NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Dissemination and Implementation Research Methods and Embedded Pragmatic Trials:

Strategies for Designing Studies That Inform Care for Diverse Populations

Participant Guide

15th Annual Conference on the Science of Dissemination and Implementation in Health

December 11, 2022

NIH PRAGMATIC TRIALS COLLABORATORY

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Dissemination & Implementation Research Methods and Embedded Pragmatic Trials: Strategies for Designing Studies That Inform Care for Diverse Populations

15th Annual Conference on the Science of Dissemination and Implementation in Health
Walter E. Washington Convention Center, Washington, DC
December 11, 2022

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
8:00-8:45 am	**What are Embedded Pragmatic Clinical Trials (ePCTs)?**	Wendy Weber	• Welcome and introduction of agenda and objectives • 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, and when a pragmatic approach can be used to answer the research question
8:45-9:05 am	**Engaging Stakeholders & Aligning with Health System Partners**	Emily O'Brien	• Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study • 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
9:05-9:30 am	**Objectives and Trial Design: An Overview of Hybrid Designs**	Emily O'Brien	• Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs
9:30-10:00 am	**Measuring Outcomes**	Emily O'Brien	• Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) • Discuss the integration of a health equity lens in evaluating outcomes

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
10:00-10:30 am	**ePCT Design**	David Murray	• Learn about cluster randomized and stepped-wedge study designs
10:30-10:45 am	**Break**		• Networking among attendees and presenters
10:45-11:15 am	**ePCT Analysis**	David Murray	• Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what principal investigators (PIs) need to know
11:15 am- 12:15 pm	**ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Emily O'Brien **Panel:** ACP PEACE: Angelo Volandes BeatPain Utah: Julie Fritz GGC4H: Margaret Kuklinski ICD-Pieces: Miguel Vazquez	• Introduce PIs of 4 ongoing ePCTs to reflect on the morning topics and discuss challenges, solutions, and lessons learned • Q & A with attendees
12:15-1:15 pm	**Lunch**		• Networking among attendees and presenters
1:15-1:45 pm	**Pilot & Feasibility Testing**	Wendy Weber	• Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions
1:45-2:15 pm	**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
2:15-3:15 pm	**ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Wendy Weber **Panel:** ACP PEACE: Angelo Volandes BeatPain Utah: Julie Fritz GGC4H: Margaret Kuklinski ICD-Pieces: Miguel Vazquez	• Introduce PIs of 4 ongoing ePCTs to reflect on the afternoon topics and discuss challenges, solutions, and lessons learned • Q & A with attendees
3:15-3:30 pm	**Break**		• Networking among attendees and presenters

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
3:30-4:30 pm	**Assembling an ePCT Team & Writing a Grant Application**	Beda Jean-Francois	• Identify skills needed for a strong study team • Learn how to develop a compelling ePCT application • Consider the diversity of the team, including inclusive practices • Tips from Collaboratory PIs
4:30-4:45 pm	**Next Steps**	Wendy Weber	• Final Q & A • Wrap-up including identifying sources for further learning

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Speaker Biographies

Julie Fritz, PhD, PT
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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.

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.

Dr. Jean-Francois earned her PhD in applied developmental psychology and a master's degree in education with an emphasis on learning and reading disabilities from the University of Miami in Coral Gables, Florida, in 1999.

Margaret Kuklinski, PhD
University of Washington
mrk63@uw.edu

Margaret Kuklinski, PhD, is associate professor and director of the Social Development Research Group (SDRG), School of Social Work, University of Washington. Her work aims to promote positive developmental outcomes by demonstrating the long-term impact of effective family-focused and community-based preventive interventions; partnering with communities, agencies, and services systems to implement and scale them; and building policy support for preventive interventions by demonstrating their benefits and costs.

Dr. Kuklinski currently serves as co–principal investigator on a multisite trial testing the feasibility and effectiveness of implementing Guiding Good Choices, a prevention program for parents of adolescents, in 3 large healthcare systems. She is also co–principal investigator on the longitudinal evaluation of the Communities That Care prevention system, which has demonstrated impact on preventing drug use and antisocial behavior from adolescence into young adulthood. Under NIDA's HEAL Prevention Initiative she cochairs the Health Economics Working Group, which is examining the cost-effectiveness of a set of projects aimed at developing effective approaches to preventing opioid misuse in adolescents and young adults.

Dr. Kuklinski received a PhD in psychology from the University of California, Berkeley, and an AB in economics from Harvard University.

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

Stephanie Morain, PhD, MPH is an assistant professor at Johns Hopkins University in the Department of Health Policy and Management in the Bloomberg School of Public Health and the Berman Institute of Bioethics. She conducts both empirical

and normative research into issues at the intersection of ethics, law, and health policy.

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

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

David Murray, PhD
Office of Disease Prevention, NIH
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David Murray, PhD, has spent his career evaluating interventions designed to improve the public health. He has focused on the design and analysis of group- or cluster-randomized trials in which groups are randomized to conditions and members of those groups are observed to assess the effect of an intervention. He wrote the first textbook on that material, published by Oxford University Press in 1998. He has worked on many of these trials, collaborating with colleagues around the country, and has conducted research to develop and test new methods for their design and analysis. After 35 years at the University of Minnesota, the University of Memphis, and the Ohio State University, Dr. Murray joined the NIH in September 2012, as the associate director for prevention and director of the Office of Disease Prevention. He is responsible for promoting and coordinating prevention research among and between NIH Institutes and Centers and other public and private entities. The Strategic Plan for the Office for 2019 through 2023 identifies 6 priorities related to portfolio analysis, evidence gaps, prevention science methods, trans-NIH research initiatives, tobacco regulatory science and prevention, health disparities, and communications. For more information, see https://prevention.nih.gov/about-odp/staff-directory/david-m-murray-phd.

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

Emily O'Brien, PhD, is an associate professor in population health sciences at the Duke University School of Medicine. An epidemiologist by training, Dr. O'Brien's research focuses on comparative effectiveness, patient-centered outcomes, and pragmatic health services research in chronic disease. Dr. O'Brien's expertise is in systematic assessment of medical therapies in real-world settings, including long-term safety and effectiveness assessment. She is the principal investigator for projects focusing on the linkage and use of secondary data, including administrative claims, clinical registries, and electronic health record data. Dr. O'Brien is the principal investigator for studies funded by the Food and Drug Administration (FDA), NIH, and PCORI. 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 *Circulation: Cardiovascular Quality and Outcomes*.

Miguel A. Vazquez, MD
UT Southwestern Medical Center
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Miguel A. Vazquez, MD, is professor of internal medicine at UT Southwestern Medical Center in Dallas and the clinical chief of the Nephrology Division at UT Southwestern and nephrology chief of service at Parkland Hospital in Dallas. His patient care specialties include chronic kidney disease, end-stage kidney disease, and kidney transplantation. He attended medical school at the University of Puerto Rico in San Juan, and moved to UT Southwestern for his internship and residency in internal medicine. He also completed his fellowship in nephrology and research in immunology and transplantation at UT Southwestern.

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

Angelo Volandes, MD, MPH
Harvard Medical School
Massachusetts General Hospital
angelo@acpdecisions.org

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.

Wendy Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH)
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Wendy Weber, ND, PhD, MPH, is the branch chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research in the National Center for Complementary and Integrative Health at NIH. She joined NCCIH as a program director in 2009. The Clinical Research Branch is responsible for the oversight of all NCCIH-supported clinical trials. Dr. Weber is the programmatic lead for the Trans-NIH Pragmatic Trials Collaboratory and the program officer for the Coordinating Center. She cochairs the Translating Research to Practice for the Treatment of Opioid Addiction Team within the NIH HEAL Initiative and oversees the Pragmatic and Implementation Studies for the Management of Pain (PRISM) program. Dr. Weber is also a member of the planning and oversight team for the NIH-DoD-VA Pain Management Collaboratory and project scientist for its Coordinating Center. She is also the coordinator for NCCIH's Clinical Trial Specific Funding Opportunity Announcements (FOAs) and point of contact for natural product–related clinical trial FOAs. Dr. Weber serves on several trans-agency committees, including serving as one of the NIH representatives to the Leadership Council for the Department of Health and Human Services Office of the Secretary Patient Centered Outcomes Research Trust Fund and as a member of the Centers for Medicare & Medicaid Services–NIH Opioid Working Group, and she leads the Evidence for Non-Pharmacological Treatments subgroup.

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

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GOAL

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

WHAT ARE EMBEDDED PRAGMATIC CLINICAL TRIALS (EPCTS)?

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

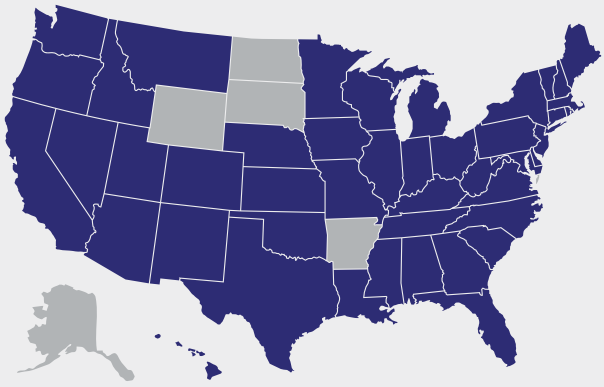
PROGRAM

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

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

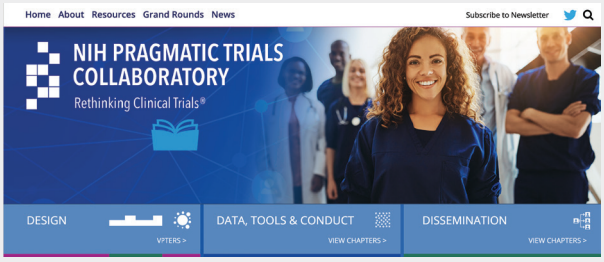
23 DEMONSTRATION PROJECTS

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



RESOURCES

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



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

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

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

Plus:

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

Visit the Living Textbook:
www.rethinkingclinicaltrials.org

HOW IS A CLINICAL TRIAL CONSIDERED PRAGMATIC?

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

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

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

Visit the Living Textbook:
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Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP PEACE)

Principal Investigators
James A. Tulsky, MD, and Angelo Volandes, MD, MPH

Sponsoring Institution
Dana-Farber Cancer Institute

Collaborators
- Massachusetts General Hospital
- Boston Medical Center
- Duke University
- Feinstein Institute for Medical Research (Northwell Health)
- Mayo Clinic

NIH Institute Providing Oversight
National Institute on Aging (NIA)

Program Official
Marcel E. Salive (NIA)

Project Scientist
Jeri Miller (National Institute of Nursing Research [NINR])

ClinicalTrials.gov Identifier
NCT03609177

ABSTRACT

Too many older Americans with advanced cancer die every year receiving aggressive interventions at the end of life that do not reflect their values, goals, and preferences. Advance care planning (ACP) is the most consistent modifiable factor associated with better end-of-life communication and goal-concordant care. However, clinicians often do not possess the communication skills needed for high-quality ACP conversations, and patients are often unable to imagine their options for medical care to make informed decisions.

The ACP PEACE Demonstration Project combines two well-tested, evidence-based complementary interventions: clinician communication skills training (VitalTalk) and patient video decision aids (ACP Decisions). This approach treats patients and clinicians as equal stakeholders, providing both with the communication skills and tools needed to optimally make informed decisions before the toughest choices arise. ACP PEACE is a pragmatic, cluster-randomized, stepped-wedge trial that will be conducted in three large healthcare systems. The study will use established electronic health record (EHR) systems at each health system to obtain outcomes. It is proposed that a higher proportion of patients in the intervention arm will complete advance care plans, have documented electronic medical orders for resuscitation preferences, be seen in palliative care consultations, and enroll in hospice. The ACP PEACE study will monitor long-term outcomes to evaluate whether patients received the care they planned for and wanted.

WHERE CAN ACP VIDEOS BE VIEWED?

View at Home

View in a Clinical Setting

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Most clinicians do not use the structured variable in the EHR that the study team planned to use to extract the primary outcome.	The study team developed a workaround that uses natural language processing to abstract the primary outcome from the free text of the clinical note in the EHR.
Some participating health systems have not established a method for patients to opt out of having their deidentified data used for research purposes.	The study team plans to use a "broadcast notification" that displays posters or other notices in healthcare settings that let patients know they can opt out if they have a concern about their deidentified data being shared for research purposes.

"Make sure you get appropriate buy-in from enough stakeholders to know that you're going to get the project done."

SELECTED PUBLICATIONS & PRESENTATIONS

- June 2019: Interview with ACP PEACE PIs in *Living Textbook*
- February 2019: PCT Grand Rounds webinar

ACP PEACE: Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly

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

ACP PEACE

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Objective

- To test implementation of an advance care planning (ACP) program that combines clinician communication skills training and patient video decision aids
- Focused on patients with advanced cancer and their clinicians in oncology settings

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Study design

- Stepped-wedge, cluster randomized trial
- 4500 patients aged 65 years and older with advanced cancer
- 36 oncology clinics in 3 healthcare systems

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Outcomes

- Advance care plans completion
- Medical orders for resuscitation preferences
- Palliative care consultations
- Hospice use
- Will also characterize detailed patient-centered outcomes in a subgroup of 450 patients, including video declarations of individual preferences

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Participating healthcare systems

- Duke Health
- Northwell Health
- Mayo Clinic

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Barriers/challenges

- Incomplete and variable content of structured data ACP documents
- Impacts of the COVID-19 pandemic
- Transition to online communication skills training
- Transition to emailing/texting/mailing links to videos
- In-person vs telehealth visits
- Revised design

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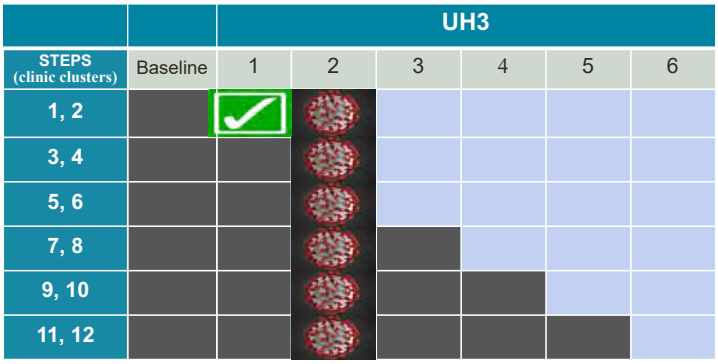
Original Design



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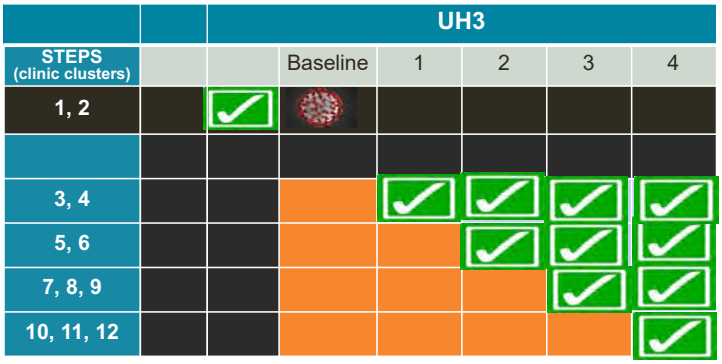
Revised Design



- Steps 1-2: ACP rates before and after intervention
- Steps 3-12: Intervention effect post-COVID-19

- **COVID-19 effect:** Will estimate pre-COVID ACP rate from original baseline plus Step 1; post-COVID ACP rate from Step 2 data. Will also examine trends over time.

