NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Dissemination & Implementation in Embedded Pragmatic Trials:

Getting the Timing Right in Real-World Research

Participant Guide

17th Annual Conference on the Science of Dissemination and Implementation in Health

Co-hosted by AcademyHealth and National Institutes of Health

December 8, 2024

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Dissemination and Implementation in Embedded Pragmatic Trials: Getting the Timing Right in Real-World Research

17th Annual Conference on the Science of Dissemination and Implementation in Health
Co-hosted by AcademyHealth and National Institutes of Health
"Moving Fast and Slow: Optimizing the Pace of Implementation"

Crystal Gateway Marriott, Arlington
December 8, 2024

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
10:00 – 10:10 a.m.	**Welcome** **Opening Remarks**	Emily O'Brien	• Welcome and introduction of agenda, objectives, and Living Textbook
10:10 – 10:40 a.m.	**What are Embedded Pragmatic Clinical Trials (ePCTs)?**	Beda Jean-Francois	• Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials • Learn about the advantages and disadvantages of ePCTs, when a pragmatic approach can be used to answer the research question • Q & A with attendees
10:40 – 11:10 a.m.	**Objectives and Trial Design: An Overview of Hybrid Designs**	Devon Check	• Overview of the 3 types of effectiveness implementation hybrid trial designs and when they may be appropriate for ePCTs • Q & A with attendees

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
11:10 – 11:40 a.m.	**Engaging with Health System and Community Partners**	Hayden Bosworth	• Describe the breadth of individuals to engage as partners and approaches for engaging them through all phases of the study • Identify skills needed for a strong study team and consider the diversity of the team, including inclusive practices • Understand the real-world priorities and perspectives of healthcare system leaders and how to obtain their support • Identify engagement practices to obtain patient and community perspectives • Highlight challenges of partnering with diverse healthcare systems • Q & A with attendees
11:40 a.m. – 12:40 p.m.	**ePCTs in Context: Small Group Work Followed by Panel Discussion with NIH Collaboratory Trial PIs**	**Moderator:** Angelo Volandes **Panel:** Andrea Cheville Julie Fritz Mike Ho Sebastian Tong	• Introduce PIs of ongoing ePCTs and hear a brief overview of each trial • Have attendees work in small groups to discuss challenges faced by ongoing ePCTs • PIs discuss how they handled the challenges from attendees' discussion, reflect on the morning topics, and discuss lessons learned • Q & A with attendees
12:40 – 1:40 p.m.	**Lunch**		• Networking among attendees and presenters
1:40 – 2:00 p.m.	**Measuring Outcomes**	Angelo Volandes	• Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) • Discuss the integration of a health equity lens in evaluating outcomes • Q & A with attendees
2:00 – 2:30 p.m.	**ePCT Design**	Jonathan Moyer	• Learn about cluster randomized and stepped-wedge study designs • Q & A with attendees

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
2:30 – 3:00 p.m.	**ePCT Analysis**	Jonathan Moyer	• Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what principal investigators (PIs) need to know • Q & A with attendees
3:00 – 3:10 p.m.	**Break**		• Networking among attendees and presenters
3:10 – 3:40 p.m.	**Pilot & Feasibility Testing**	Beda Jean-Francois	• Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions • Q & A with attendees
3:40 – 4:10 p.m.	**Ethical & Regulatory Oversight Considerations**	Stephanie Morain	• Learn about the regulatory and ethical challenges of conducting ePCTs • Discuss unique needs of historically underrepresented and mistreated groups • Q & A with attendees
4:10 – 4:40 p.m.	**Writing a Compelling Grant Application**	Beda Jean-Francois	• Learn how to develop a compelling ePCT application • Tips from Collaboratory PIs • Q & A with attendees
4:40 – 5:40 p.m.	**ePCTs in Context: Small Group Work Followed by Panel Discussion with NIH Collaboratory Trial PIs**	**Moderator:** Stephanie Morain **Panel:** Andrea Cheville Julie Fritz Mike Ho Sebastian Tong	• Have attendees work in small groups to discuss challenges faced by ongoing ePCTs • PIs discuss how they handled the challenges from attendees' discussion, reflect on the afternoon topics, and discuss lessons learned • Q & A with attendees
5:40 – 5:50 p.m.	**Closing Remarks**	Emily O'Brien	• Wrap-up including identifying sources for further learning

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Speaker Biographies

Hayden B. Bosworth, PhD
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Hayden B. Bosworth, PhD, is a health services researcher and implementation scientist. He is currently a professor of population health sciences, medicine, psychiatry, and nursing at Duke University and the vice chair of research in the Department of Population Health Sciences. He is also the deputy director of the Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT) (COIN) at the Durham Veterans Affairs Medical Center and adjunct professor in the Department of Health Policy and Administration in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. His research interests comprise 3 overarching areas of research: 1) conducting clinical research that improves chronic disease self-management care; 2) implementing research to improve access to quality of care; and 3) eliminating health care disparities. Dr. Bosworth has expertise in developing and implementing scalable/sustainable interventions to improve health behaviors and reduce the burden of chronic diseases. These trials/programs focus on motivating individuals to initiate health behaviors and sustain them long term. He also has ample experience in conducting observational studies examining healthcare use and predictors of medication nonadherence. Current examples of his work include a multisite trial evaluating a nurse-administered intervention to extend the HIV treatment cascade for cardiovascular disease prevention (EXTRA-CVD) and a similar study being conducted in the VA (VA-EXTRA-CVD).

Dr. Bosworth is the recipient of numerous awards, including an American Heart Association Established Investigator award, a VA Senior Career Scientist Award, and the Under-Secretary's Award for Outstanding Achievement in Health Services Research. He has been the principal investigator of over 30 trials resulting in over 450 peer-reviewed publications and 4 books. His work has been implemented in Medicaid of North Carolina, the UK National Health System, Kaiser Permanente, the Veterans Health Administration, as well as by a number of health care payers such as Humana.

In addition to his research experience, mentoring is an area to which he has devoted significant effort. He has mentored over 140 graduate students, postdoctoral fellows, and junior faculty, including 28 career development awardees over the last 10 years. In addition, he is the principal investigator of a K12 National Heart, Lung, and Blood Institute–funded grant to train faculty in dissemination and implementation.

Devon Check, PhD
Duke University School of Medicine
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Devon Check, PhD, is a health services and implementation researcher. She is an Assistant Professor in the Department of Population Health Sciences at Duke and a member of the Duke Cancer Institute. Her primary research interests are quality of care and implementation of evidence-based practices in oncology. Dr. Check's work combines quantitative and qualitative methods to understand and address barriers to the delivery of high-quality, equitable care during and after cancer treatment. Dr. Check also has methodological expertise in implementation science, including hybrid effectiveness-implementation trial design. She co-leads the Implementation Science Core Working Group as part of the Coordinating Center for the NIH Pragmatic Trials Collaboratory.

Andrea Cheville, MD, MS
Mayo Clinic
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Dr. Andrea Cheville is a Professor of Physical Medicine and Rehabilitation and is the medical director for the Patient-Centered Outcomes Program in the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery at Mayo Clinic in Rochester, MN. She is a former Chair of the Department of Physical Medicine and Rehabilitation at Mayo Clinic, Rochester, MN. She received her MD degree from Harvard Medical School in 1993 and her Master of Science in Clinical Epidemiology degree from the University of Pennsylvania in 2006. She is board-certified in Physical Medicine and Rehabilitation, Pain Medicine, and Palliative Care. She has received funding from the National Institutes of Health, National Cancer Institute, and the U.S. Department of Defense. She was elected to the National Institute of Medicine in October 2016. Her areas of clinical and research interest are lymphedema and cancer rehabilitation, palliative medicine, and patient-reported outcomes. She has over 200 articles published in peer-reviewed journals.

Julie Fritz, PhD, PT
University of Utah
Julie.fritz@utah.edu

Julie Fritz, PhD, PT, is a distinguished professor in the Department of Physical Therapy and Athletic Training and the associate dean for research in the College of Health at the University of Utah located in Salt Lake City. Her research has focused on examining nonpharmacologic treatments for individuals with spinal pain, including clinical trials and health services research. Currently, Dr. Fritz is leading projects funded by PCORI and the NIH including projects funded under the NIH HEAL Initiative addressing pain management and opioid use. She also leads a trial within the NIH-VA-DoD Pain Management Collaboratory investigating nonpharmacologic pain management in the Military Health System.

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) and a Senior Clinician Investigator at the 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 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 also serves as the medical director for the IMPROVE Program at Kaiser Permanente Colorado.

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 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.

Beda Jean-Francois, PhD
National Center for Complementary and Integrative Health (NCCIH)
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Beda Jean-Francois, PhD, is a program director in the Clinical Research Branch in the Division of Extramural Research of the NCCIH. She oversees a portfolio of clinical research, including health disparities, pediatric research on mental and emotional well-being, maternal morbidity and mortality, and pragmatic clinical trials. Additionally, she contributes to the Mental, Emotional, and Behavioral (MEB) initiatives as well as the NIH Pragmatic Trials Collaboratory, the NIH HEAL Initiative, and the Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) program.

Dr. Jean-Francois is especially passionate about reducing children's health disparities. Other research interests include life-course perspective on health and disease, behavioral health prevention services, health information technology, reproductive health equity, and childhood obesity. Before joining NCCIH, Dr. Jean-Francois served as an NIH health scientist administrator at the National Institute on Minority Health and Health Disparities (NIMHD) since 2017. While at NIMHD, she served as a co-lead for the data coordinating center for the trans-NIH Rapid Acceleration of Diagnostics for Underserved Populations (RADxUP), which is a consortium of more than 85 multidisciplinary grantees working to target disparities in COVID-19 morbidity and mortality. She developed multiple funding opportunities, including Effectiveness of School-Based Health Centers to Advance Health Equity, Addressing Racial Disparities in Maternal Mortality and Morbidity, and Leveraging Health Information Technology to Address Health Disparities. Additionally, she served as project scientist for Center of Excellence research grants to promote research in health disparities and the training of a diverse scientific workforce.

Stephanie Morain, PhD, MPH
Johns Hopkins University
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Stephanie Morain, PhD, is a core faculty member at the Berman Institute of Bioethics, and an associate professor in the Department of Health Policy and Management at the Bloomberg School of Public Health. She conducts both empirical and normative research into issues at the intersection of ethics, law, and health policy. Dr. Morain's work examines political and ethical issues concerning the scope of government authority in public health and the role of stakeholder opinion in shaping decision-making in public health policy. Specific research interests include the ethics and politics of disease control and injury prevention; public health law; and ethical and policy challenges presented by the transition to learning health care systems. She was most recently an assistant professor in the Center for Medical Ethics and Health Policy at Baylor College of Medicine.

A former Hecht-Levi Postdoctoral Fellow at the Berman Institute, Dr. Morain received her BA from Lafayette College with a dual major in Biology and History, Government, & Law, her MPH from Columbia University's Mailman School of Public Health, and her PhD from Harvard University's Interfaculty Initiative in Health Policy.

Jonathan Moyer, PhD
NIH Office of Disease Prevention
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Jonathan Moyer, PhD, is a statistician with the NIH Office of Disease Prevention and focuses on efforts to enhance the rigor and reproducibility of NIH-funded prevention research by promoting the use of the best available research methods. This includes expanding the resources available on NIH's Research Methods Resources website, providing guidance on the Methods: Mind the Gap Webinar Series, and collaborating with NIH Institutes and Centers on projects that require group randomization or delivery of interventions to groups.

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

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

Sebastian Tong, MD, MPH
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Sebastian Tong is a practicing family physician and addiction medicine specialist. He is an Assistant 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 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
Harvard Medical School
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Angelo Volandes, MD, MPH, is a physician, researcher, filmmaker, and author. He is an associate professor at Harvard Medical School and Massachusetts General Hospital, and co-founder of ACP Decisions Nonprofit Foundation. He is an internationally recognized expert on the use of video decision support tools, decision science, and ethics. He leads an internationally recognized group of innovators and video artists who create video support tools to better inform patients about their options for medical care.

His work has been funded by the National Institute on Aging, the National Cancer Institute, the National Institute of Nursing Research, the National Heart, Lung, and Blood Institute, the NIH Common Fund, the Agency for Healthcare Research and Quality, the Alzheimer's Foundation, and the Gordon and Betty Moore Foundation, among others.

Dr. Volandes's work has been featured in major publications and national media and he is the author of *The Conversation: A Revolutionary Plan for End-of-Life Care*. He lectures widely around the country.

Born and raised in Brooklyn, New York, he is a proud product of the New York City public school system. He went on to receive his undergraduate degree in philosophy from Harvard, a medical degree from Yale, and a master's degree in public health from Harvard. In 2005, he was named the Edmond J. Safra Fellow at the Harvard University Center for Ethics.

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GOAL

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

WHAT ARE EMBEDDED PRAGMATIC CLINICAL TRIALS (EPCTS)?

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

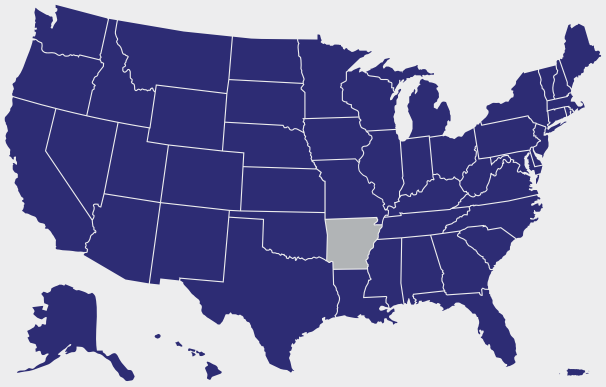
PROGRAM

NIH COLLABORATORY TRIALS: ePCTs that address questions of major public health importance and provide proof of concept for innovative pragmatic research designs

CORES: Working groups that support the conduct of NIH Collaboratory Trials and generate guidance addressing implementation challenges

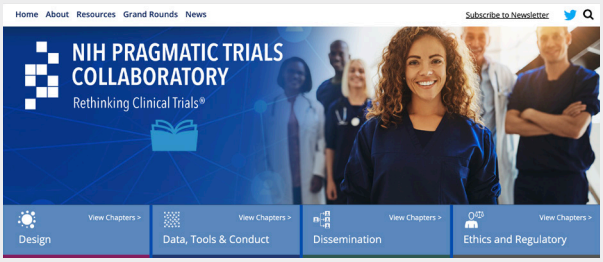
32 NIH COLLABORATORY TRIALS

- Conducted in partnership with healthcare systems
- Studying diverse clinical areas spanning 14 NIH Institutes and Centers
- >1100 clinical sites across 49 US States and Puerto Rico; >940,000 active subjects



RESOURCES

Living Textbook of Pragmatic Clinical Trials
Comprehensive resource on ePCTs



DESIGN describes how to plan an ePCT, including biostatistical and study design considerations, using electronic health record data, and building study teams and partnerships

DATA, TOOLS & CONDUCT describes tips for study startup, participant recruitment, data collection, and intervention delivery and monitoring

DISSEMINATION describes data sharing, dissemination, and implementation approaches

ETHICS AND REGULATORY describes issues related to privacy, informed consent, collateral findings, data and safety monitoring, and more

Plus:

- Grand Rounds webinars and podcasts
- Monthly NIH Collaboratory newsletter

Visit the Living Textbook: www.rethinkingclinicaltrials.org

This work was supported within the National Institutes of Health (NIH) Pragmatic Trials Collaboratory through cooperative agreement U24AT009676 from the National Center for Complementary and Integrative Health, the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Institute on Aging, the National Heart, Lung, and Blood Institute, the National Institute of Nursing Research, the National Institute of Minority Health and Health Disparities, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the NIH Office of Behavioral and Social Sciences Research, and the NIH Office of Disease Prevention. This work was also supported by the NIH through the NIH HEAL Initiative under award number U24AT010961.

HOW IS A CLINICAL TRIAL CONSIDERED PRAGMATIC?

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

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

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

Visit the Living Textbook:
www.rethinkingclinicaltrials.org

DCRI COMMUNICATIONS 26JAN2024

Case Studies

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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; and
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 Institute Providing 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 2 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
Assistant Professor of Family Medicine
Associate Director, WWAMI region Practice and Research Network
University of Washington

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Objectives

To adapt and test a nurse care management (NCM) model to provide comprehensive 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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Study aims

- Engage patients, clinicians, and care managers from 2 health systems in a learning collaborative to pilot the NCM model
- Adapt infrastructure and workflows to implement the intervention program and engage the partnering health systems in developing relationships with community partners and identifying care managers
- In the UH3 phase, conduct a randomized controlled trial of the adapted NCM model vs usual care in rural-dwelling patients with chronic pain

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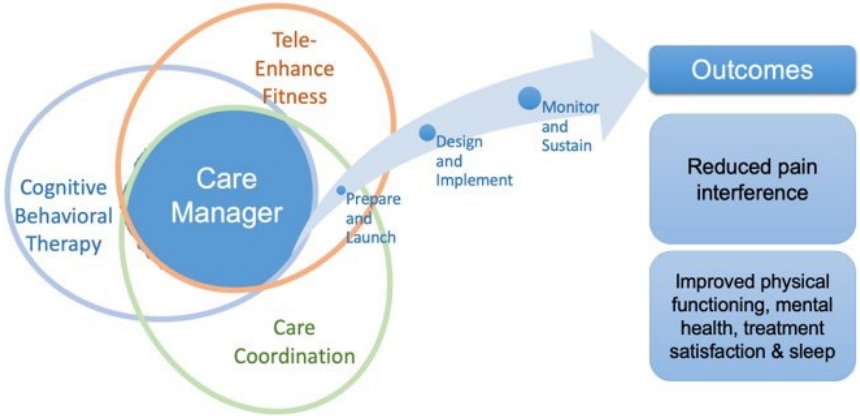
Strategy

- Type 2 hybrid effectiveness-implementation trial



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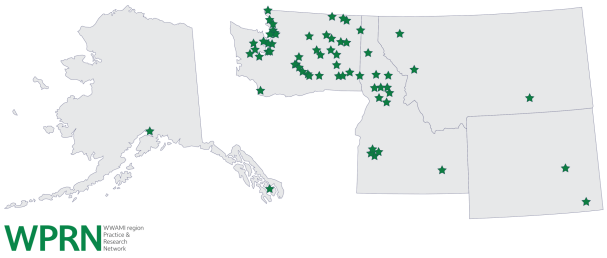
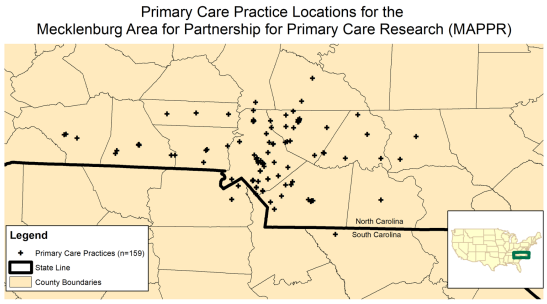
Setting





Intervention details

Individual component	Description
Care Coordination	• Assessing patients for social service, behavioral health, and specialty care needs • Linking patients with community resources • Tracking and supporting patients when care received outside health system • Coordinating behavioral health and specialty care • Using PainTracker to develop goals of care, track progress, and refine treatment plans
Cognitive Behavioral Therapy	• 6-10 weekly to every-other-week sessions with care manager to develop strategies to change maladaptive cognition and behaviors around pain
Tele-Enhance Fitness	• Remotely delivered, instructor-led, group exercise program for 1-hour, 2-3 times weekly

Barriers/challenges

Workforce

- Nursing workforce shortage
- Overall workforce shortage

Trust/polarization

- Urban-rural divide
- Framing of research outcomes, variables, and intervention

Regulatory

- Lack of familiarity
- Different expectations

Solutions/lessons learned

Workforce

- Flexibility in care manager background
- Defer site participation, discuss intervention as strategy to alleviate workforce shortage

Trust/polarization

- Use local staff for most contact
- Partner with staff/investigators who understand rural issues, build on existing relationships
- Open listening/discussion

Regulatory

- Open discussion
- Flexibility in trial design, identifying core elements of intervention

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BEATPAIN Utah

Nonpharmacologic Pain Management in Federally Qualified Health Center Primary Care Clinics (BeatPain Utah)

Principal Investigator
Julie Fritz, PhD, PT

Sponsoring Institution
University of Utah

Collaborator
Association for Utah Community Health

NIH Institute Providing Oversight
National Institute of Nursing Research (NINR)

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

Project Scientist
Joe Bonner, PhD (National Institute of Child Health and Human Development [NICHD]/National Center for Medical Rehabilitation Research [NCMRR])

ClinicalTrials.gov Identifier
NCT04923334

ABSTRACT

Chronic pain is a growing concern for society, contributing substantially to the ongoing opioid epidemic. Back pain is the most common chronic pain diagnosis and is the most common reason for prescribing opioids. Clinical practice guidelines and opioid prescribing recommendations make it clear that nonpharmacologic pain treatments are preferable to opioids for patients with back pain, yet overprescribing of opioids to individuals with back pain persists. Primary care providers serving rural and low-income communities face specific challenges to providing nonpharmacologic pain care. Nonpharmacologic care providers are often absent from these communities, and even if present may be inaccessible to patients with limited resources. Many rural and low-income communities are served by federally qualified health centers (FQHCs). FQHCs often serve communities at the forefront of the opioid crisis but too often lack options to provide accessible nonpharmacologic alternatives to the patients they serve.

