clinics 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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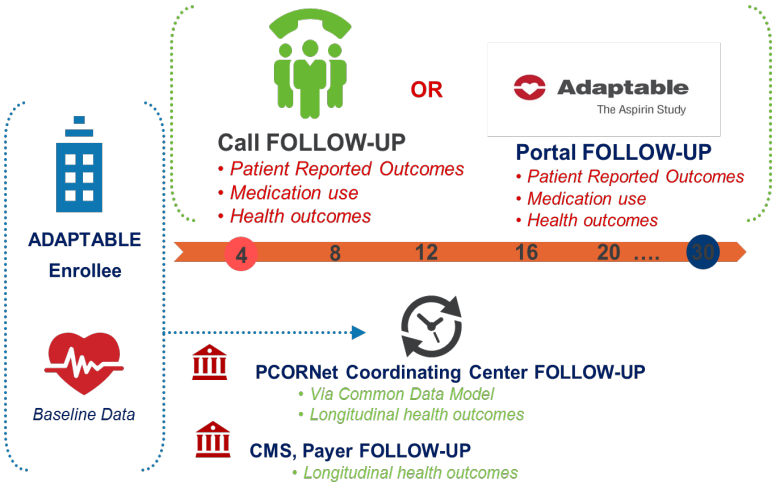
Enabling pragmatic research

E-screening, e-enrollment, and 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

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Data quality assessment

- Identify variation between populations at different sites or in different 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
- Design trials to minimize new data collection
- Talk to patients and stakeholders when identifying outcomes
- Engage EHR and data experts when defining endpoints
- Budget for data and systems experts at each site (…then double it)
- Carefully consider bias and take steps to promote generalizability
- Develop a data quality assessment plan to improve the value of the data and detect and address data issues early

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Q&A

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Knowledge checkpoint

- Getting longitudinal data from an insurance carrier does not require explicit consent from the patient.
  - True
  - False

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Knowledge checkpoint

- Suicide attempts would be a good endpoint to use in pragmatic clinical trials since they are routinely documented.
  - True
  - False

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Knowledge checkpoint

- Mobile devices are promising means of obtaining data although presently largely imperfect measures.
  - True
  - False

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Resources

Innovative Methods for ePCTs

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

- Approaches to Patient Follow-Up for Clinical Trials: What's the Right Choice for Your Study? (Keith Marsolo, PhD)
- Thoughts From the Phenotypes, Data Standards & Data Quality Core (Rachel Richesson, PhD, MPH)
- Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings From the HARMONY-Outcomes EHR Ancillary Study (Lesley Curtis, PhD; Emily O'Brien, PhD)
- Update From the Phenotypes, Data Standards, and Data Quality Core of the NIH Health Care Systems Research Collaboratory (Rachel Richesson, PhD)
- Leveraging Real-World Data in a Multinational Trial: Results From the Other eHARMONY [HARMONY Outcomes EHR Ancillary Study] (Lesley Curtis, PhD; Bradley Hammill, PhD; Sudha Raman, PhD)
- Keys to Success in the Evolving EHR Environment (Keith Marsolo, PhD; Teresa Zayas-Cabán, PhD; George (Holt) Oliver, MD, PhD; Christopher A. Longhurst, MD, MS; Rachel Richesson, PhD, MPH)

- FDA Draft Guidance on Real-World Evidence (John Concato, MD, MS, MPH)
- Navigating the Use of Patient-Reported Outcomes in Research and Practice: The PROTEUS Consortium (Claire Snyder, PhD; Norah Crossnohere, PhD; Anne Schuster, PhD)
- Searching for a Unicorn: Understanding Stakeholder Perspectives When Selecting Outcomes for Outpatient Trials (Christopher Lindsell, PhD)
- Enabling Patient-Reported Outcome Measures (PROMs) in Clinical Trials, Exemplified by Cardiovascular Trials (Theresa Coles, PhD; Kevin Weinfurt, PhD)
- Validating a Computable Phenotype: Should Results Change a Trial's Pre-Specified Primary Outcome? (Gregory E. Simon, MD, MPH, Susan M. Shortreed, PhD)

Key Journal Articles

- Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: Conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health*. 2011 Mar;38(2):65-76. PMID: 20957426.
- Curran GM. Implementation science made too simple: A teaching tool. *Implement Sci Commun*. 2020 Feb 25;1:27. PMID: 32885186.
- Lewis CC, Fischer S, Weiner BJ, Stanick C, Kim M, Martinez RG. Outcomes for implementation science: An enhanced systematic review of instruments using evidence-based rating criteria. *Implement Sci*. 2015 Nov 4;10:155. PMID: 26537706.
- Richesson RL, Green BB, Laws R, et al. Pragmatic (trial) informatics: A perspective from the NIH Health Care Systems Research Collaboratory. *J Am Med Inform Assoc*. 2017 Sep 1;24(5):996-1001. PMID: 28340241.
- Weber GM, Mandl KD, Kohane IS. Finding the missing link for big biomedical data. *JAMA*. 2014 Jun 25;311(24):2479-80. PMID: 24854141.
- Hersh WR, Weiner MG, Embi PJ, et al. Caveats for the use of operational electronic health record data in comparative effectiveness research. *Med Care*. 2013 Aug;51(8 Suppl 3):S30-7. PMID: 23774517.
- Richesson RL, Rusincovitch SA, Wixted D, et al. A comparison of phenotype definitions for diabetes mellitus. *J Am Med Inform Assoc*. 2013 Dec;20(e2):e319-26. PMID: 24026307.

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ePCTs in Context

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ePCTs in Context

Small Group Work and Panel Discussion With NIH Collaboratory Trial Investigators

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Learning goals

- Hear a brief description of the NIH Collaboratory Trials being used as case studies for the small group activity
- Small group discussion
  - Breakout into small groups
  - Each group discusses 1 question
  - Report back to the group
- Panelists discuss how they handled the challenges
- Reflect on the challenges, solutions, and lessons learned, to include Q&A

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NIH Collaboratory Trial panelists

- Sebastian Tong, MD, MPH — AIM-CP
- Michael Ho, MD, MPH — Chat 4 Heart Health

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Small group discussion

AIM-CP

- **Scenario**: The study was designed to implement remote nurse care management approach for chronic pain in rural communities, including tele-visit for care coordination, cognitive behavioral therapy, and referral to a virtual exercise program. However, when enrolling patients in the pilot phase, many patients who would otherwise be eligible declined due to lack of broadband access, inability to use digital devices, and no access to devices to connect to audiovisual meetings.
- **Discussion Prompt:** What changes to the study could help increase enrollment?

Chat 4 Heart Health

- **Scenario**: The trial was designed to use an opt-out enrollment approach, whereby eligible patients identified through the EHR would be automatically included unless they declined participation. Just before the pilot year, the FCC introduced new rules requiring opt-in consent for text messaging. As a result, participating health systems determined verbal consent would now be required before sending study-related text messages. The original enrollment target was approximately 2,100 patients.
- **Discussion Prompt:** Given this regulatory change, how would you redesign or adapt the patient enrollment strategy to meet study goals while remaining compliant?

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Reflection on today's topics

- Opportunities for pragmatic research
- Engaging and aligning with partners
- Design considerations
- Innovative methods

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Resources

ePCTs in Context

- AIM-CP: Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients with Chronic Pain
- Chat 4 Heart Health: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors

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Closing Remarks

SPEAKER

Emily O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Closing Remarks

Emily O'Brien, PhD
Associate Professor in Population Health Sciences
Duke University School of Medicine

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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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