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Data Challenges

TABLE 3. CHART REVIEW CONTENT OF STRUCTURED DATA ADVANCE CARE PLANNING DOCUMENTS BY CLASSIFICATION

Chart review classification N = *total number of documents*	*Site 1 (N = 55)*[a]	*Site 2 (N = 176)*[a]	*Site 3 (N = 132)*[a]	*Overall (N = 363)*
1. Data elements that represent unique advance care planning documents (correct)				
Advance directive/description of EOL wishes	14 (25.5)	104 (59.1)	1 (0.8)	119 (32.8)
MOLST/out of hospital code status	0 (0.0)	17 (9.7)	7 (5.3)	24 (6.6)
Post-mortem instructions	0 (0.0)	4 (2.3)	0 (0.0)	4 (1.1)
HCP/DPOA for health care	13 (23.6)	22 (12.5)	33 (25.0)	68 (18.7)
Total correct documents	**27 (49.1)**	**147 (83.5)**	**41 (31.1)**	**215 (59.2)**
2. Data elements that represent blank, not available/completed documents, or those that do not represent ACP (incorrect)				
Blank or incomplete document	0 (0.0)	4 (2.3)	2 (1.5)	6 (1.7)
Reports as asked, but not completed	0 (0.0)	0 (0.0)	29 (22.0)	29 (8.0)
Reports as available, but document not present	18 (32.7)	1 (0.6)	13 (9.8)	32 (8.8)
Wrong document (i.e., Consent Form, Procedural Safety Checklist, HIPAA Release)	2 (3.6)	11 (6.2)	6 (4.5)	19 (5.2)
Total incorrect documents	**20 (36.4)**	**16 (9.1)**	**50 (37.9)**	**86 (23.7)**
3. Duplicate documents (identical to another form)	**8 (14.5)**	**13 (7.4)**	**41 (31.1)**	**62 (17.1)**

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Solutions/lessons learned

- Online trainings and viewings are highly acceptable
- Hybrid is here to stay (in-person and telehealth)
- Redundancy in intervention exposure (EHR, text, in-person, waiting room, etc)
- Stepped-wedge design is not the design of choice
- "We argue that the mere popularity and novelty of the SW-CRT should not be a factor in its adoption. In situations when a conventional parallel-CRT is feasible it is likely to be the preferred design."

Ellenberg SS. The stepped-wedge clinical trial: evaluation by rolling deployment. *JAMA*. 2018 Feb 13;319(6):607-608. doi: 10.1001/jama.2017.21993. PMID: 29450512.

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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/National Center for Medical Rehabilitation Research)

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 healthcare 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." — Dr. Julie Fritz

PRESENTATIONS & ABSTRACTS

- Video Interview: BeatPain Utah Takes Pragmatic Research to New Frontiers (August 23, 2021)
- Presentation: Presentation to the NIH Collaboratory Steering Committee (April 15, 2021)

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

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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

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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

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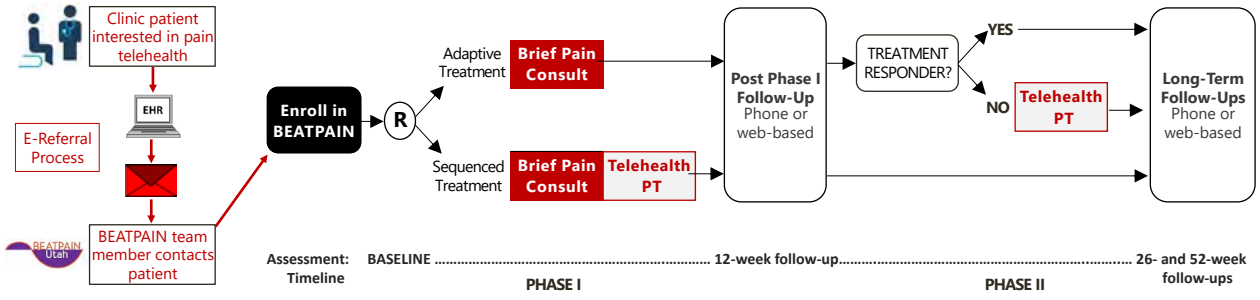
Study design



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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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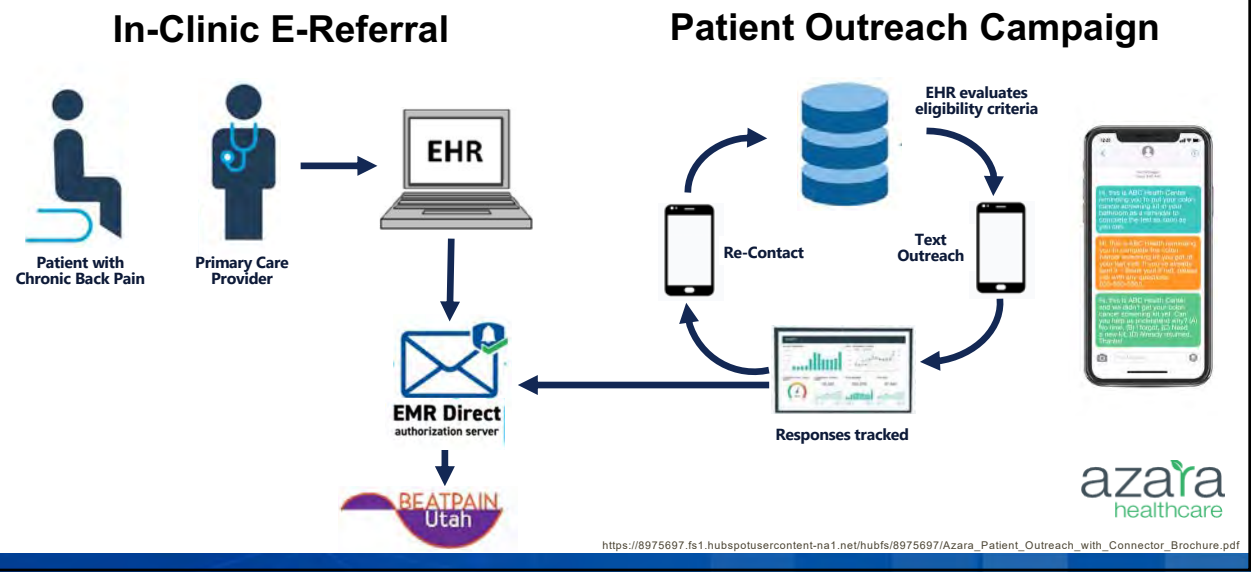
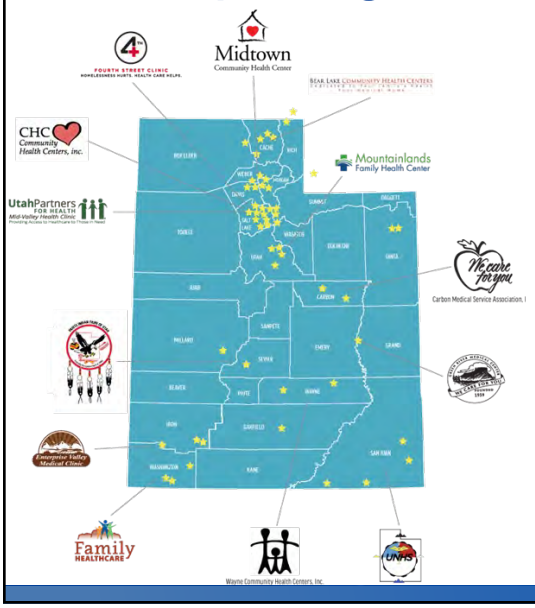
Implementation strategies



Participating healthcare systems



AUCH ASSOCIATION FOR UTAH COMMUNITY HEALTH

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

- Cumulative impact of successive COVID-19 waves
- Staffing challenges for providers and support personnel
- “Research fatigue” in FQHC settings
- Restrictions on in-person opportunities for clinic staff training and engagement
- Building trust between the academic medical center and FQHC leadership, staff, and communities served

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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
- Ongoing research staff training on cultural competencies and justice considerations for FQHC clinics and the communities they serve

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Guiding Good Choices for Health (GGC4H)

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

Sponsoring Institution
University of Washington

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

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

Program Official
Robin Boineau (NCCIH)

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

ClinicalTrials.gov Identifier
NCT04040153

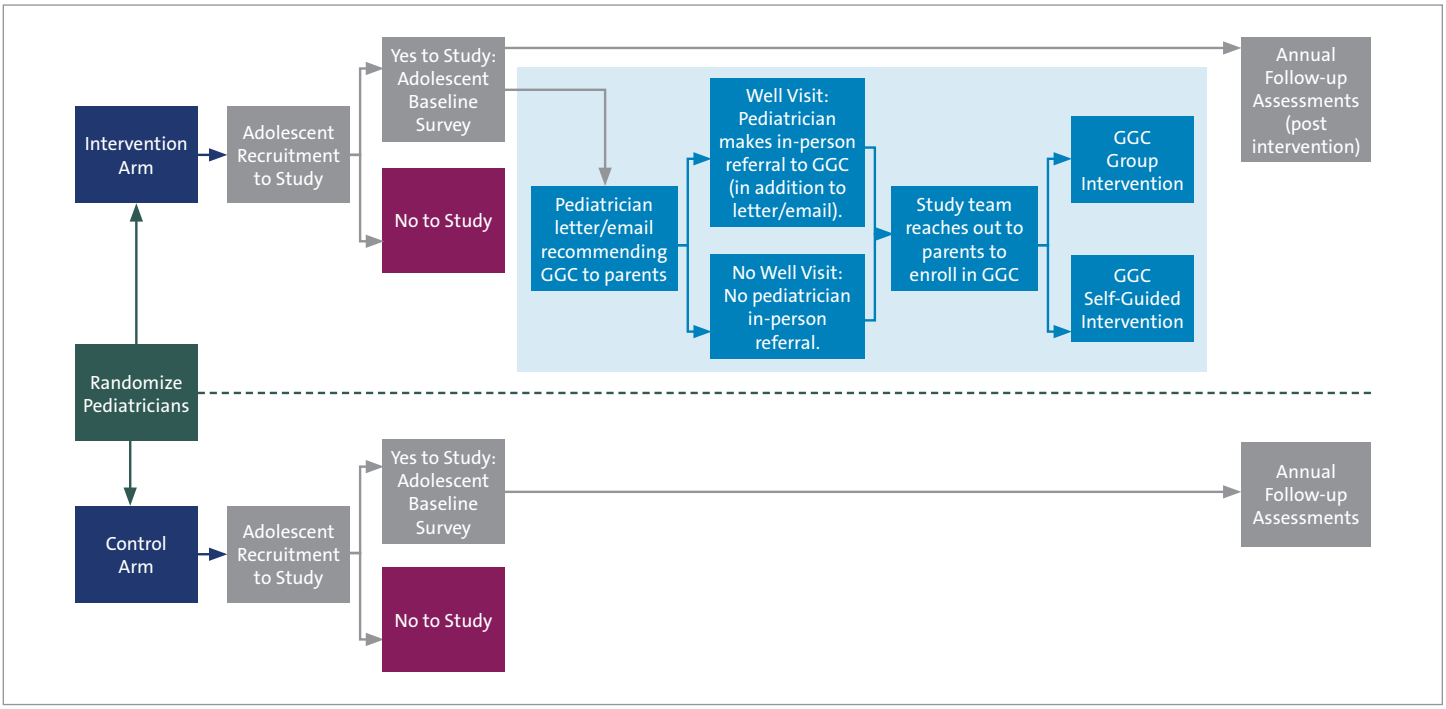
ABSTRACT

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

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

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

GGC4H Effectiveness Design



WHAT WE'VE LEARNED SO FAR

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

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

SELECTED PUBLICATIONS & PRESENTATIONS

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

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

Margaret Kuklinski, PhD
Associate Professor of Social Work
University of Washington

GUIDING GOOD CHOICES

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Objectives

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

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Guiding Good Choices (GGC)

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

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

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Study design

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

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Barriers/challenges

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

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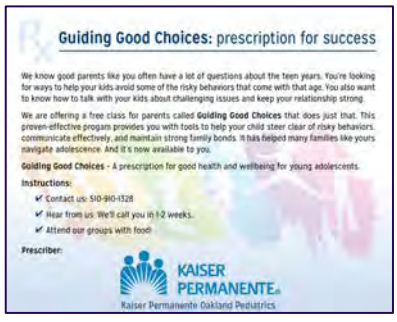
Pragmatic implementation: Key leader support

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

Pediatrician referral "scripts"

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

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



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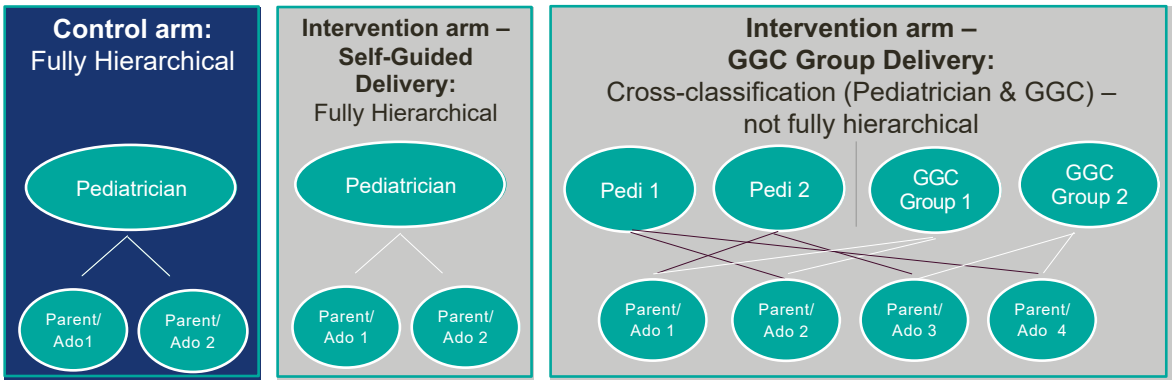
Pragmatic implementation: study design



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

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

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

- Developed Adolescent Behavioral Health Survey to collect data on behavioral health outcomes; widely used, validated measures
- Administered online or by telephone with trained interviewers

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COVID-19 → Virtual GGC

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

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

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

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Solutions/lessons learned

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

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ICD-Pieces: Improving Chronic Disease Management with Pieces™