BeatPain Utah is an embedded pragmatic clinical trial that will compare the effectiveness of nonpharmacologic intervention strategies for patients with back pain seeking care in FQHCs throughout the state of Utah. The strategies evaluated are designed to overcome the barriers specific to rural and low-income communities served by FQHC clinics through the innovative use of e-referral and telehealth resources. The BeatPain Utah interventions include:

- A telehealth strategy that provides a brief pain teleconsult along with phone-based physical therapy.
- An adaptive strategy that provides the brief pain teleconsult first, followed by phone-based physical therapy among patients who are nonresponsive to treatment.

The study will also evaluate implementation outcomes to inform future efforts to scale effective strategies into other low-resource health care settings.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Choosing analysis procedures that will best account for therapist effects in the study	The study team met internally to modify the statistical analysis and reporting plan to manage this concern. The NIH Collaboratory's Biostatistics and Study Design Core Working Group devoted 2 meetings to helping the study team with solutions for this concern.
Working with FQHC primary care clinics that have been particularly stressed by the demands of the COVID-19 public health emergency in low-resource settings	The study team adapted some of its engagement procedures and remains in regular communication with study sites to balance advancing the project with the demands that clinics are facing related to COVID-19, including both clinical services and retaining clinical personnel.

"Accelerating the real-world applicability of our research is particularly critical in this area of clinical research. To address the needs of populations that need resources—and they need them now—a pragmatic trial that focuses on real-world solutions was a particularly attractive option."

SELECTED PUBLICATIONS & PRESENTATIONS

- PCT Grand Rounds Presentation: BeatPain Utah: Partnering With Community Health Centers Within a Socio-Technical Framework (2023)
- Presentation: Presentation to the NIH Pragmatic Trials Collaboratory Steering Committee (2023)
- Article (Study Design): BeatPain Utah: Study Protocol for a Pragmatic Randomised Trial Examining Telehealth Strategies to Provide Non-pharmacologic Pain Care for Persons With Chronic Low Back Pain Receiving Care in Federally Qualified Health Centers (2022)

Access the complete set of BeatPain Utah resources.

BeatPain Utah: Nonpharmacologic Pain Management in Federally Qualified Health Centers Primary Care Clinics

Julie M. Fritz, PhD, PT
Distinguished Professor of Physical Therapy and Athletic Training
University of Utah

BEATPAIN Utah

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Objectives

- Compare effectiveness of nonpharmacologic interventions for patients with back pain seeking care in federally qualified health centers (FQHCs) in Utah
  - Telehealth strategy that provides a brief pain consult along with telehealth physical therapy
  - Adaptive strategy that provides the brief pain consult first, followed by telehealth physical therapy for patients who are non-responders
- Strategies are designed to overcome barriers specific to rural and lower-income communities served by FQHC clinics
- Study also evaluates implementation outcomes to inform future efforts to scale effective strategies into other settings

NIH PRAGMATIC TRIALS COLLABORATORY
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Goal and strategy

- Improve pain management and reduce reliance on opioids for patients with chronic back pain in FQHCs in Utah
- Hybrid type I effectiveness-implementation trial
  - Compare the effectiveness of first-line nonpharmacologic pain treatments using telehealth to overcome access barriers, improve patient-centered outcomes, and reduce opioid use
  - Collect implementation outcomes for EHR-based, e-referral process and telehealth care

NIH PRAGMATIC TRIALS COLLABORATORY
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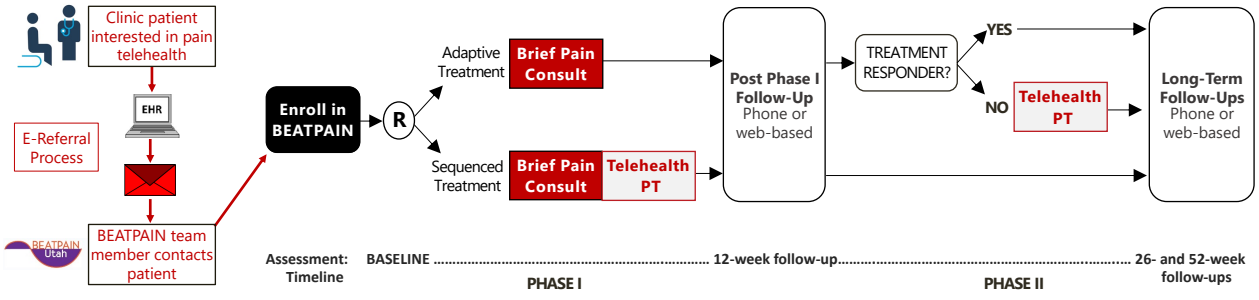
Study design



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Study aims

- Compare effectiveness of brief pain consult with or without telehealth PT (pain impact [PEG] as primary outcome; opioid use as secondary outcome)
- Compare effectiveness of telehealth PT as first-line care vs stepped care strategy as second-line care for patients who do not respond to brief pain consult
- Examine results of Aims 1 and 2 in predefined patient subgroups based on gender, HICP, and current opioid use
- Explore implementation outcomes for telehealth services (acceptability, adoption, feasibility, fidelity)

Interventions

Brief Pain Consult

- Two sessions provided in ~1 week
- Provided to all participants and nonparticipating referrals as standard of care
- Cognitive-behavioral approach to reduce maladaptive pain beliefs, increase physical activity

Telehealth Physical Therapy

- 10 weekly sessions
- Provided in Phase I or Phase II (non-responders) for enrolled participants
- Builds on BPC intervention, exercise program, goal setting, motivation and problem-solving approach

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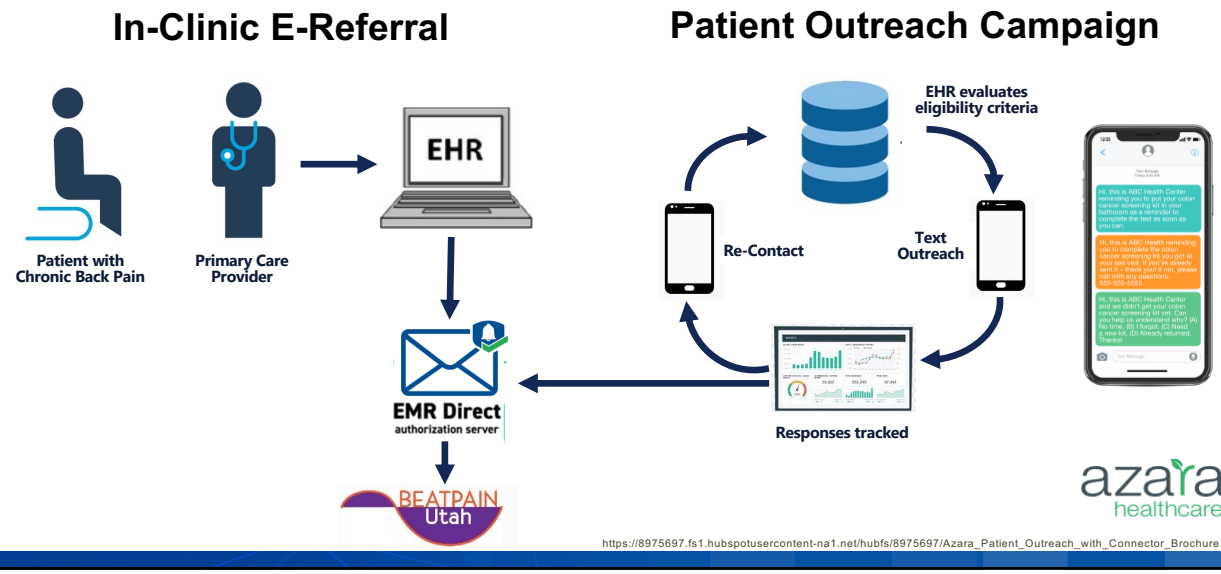
Implementation strategies



https://8975697.fs1.hubspotusercontent-na1.net/hubfs/8975697/Azara_Patient_Outreach_with_Connector_Brochure.pdf

Participating healthcare systems

AUCH ASSOCIATION FOR UTAH COMMUNITY HEALTH

U HEALTH UNIVERSITY OF UTAH

- **49%** Hispanic/Latino Ethnicity
- **9%** American Indian/Alaska Native
- **37%** Best served in a language other than English
- **66%** At or below 100% of the Federal Poverty Guidelines
- **49%** Uninsured
- **17%** Medicaid
- **10 Clinics in frontier counties** (<6 persons per sq. mile)
- **18 Clinics in rural counties** (6-100 persons per sq. mile)

Barriers/challenges

- Slower than anticipated start due to COVID
- Staffing challenges for providers and support personnel
- “Research fatigue” in FQHC settings
- Challenges in using text messaging to inform patients
- Building trust between the academic medical center and FQHC leadership, staff, and communities served
- Bringing in new FQHCs from surrounding states through the NIH CARE for Health™ program

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Solutions/lessons learned

- Improved coordination and communication among project teams conducting research in Utah FQHCs
- Greater use of population-based strategies to identify and offer referral to patients with chronic low back pain
- Knowing when to step back
- Adaptations to local needs
- Ongoing research staff training on cultural competencies and justice considerations for FQHC clinics and the communities they serve

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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
Lawrence Fine, MD, DrPH (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)

See the complete set of Chat 4 Heart Health resources.

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

Michael Ho, MD, PhD
Adjoint Professor of Medicine, University of Colorado School of Medicine
Kaiser Permanente Colorado

Chat for Heart Health

NIH PRAGMATIC TRIALS COLLABORATORY
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Objective

Improve control of cardiovascular disease risk factors using a multilevel intervention leveraging mobile phone-based text messages integrated within healthcare systems to improve control of the American Heart Association's Life's Essential 8 (LE8) lifestyle factors

Strategy

- 5-year multilevel intervention to test comparative effectiveness of 3 strategies:
  - Generic text messages
  - Interactive AI-based chatbot text messaging
    - Uses evidence-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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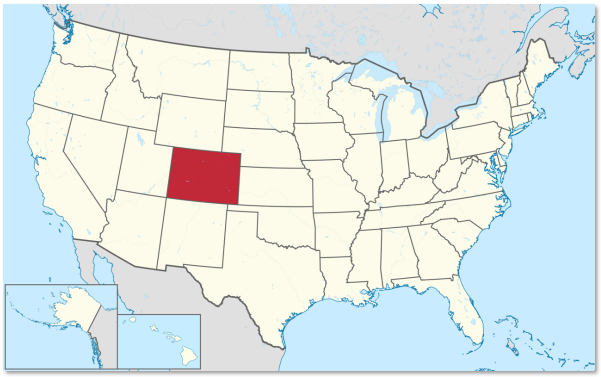
Setting

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



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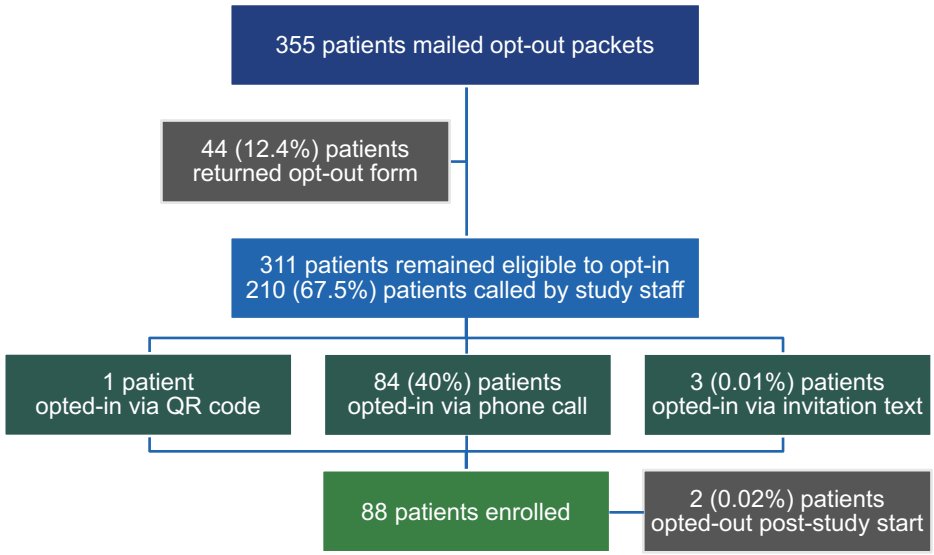
Patient identification and enrollment

Patients meeting inclusion criteria identified through EHR

Staff mail patient a packet
- Study info, opt-out form, opt-in form with QR code and phone number

Staff called patients who did not opt-out or opt-in
- Patients not reached were texted an invitation to participate

Enrolled patients can opt-out any time by texting STOP



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Barriers/challenges

- FCC regulatory change that impacts the study's ability to use an opt-out enrollment approach

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Solutions/lessons learned

- Flexibility in study design

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Nonpharmacologic Options in Postoperative Hospital-based and Rehabilitation Pain Management (NOHARM)

Principal Investigators
Andrea Cheville, MD; Jon Tilburt, MD

Sponsoring Institution
Mayo Clinic Rochester, MN

Collaborators
- Mayo Clinic Rochester
- Mayo Clinic Florida
- Mayo Clinic Arizona
- Mayo Clinic Upper Midwest Health System

NIH Institute Providing Oversight
National Institute on Aging (NIA)

Program Official
Marcel Salive, MD (NIA)

Project Scientist
Theresa Cruz, PhD (National Institute of Child Health and Human Development [NICHD])

ClinicalTrials.gov Identifier
NCT04570371

ABSTRACT

Prescriptions for narcotic pain relief after surgery result in unintended prolonged opioid use for hundreds of thousands of Americans. That trend fuels an excess supply of opioids that can lead to dependence, addiction, diversion, and overdoses on a national scale. Nonpharmacologic pain care is effective and recommended by guidelines for perioperative pain while offering a more favorable risk-benefit ratio. However, nonpharmacologic pain care is rarely used as first- or second-line therapy after surgery. Patient and clinician decision support interventions are effective in encouraging patient-centered and guideline-concordant care, but these strategies have not been tested pragmatically as a bundle in everyday postoperative pain care.

The NOHARM trial will test an EHR-embedded, bundled intervention comprised of patient- and clinician-facing decision support components that enable patients to integrate nonpharmacologic pain care (NPPC) into their perioperative management. NOHARM will employ a stepped-wedge, cluster-randomized pragmatic clinical trial design. Clusters throughout Mayo Clinic Enterprise spanning 6 institutions in 4 states will participate. The NOHARM trial will evaluate whether pain and function, assessed with PROMIS tools, can be improved while honoring patient values and deemphasizing opioids in pain management.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Accurately identifying and assigning the intervention to eligible patients within the electronic health record (EHR) in an automated way	The study implemented appropriate ordering, referring, and prescribing (ORP) codes for automatic assignment.
Helping clinic staff know which patients are enrolled in the NOHARM trial	The study added a banner in the Epic system to help clinical teams easily identify NOHARM patients.
Identifying and accounting for the number and variability of clusters based on size, geography, and median pain burden of the patient population	The team worked with the Collaboratory's Biostatistics and Study Design Core to plan a "constrained randomization" design, which will help with managing varied cluster sizes, geographic locations, and practice volumes as part of the stepped-wedge cluster-randomized trial.
Modifying the primary outcome measure due to incomplete ascertainment	The team determined that pain interference and physical function measures would be co-primary endpoints at 1, 2, and 3 months.

"We are excited to bring our novel use of the EHR as a critical and central intervention component and to bring that approach to the Collaboratory so we can both teach and learn."

SELECTED PRESENTATIONS

- Presentation: Presentation to the NIH Pragmatic Trials Collaboratory Steering Committee (2023)
- Article (Study Design): Non-pharmacological Options in Postoperative Hospital-Based and Rehabilitation Pain Management (NOHARM): Protocol for a Stepped-Wedge Cluster-Randomized Pragmatic Clinical Trial (2022)
- PCT Grand Rounds Presentation: Learning While Sprinting: A One-Year Retrospective from the NOHARM Pragmatic Trial (2020)

Access the complete set of NOHARM resources.