Principal Investigators
Miguel Vazquez, MD

Sponsoring Institution
University of Texas Southwestern Medical Center

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

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

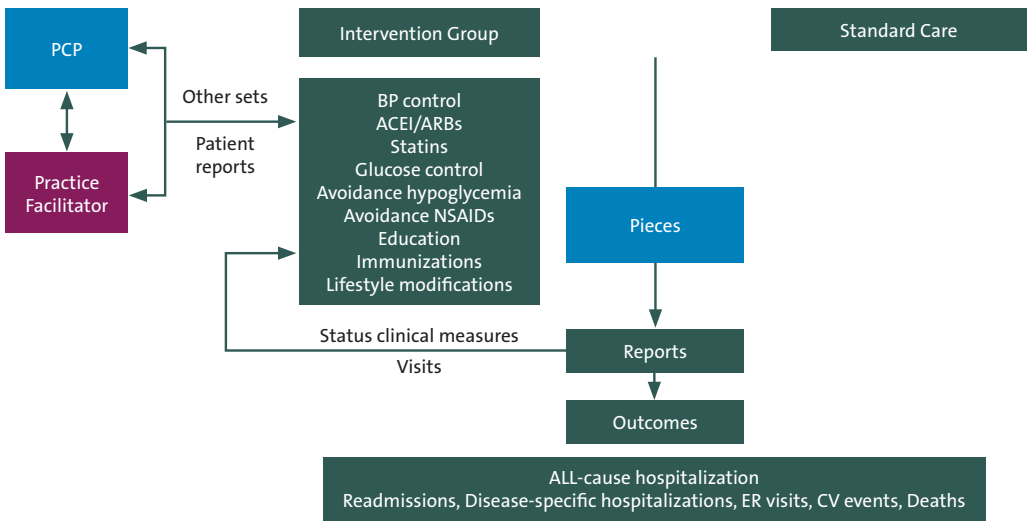
ClinicalTrials.gov Identifier
NCT02587936

ABSTRACT

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

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

GGC4H Effectiveness Design



WHAT WE'VE LEARNED SO FAR

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

1=litte difficulty; 5=extreme difficulty

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

SELECTED PUBLICATIONS & PRESENTATIONS

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

ICD-Pieces: Improving Chronic Disease Management With Pieces

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

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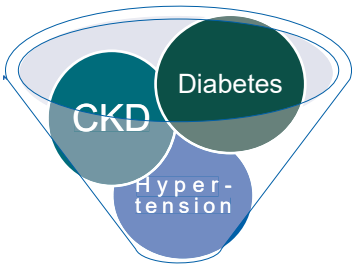
Multiple chronic conditions

->**Common**
->**Serious Complications**



->**Under-recognized**
->**Treatable**

Opportunity to Advance Care

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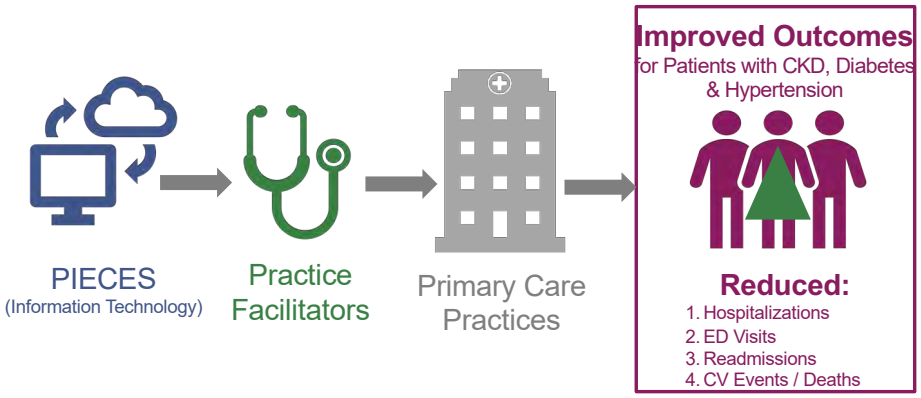
Hypothesis



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Study design

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

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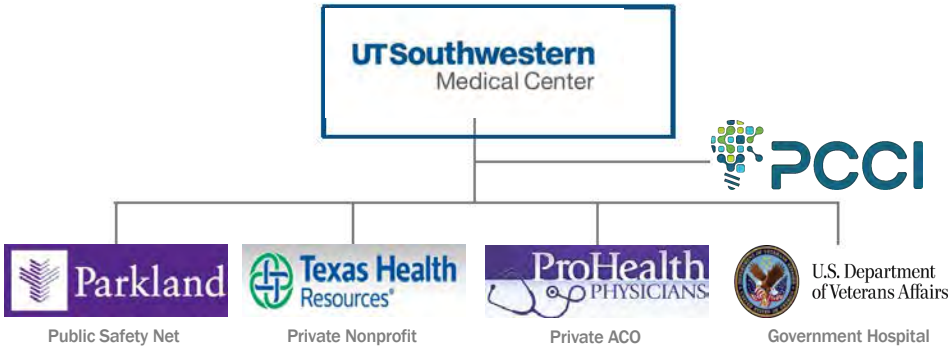
Participating healthcare systems



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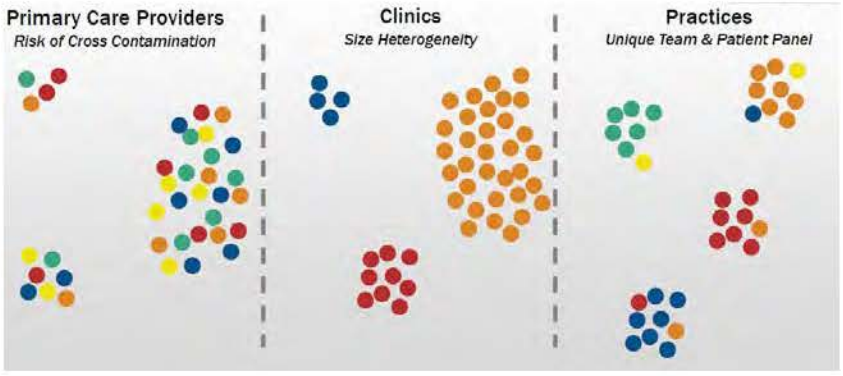
Study design: cluster randomization



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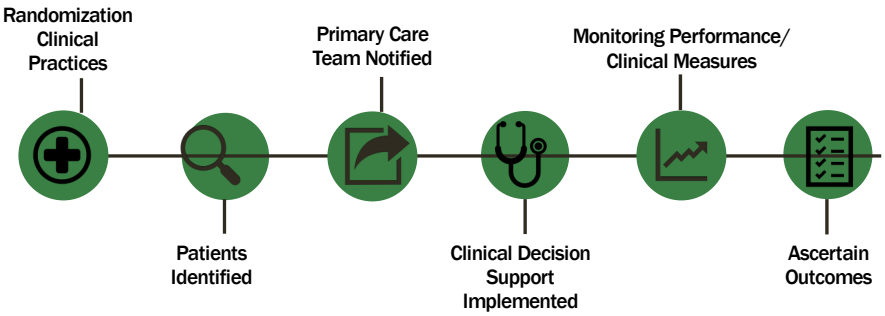
Study conduct



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Potential barriers

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

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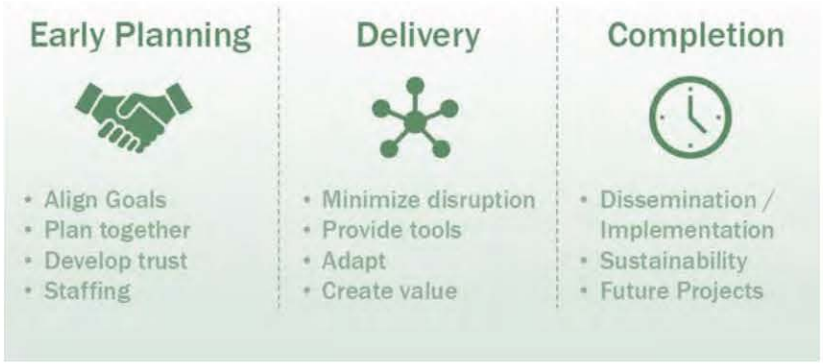
Lessons learned



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Welcome

Speaker

Wendy J. Weber, ND, PhD, MPH

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

Welcome

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

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Workshop learning objectives

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

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Workshop sessions

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

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Workshop sessions (continued)

- Measuring Outcomes (Emily O'Brien)
- ePCT Design (David Murray)
- ePCT Analysis (David Murray)
- Pilot & Feasibility Testing (Wendy Weber)

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Workshop sessions (continued)

- Ethical & Regulatory Oversight (Stephanie Morain)
- ePCTs in Context: Panel Discussion With Demonstration Project PIs
- Assembling an ePCT Team & Writing a Compelling Grant Application (Beda Jean-Francois)
- Next Steps (Wendy Weber)

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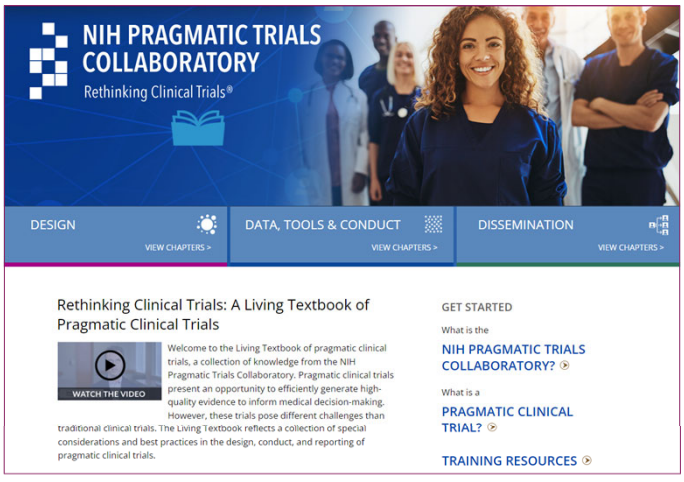
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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What Are Embedded PCTs?

Speaker

Wendy J. Weber, ND, PhD, MPH

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

What Are Embedded PCTs?

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

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1

Learning goals

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

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2

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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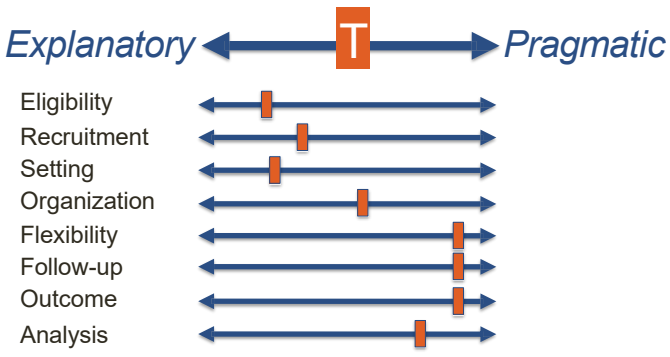
3

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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4

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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5

ePCT characteristics

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

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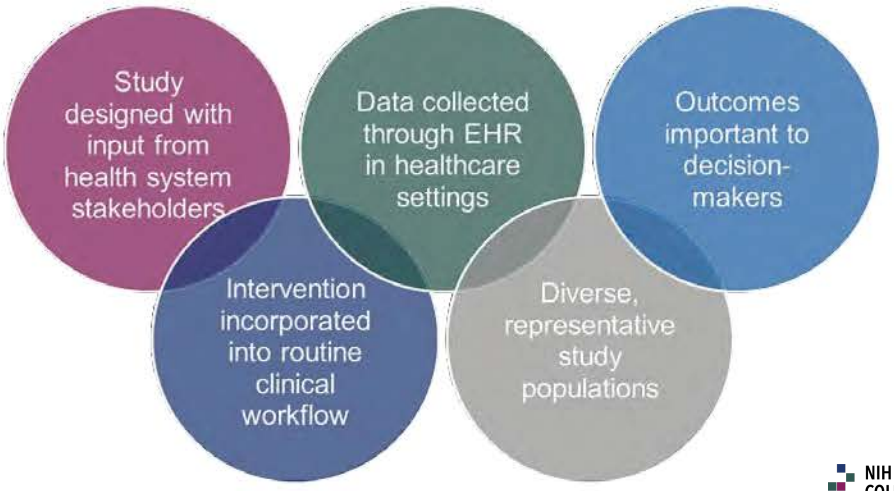
6

ePCTs bridge clinical care into research



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7

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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8

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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9

Use existing workflows

The more complicated the intervention is to the existing workflow, the more difficult it is to get compliance—you can't just add on a new thing, you have to change what happens on the floor.

– Vincent Mor, PhD (PROVEN)

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10

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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11

Important things to do

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

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Resources:

What Are Embedded PCTs (ePCTs)?

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Engaging Stakeholders & Aligning With Health System Partners

Speaker

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

Engaging With Stakeholders & Aligning With Health System Partners

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

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Learning goals

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

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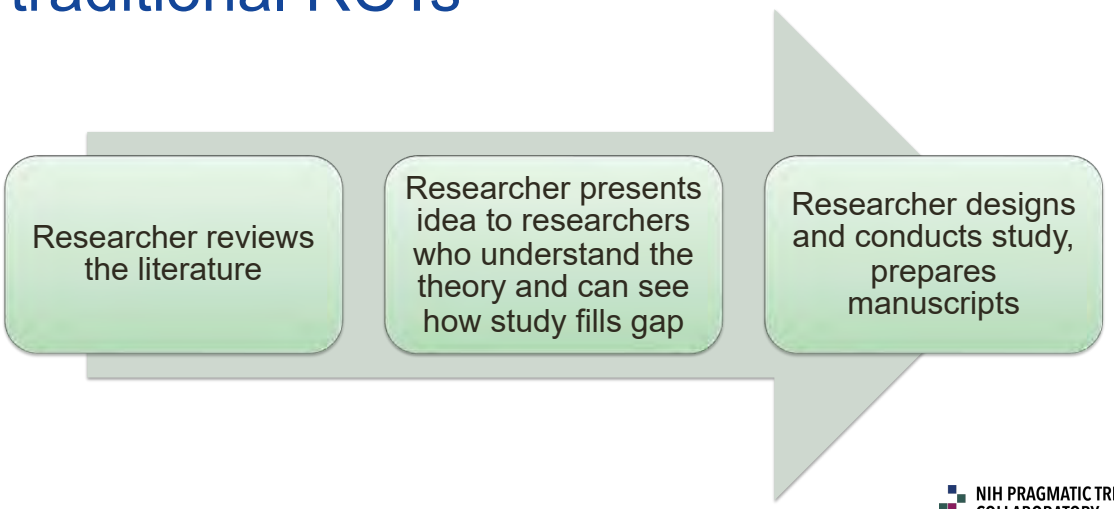
How researchers approach stakeholders in traditional RCTs



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Researchers partner with stakeholders in ePCTs differently.

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

– Greg Simon, MD, MPH (SPOT)

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Important things to know

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

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Who will be impacted? Who are the decision makers?

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

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

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Roles of stakeholders

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

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Roles of stakeholders

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

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Choosing a salient question

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

Source: Greg Simon, MD, MPH

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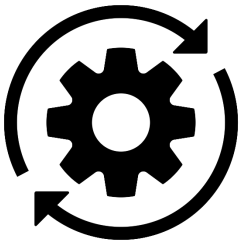
Designing the intervention for sustainment



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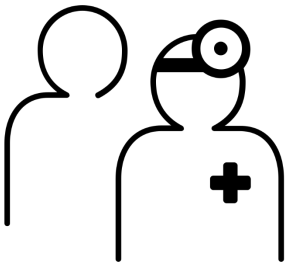
Designing the intervention to minimize burden for patients and clinicians



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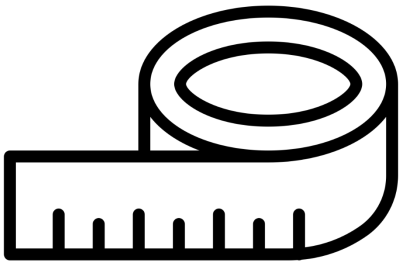
Selecting outcome measures



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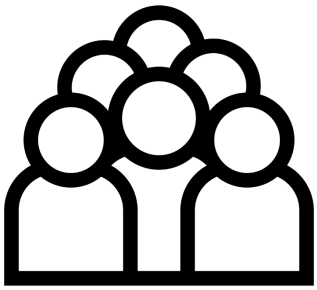
Determining inclusion and exclusion criteria



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Roles of stakeholders

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

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Develop recruitment strategies

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Serve as study champions

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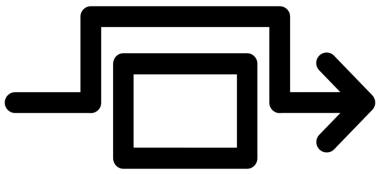
Track challenges and adaptations



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Interpret study results

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Roles of stakeholders

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

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

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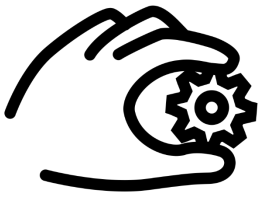
Support implementation or de-implementation



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Consider changes to policies and guidelines

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Roles of stakeholders

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

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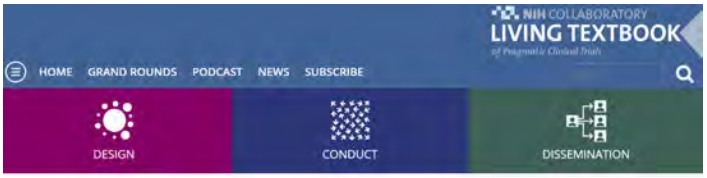
Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

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



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Resources: Journal articles

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

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Important things to do

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

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Questions?

Stakeholder roles in:

<u>Design</u>
- Question
- Intervention
- Outcomes
- Population

<u>Conduct</u>
- Recruitment
- Advocacy
- Challenges
- Interpretation

<u>Dissemination</u>
- Messaging
- Venues
- Implementation
- Guidelines

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Extra slides

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How to engage stakeholders

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

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Identify and form collaborations

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

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

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Get to know each other

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

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Pilot and assess stakeholders' capacity and capabilities

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

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Resources:

Engaging All Stakeholders & Aligning With Healthcare System Partners

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

Other

- Health Care Services Research Network website

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Objectives and Trial Design: An Overview of Hybrid Designs

Speaker

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

Trial Objectives and Design: An Overview of Hybrid Designs

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

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Learning goals

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

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Hybrid trial designs

- Trials with a focus on both clinical (patient) and implementation outcomes

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Why hybrid trial designs?

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

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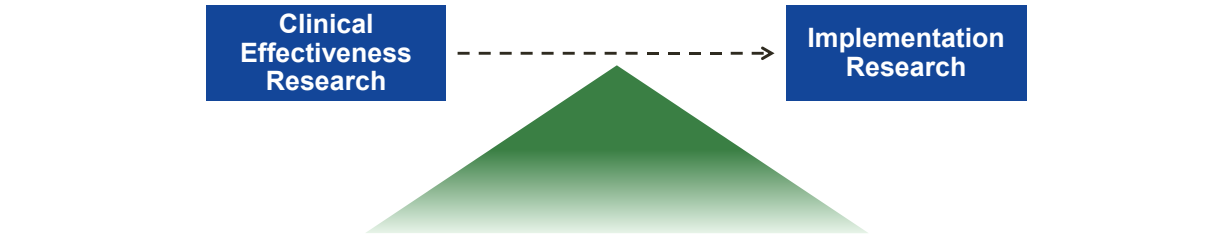
Types of hybrids



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

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Type 1

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

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Type 1 example: PPACT

Contemporary Clinical Trials 67 (2018) 91–99

Contents lists available at ScienceDirect

Contemporary Clinical Trials

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

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

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

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Type 1 example: PPACT

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

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Type 2

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

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Type 2 example: STOP CRC

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

Implementation Science

METHODOLOGY Open Access

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

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

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Type 2 example: STOP CRC

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

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Type 3

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

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Type 3 example: ENABLE

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

Implementation Science

STUDY PROTOCOL Open Access

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

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

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Concluding points

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

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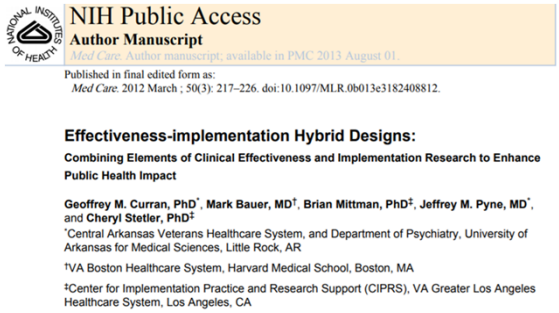
Concluding points

- 3 If you want to learn more…



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

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

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

Geoffrey M. Curran, PhD[*], **Mark Bauer, MD**[†], **Brian Mittman, PhD**[‡], **Jeffrey M. Pyne, MD**[*], and **Cheryl Stetler, PhD**[‡]
[*]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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Resources:

Objectives and Trial Design: An Overview of Hybrid Designs

Living Textbook readings

- Hybrid Design

Key journal articles

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

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

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Measuring Outcomes

Speaker

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

Measuring Outcomes

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

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Learning goals

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

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2

Endpoints and outcomes

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

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3

Important things to know

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

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Choosing and specifying ePCT endpoints

Endpoints and outcomes should be available as part of routine care

- Acute MI
- Broken bone
- Hospitalization

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

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Key questions for choosing endpoints

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

Does it require hospitalization?

Will the endpoint be medically attended?

Is the treatment generally provided in inpatient or outpatient settings?

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Data sources for endpoints in ePCTs

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

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

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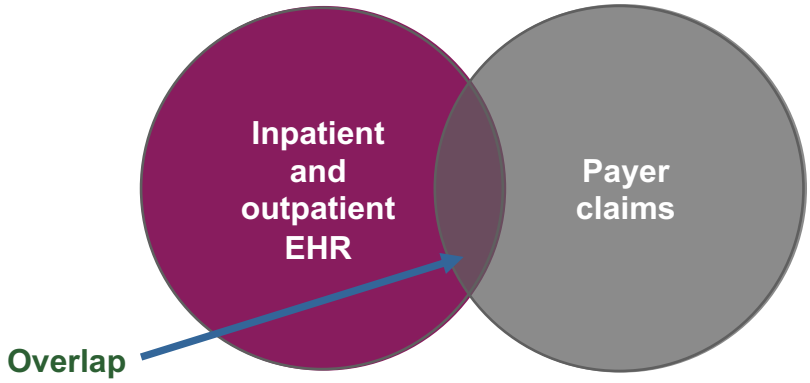
Where is the signal?

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



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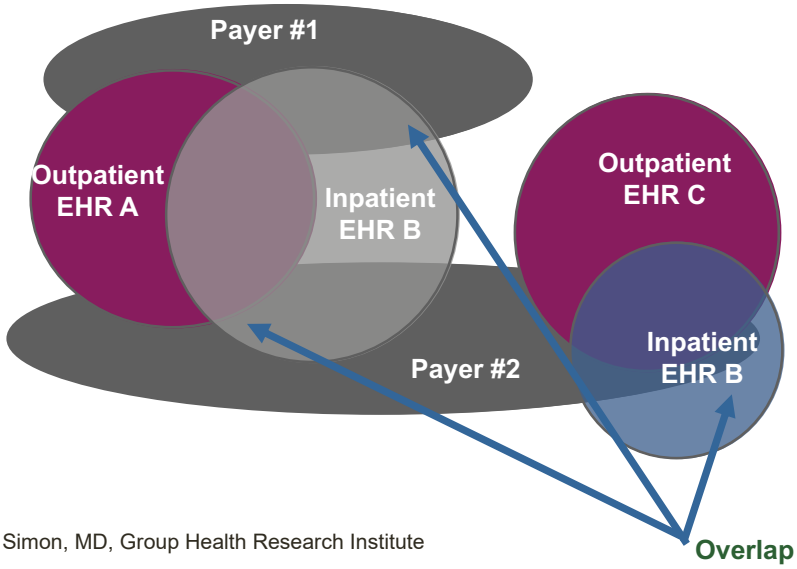
Reality is not straightforward



Source: Greg Simon, MD, Group Health Research Institute

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Longitudinal data linkage

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

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Data sources for endpoints in ePCTs

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

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It's a balancing act

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

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

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Outcomes measured via direct patient report

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

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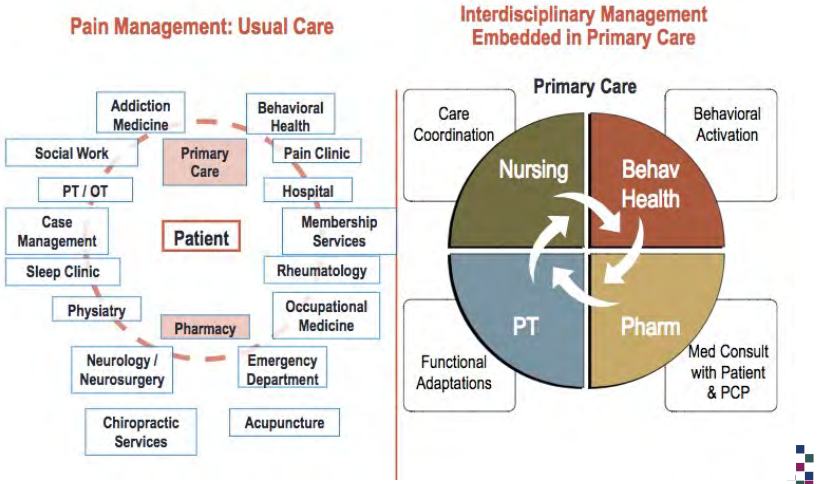
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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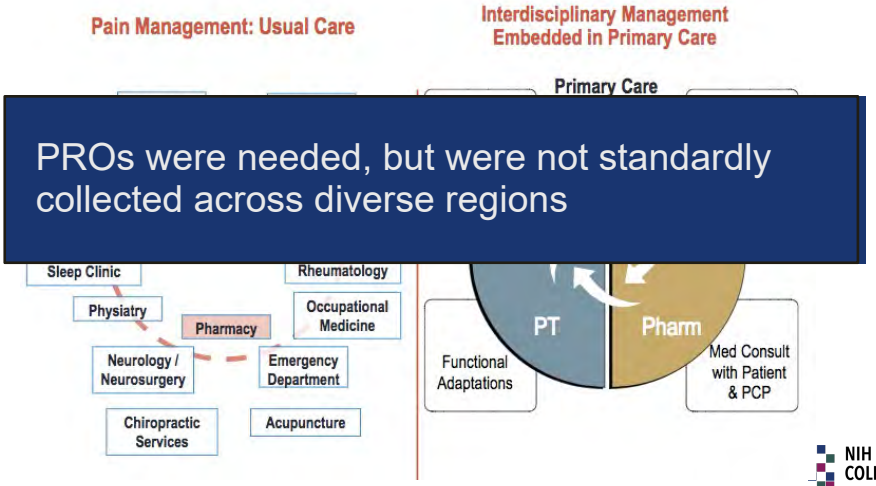
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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Case example: PPACT

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

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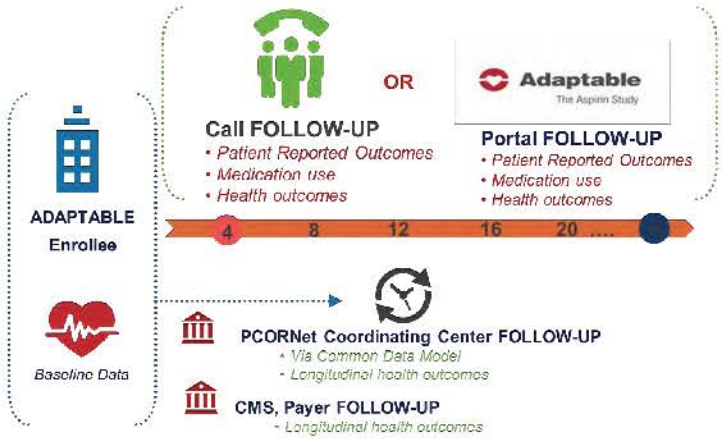
Enabling pragmatic research: e-screening, e-enrollment & e-follow-up



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Mobile devices for outcome measurement

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

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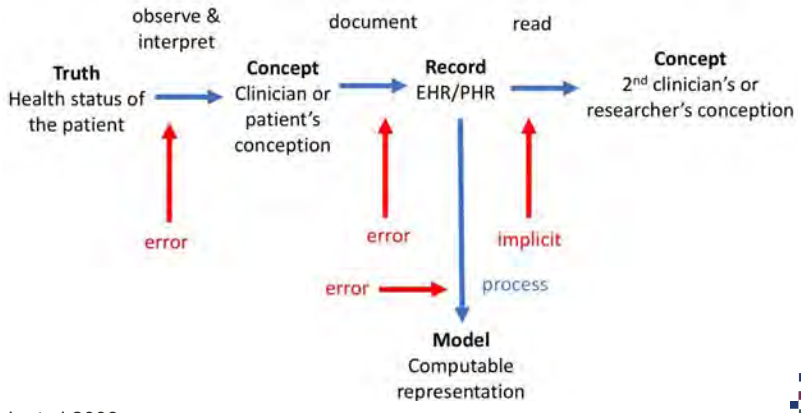
Data is a surrogate for clinical phenomena

Error Impact on Trials



Adapted from Hripcsak et al 2009

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Data quality assessment

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

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Important things to do

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

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Concluding points

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

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Resources:

Measuring Outcomes

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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ePCT Design

Speaker

David M. Murray, PhD

Associate Director for Prevention
Director, Office of Disease Prevention
National Institutes of Health

ePCT Experimental Design and Analysis

David M. Murray, PhD
Associate Director for Prevention
Director, Office of Disease Prevention
National Institutes of Health (NIH)

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Learning goals

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

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Design Considerations

Embedded Pragmatic Clinical Trials

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Important things to know

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

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NIH Collaboratory ePCT: STOP CRC

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

stop screen to prevent colon cancer

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

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Reasons to randomize clusters instead of individuals

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

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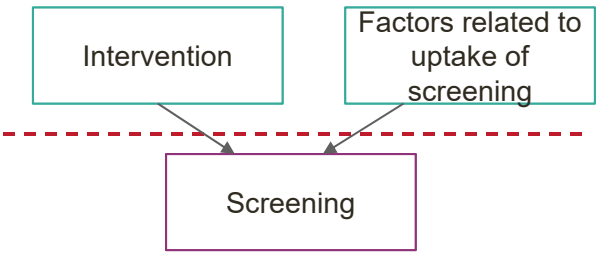
STOP CRC cluster randomization

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



Level 1: Individual-level outcomes nested within clinics

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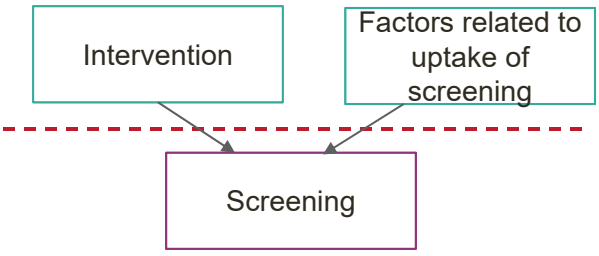
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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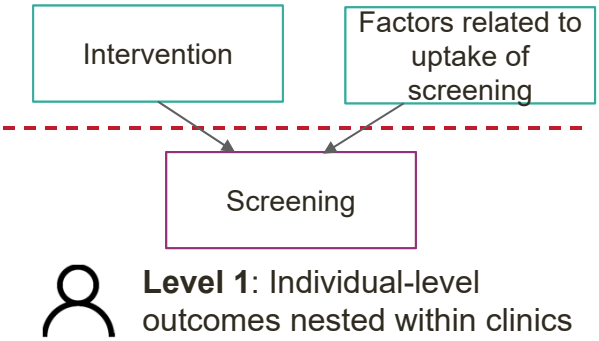
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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Understanding outcome clustering