NOHARM: Nonpharmacological Options in post-operative Hospital-based And Rehabilitation pain Management pragmatic trial

Andrea Cheville, MD, MSCE
Professor of Physical Medicine and Rehabilitation
Mayo Clinic

NIH PRAGMATIC TRIALS COLLABORATORY
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Objective

- Evaluate whether pain and function, assessed with PROMIS tools, can be improved while honoring patient values and de-emphasizing opioids in pain management

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Strategy

- Test an EHR-embedded, bundled intervention of patient- and clinician-facing decision support components that enable patients to integrate nonpharmacologic pain care into their perioperative management
- Stepped-wedge, cluster randomized pragmatic trial design

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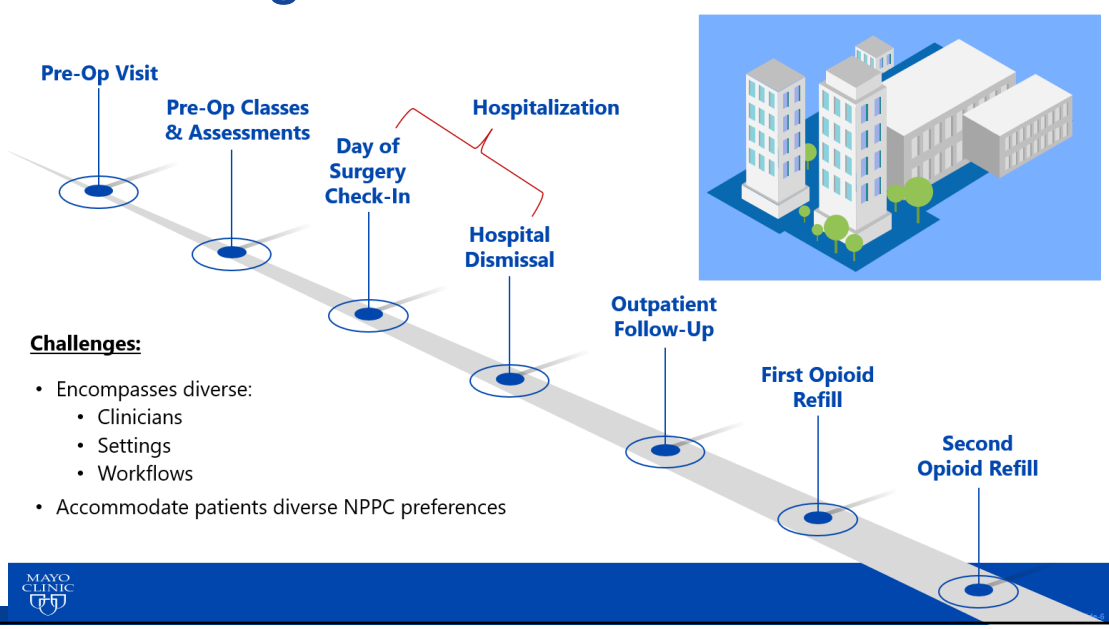
EHR to integrate NPPC use



Challenges:

- Encompasses diverse:
  - Clinicians
  - Settings
  - Workflows
- Accommodate patients diverse NPPC preferences

RIALS

MAYO CLINIC

Setting

- Clusters throughout Mayo Clinic Enterprise, spanning 6 institutions and 4 states

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Study design

	Tranche 1 **Rochester** Cardiac, C-Section **Florida** **Eau Claire** Ortho, Colorectal, Gyn, C-section **LaCrosse** Gyn, C-Section	Tranche 2 **Rochester** Ortho, Gyn, Lung **Arizona** Lung, Cardiac **Mankato** Colorectal	Tranche 3 **Rochester** Colorectal **Florida** Transplant **Arizona** Colorectal, Gyn, Transplant	Tranche 4 **Florida** Colorectal, Gyn, Lung, Cardiac **Eau Claire** Lung, Cardiac **Mankato** C-Section	Tranche 5 **Rochester** Transplant **Arizona** Ortho **Mankato** Ortho **LaCrosse** Ortho, Colorectal
Control condition	Data Collection 10/16/2020				
Step 1	Go live 3/1/2021				
Step 2		Go live 10/1/2021			
Step 3			Go live 5/1/2022		
Step 4				Go live 12/1/2022	
Step 5					Go live 7/1/2023

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Nonpharmacological pain care (NPPC)

Movement	Relaxation	Physical
• Walking • Yoga • Tai Chi	• Meditation • Relaxed breathing • Music listening • Guided imagery • Muscle relaxation • Aromatherapy	• Acupressure • Massage • Cold or heat • TENS

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Intervention

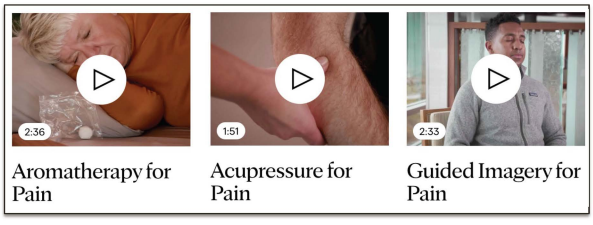
Prompt clinicians via CDS to:

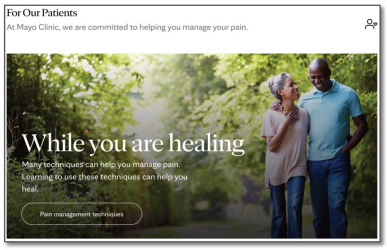
- Introduce NOHARM NPPC
- Normalize use
- Support options
- Direct patients to NOHARM resources

EHR

Direct patients via portal-based messages to:

- Learn about NPPC and opioid harms/benefits
- Select preference-concordant NPPC options
- Troubleshoot and advance NPPC use
- Access resources





Barriers/challenges

- Unpredictable EHR instability
  - Intervention assignment logic
  - PROM assignment logic
- Consistency of staffing and staff engagement
  - Turnover, cross-coverage, use of locums
- Competing staff demands
- Variable administrative and allied health engagment
- EHR data abstraction and curation

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Solutions/lessons learned

- Critical importance of scheduled, standardized EHR functionality checks
- Continued engagement and implementation
  - Effective approaches are contextual
  - Chocolate is a powerful catalyst
- Delicate balance between clinician buy-in and annoyance
- “Passive” and “scalable” are relative terms
- Culture

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Nudge

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

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

Sponsoring Institution
University of Colorado

ClinicalTrials.gov Identifier
NCT03973931

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

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

Program Official
Lawrence Fine, MD, DrPH (NHLBI)

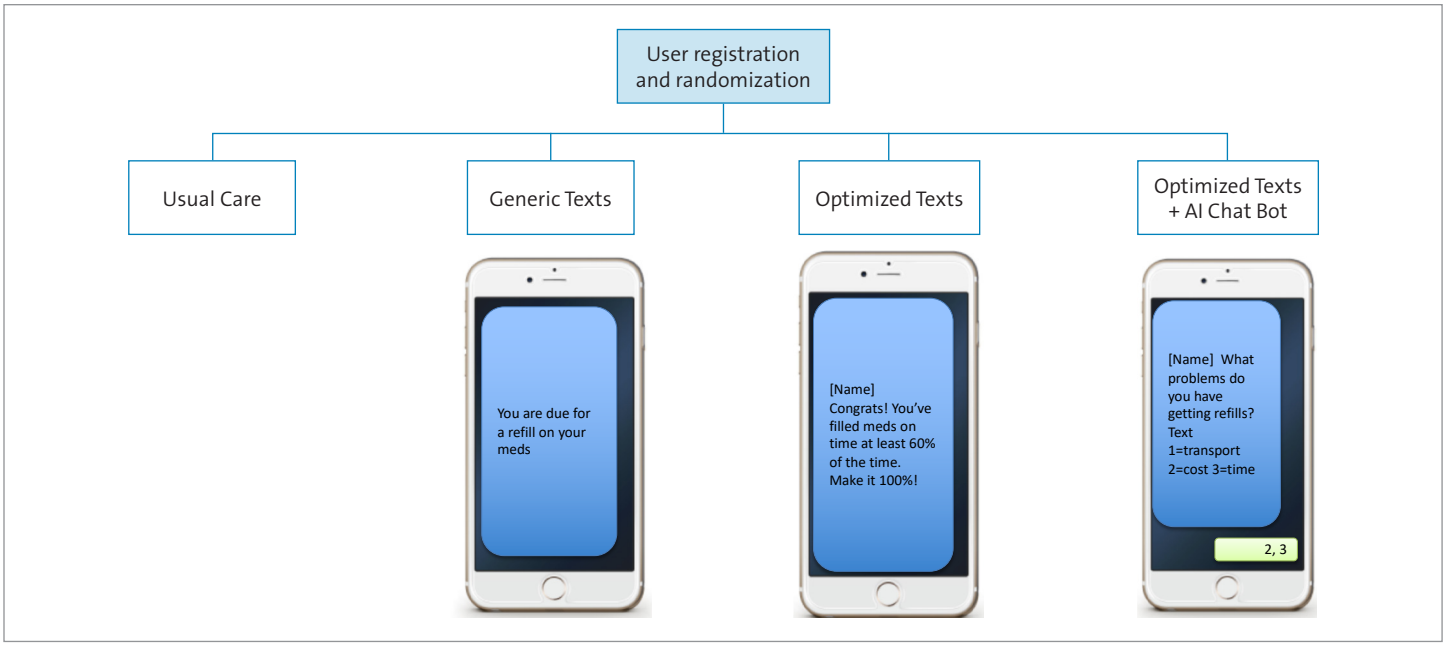
Project Scientist
Nicole Redmond, MD, PhD, MPH (NHLBI)

ABSTRACT

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

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

INTERVENTION ARMS FOR THE PRAGMATIC TRIAL



WHAT WE'VE LEARNED SO FAR

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

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

SELECTED PUBLICATIONS & PRESENTATIONS

- Presentation: Presentation to the NIH Pragmatic Trials Collaboratory Steering Committee (2023)
- Article (Study Design): The NUDGE Trial Pragmatic Trial to Enhance Cardiovascular Medication Adherence: Study Protocol for a Randomized Controlled Trial (2021)
- Article: Leave Me Out: Patients' Characteristics and Reasons for Opting Out of a Pragmatic Clinical Trial Involving Medication Adherence (2021)

Access the complete set of Nudge resources.

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

Michael Ho, MD, PhD
Adjoint Professor of Medicine, University of Colorado School of Medicine
Kaiser Permanente Colorado

Nudge

NIH PRAGMATIC TRIALS COLLABORATORY
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Objective

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

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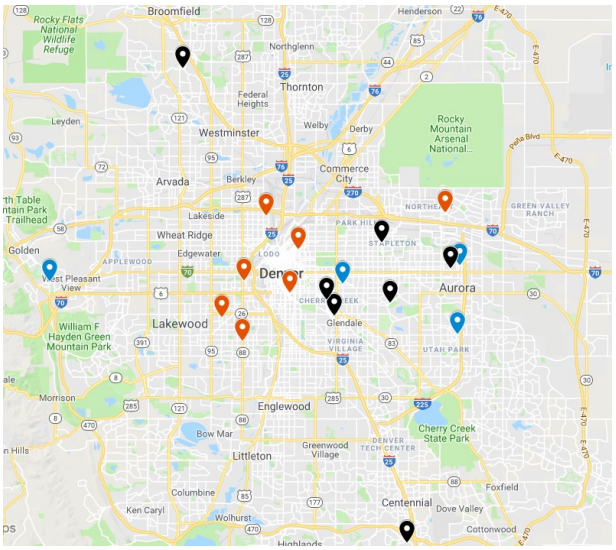
Study setting

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



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Patient population

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

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

- English or Spanish-speaking

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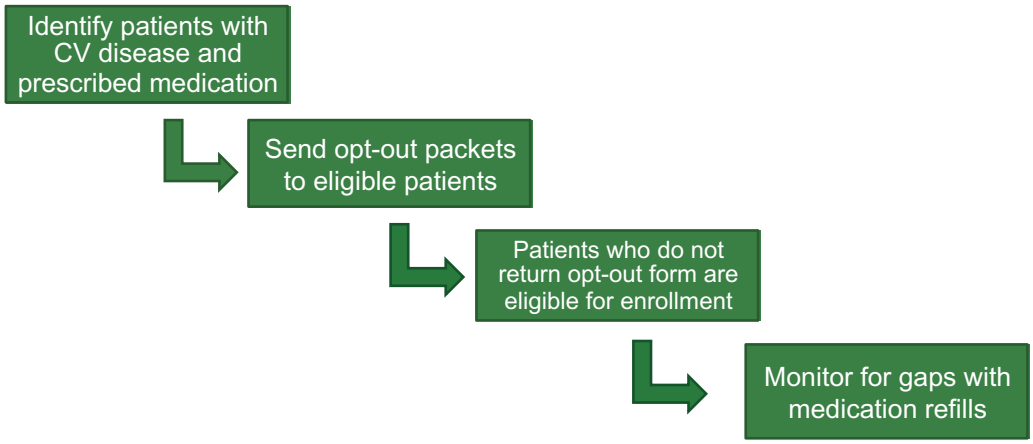
Opt-out study design



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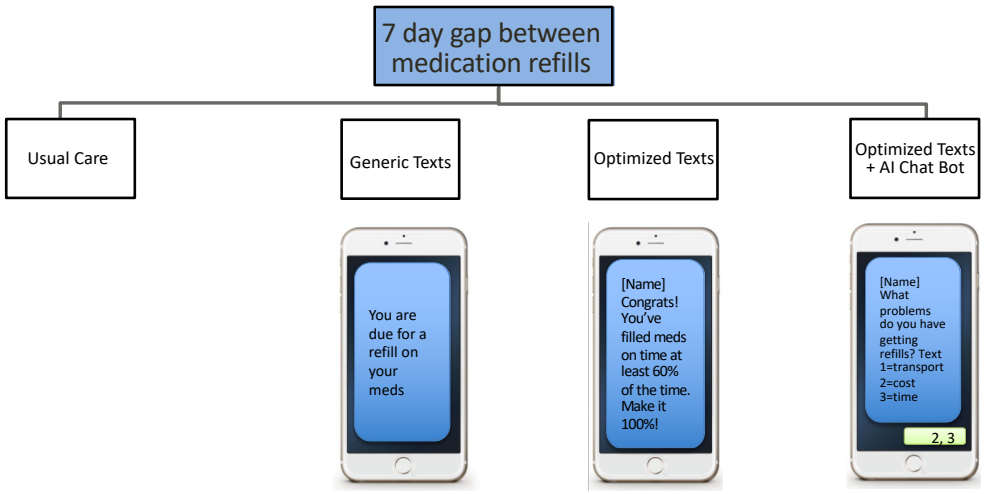
Intervention arms



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Types of nudges employed in this study

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

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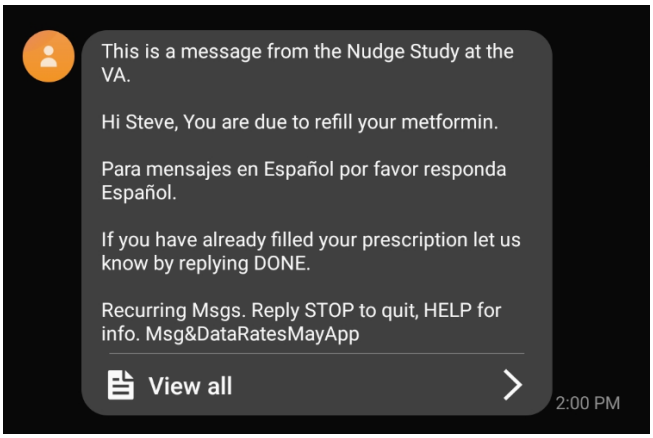
Sample generic message



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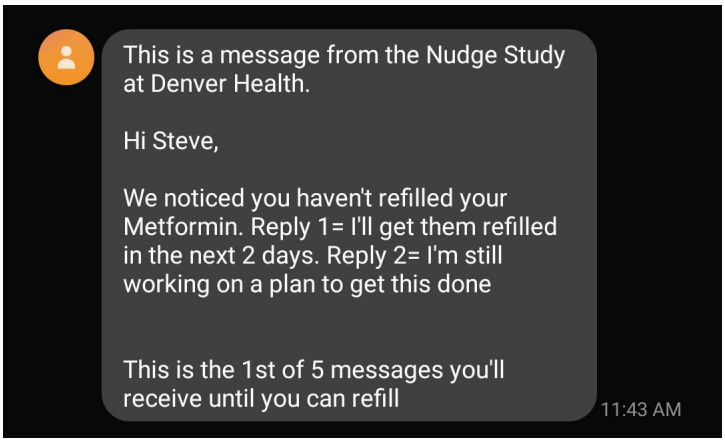
Sample optimized message



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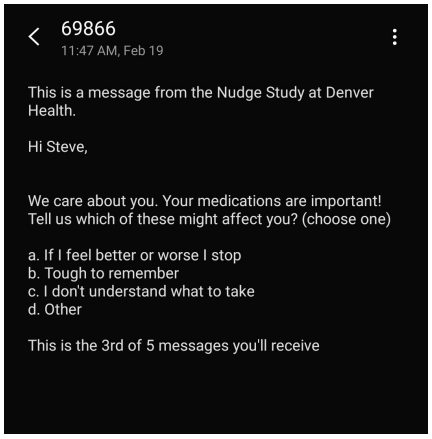
Sample optimized + AI chatbot message



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Barriers/challenges

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

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Solutions/lessons learned

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

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Welcome and Opening Remarks

Speaker

Emily O'Brien, PhD

Associate Professor of Population Health Sciences
Department of Population Health Sciences
Duke University School of Medicine

Welcome

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

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Workshop learning objectives

1. Identify areas of synergy between embedded pragmatic clinical trials and implementation research.
2. Introduce participants to the unique characteristics and challenges of designing, conducting, and implementing pragmatic clinical trials embedded in diverse healthcare systems, and describe opportunities for integrating implementation research methods into these trials.
3. Increase the capacity of health researchers to address important clinical questions with embedded pragmatic clinical trials and share lessons from implementation science for supporting intervention adoption, sustainment, scale-up, and/or deimplementation.

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Workshop sessions - Morning

- What Are Embedded Pragmatic Clinical Trials?
  - Beda Jean-Francois
- Objectives and Trial Design: An Overview of Hybrid Designs
  - Devon Check
- Engaging with Health System and Community Partners
  - Hayden Bosworth
- ePCTs in Context: Small Group Work Followed by Panel Discussion with NIH Collaboratory Trial PIs
  - Angelo Volandes

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Workshop sessions – Afternoon

- Measuring Outcomes
  - Angelo Volandes
- ePCT Design and Analysis
  - Jonathan Moyer
- Pilot & Feasibility Testing
  - Beda Jean-Francois
- Ethical & Regulatory Oversight Considerations
  - Stephanie Morain

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Workshop sessions – Afternoon continued

- Writing a Compelling Grant Application
  - Beda Jean-Francois
- ePCTs in Context: Small Group Work Followed by Panel Discussion with NIH Collaboratory Trial PIs
  - Stephanie Morain
- Closing Remarks
  - Emily O'Brien

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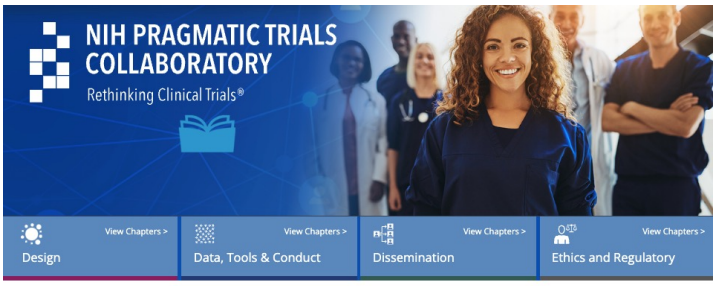
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials

WATCH THE VIDEO

Welcome to the Living Textbook of pragmatic clinical trials, a collection of knowledge from the NIH Pragmatic Trials Collaboratory. Pragmatic clinical trials present an opportunity to efficiently generate high-quality evidence to inform medical decision-making. However, these trials pose different challenges than traditional clinical trials. The Living Textbook reflects a collection of special considerations and best practices in the design, conduct, and reporting of pragmatic clinical trials.

GET STARTED

What is the NIH PRAGMATIC TRIALS COLLABORATORY?

What is a PRAGMATIC CLINICAL TRIAL?

TRAINING RESOURCES

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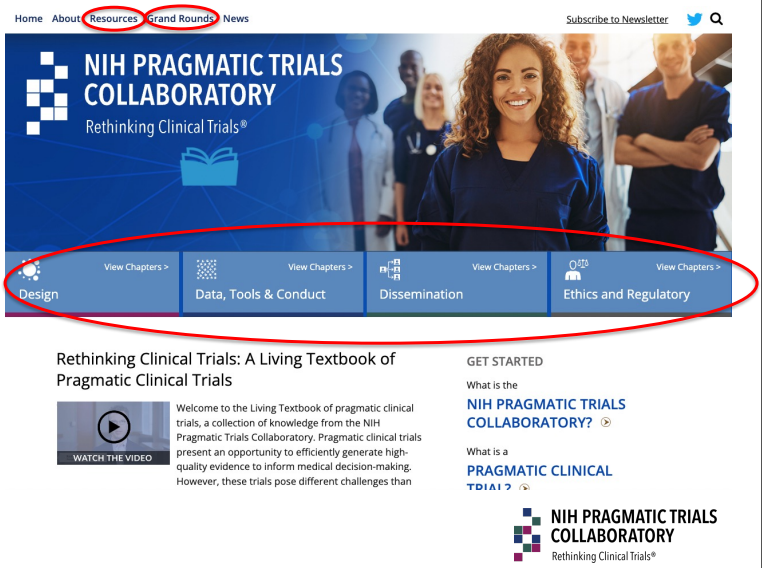
Key Resources

- Living Textbook
- Grand Rounds Hub
- Training Resources

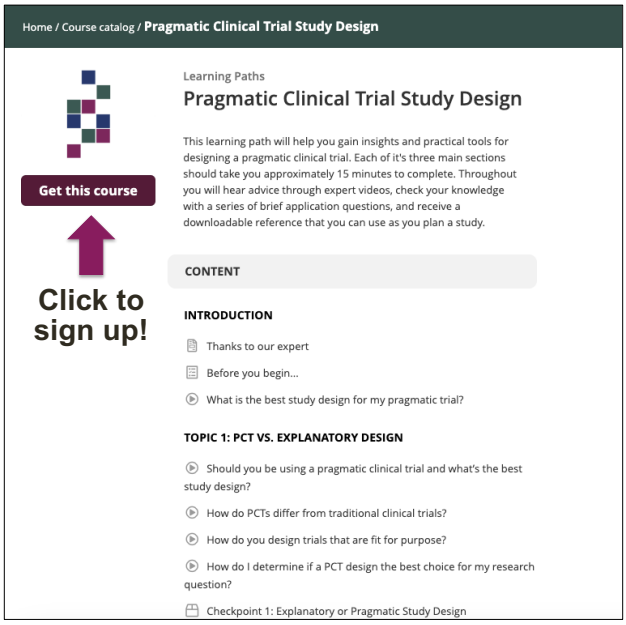


New Self-Paced Learning Path on Study Design

Free | Earn Certificate

1-Hour Course Includes

- Expert-led content, reference materials, and knowledge checkpoints
- Insights on how to:
  - Select the most appropriate study design for a pragmatic trial
  - Make decisions about randomization
  - Choose between parallel and stepped-wedge design
- Visit rethinkingclinicaltrials.org/training-resource/

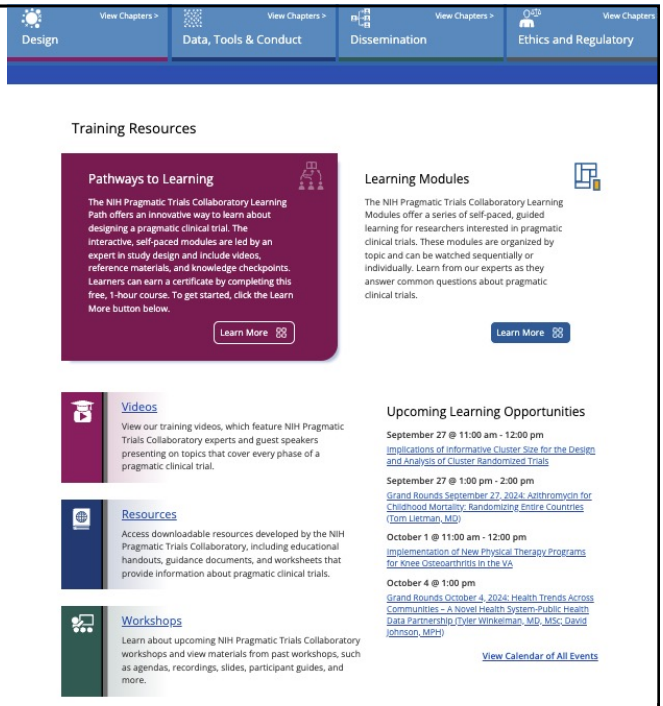


Training Resources
rethinkingclinicaltrials.org

Website Features Include:

- 8 self-paced, guided video learning modules on conducting pragmatic clinical trials
- Enhanced video library indexed by topic
- Workshops page content from program workshops
- Resources page with handouts, guides, and worksheets
- Upcoming learning events and workshops

Learn more:



About you

- What best matches your professional position?
  - Academic Faculty
  - Clinician or Health Care systems Leadership
  - Research Support Staff
  - Student or Trainee
  - Other

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About you

- Where are you in your career track?
  - Student
  - Post-Doctoral Fellow
  - New faculty (K award, Early Stage Investigator, etc.)
  - Established Faculty (Associate or Full Professor)
  - Other

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About you

- What is your experience conducting pragmatic trials in health care 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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What Are Embedded Pragmatic Clinical Trials (ePCTs)?

Speaker

Beda Jean-Francois, PhD

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

What Are Embedded PCTs?

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

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Learning goals

- Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials
- Learn about the advantages and disadvantages of ePCTs, when a pragmatic approach can be used to answer the research questions
- Identify key areas of convergence between ePCTs and D&I research

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Important things to know

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

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Why conduct ePCTs?

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

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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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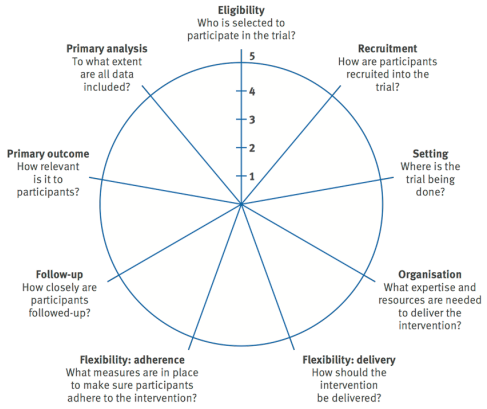
Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) Wheel



Adapted from BMJ 2015;350:h2147
https://www.precis-2.org/

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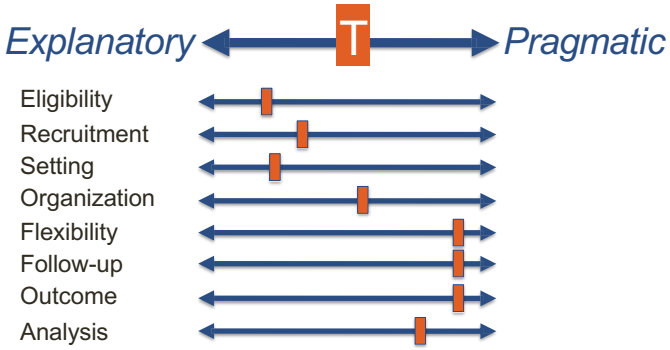
Trials vary across a spectrum of explanatory and pragmatic elements

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



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What is a Pragmatic Clinical Trial?

There is a need for "a different context to clinical research that could speed the discovery and implementation of evidence-based advancements to healthcare delivery. Pragmatic clinical trials (PCTs) are a promising type of trial conducted within real-world health care delivery systems"
(Tuzzio and Larson 2019).

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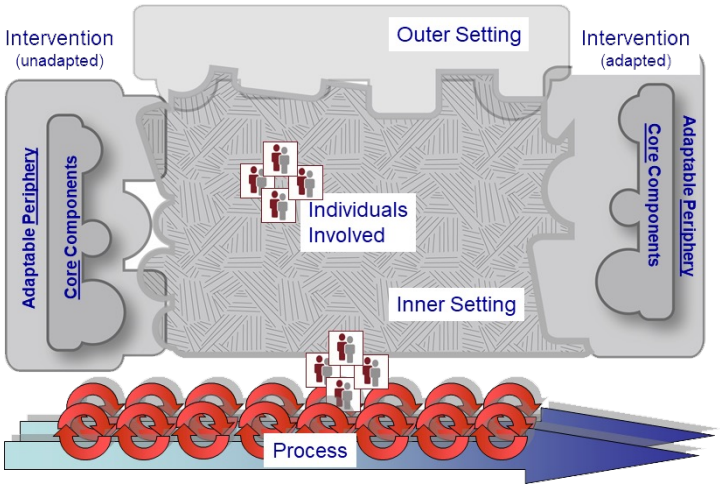
Frameworks

Consolidated Framework for Implementation Research



Front. Public Health, 29 March 2019 | https://doi.org/10.3389/fpubh.2019.00064
Front. Public Health, 27 April 2015 | https://doi.org/10.3389/fpubh.2014.00143

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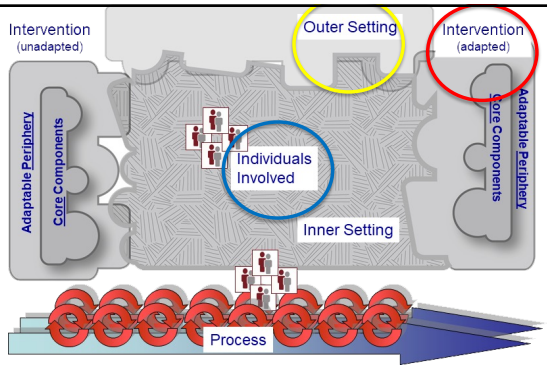

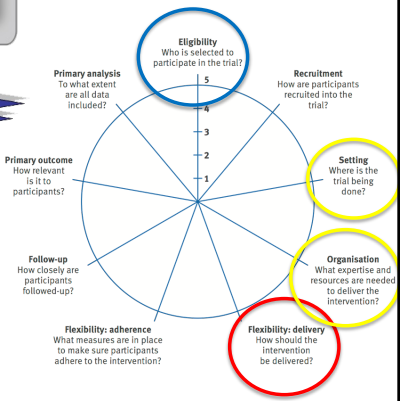

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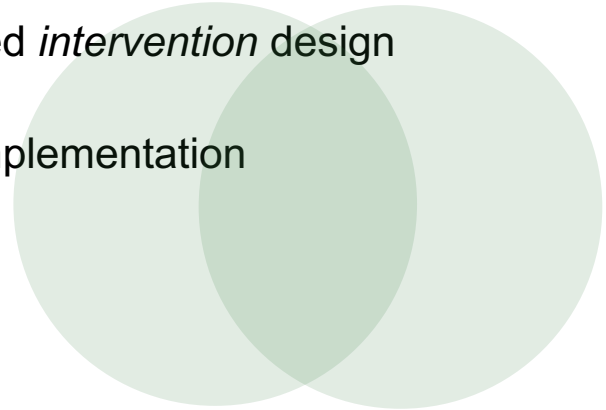
Key areas of convergence with ePCTs

- Pragmatic/stakeholder-engaged *intervention* design
- Study design that considers implementation
- Regulatory concerns



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Who are your stakeholders?

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

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

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Opportunities

- Pragmatic trials can be improved by including implementation strategies
- Hybrid designs offer the opportunity to evaluate effectiveness and implementation strategies
- Multidisciplinary teams improve pragmatic research and dissemination/implementation research

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It's a balancing act

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

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

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Listen to the frontline

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

– Greg Simon, MD, MPH (SPOT)

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Important things to do

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

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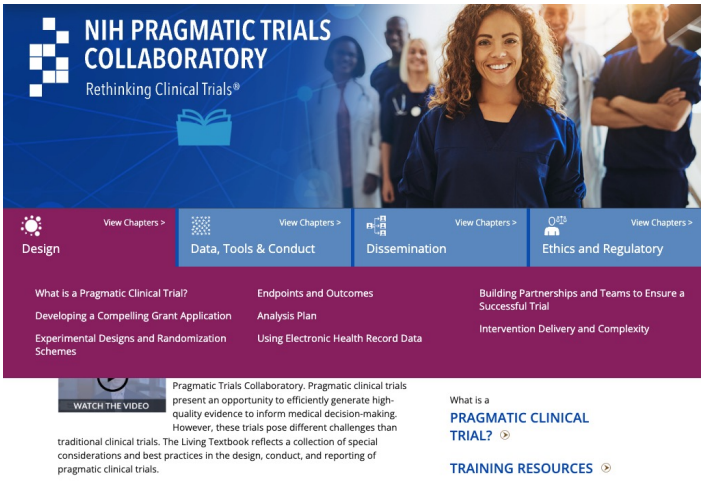
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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Knowledge Checkpoint

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

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Resources:

What Are Embedded PCTs (ePCTs)?

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Objectives and Trial Design: An Overview of Hybrid Designs

Speaker

Devon Check, PhD

Assistant Professor of Population Health Sciences
Department of Population Health Sciences
Duke University School of Medicine

Trial Objectives and Design: An Overview of Hybrid Designs

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

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Learning goals

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

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Important things to know

- Hybrid trial designs are trials with a focus on both clinical effectiveness and implementation outcomes
- ePCTs are usually hybrid type 1 or 2
- Choosing the appropriate hybrid trial design for an ePCT involves considering the research objectives, specifically the balance between understanding effectiveness and optimizing implementation strategies

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Why hybrid trial designs?

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

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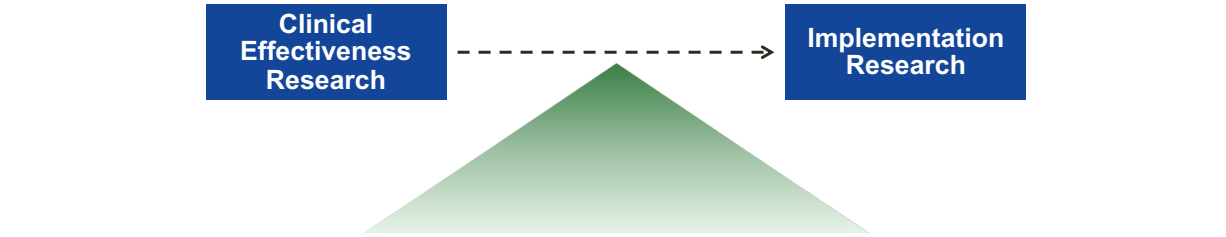
Types of hybrids



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

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Type 1

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

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Type 1 example: PPACT

Contemporary Clinical Trials 67 (2018) 91–99

Contents lists available at ScienceDirect

Contemporary Clinical Trials

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

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

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

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Type 1 example: PPACT

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

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Type 2

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

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Type 2 example: STOP CRC

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

Implementation Science

METHODOLOGY Open Access

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

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

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Type 2 example: STOP CRC

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

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Type 3

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

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Type 3 example: ENABLE

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

Implementation Science

STUDY PROTOCOL Open Access

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

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

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Concluding points

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

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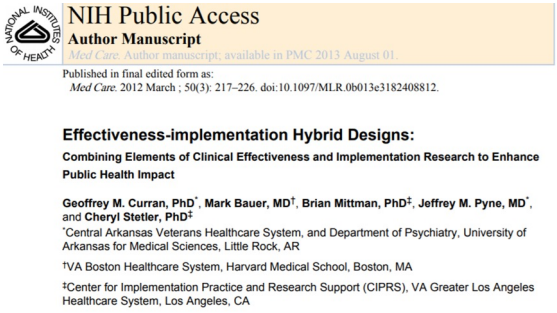
Concluding points

- If you want to learn more…

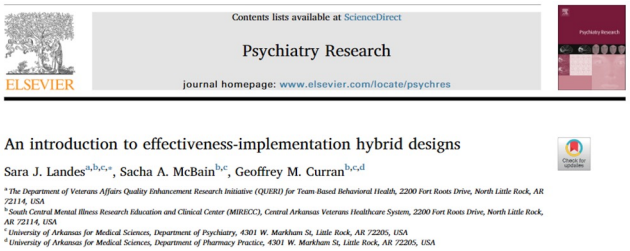


NIH Public Access
Author Manuscript
Med Care. Author manuscript; available in PMC 2013 August 01.

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

Effectiveness-implementation Hybrid Designs:
Combining Elements of Clinical Effectiveness and Implementation Research to Enhance Public Health Impact

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



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

An introduction to effectiveness-implementation hybrid designs

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

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Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

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Question & Answer

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Resources:

Objectives and Trial Design: An Overview of Hybrid Designs

Key journal articles

- Curran et al., 2012. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact.
- Landes, McBain, Curran. 2019. An introduction to effectiveness-implementation hybrid designs.