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

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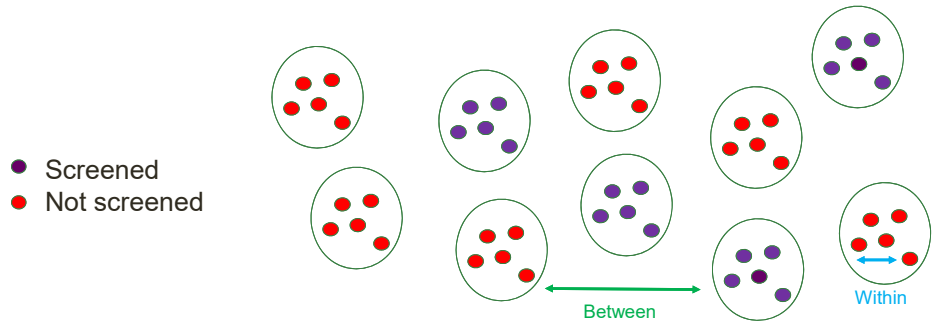
Understanding outcome clustering: complete clustering (ICC =1)



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

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

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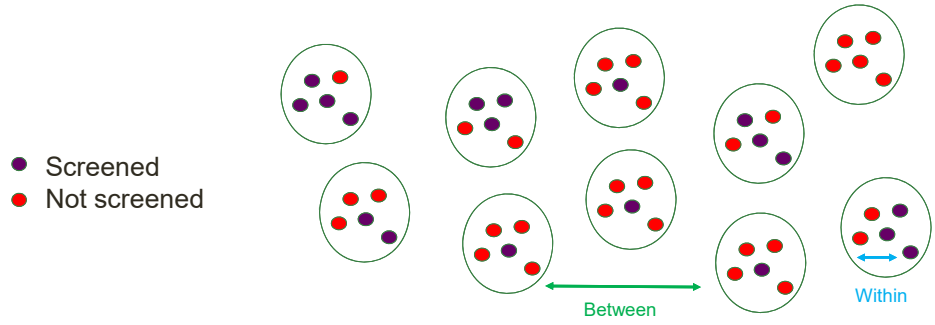
Understanding outcome clustering: some clustering (0 < ICC < 1)



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

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

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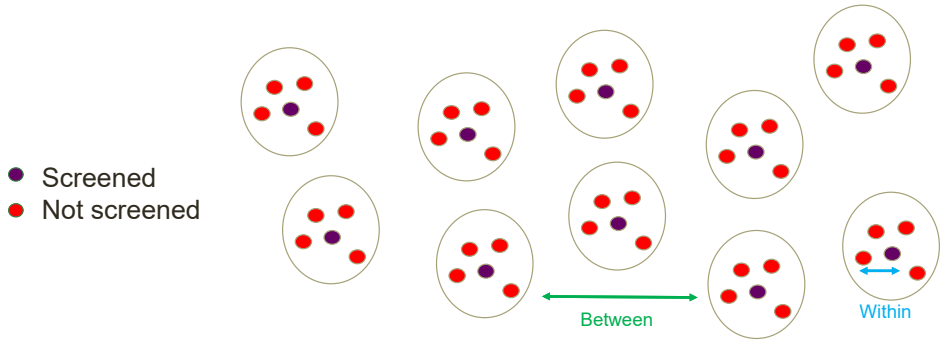
Understanding outcome clustering: no clustering (ICC=0)



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

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

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Summary of design issues for CRTs

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

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Methods for pragmatic trials

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

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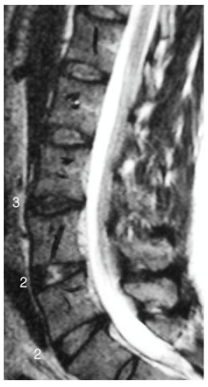
NIH Collaboratory ePCT: LIRE



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

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

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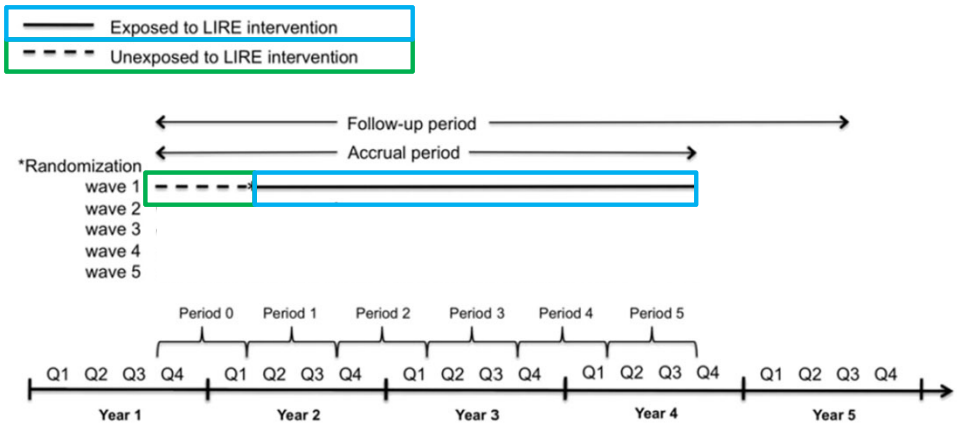
NIH Collaboratory ePCT: LIRE



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

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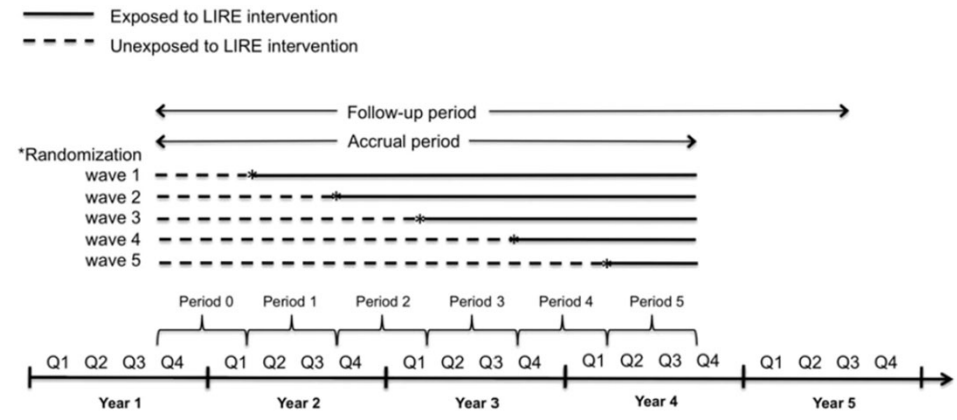
NIH Collaboratory ePCT: LIRE



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

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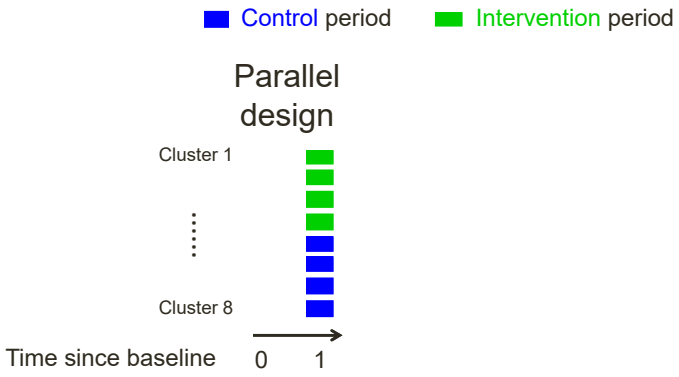
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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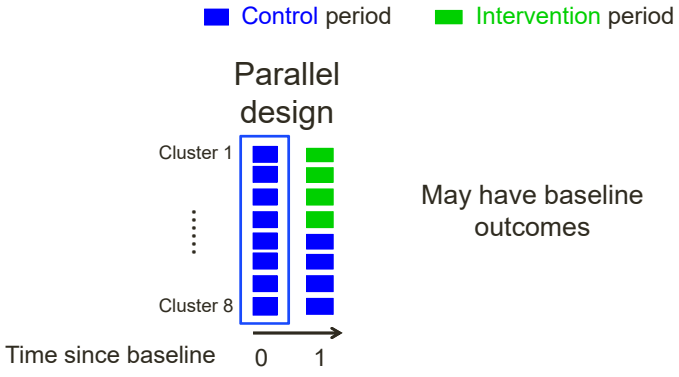
Types of CRT designs

Examples with 8 clusters: 1-year intervention



May have baseline outcomes

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

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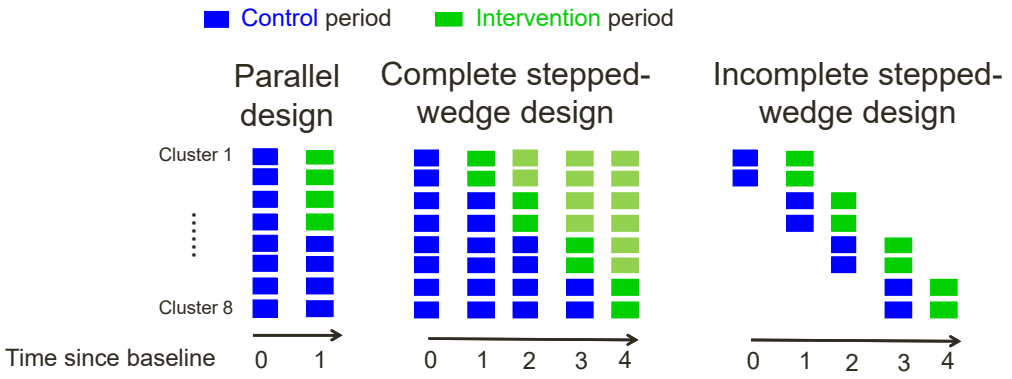
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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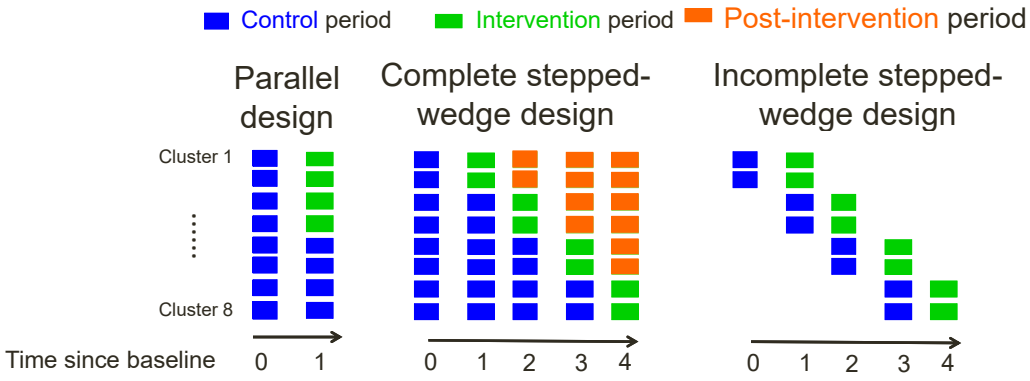
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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Summary of design issues

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

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NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

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

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

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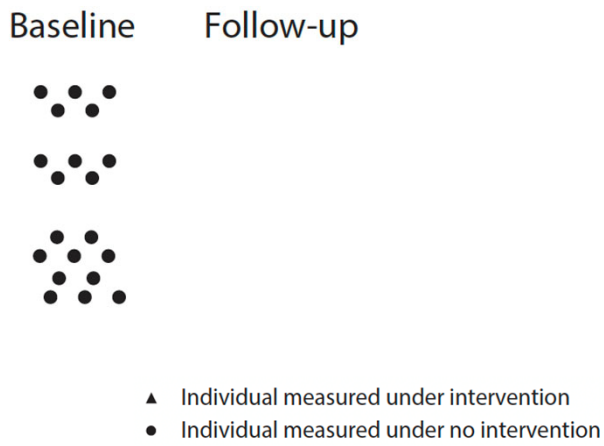
NIH Collaboratory ePCT: OPTIMUM



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

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Summary of design issues

- Many design features common to RCTs are available to IRGTTs:
  - Cohort, but not easy to conceive of a cross-sectional design;
  - Single-factor designs and factorial designs
  - A priori stratification, or other restricted randomization procedures such as minimization to create comparable treatment arms
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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How to choose the right design?

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How to choose the right design?

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

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

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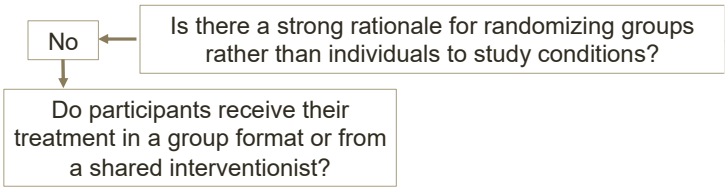
How to choose the right design?



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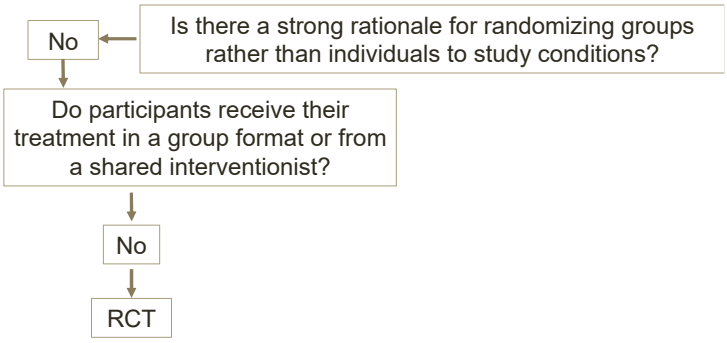

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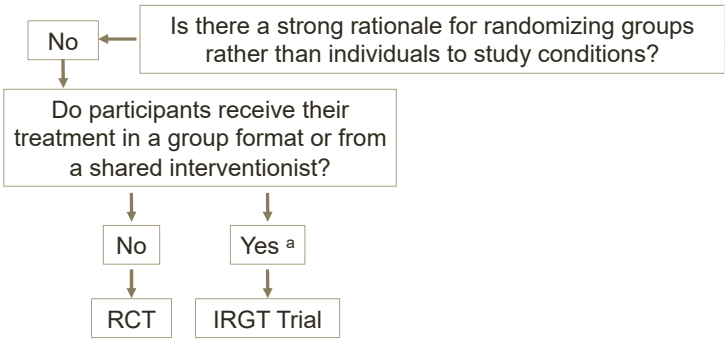

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

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

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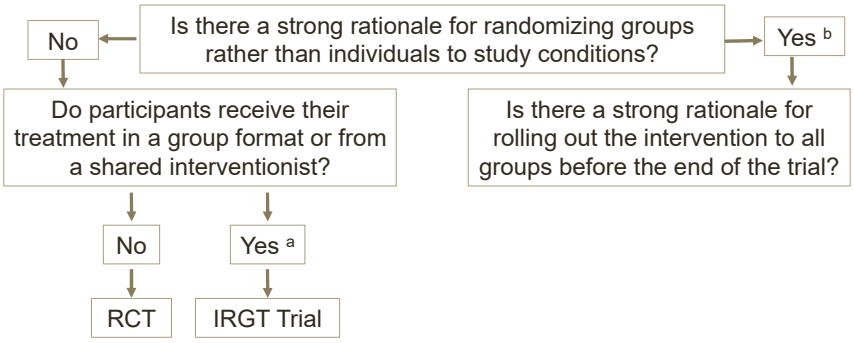
How to choose the right design?