Additional resources

- Designing With Implementation and Dissemination in Mind: Hybrid Designs

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Engaging with Health System and Community Partners

Speaker

Hayden Bosworth, PhD

Professor of Population Health Sciences
Department of Population Health Sciences
Duke University School of Medicine

Engaging with Health System and Community Partners

Hayden Bosworth, PhD
Professor of Population Health Sciences
Department of Population Health Sciences
Duke University School of Medicine

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Learning goals

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

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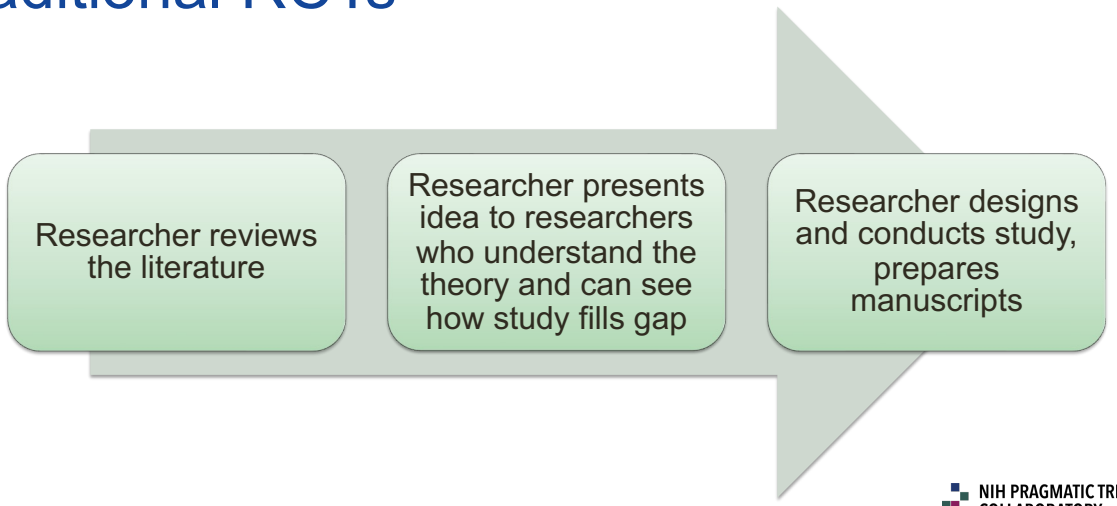
How researchers approach partners in traditional RCTs



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ePCTs work differently.

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

– Greg Simon, MD, MPH (SPOT)

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Important things to know

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

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Who will be impacted? 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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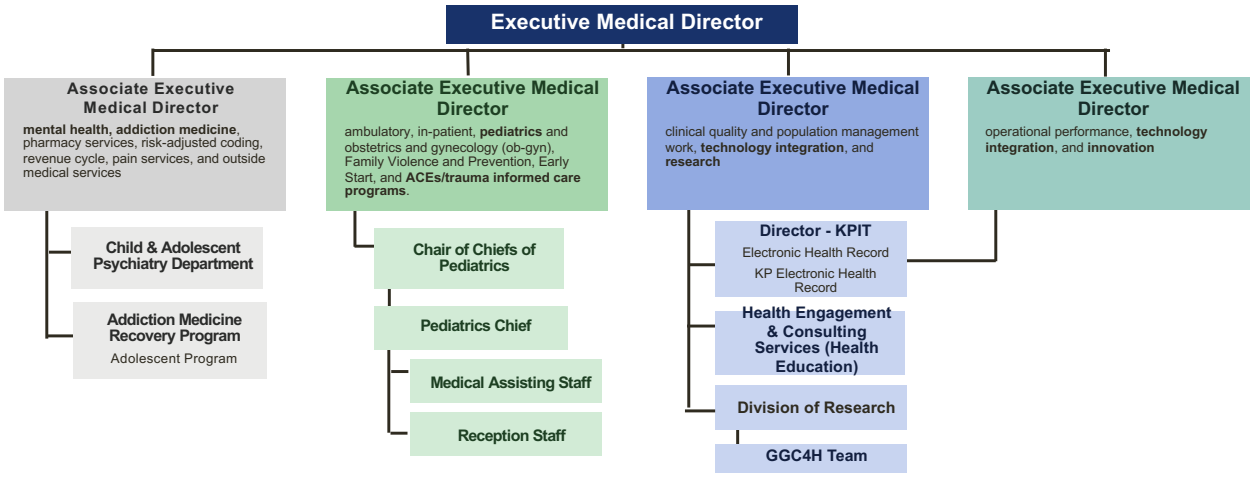
Kaiser Permanente Northern California



<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**
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Choosing a salient question

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

Source: Greg Simon, MD, MPH

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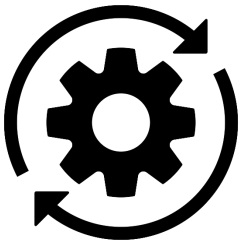
Designing the intervention for sustainment



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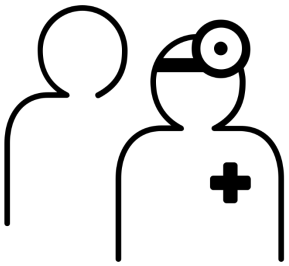
Designing the intervention to minimize burden for patients and clinicians



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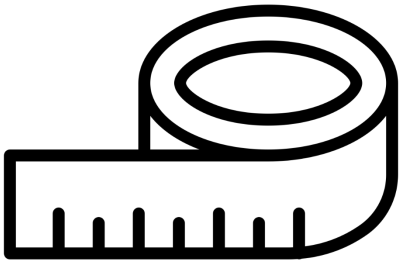
Selecting outcome measures



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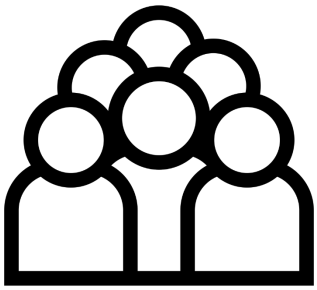
Determining inclusion and exclusion criteria



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Roles of 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 "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 name by patient
  - Chat 4 Heart Health

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Serve as study champions

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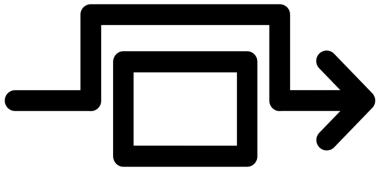
Track challenges and adaptations



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Interpret study results

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Roles of partners

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

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Determine key messages for different groups and

identify avenues for dissemination

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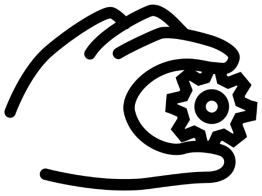
Support implementation or de-implementation



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Consider changes to policies and guidelines

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Roles of ePCT partners

1. Design
- Question
- Intervention
- Outcomes
- Population

2. Conduct
- Recruitment
- Advocacy
- Challenges
- Interpretation

3. Dissemination
- Messaging
- Venues
- Implementation
- Guidelines

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Important things to do

- Engage partners early and often
- Set expectations to work collaboratively and build trust from the beginning
- Use familiar language that partners understand
- Get to know your partners' values, priorities, and expectations
- Assess health system 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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Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

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Knowledge Checkpoint

- Why is it essential to engage partners early, even before the study design phase?
  - To meet regulatory requirements
  - To build relationships and ensure alignment with healthcare system goals
  - 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?
  - Only clinicians
  - Patients and caregivers, healthcare organization leaders, policymakers
  - Laboratory staff only

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Knowledge Checkpoint

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

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Question & Answer

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Resources:

Engaging With Health System and Community Partners

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

Other

- Health Care Services Research Network website

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ePCTs in Context: Small Group Work and Panel Discussion with Trial Investigators

Moderator

Angelo Volandes, MD, MPH

Associate Professor of Medicine
Harvard Medical School
Massachusetts General Hospital

ePCTs in Context

Small Group Work and Panel Discussion With Trial Investigators

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NIH Collaboratory Trial Panelists

- Andrea Cheville, MD
  - NOHARM
- Julie Fritz, PhD, PT
  - BeatPain Utah
- Michael Ho, PhD, MD
  - Nudge, Chat 4 Heart Health
- Sebastian Tong, MD, MPH
  - AIM-CP

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Learning goals

- Introduction of Panelists and Overview of Trials
- 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 & lessons learned of the morning topics, to include Q&A

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Small Group Discussion

AIM-CP: Engaging with Health System and Community Partners

- AIM-CP is partnering with clinics to implement a nurse care management model to address chronic pain among patients in rural settings; the research team is based in an urban setting and was advised by rural partners that building trust with patients could be difficult. **How would you approach this challenge?**

BeatPain Utah: Enrollment and Engagement of Participants

- BeatPain Utah researchers, based at an academic medical center, needed to build trust with Federally Qualified Health Center (FQHC) leadership and staff. **How would you approach this challenge?**

NOHARM: Engaging with Health System Partners

- NOHARM found that there were frequent staffing changes at participating sites. **How would you approach this challenge?**

Nudge: Engaging with Health System Partners

- Clinical priorities often supersede research projects. **What strategies would you use to overcome this challenge?**

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Reflection on Morning Topics

- What are embedded pragmatic clinical trials (ePCTs)?
- Objectives and trial design
- Engaging with health system and community partners

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Question & Answer

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Resources:

ePCTs in Context: Panel Discussion

AIM-CP

- UG3 Project: Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients with Chronic Pain (AIM-CP)

BeatPain Utah

- UH3 Project: Nonpharmacologic Pain Management in Federally Qualified Health Centers Primary Care Clinics (BeatPain Utah)

Chat 4 Heart Health

- UH3 Project: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors (Chat 4 Heart Health)

NOHARM

- UH3 Project: Nonpharmacologic Options in Postoperative Hospital-based and Rehabilitation Pain Management (NOHARM)

Nudge

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

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Measuring Outcomes

Speaker

Angelo Volandes, MD, MPH

Associate Professor of Medicine
Harvard Medical School
Massachusetts General Hospital

Measuring Outcomes

Angelo Volandes, MD, MPH
Associate Professor of Medicine
Harvard Medical School and Massachusetts General Hospital

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Learning goals

- Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
- Discuss the integration of a health equity lens in evaluating outcomes

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Outcome, Measure, Endpoint

- An outcome usually refers to a variable of interest or a meaningful aspect of health (such as oxygen volume or fatigue).

- A measure usually refers to a specific and 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 measures (PROM)	Observer-reported outcome measures (ObsRO)
Clinician-reported outcome measures (ClinRO)	Performance outcome measures (PerfO)

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Outcome, Measure, Endpoint

- An endpoint usually refers to a precisely defined variable that is statistically analyzed to address a particular research question.

Example:

- Change from baseline at 6 weeks in mean PROMIS Fatigue score.
- Mean differences in PROMIS Fatigue scores between patients in treatment and standard of 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 (i.e., pragmatic)
- Researchers do not control the design or data collected in EHR systems

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Choosing and specifying ePCT endpoints

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

- Acute MI
- Broken bone
- Hospitalization

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

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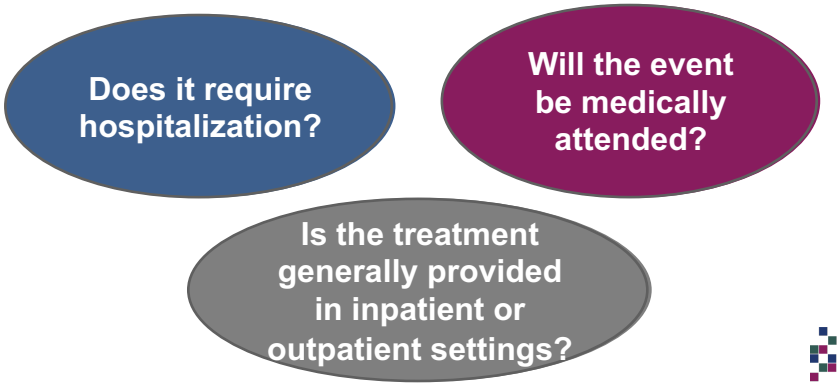
Key questions for choosing endpoints

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



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Data sources for endpoints in ePCTs

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

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

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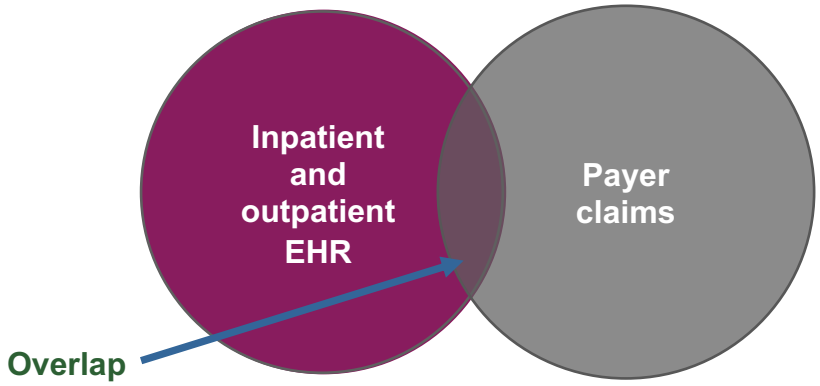
Where is the signal?

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



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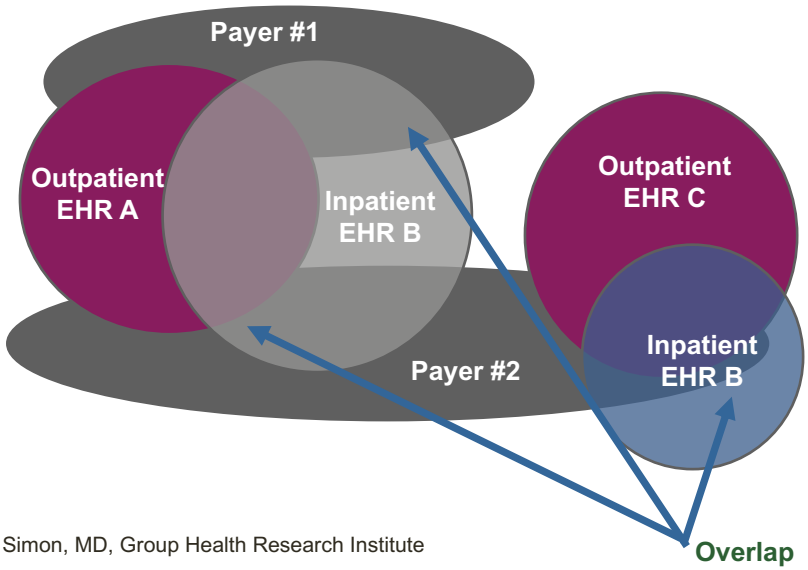
Reality is not straightforward



Source: Greg Simon, MD, Group Health Research Institute

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Longitudinal data linkage

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

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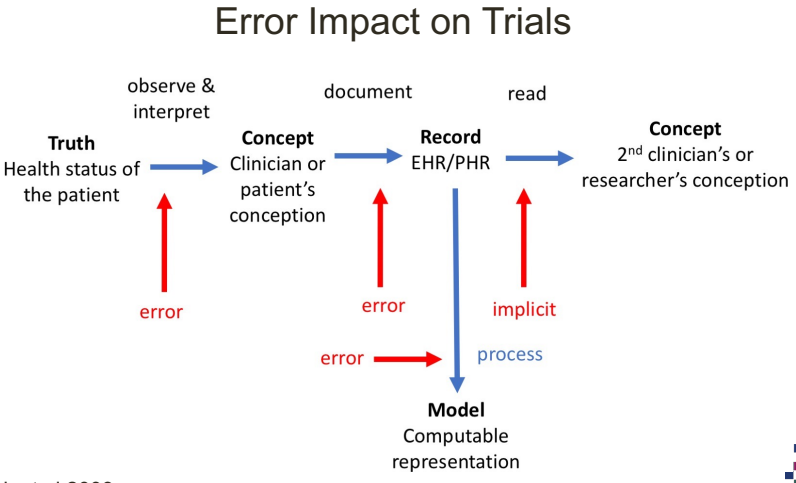
Data is a surrogate for clinical phenomena



Adapted from Hripcsak et al 2009

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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 of standard clinical practice:

- Patient reported data

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It's a balancing act

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

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

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Outcomes measured via direct patient report

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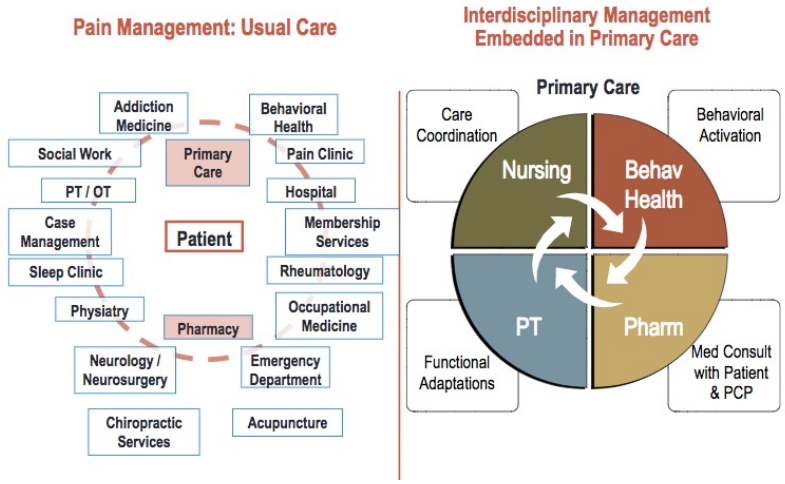
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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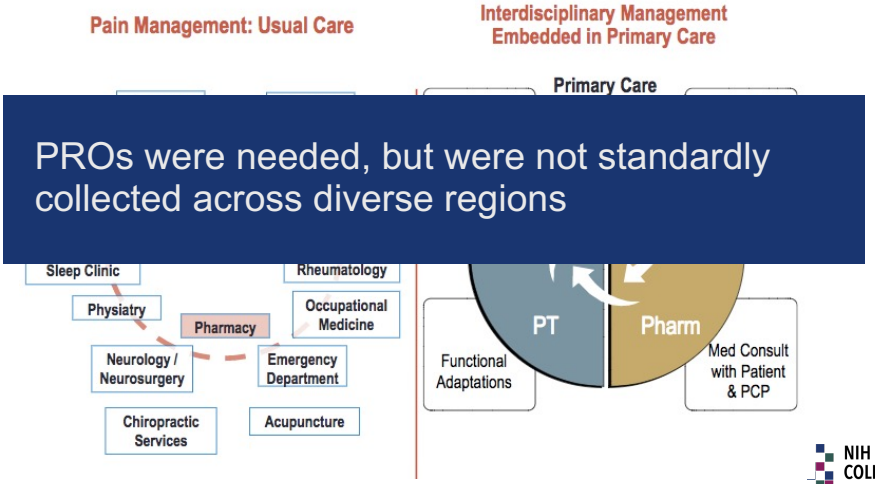
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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Case example: PPACT

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

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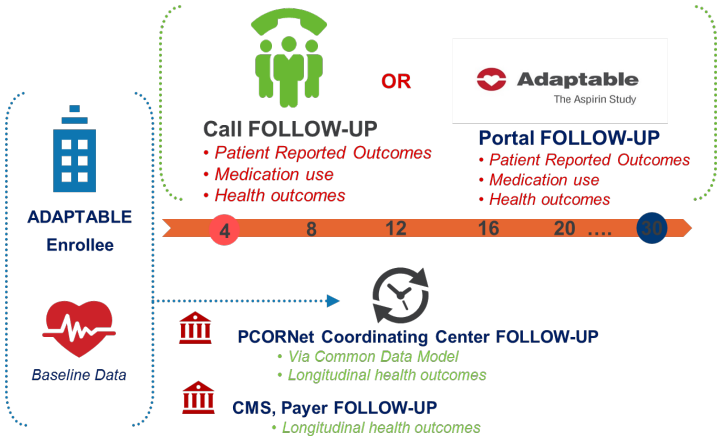
Enabling pragmatic research: e-screening, e-enrollment & e-follow-up



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Mobile devices for outcome measurement

- Smartphones, tablet computers, and portable, implantable, or wearable medical devices (mHealth)
  - Some mHealth devices transmit data to a data warehouse every night
  - Largely considered imperfect measures

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A Health Equity Lens

- "As the number of ePCTs using EHR-derived data grows, so does the risk that research will become more vulnerable to biases due to differences in data capture and access to care for different subsets of the population, thereby propagating inequities in health and the healthcare system"
- **Challenges:**

Alerts | Author Instructions | Submit | About JAMIA Journal of the American Medical Informatics Association

J Am Med Inform Assoc. 2023 Sep; 30(9): 1561–1566. PMCID: PMC10436149
Published online 2023 Jun 26. doi: 10.1093/jamia/ocad115 PMID: 37364017

Potential bias and lack of generalizability in electronic health record data: reflections on health equity from the National Institutes of Health Pragmatic Trials Collaboratory

Andrew D Boyd, Rosa Gonzalez-Guarda, Katharine Lawrence, Crystal L Patil,

J Am Med Inform

Data loss due to variable use of technology

Incomplete and variable capture of data on social determinants of health

Lack of representation from vulnerable populations that do not access or receive treatment

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A Health Equity Lens

Contemporary Clinical Trials
Volume 130, July 2023, 107238

Short Communication

Equity and bias in electronic health records data

Andrew D. Boyd [a], Rosa Gonzalez-Guarda [b], Katharine Lawrence [c],

Recommendations to reduce bias:

- Collect demographic and social determinants of health
- Evaluate and address data collection barriers across diverse populations
- Utilize community-engaged approaches
- Evaluate the reading level of all patient-facing data collection tools (e.g. PROMs) and consider translation/cross-cultural validation

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Data quality assessment

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

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Important things to do

- Ask questions that the data will support
- 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 (… and then double it)
- Carefully consider bias and take steps to promote equity
- Develop a robust data quality assessment plan to improve value of data and to detect and address data issues – early in data collection

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Concluding points

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

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Resource: The Living Textbook

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Question & Answer

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Resources:

Measuring Outcomes

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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ePCT Design and Analysis

Speaker

Jonathan Moyer, PhD

Statistician, National Institutes of Health
Office of Disease Prevention

ePCT Experimental Design and Analysis

Jonathan Moyer, PhD
Statistician, National Institutes of Health
Office of Disease Prevention

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Learning goals

- Learn about cluster randomized and stepped-wedge study designs
- Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know

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Important things to know

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

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Design Considerations

Embedded Pragmatic Clinical Trials

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

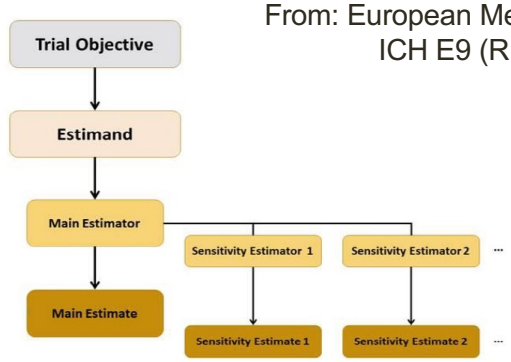

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Methods for pragmatic trials

- Pragmatic trials do not require a completely different set of research designs, measures, analytic methods, etc.
- During study design:
  - State hypotheses
  - Pre-specify analyses
  - Calculate sample size needed for desire power
  - Consider restricted randomization (e.g., stratified randomization)
  - Determine data on participant characteristics to be collected
  - Anticipate sources of heterogeneity
- Randomized trials will provide the strongest evidence.
  - What kind of randomized trial depends on the research question and how the intervention will be delivered

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NIH Collaboratory ePCT: STOP CRC

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

stop screen to prevent colon cancer

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

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Reasons to randomize clusters instead of individuals

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

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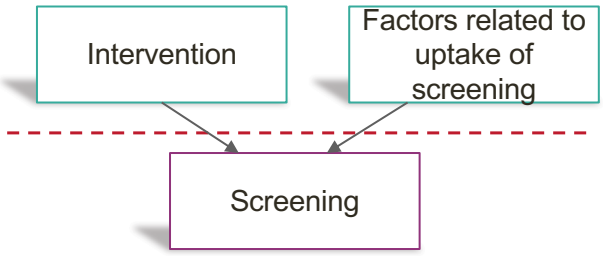
STOP CRC cluster randomization

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



Level 1: Individual-level outcomes nested within clinics

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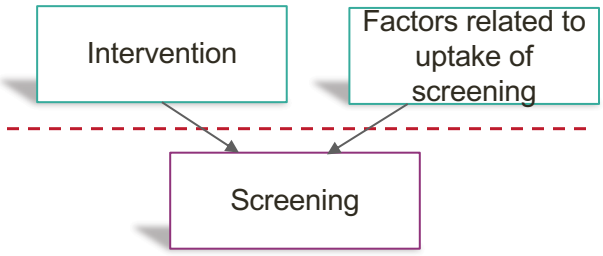
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (i.e., to *cluster*)
- Reduces power to detect treatment effect if same sample size used as under individual randomization

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Understanding outcome clustering

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

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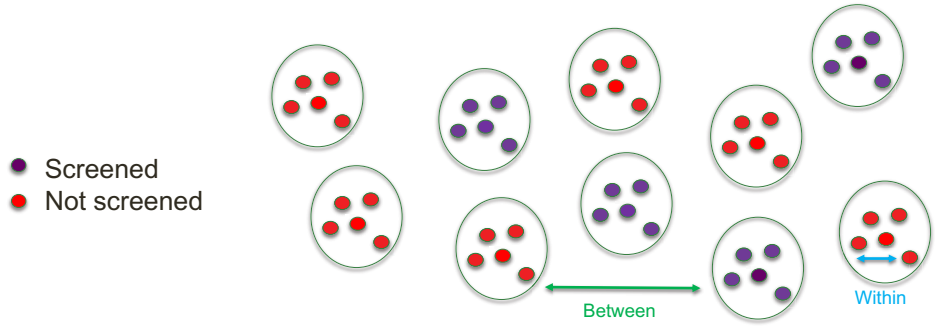
Understanding outcome clustering: complete clustering (ICC =1)



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

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

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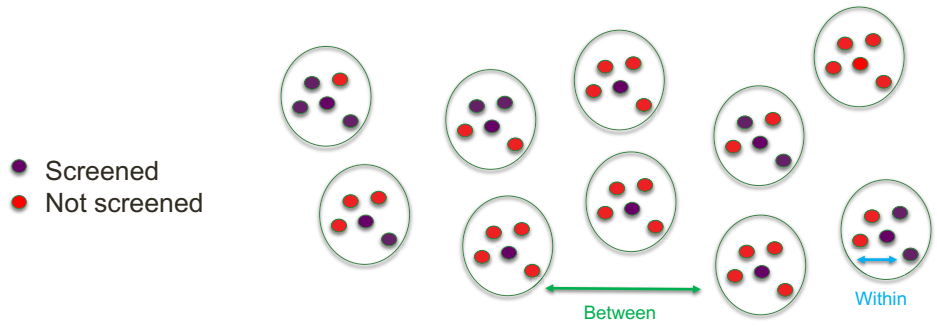
Understanding outcome clustering: some clustering (0 < ICC < 1)



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

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

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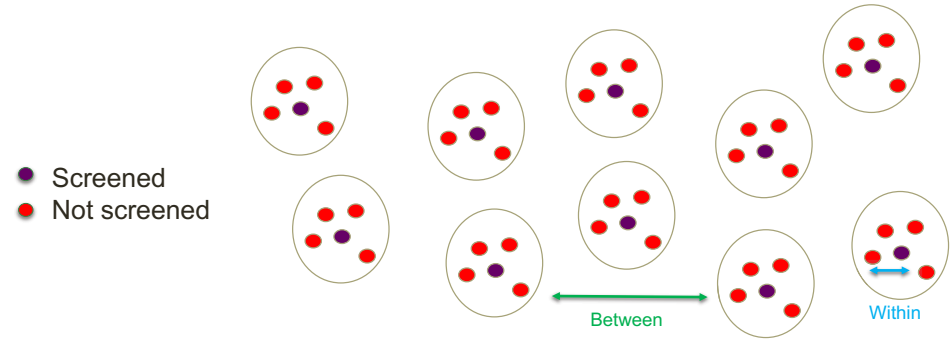
Understanding outcome clustering: no clustering (ICC=0)



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

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

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Summary of design issues for CRTs

- All the design features common to RCTs are available to CRTs with the added complication of an extra level of nesting:
  - Cohort and cross-sectional designs
  - Post only, pre-post, and extended designs
  - Single-comparison designs and factorial designs
  - Restricted randomization (stratification, constrained randomization, etc.)
- Most CRTs are “small”, ie, total # clusters (C) <50
  - Small number of independent units may result in low power
  - Randomization may not evenly distribute potential confounders
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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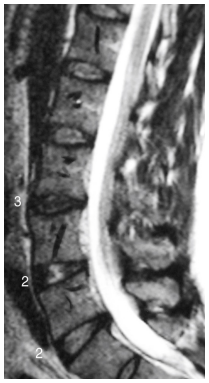
NIH Collaboratory ePCT: LIRE



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

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

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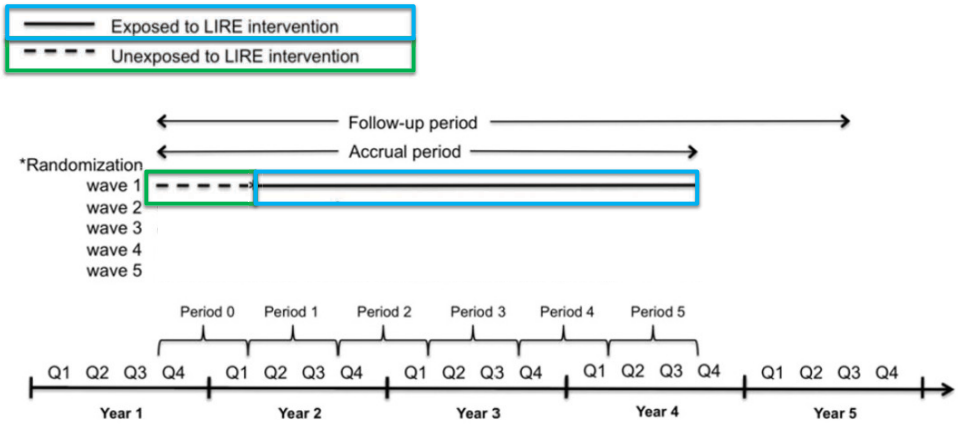
NIH Collaboratory ePCT: LIRE



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

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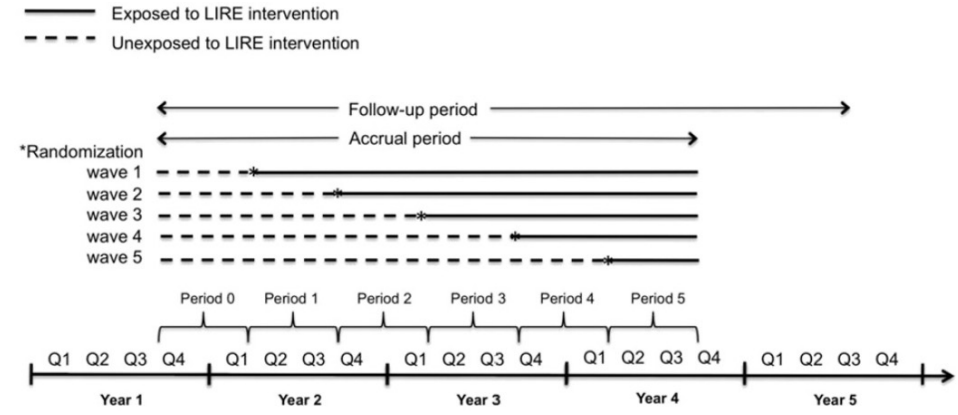
NIH Collaboratory ePCT: LIRE



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

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Summary of design issues for SW-CRTs

- Many design features common to RCTs are available to SW-CRTs:
  - Cohort and cross-sectional designs.
  - Single-comparison designs and factorial designs.
  - Restricted randomization to create comparable sequences.
- Clusters crossed with study condition, which minimizes confounding
  - Intervention effects confounded with time by design – always adjust for time!
  - SW-CRTs inherently more complicated than parallel CRTs.
- A SW-CRT may be an acceptable alternative to a parallel CRT if…
  - Intervention is being rolled out to all groups as part of system-wide implementation.
  - Cannot implement intervention in many groups at same time.
    - Consider a staggered start parallel CRT.
  - External events are unlikely to affect the outcomes (disruption!)
- Accounting for the pattern of the intervention effect over time:
  - The common assumption of an immediate, sustained intervention effect may yield biased estimates.
  - In the absence of evidence to the contrary, it is reasonable to assume intervention effect changes with exposure time.
  - Important to define intervention effect in this case – e.g., average at one point in time, average over more than one time.

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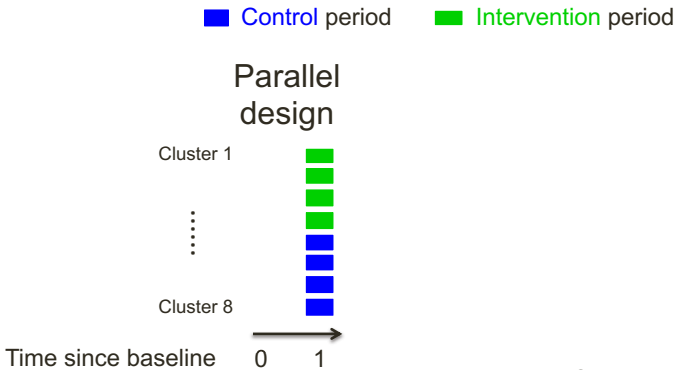
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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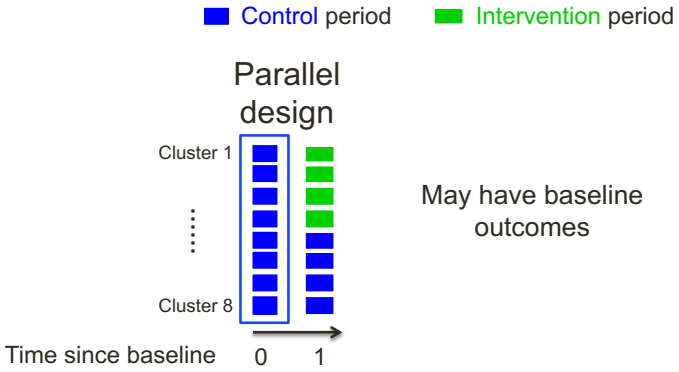
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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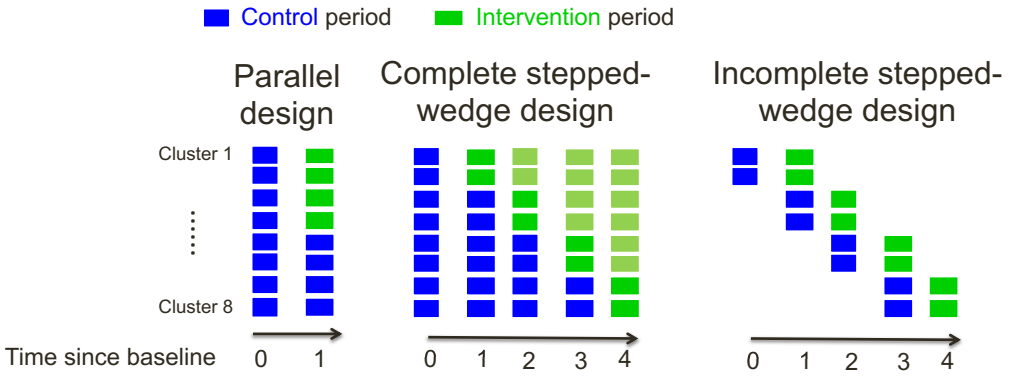
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

- Optimizing Pain Treatment In Medical settings Using Mindfulness (OPTIMUM)
- Goal: to reduce pain and pharmacologic medications via a group-based mindfulness-based stress reduction (MBSR) program
- Study population: individuals with chronic lower back pain
- Unit of randomization: individual
  - Participants randomized to control and intervention conditions
  - No correlated outcomes before randomization
- Control condition: No post randomization correlation between outcomes for control participants
- Group-based online intervention → groups must be formed by study team
  - Post randomization interactions between participants!
- Individually-randomized group treatment (IRGT) trial
  - Post randomization groupings induce correlated outcomes

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

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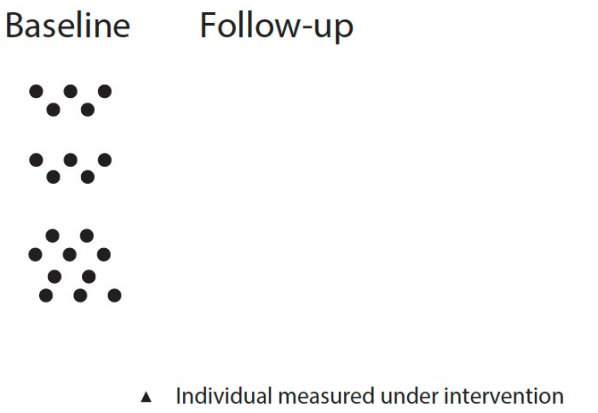
NIH Collaboratory ePCT: OPTIMUM



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

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Summary of design issues for IRGT trials

- Many design features common to RCTs are available to IRGT trials:
  - Cohort, but not easy to conceive of a cross-sectional design
  - Single-comparison designs and factorial designs
  - Restricted randomization procedures
- Clustering emerges post randomization
  - Could be due to a shared agent, participation in a group-based intervention, etc.
    - Fully Nested: Agents in both arms and nested within arm
    - Partially Nested: Agents in one arm only – participants in the other arm (usually control) are not clustered
    - Crossed: Agents interact with participants in both arms
  - Individual randomization, but ICC has a similar impact as it does for CRTs
  - Impact of ICC due to shared agent or group-based intervention often overlooked
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the design, with sufficient power for a valid analysis, and avoid threats to internal validity

More information: Moyer JC et al. 2024. *Stat Med*. 43(25):4796-4818.