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

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

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

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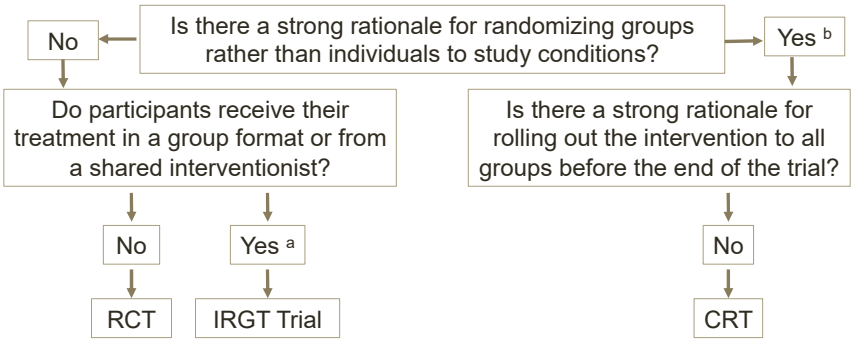

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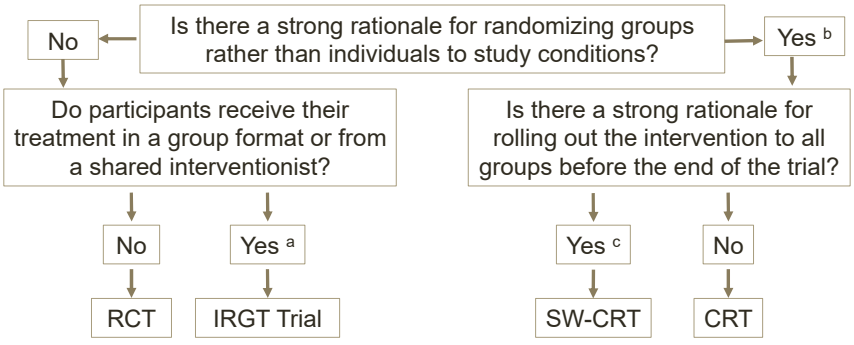

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

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

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

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

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Implications of design choice

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

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Implications of design choice

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

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The need for these designs

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

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Clustering: Impact on power

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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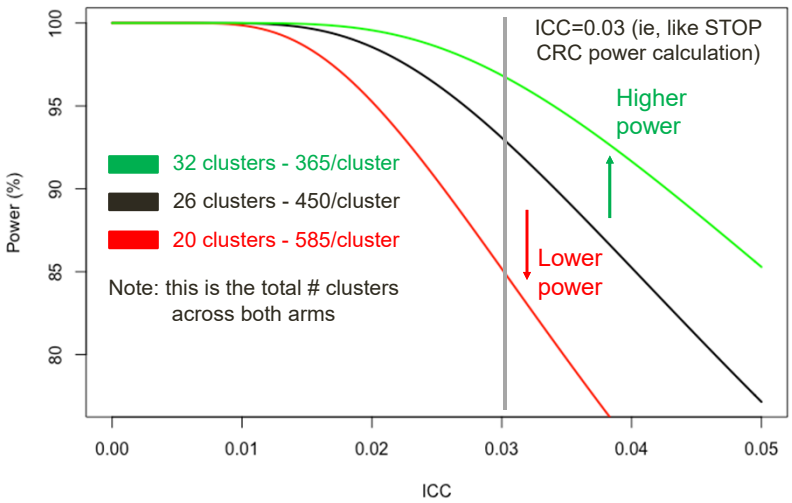
Clustering: Impact on power in STOP CRC



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

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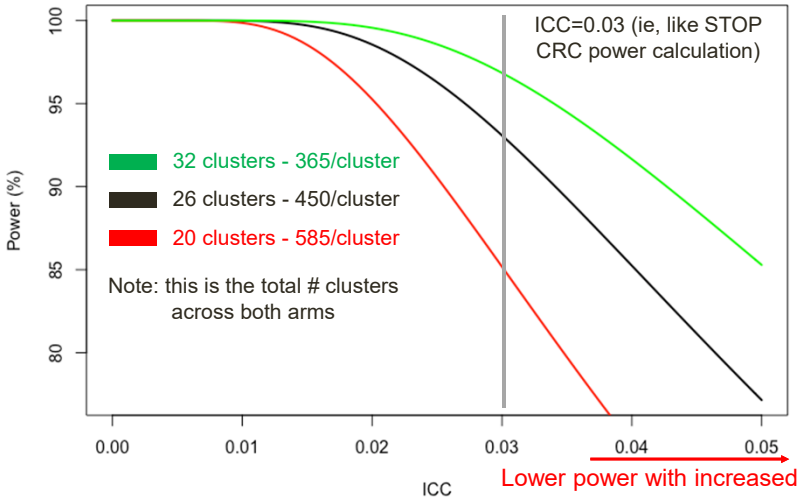
Clustering: Impact on power in STOP CRC



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Summary: Important things to know

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

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Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at
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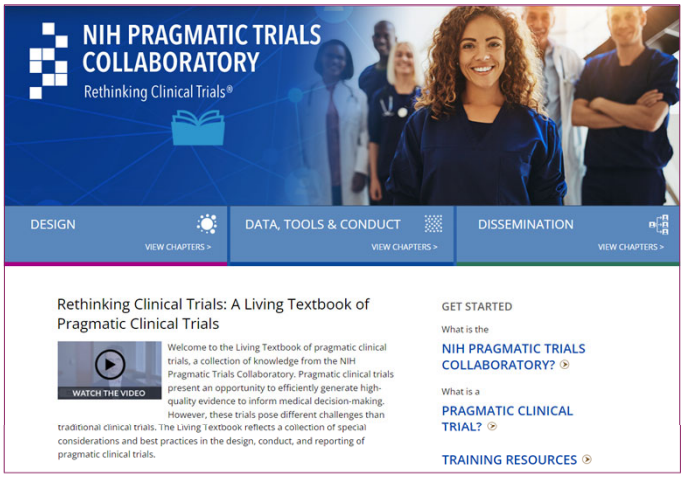

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Additional resources

- 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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ePCT Analysis

Speaker

David M. Murray, PhD

Associate Director for Prevention
Director, Office of Disease Prevention
National Institutes of Health

ePCT Experimental Design and Analysis

David M. Murray, PhD
Associate Director for Prevention
Director, Office of Disease Prevention
National Institutes of Health (NIH)

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Learning goals

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

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Analysis Considerations

Embedded Pragmatic Clinical Trials

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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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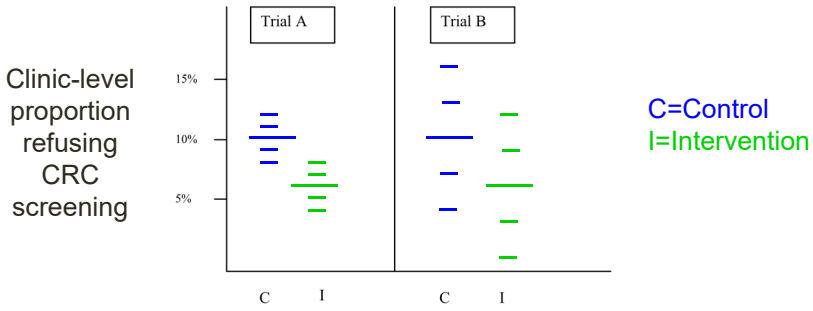
Clustering in CRTs: Implications for analysis



- 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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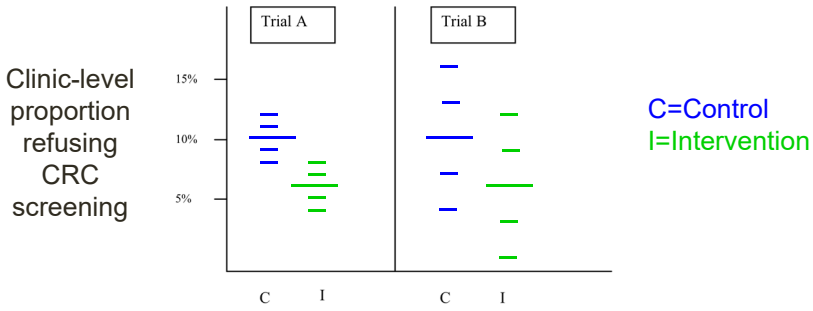

Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

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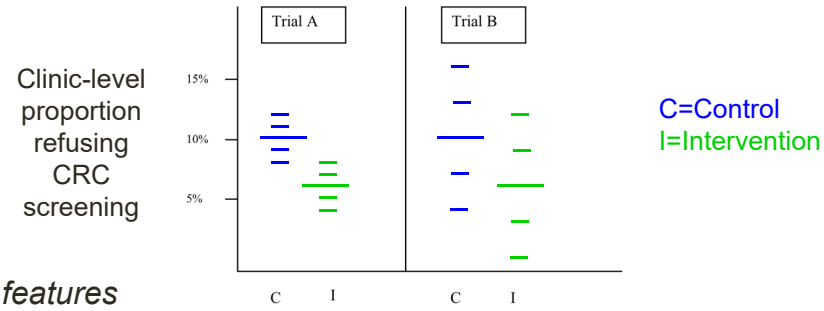

Study features

- 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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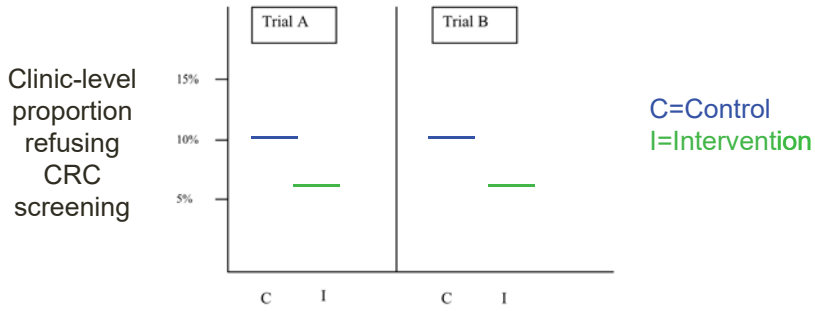

- If ignore clustering: p-value = **0.02** for both trials
- Comparison of 10% (50/500) vs 6% (30/500) by chi-sq. test

Adapted from Hayes & Moulton (2009)

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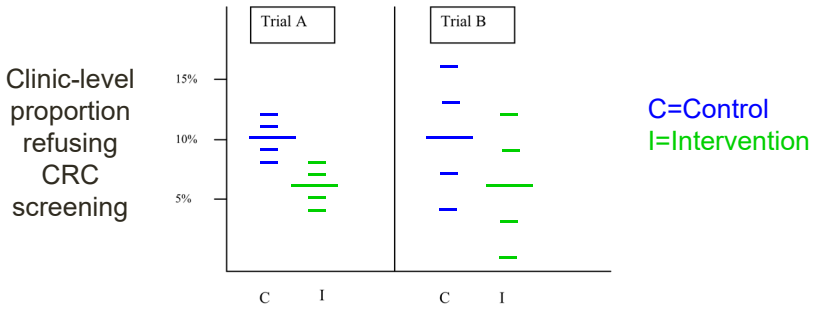

- Trial B p-value accounting for clustered design = **?**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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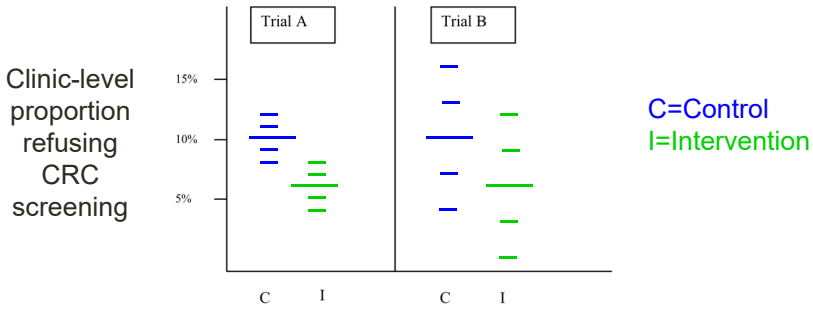
Clustering in CRTs: Implications for analysis



- 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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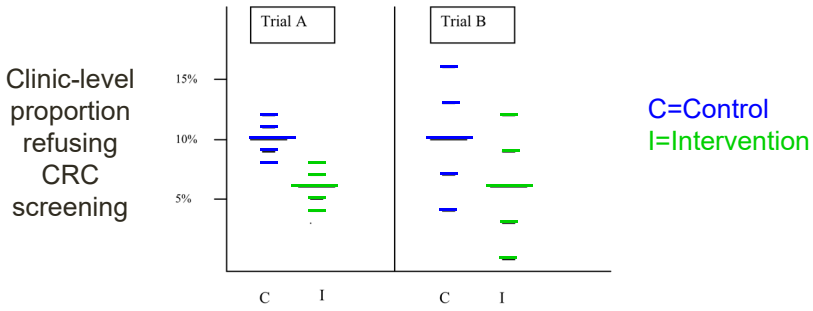
Clustering in CRTs: Implications for analysis



- 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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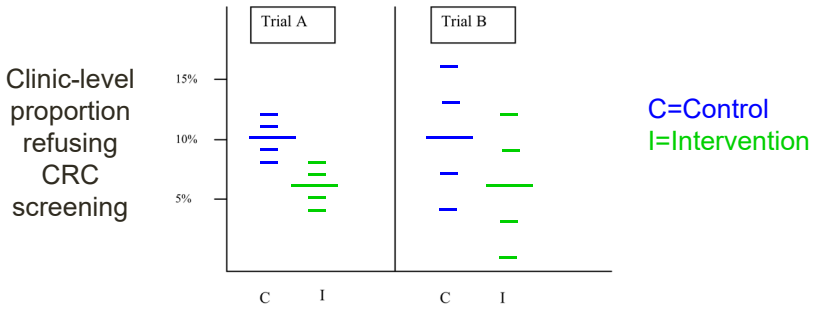
Clustering in CRTs: Implications for analysis



- 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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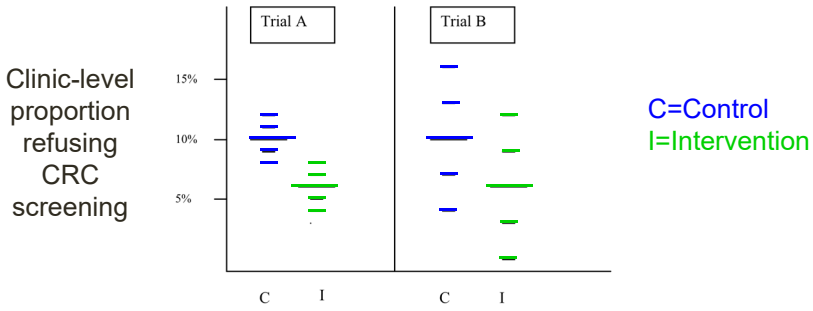

- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

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

Adapted from Hayes & Moulton (2009)

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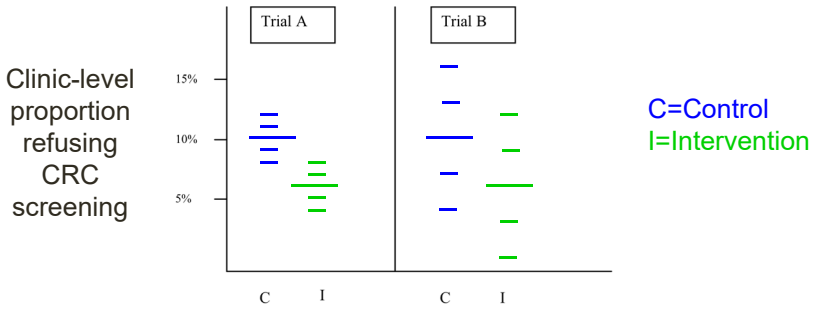
Clustering in CRTs: Implications for analysis



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

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

Adapted from Hayes & Moulton (2009)

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Summary: Analysis of two example CRTs

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

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Analysis of CRTs, including SW-CRTs

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

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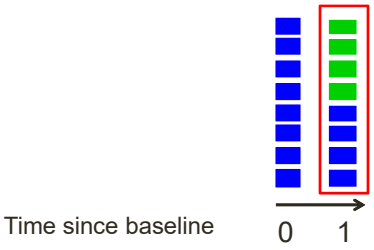
Analysis of CRTs, including SW-CRTs

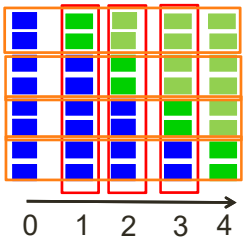
Parallel design

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



Complete SW design

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



Control period Intervention period

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

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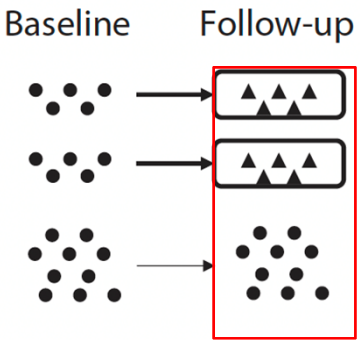
Analysis of IRGT trials



▲ Individual measured under intervention
● Individual measured under no intervention

Parallel design

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

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

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Analysis of IRGT trials

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

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Analysis of CRTs, SW-CRTs, and IRGTTs

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

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Analysis of CRTs, SW-CRTs, and IRGTTs

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

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Strategies to protect the analysis

Avoid model misspecification

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

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Strategies to protect the analysis

Avoid low power

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

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Challenges of pragmatic study design

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

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NIH Collaboratory: examples of analytic challenges and trade-offs

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

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

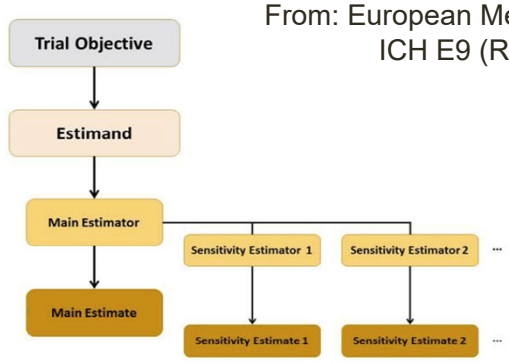

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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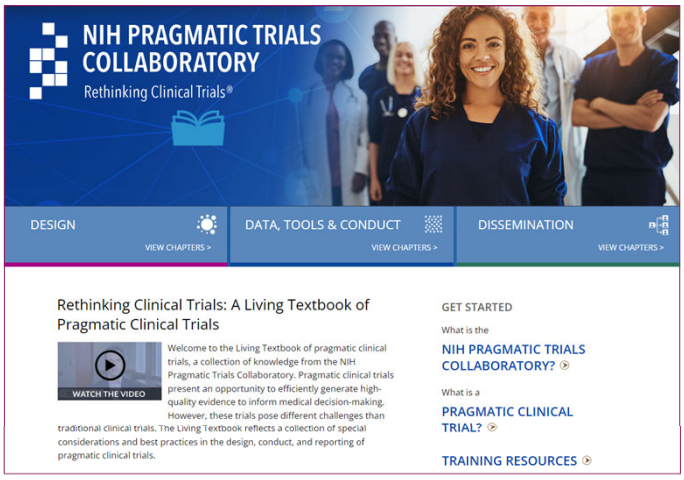

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- Murray DM. Design and Analysis of Group-Randomized Trials. New York, NY: Oxford University Press; 1998.
- Pragmatic Trials: A Workshop Handbook
- Statistical lessons learned for designing cluster randomize pragmatic clinical trials from the NIH Healthcare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

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ePCTs in Context: Panel Discussion With Demonstration Project PIs

Moderator

Emily C. O'Brien, PhD

Associate Professor of Population Health Sciences
Duke University

ePCTs in Context

Panel Discussion With Demonstration Project Investigators

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

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Challenges, solutions & lessons learned

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

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ePCT examples

- **ACP PEACE** (Angelo Volandes, MD, MPH)
- **BeatPain Utah** (Julie Fritz, PhD, PT)
- **GGC4H** (Margaret Kuklinski, PhD)
- **ICD-Pieces** (Miguel Vazquez, MD)

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Pilot & Feasibility Testing

Speaker

Wendy J. Weber, ND, PhD, MPH

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

Pilot & Feasibility Testing

Wendy J. Weber, ND, PhD, MPH
Branch Chief, Clinical Research in Complementary and Integrative Health Branch
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Learning goals

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

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Important things to know

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

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ePCTs are not efficacy trials

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

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During the pilot phase

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

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Build partnerships

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

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Aspects of feasibility that can be piloted

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

Use what you learn to design the ePCT

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Evaluate power calculations

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

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Quantify feasibility for pilot study aims

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

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

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Quantifying example 1

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

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

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Quantifying example 2

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

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

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Quantifying example 3

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

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

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Ensuring trial readiness

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

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Readiness checklist

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

Implementation Readiness Checklist available on the Living Textbook

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In the end, good planning will help

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

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Important things to do

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

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Resources

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

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

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Resources:

Pilot and Feasibility Testing

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Ethical & Regulatory Oversight Considerations

Speaker

Stephanie Morain, PhD, MPH

Assistant Professor
Johns Hopkins Bloomberg School of Public Health and
Berman Institute of Bioethics
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Ethical & Regulatory Oversight Considerations

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and Berman Institute of Bioethics

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Learning goals

- Recognize regulatory and ethical challenges associated with ePCTs (and resources for addressing them!)
- Identify PCT-related considerations for research with historically underrepresented groups

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Important things to know

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

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ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions

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Evolving understanding of ethical/regulatory issues for ePCTs

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

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Article

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

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Informed Consent, Waivers, and Alterations

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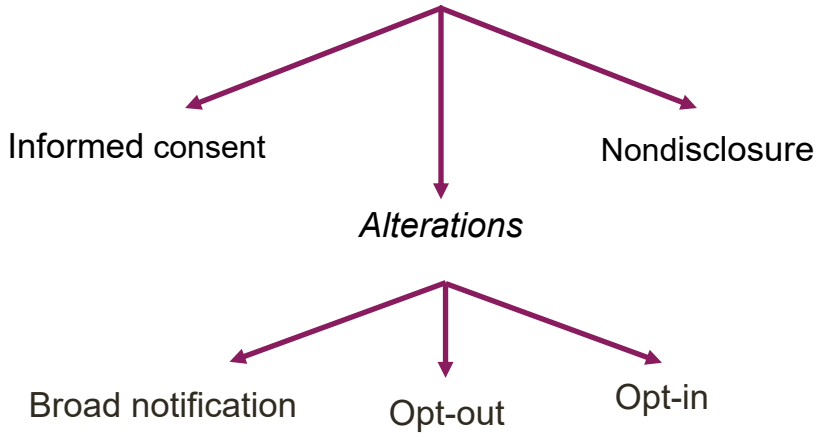
Approaches to notification & authorization



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Criteria for waiver/alteration of consent

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

Common Rule: 45 CFR 46.116(f)

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Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

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

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Distinguishing research risks

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

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Regulatory permissible ≠ ethically optimal

- Regulatory criteria for waivers and alterations identical…but they are <u>ethically</u> 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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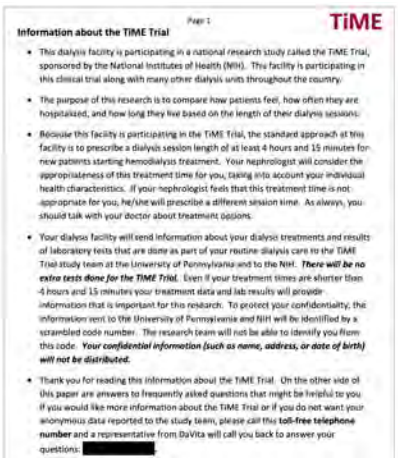
Examples: information sheets or flyers



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 the **toll-free telephone number** and a representative from DaVita will call you back to answer your questions: [redacted]

Page 2

Frequently Asked Questions About Research and About the TiME Trial

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

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

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

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

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

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

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

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

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Data and Safety Monitoring

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

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

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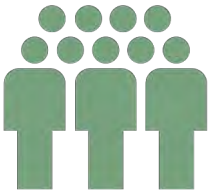
Data monitoring committee

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



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Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct
- Are interim analyses actionable?
- Differential data collection/contact by study arm

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

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Unique considerations for monitoring ePCTs

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

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

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Identifying Direct and Indirect Participants

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Regulatory perspective: Who are the subjects in ePCTs?

Definition of human subject

- Human subject means a living individual about whom an investigator conducting research:
  - obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

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

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Regulatory perspective: Who are the subjects in ePCTs?

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

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

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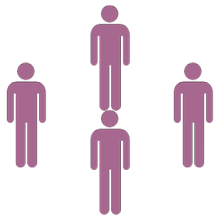
Ethical perspective:
Whose rights and welfare need to be protected?



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

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Types of participants in an ePCT

Direct Indirect

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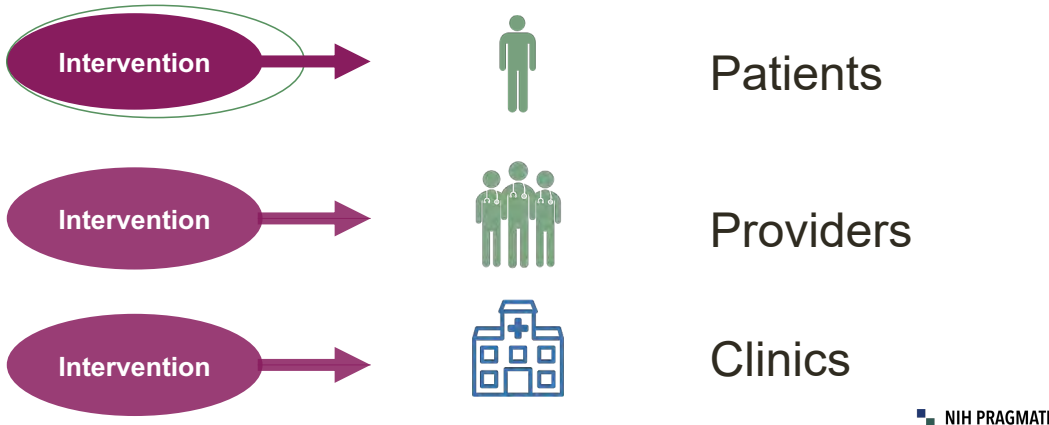
Direct participants

Immediate or mediated targets of the intervention



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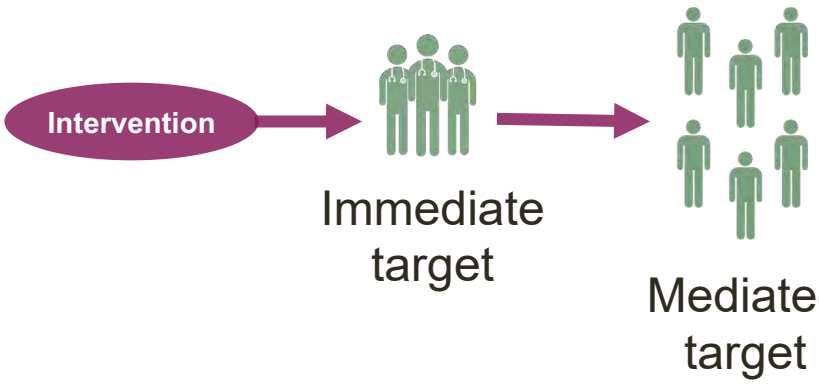
Direct participant



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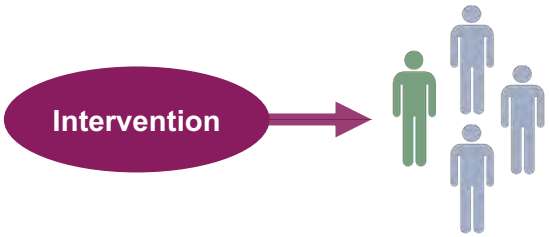
Indirect participants

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



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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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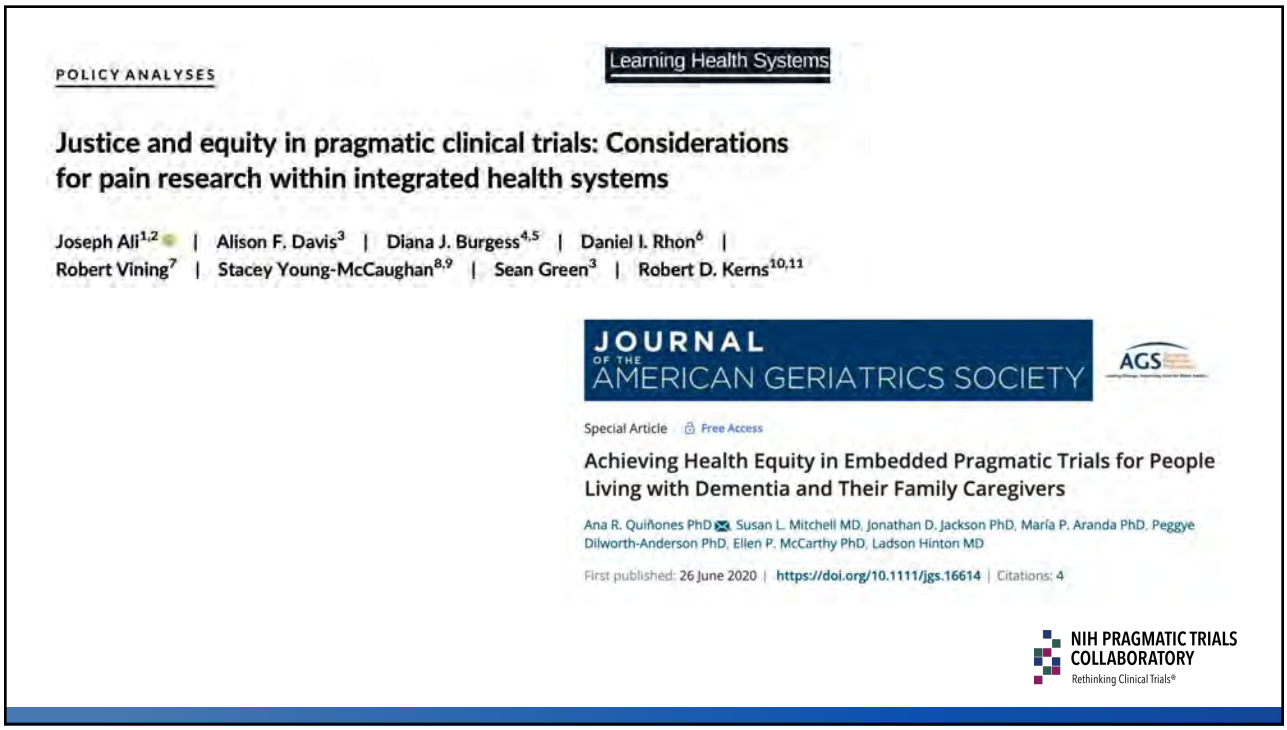

POLICY ANALYSES

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

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Special Article | Free Access

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

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

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

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Important things to do

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

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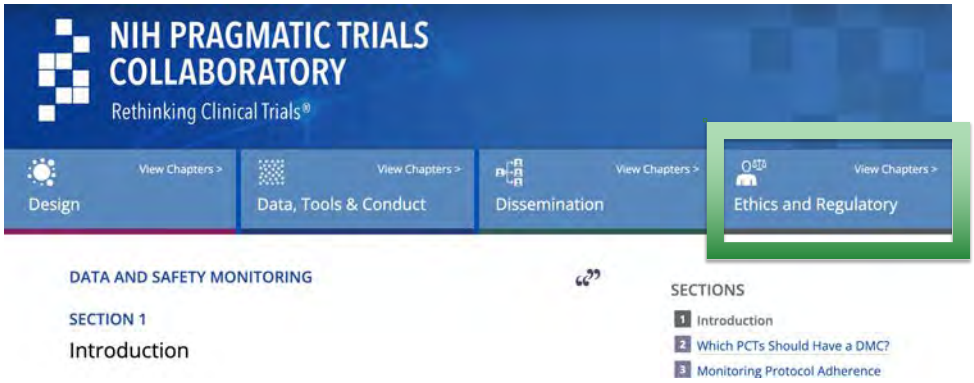
Important things to do

- Make use of existing resources!