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Clustering: Impact on power

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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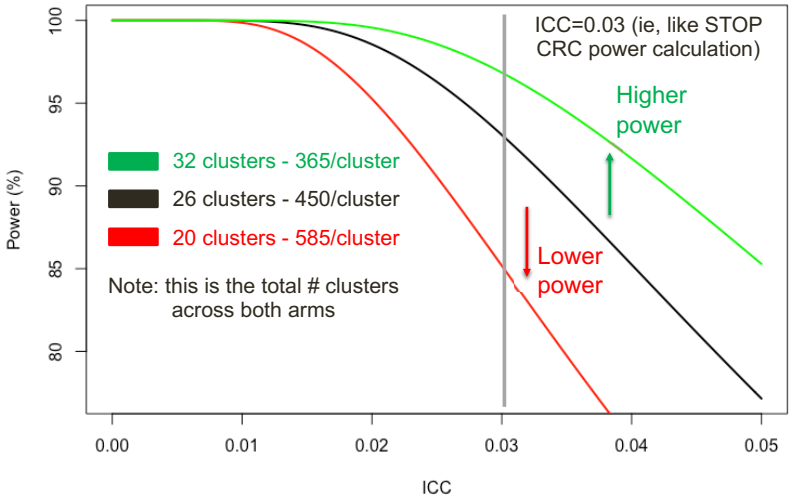
Clustering: Impact on power in STOP CRC



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

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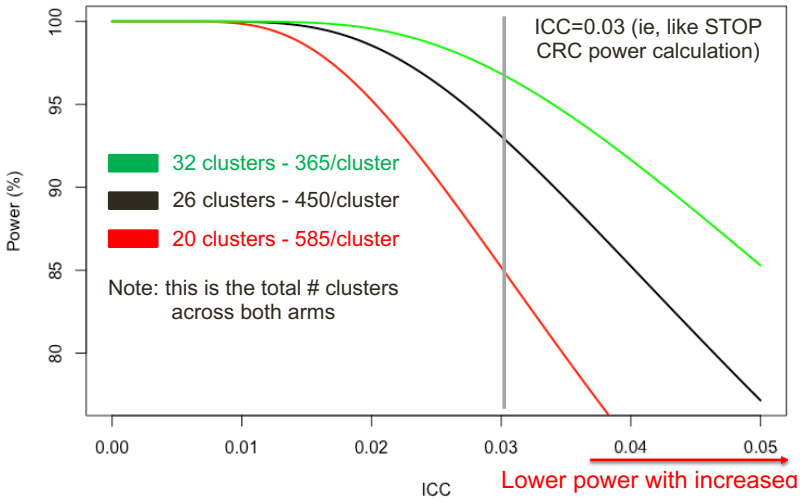
Clustering: Impact on power in STOP CRC



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

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Knowledge Checkpoint

Researchers are interested in the effect of participation in support groups vs. usual care on weight loss. Participants in the intervention attend group meetings, while usual care involves no group meetings. Out of 20 enrolled participants, 10 are randomly assigned to the intervention arm and attend support groups. Two therapists each lead a support group that meets on different weekday nights. Participant BMI will be measured at baseline (before randomization) and at 3 months.

- What design is this trial?
- Researchers powered this study assuming an RCT 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 two therapists, or increase the number of therapists leading support groups?

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Question & Answer

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Analysis Considerations

Embedded Pragmatic Clinical Trials

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Learning goals

- Learn about cluster randomized and stepped-wedge study designs
- Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know

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Two example CRTs inspired by STOP CRC

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

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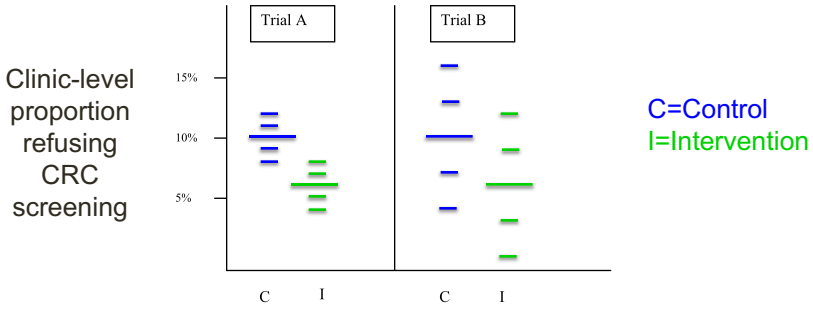
Clustering in CRTs: Implications for analysis



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

Overall screening refusal proportion in both trials: 10% vs 6%

Question: is intervention effective?

Adapted from Hayes & Moulton (2009)

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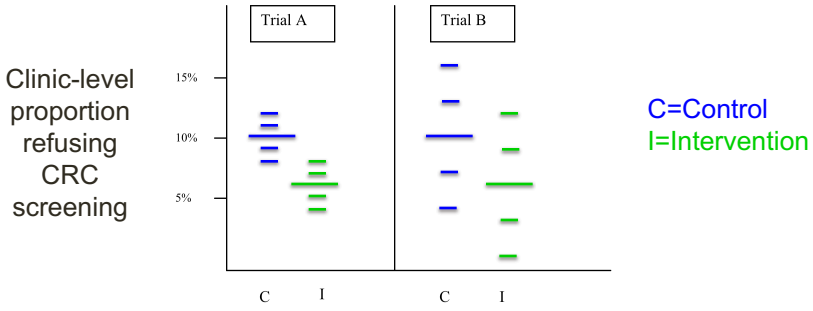
Clustering in CRTs: Implications for analysis



Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

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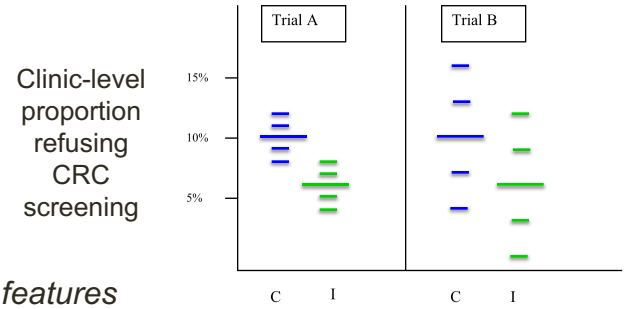
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

Study features

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

Adapted from Hayes & Moulton (2009)

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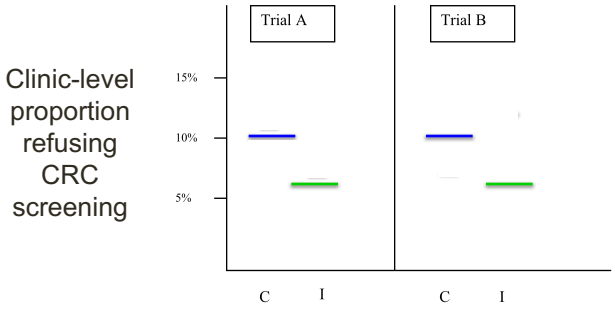
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

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

Adapted from Hayes & Moulton (2009)

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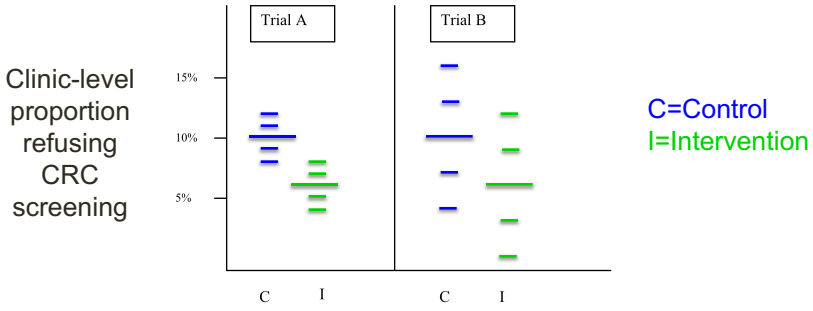
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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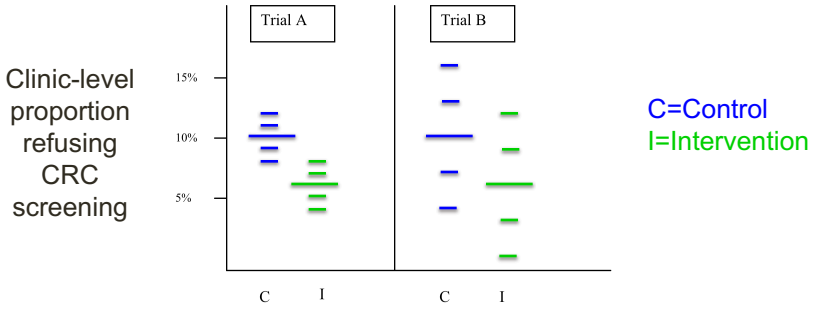
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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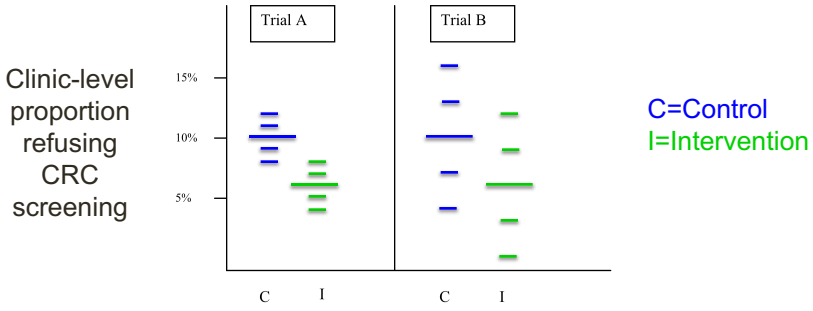
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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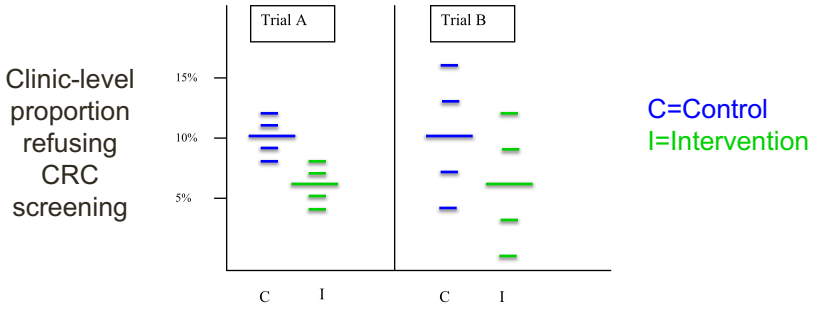
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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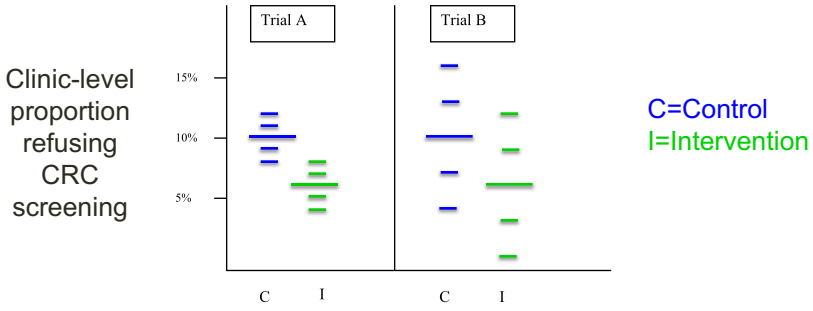
Clustering in CRTs: Implications for analysis



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

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

Adapted from Hayes & Moulton (2009)

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Summary: Analysis of two example CRTs

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

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Analysis of CRTs, including SW-CRTs

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

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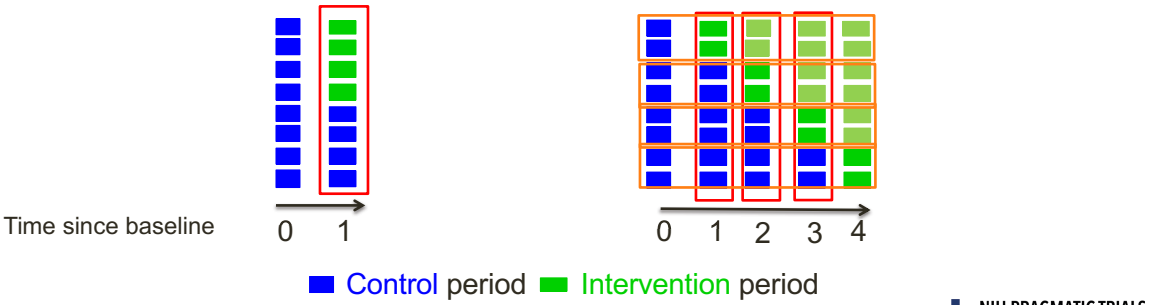
Analysis of CRTs, including SW-CRTs

Parallel design

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

Complete SW design

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



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

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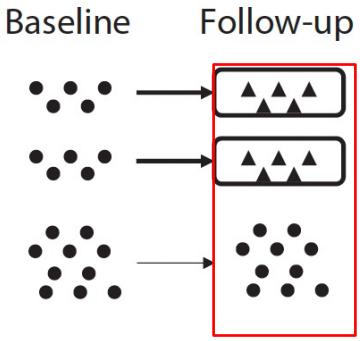
Analysis of IRGT trials



Parallel design

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

▲ Individual measured under intervention
● Individual measured under no intervention

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

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Analysis of IRGT trials

- Analyze individual-level data accounting for clustering
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
- Considerations on clustering
  - Clustering in both arms: if both conditions group-based & may need different degree of clustering in two arms
  - Clustering in intervention arm only: if intervention group-based but control condition not
  - Clustering due to shared agents or group-based intervention delivery often overlooked

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Analysis of CRTs, SW-CRTs, and IRGTs

- Clustering must be accounted for in analysis
- Challenges in “small” trials (# clusters < 50)
  - Intervention effect SE may be under-estimated
    - Mixed Models: degree of freedom
    - GEE: small sample adjustments corrections
  - Ignoring can lead to inflated Type I error
    - Type I error rate may be 30-50% in a CRT, even with small ICC
    - Type I error rate may be 15-25% in an IRGT, even with small ICC

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Strategies to protect the analysis

Avoid model misspecification

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

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Strategies to protect the analysis

Avoid low power

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

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NIH Collaboratory: examples of analytic challenges and trade-offs

- Stepped wedge designs "roll out" over time and are more susceptible to disruption!
- Parallel cluster randomized designs are simple and powerful, but still need to address "clustering" for design and analysis.
- Individually randomized group treatment trial designs have benefits of individual-level randomization, but still need to address clustering due to shared agents or group-based interventions in design and analysis.

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Knowledge Checkpoint

Researchers are interested in the effect of participation in support groups vs. usual care on weight loss. Participants in the intervention attend group meetings, while usual care involves no group meetings. Out of 20 enrolled participants, 10 are randomly assigned to the intervention arm and attend support groups. Two therapists each lead a support group that meets on different weekday nights. Participant BMI will be measured at baseline (before randomization) and at 3 months.

- What are some sources of variation and correlation that should be accounted for in the analysis?

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Effectiveness-Implementation Hybrid Trial Designs

Embedded Pragmatic Clinical Trials

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

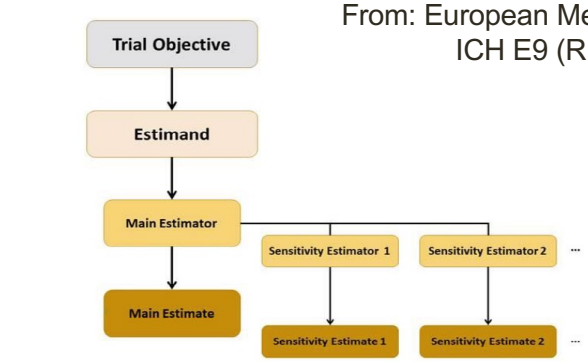

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Effectiveness and Implementation

- Trials often study both effectiveness and implementation outcomes.
- Effectiveness outcomes focus on how successful the trial was in addressing a health issue
  - Measured health outcomes, functional ability, quality of life, etc.
- Implementation outcomes focus on how the trial was implemented and delivered
  - Acceptability, adoption, appropriateness, cost, feasibility, fidelity, reach, etc.

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Hybrid Designs

- Curran et al. (2012) introduced the hybrid effectiveness-implementation designs
  - Hybrid Type I tests a clinical intervention while gathering information on implementation
  - Hybrid Type II simultaneously tests a clinical intervention and an implementation intervention or strategy
  - Hybrid Type III tests an implementation intervention or strategy while gathering information on effectiveness
- "Hybrid Design" is in hindsight a somewhat unfortunate choice of words
  - Suggests that implementation research had different methods than other research and might not be held to the same standard as other research
  - The same rigorous methods for implementation research that we use for other research, changing only the focus

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Hybrid Studies

- Curran et al (2022) updated their original description of hybrid designs, labeling them as **hybrid studies** without offering designs for each type.
- The usual trial evaluates a single intervention strategy delivered with a single implementation strategy as a package and it is not possible to distinguish the effects of the two strategies.
- In contrast, implementation trials compare intervention strategies and/or implementation strategies.