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Resources:

Ethical and Regulatory Considerations

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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ePCTs in Context: Panel Discussion With Demonstration Project PIs

Moderator

Wendy J. Weber, ND, PhD, MPH

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

ePCTs in Context

Panel Discussion With Demonstration Project Investigators

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

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Challenges, solutions & lessons learned

- Afternoon topics
  - Pilot and feasibility testing
  - Ethical and regulatory oversight considerations

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ePCT examples

- **ACP PEACE** (Angelo Volandes, MD, MPH)
- **BeatPain Utah** (Julie Fritz, PhD, PT)
- **GGC4H** (Margaret Kuklinski, PhD)
- **ICD-Pieces** (Miguel Vazquez, MD)

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Assembling an ePCT Team & Writing a Grant Application

Speaker

Beda Jean-Francois, PhD

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

Assembling an ePCT Team & Writing a Compelling Grant Application

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

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Learning goal

- Identify skills needed for a strong study team

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Important things to know

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

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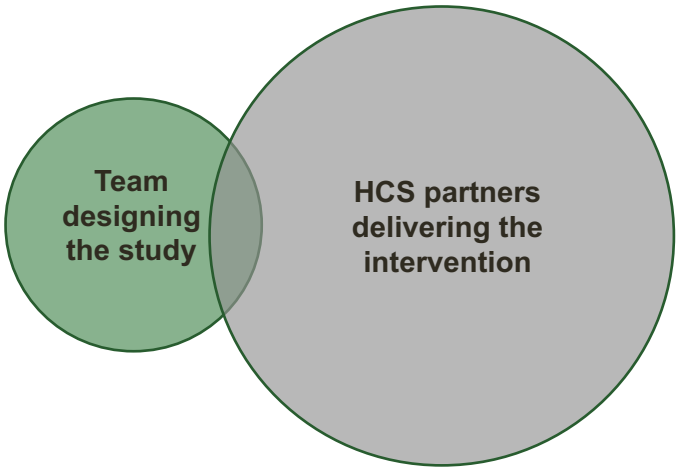
Who is involved?



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Potential team members

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

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Important things to do

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

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What skills will be needed?

- Best skill set depends on the study aims and how the intervention will be embedded in the healthcare system workflow
- Questions to ask:
  - What clinical specialties will be needed to carry out the intervention?
  - What roles will support clinic operations?
  - Who will be the liaison between HCS departments for interventions that are multidisciplinary?
  - What aspects of the trial will require IT staff expertise?
  - Will the trial need training videos, online materials, or toolkits?

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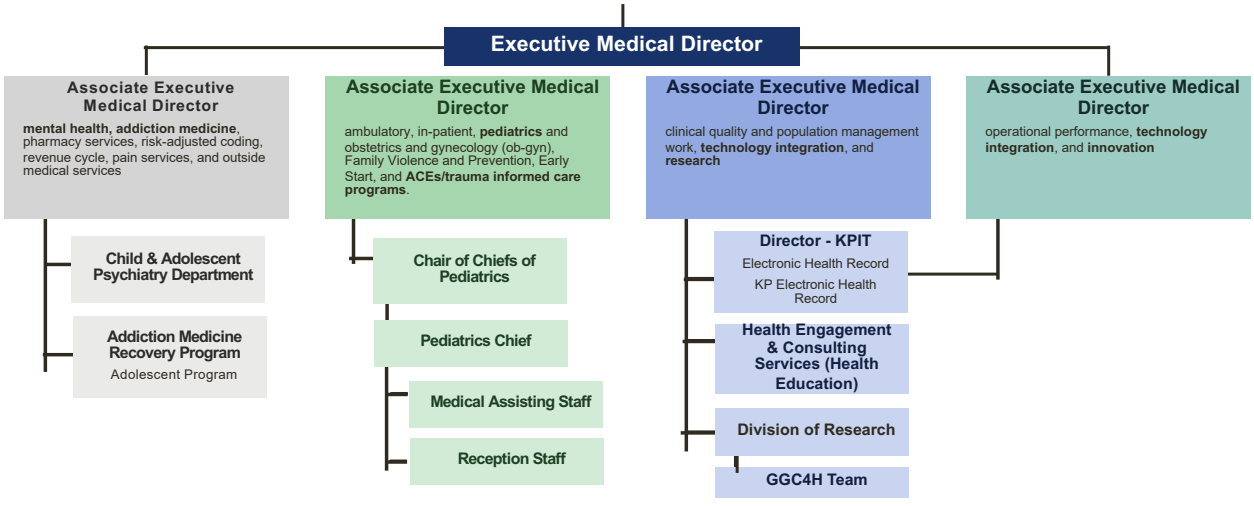
Kaiser Permanente Northern California



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

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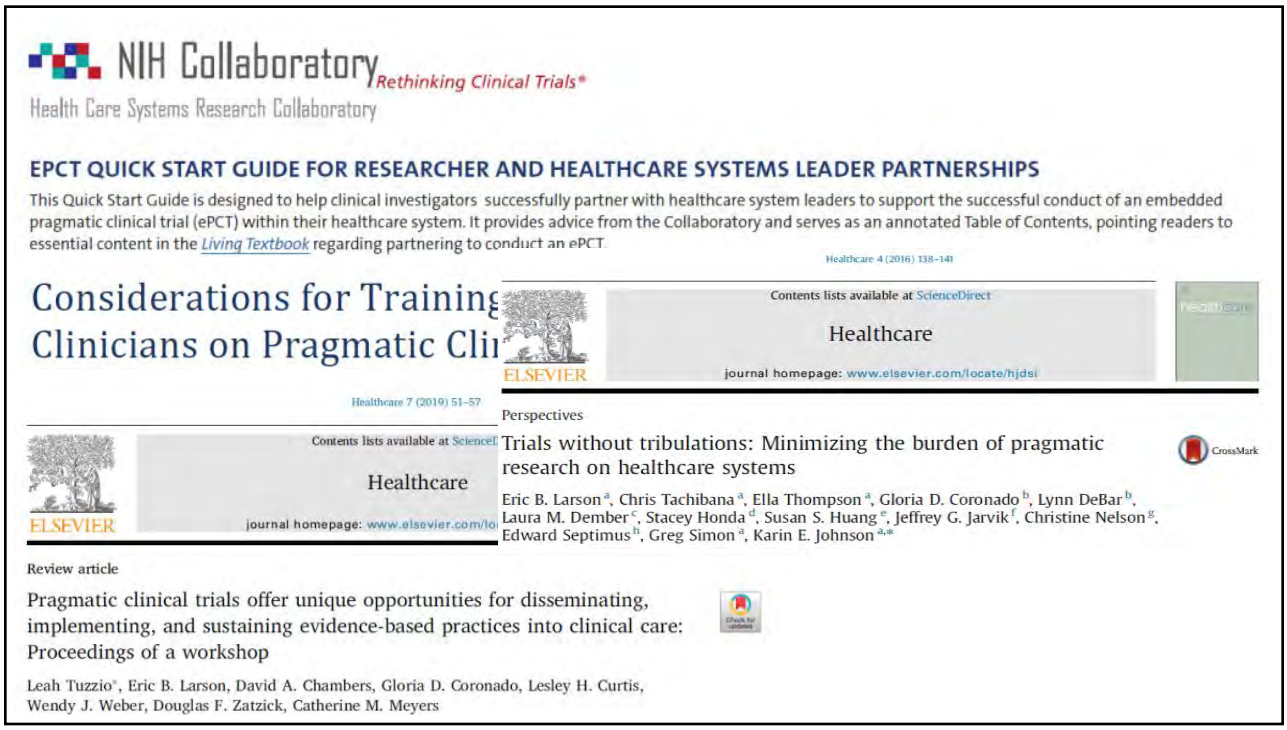
NIH Collaboratory
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Health Care Systems Research Collaboratory

EPCT QUICK START GUIDE FOR RESEARCHER AND HEALTHCARE SYSTEMS LEADER PARTNERSHIPS

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

Considerations for Training Clinicians on Pragmatic Cli

Healthcare 7 (2019) 51–57

Contents lists available at ScienceD

Healthcare

journal homepage: www.elsevier.com/lo

Healthcare 4 (2016) 138–141

Contents lists available at ScienceDirect

Healthcare

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

Perspectives

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

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

Review article

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

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

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Writing a Compelling Grant Application

Is the question compelling, balanced team, right population, clinical sites with study population, and an approach which is clearly communicated?

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Learning goals 

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

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

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Find the right NIH program official

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

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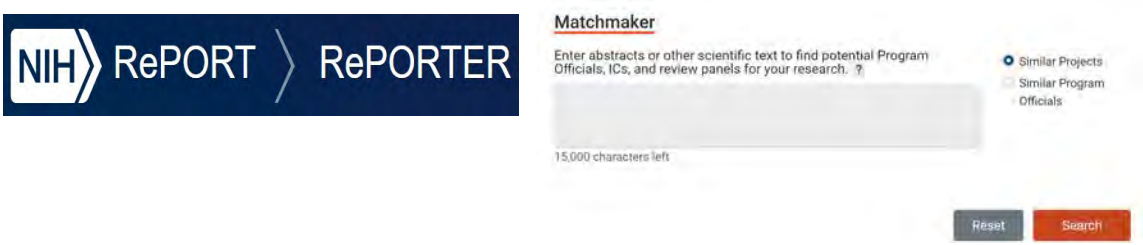
NIH RePORTER matchmaker tool

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



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Matchmaker results (example)

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

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Find the right FOA

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

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NIH scientific contacts

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

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Tailor the application

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

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Common application pitfalls

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

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Application dos

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

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Application don’ts

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

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Strategies for success

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

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NIH online resources

https://researchmethodsresources.nih.gov/

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

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Think through team diversity

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

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Important things to do

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

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Resources:

Writing a Compelling Grant Application

Living Textbook readings

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

Key journal articles

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

Other

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

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Resources:

ePCTs in Context: Panel Discussion

Nudge

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

ICD-Pieces

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

GGC4H

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

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Next Steps

Speaker

Wendy J. Weber, ND, PhD, MPH

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

Next Steps:
Embedded Pragmatic Clinical Trials

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

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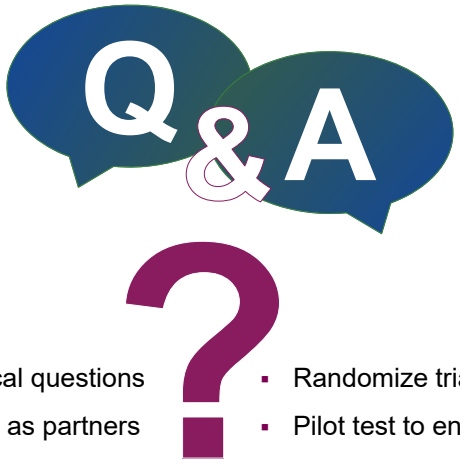

- Answer real-world clinical questions
- Engage health systems as partners
- Design your trial for both patient and implementation outcomes
- Choose meaningful and pragmatic endpoints and outcomes
- Randomize trials for the strongest evidence
- Pilot test to ensure trial readiness
- Consider ethical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

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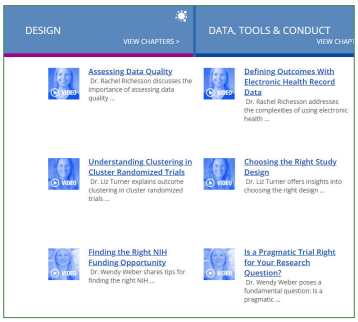
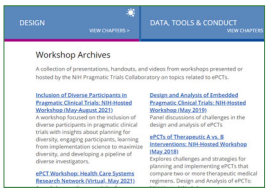
Sources for further learning

- Living Textbook video modules
  - https://rethinkingclinicaltrials.org/training-resources/living-textbook-video-modules/
- EHR video modules
  - https://rethinkingclinicaltrials.org/training-resources/ehr-workshop-video-modules/
- Online Training Workshops
  - https://rethinkingclinicaltrials.org/training-resources/
- Grand Rounds
  - https://rethinkingclinicaltrials.org/grand-rounds-hub/
- eNewsletter
  - https://rethinkingclinicaltrials.org/newsletter-subscribe/





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Considerations for Planning Your Embedded Pragmatic Clinical Trial

1. ePCT Aims and Significance

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

2. Engaging All Stakeholders and Aligning with Healthcare System Partners

- Who are your stakeholders?
- Does your intervention add long-term value to the health system and its patients?
- Important things to do:
  - Engage stakeholders early and often
  - Set expectations to work collaboratively and build trust from the beginning
  - Use familiar language that stakeholders understand
  - Get to know your stakeholders' values, priorities, and expectations
  - Assess your partners' capacity and capabilities
  - Track goals reached, challenges, and adaptations throughout the life cycle of your ePCT
  - Show appreciation and celebrate accomplishments early and often to have sustained partnerships

3. Measuring Outcomes

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

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

4. ePCT Design and Analysis

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

6. Pilot and Feasibility Testing

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

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

7. Ethical and Regulatory Oversight Considerations

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

8. Dissemination and Implementation

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

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

9. Assembling Your ePCT Team

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

10. Writing the Grant Application

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

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