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Hybrid Study Design Prototypes

- Stevens et al (2023) outline three design prototypes
- Type I (Effectiveness) requires at minimum a two-arm trial:
  1. No Intervention
  2. Intervention
  - ➢ Compare: No Intervention vs. Intervention
- Type II (both) requires at minimum a three-arm trial:
  1. No Intervention
  2. Intervention
  3. Intervention with Enhanced Implementation Strategy
  - ➢ Compare: No Intervention vs. Intervention vs. Intervention with Enhanced Implementation Strategy
- Type III (Implementation) requires at minimum a two-arm trial:
  1. Intervention
  2. Intervention with Enhanced Implementation Strategy
  - ➢ Compare: Intervention vs. Intervention with Enhanced Implementation Strategy

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Other Issues in Hybrid Studies

- Addressing clustered outcomes
  - Usual issues with ICC, small effective sample size, etc
  - Implementation outcomes are often cluster-level outcomes
- Masking of study arms
  - Routine in most clinical trials, helps guard against bias
  - However, many implementation outcomes serve as process variables (e.g. reach, adoption, fidelity)
  - Need to put into place practices that protect against bias but allow dedicated implementation staff to encourage adherence to study protocol and allow for feedback to stakeholders
- Adaptation of the intervention
  - Uncommon in most clinical trials
  - Adaptive interventions allow adaptations of the intervention using a prespecified process that describe what and when changes can be made
  - Limited guidance for implementation studies (Murray et al 2023):
    - Anticipated changes to the protocol should be pre-specified, as with any other adaptive intervention
    - Protocol changes should be approved of in advance

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Resource: The Living Textbook

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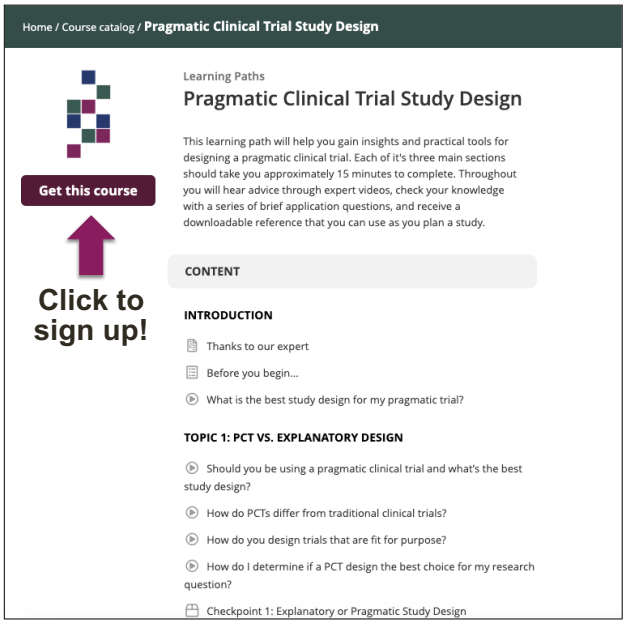
- Expert-led content, reference materials, and knowledge checkpoints
- Insights on how to:
  - Select the most appropriate study design for a pragmatic trial
  - Make decisions about randomization
  - Choose between parallel and stepped-wedge design

– Visit rethinkingclinicaltrials.org/training-resource/



Summary: Important things to know

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

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NIH resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  - https://prevention.nih.gov/GRTcourse
  - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
  - https://prevention.nih.gov/MindTheGap
    - Deconstruction of the Type 2 Hybrid Effectiveness-Implementation Study Design that Uses Two Randomized Controlled Trials (June Stevens, March 20, 2024)
    - Toward Causal Inference in Cluster Randomized Trials: Estimands and Reflection on Current Practice (Fan Li, November 3, 2022)
    - Robust Inference for Stepped Wedge Designs (Jim Hughes, May 17, 2022)
    - When is the Stepped Wedge Study a Good Study Design Choice? (Karla Hemming, January 21, 2022)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs, IRGTs, SWGRTs and a sample size calculator for each
  - Information on hybrid effectiveness-implementation studies

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Recommended reading

- Brown CH et al. Accounting for context in randomized trials after assignment. Prev Sci. 2022. PMID: 36083435.
- Curran GM et al. Reflections on 10 years of effectiveness-implementation hybrid studies. Front Health Serv. 2022. PMID: 36925811.
- Hemming K, Taljaard M. Reflection on modern methods: When is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol. 2020. PMID: 32386407.
- Hemming K, Taljaard M. Key considerations for designing, conducting and analysing a cluster randomized trial. Int J Epidemiol. 2023. PMID: 37203433.
- Hughes JP et al. Sample size calculations for stepped wedge designs with treatment effects that may change with the duration of time under intervention. Prev Sci. 2023. PMID: 37728810.
- Kenny A et al. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. Stat Med. 2022. PMID: 35774016.
- Kahan BC et al. Estimands in cluster-randomized trials: Choosing analyses that answer the right question. Int J Epidemiol. 2022. PMID: 35834775.
- Murray DM et al. Essential ingredients and innovations in the design and analysis of group-randomized trials. Ann Rev Public Health. 2020. PMID: 31869281
- Murray DM et al. Implementation Research at NHLBI: Methodological and Design Challenges and Lessons Learned from the DECIPHeR Initiative. Ethn Dis. 2023. PMID: 38846726.
- Stevens J et al. Design of a dual randomized trial in a type 2 hybrid effectiveness-implementation study. Implement Sci. 2023. PMID: 37996884.

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Question & Answer

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Resources:

ePCT Experimental Design & Analysis

Living Textbook readings

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

NIH Research Methods

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

Collaboratory Grand Rounds webinar recordings & slides

- Lessons Learned from the NIH Collaboratory Biostatistics and Design Core

Key journal articles

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

Additional resources

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

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Pilot & Feasibility Testing

Speaker

Beda Jean-Francois, PhD

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

Pilot & Feasibility Testing

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Learning goals

- Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions

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Important things to know

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

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ePCTs are not efficacy trials

- ePCTs bridge research into clinical care
- Intervention is integrated into real-world healthcare settings
- Involves streamlined data collection
- Pragmatic does not always mean low cost

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During the pilot phase

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

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Build partnerships

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

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Aspects of feasibility that can be piloted

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

Use what you learn to design the ePCT

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Evaluate power calculations

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

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Quantify feasibility for pilot study aims

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

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

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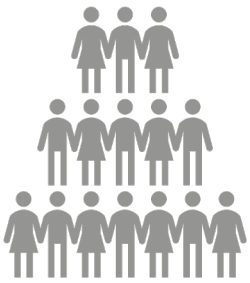
Quantifying example 1



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

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

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Quantifying example 2

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

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

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Quantifying example 3

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

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

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Ensuring trial readiness

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

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Readiness checklist

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

Implementation Readiness Checklist available on the Living Textbook

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In the end, good planning will help

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

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Important things to do

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

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Resources

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

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

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Resource: The Living Textbook

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Question & Answer

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Resources:

Pilot and Feasibility Testing

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Ethics & Regulatory Oversight Considerations

Speaker

Stephanie Morain, PhD, MPH

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

Ethical & Regulatory Oversight Considerations

Stephanie Morain, PhD, MPH
Associate Professor
Johns Hopkins Bloomberg School of Public Health
and Berman Institute of Bioethics

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Learning goals

- Learn about the regulatory and ethical challenges of conducting ePCTs
- Discuss unique needs of groups historically underrepresented in research

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Important things to know

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

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ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions

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Evolving understanding of ethical/regulatory issues for ePCTs

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

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Article

CLINICAL TRIALS

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Exploring the ethical and regulatory issues in pragmatic clinical trials

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

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

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

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Evolving understanding of ethical/regulatory issues for ePCTs

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

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Informed Consent, Waivers, and Alterations

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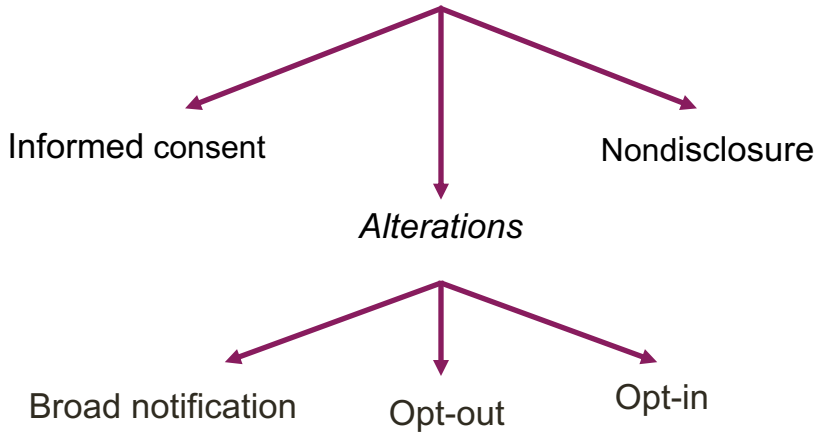
Approaches to notification & authorization



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Knowledge Checkpoint

- True or false: The same regulatory criteria apply for both waivers and alterations of consent.

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Knowledge Checkpoint

- Which of the following is NOT an acceptable justification for waiving or altering informed consent?

  a. Research involves no more than minimal risk

  b. Research could not practicably be carried out without the waiver or alteration

  c. Refusals to participate could bias the study results

  d. Waiver or alteration will not adversely affect the rights and welfare of the subject

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Criteria for waiver/alteration of consent

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

Common Rule: 45 CFR 46.116(f)

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Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

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

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Distinguishing research risks

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

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Regulatory permissible ≠ ethically optimal

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

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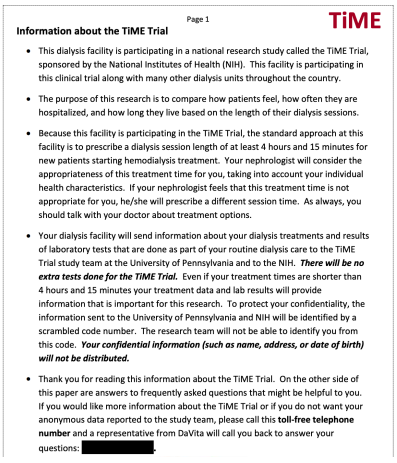
Examples: Information sheets or flyers

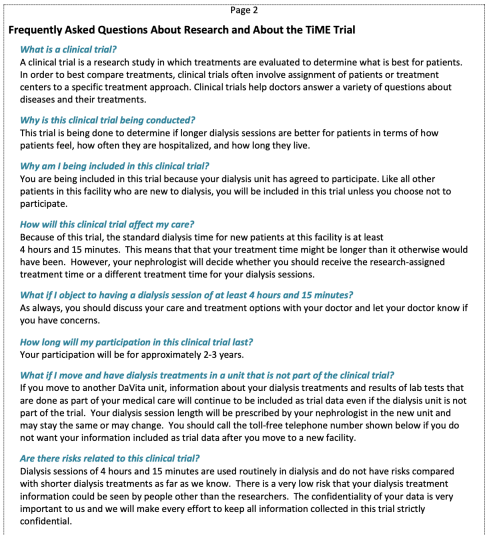


Page 1

TiME

Information about the TiME Trial

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



Page 2

Frequently Asked Questions About Research and About the TiME Trial

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

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

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

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

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

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

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

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

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Discussion

- Why might a study team notify patients about a PCT, even if the study meets the regulatory criteria for a waiver of consent?

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Data and Safety Monitoring

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

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

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Data monitoring committee

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

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Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct & implications for early termination
- Differential data collection/contact by study arm

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

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Unique considerations for monitoring ePCTs

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

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

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Data Sharing & PCTs

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Increasing expectation for sharing clinical trials data

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Challenges for Sharing PCT Data

Often conducted with waivers or alterations of informed consent

Use of extant data (e.g., EHR, claims)

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If PCT uses a waiver/alteration of consent…

- Cannot assume sharing data is consistent with preferences of patient-subjects
- Cannot rely on informed consent to fulfill ethical obligation of respect

What does it mean to <u>respect</u> patient-subjects in the context of (not) sharing data from a PCT conducted under a waiver/alteration of informed consent?

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Implications of Embeddedness for PCT Data Sharing

- Data may be “about” those beyond patient-subjects
- Increased risk of privacy violations
- Increased risk of biased/misleading analyses
- Data may be controlled by a third party (e.g, CMS)

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PCTs and Underrepresented Groups

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PCTs, equity, and underrepresented groups

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

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Promoting equity and representativeness

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

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POLICY ANALYSES

Learning Health Systems

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

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

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

Special Article | Free Access

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

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

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

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Important things to do

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

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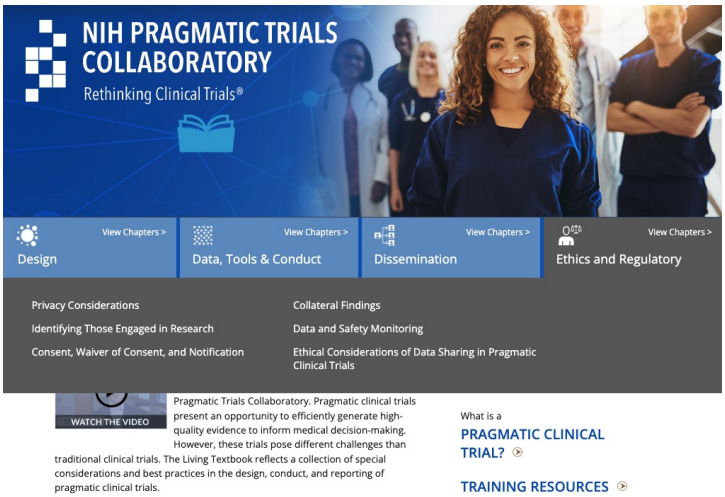
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



Question & Answer

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Resources:

Ethical and Regulatory Considerations

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Writing a Compelling Grant Application

Speaker

Beda Jean-Francois, PhD

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

Writing a Compelling Grant Application

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Learning goal

- Learn how to develop a compelling ePCT application
- Tips from NIH Collaboratory Trial PIs

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Important things to know

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

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National Institutes of Health

NIH
National Institutes of Health

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

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Find the right NIH program official

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

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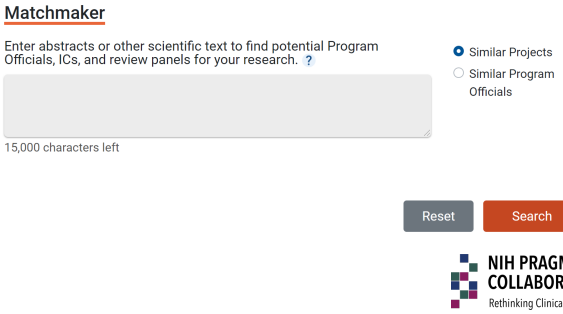
NIH RePORTER matchmaker tool

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



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Matchmaker results (example)

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

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Find the right NOFO

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

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NIH scientific contacts

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

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Tailor the application

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

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Common application pitfalls

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

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Application dos

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

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Application don’ts

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

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Strategies for success

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

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NIH online resources

https://researchmethodsresources.nih.gov/

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

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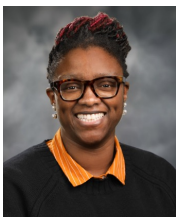
Think through team diversity

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

NIH Pragmatic Trials Collaboratory Fellowship



Dr. Stephanie Ibemere
Implementation Science Core
GRACE Demonstration Project

Dr. Kaitlyn McLeod
Health Equity Core
Nudge Demonstration Project

- Early career investigators from underrepresented minoritized (URM) groups
- 1 year fellowship (July 2023-June 2024)
- Embedded in Core Working Group and research with a Demonstration Project
- Curriculum focused on pragmatic clinical trials
- Both fellows continue to engage with Core Working Groups
- Stephanie has submitted a diversity supplement to extend her fellowship
- Kaitlyn is a first-year cardiovascular medicine fellow and is working on a manuscript with the Health Equity Core

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Important things to do

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

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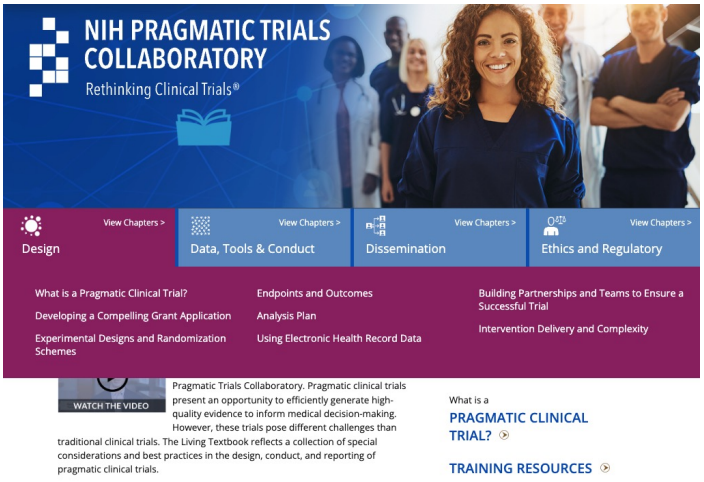
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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Tips from the Demonstration Projects

- What is 1 key tip you would recommend for developing a strong UG3 or UH3 pragmatic grant proposal?

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Question & Answer

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Resources:

Writing a Compelling Grant Application

Living Textbook readings

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

Key journal articles

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

Other

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

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ePCTs in Context: Small Group Work and Panel Discussion with Trial Investigators

Moderator

Stephanie Morain, PhD, MPH

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

ePCTs in Context

Small Group Work and Panel Discussion With Trial Investigators

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

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NIH Collaboratory Trial Panelists

- Andrea Cheville, MD
  - NOHARM
- Julie Fritz, PhD, PT
  - BeatPain Utah
- Michael Ho, PhD, MD
  - Nudge, Chat 4 Heart Health
- Sebastian Tong, MD, MPH
  - AIM-CP

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Learning goals

- 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 & lessons learned of the afternoon topics, to include Q&A

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Small Group Discussion

AIM-CP: Assessing Feasibility

- AIM-CP is partnering with health systems in rural areas that may lack familiarity with conducting research and have different expectations related to research activities. **How would you approach this challenge?**

BeatPain Utah: Assessing Feasibility

- The pilot phase demonstrated that the patients in BeatPain Utah had less predictable work hours, multi-generational homes or housing instability, and limited tech for video visits. **What strategies would you use to overcome these obstacles?**

Chat 4 Heart Health: Regulatory Oversight Considerations

- The Nudge trial was approved for an opt-out approach, where patients received a letter in the mail and were automatically enrolled in the study unless they opted-out. Chat 4 Heart Health was approved for the same approach, but the Federal Communications Commission changed a rule to state that recipients of text messages must opt-in to receive them. **How would you approach this challenge?**

NOHARM: Measuring Outcomes

- NOHARM researchers wanted to measure changes in a pain score as their primary outcome but realized obtaining complete patient-reported data over time could be a barrier. **How would you approach this challenge?**

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Reflecting on the Afternoon Topics

- Measuring outcomes
- ePCT design and analysis
- Pilot and feasibility testing
- Ethical and regulatory oversight considerations
- Writing a grant application

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Question & Answer

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Resources:

ePCTs in Context: Panel Discussion

AIM-CP

- UG3 Project: Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients with Chronic Pain (AIM-CP)

BeatPain Utah

- UH3 Project: Nonpharmacologic Pain Management in Federally Qualified Health Centers Primary Care Clinics (BeatPain Utah)

Chat 4 Heart Health

- UH3 Project: Using Artificially Intelligent Text Messaging Technology to Improve American Heart Association's Life's Essential 8 Health Behaviors (Chat 4 Heart Health)

NOHARM

- UH3 Project: Nonpharmacologic Options in Postoperative Hospital-based and Rehabilitation Pain Management (NOHARM)

Nudge

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

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Closing Remarks

Speaker

Emily O'Brien, PhD

Associate Professor of Population Health Sciences
Department of Population Health Sciences
Duke University School of Medicine

Closing Remarks: Embedded Pragmatic Clinical Trials

Emily O'Brien, PhD
Associate Professor of Population Health Sciences
Department of 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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