NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Driving Tomorrow's Outcomes Through Clinical Research in Real-World Settings:

Essentials of Embedded Pragmatic Clinical Trials Workshop

Participant Guide

2023 AcademyHealth

Annual Research Meeting

June 23-24, 2023

Table of Contents

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Driving Tomorrow's Outcomes Through Clinical Research in Real-World Settings: Essentials of Embedded Pragmatic Clinical Trials Workshop

2023 AcademyHealth Annual Research Meeting
Seattle, WA
June 23-24, 2023

JUNE 23, 2023			
DURATION	**AGENDA TOPIC**	**SPEAKERS**	**GOALS**
8:15 - 8:30 a.m.	**Welcome** **Opening Remarks**	Kevin Weinfurt	• Welcome and introduction of agenda, objectives, and Living Textbook
8:30 - 9:15 a.m.	**What are Embedded Pragmatic Clinical Trials (ePCTs)?**	Wendy Weber	• Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials • Learn about the advantages and disadvantages of ePCTs, when a pragmatic approach can be used to answer the research question. • Q & A with attendees
9:15 - 10:15 a.m.	**Engaging Stakeholders & Aligning with Health System Partners**	Emily O'Brien	• Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study • Identify skills needed for a strong study team and consider the diversity of the team, including inclusive practices • Understand the real-world priorities and perspectives of healthcare system leaders and how to obtain their support • Identify engagement practices to obtain patient and community perspectives • Highlight challenges of partnering with diverse healthcare systems • Q & A with attendees
10:15 - 10:30 a.m.	**Break**		• Networking among attendees and presenters

JUNE 23, 2023			
DURATION	**AGENDA TOPIC**	**SPEAKERS**	**GOALS**
10:30 - 11:15 a.m.	**Objectives and Trial Design: An Overview of Hybrid Designs**	Hayden Bosworth	• Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs • Q & A with attendees
11:15 a.m. - 12:00 p.m.	**Measuring Outcomes**	Emily O'Brien	• Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) • Discuss the integration of a health equity lens in evaluating outcomes • Q & A with attendees
12:00 - 1:00 p.m.	**Lunch**		• Networking among attendees and presenters
1:00 - 1:45 p.m.	**ePCT Design**	Patrick Heagerty	• Learn about cluster randomized and stepped-wedge study designs • Q & A with attendees
1:45 - 2:30 p.m.	**ePCT Analysis**	Patrick Heagerty	• Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what principal investigators (PIs) need to know • Q & A with attendees
2:30 - 2:45 p.m.	**Break**		• Networking among attendees and presenters
2:45 - 4:15 p.m.	**ePCTs in Context: Small Group Work Followed by Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Kevin Weinfurt **Panel:** Margaret Kuklinski Angelo Volandes Michael Parchman	• Have attendees work in small groups to discuss challenges faced by ongoing ePCTs • Introduce PIs of ongoing ePCTs to discuss how they handled the challenges from attendees' discussion, reflect on the morning topics, and discuss lessons learned • Q & A with attendees
4:15 - 4:25 p.m.	**Closing Remarks/Adjourn**	Kevin Weinfurt	• Summary of Day 1. • What to expect on Day 2

JUNE 24, 2023			
DURATION	**AGENDA TOPIC**	**SPEAKERS**	**GOALS**
8:00 - 8:15 a.m.	**Welcome** **Opening Remarks** **Introductions**	Kevin Weinfurt	• Review of Day 1. • Meeting goals and expectations
8:15 - 9:00 a.m.	**Pilot & Feasibility Testing**	Wendy Weber	• Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions • Q & A with attendees
9:00 - 9:45 a.m.	**Ethical & Regulatory Oversight Considerations**	Stephanie Morain	• Learn about the regulatory and ethical challenges of conducting ePCTs • Discuss unique needs of historically underrepresented and mistreated groups • Q & A with attendees
9:45 – 9:55 a.m.	**Break**		• Networking among attendees and presenters
9:55 - 10:40 a.m.	**Writing a Compelling Grant Application**	Beda Jean-Francois	• Learn how to develop a compelling ePCT application • Tips from Collaboratory PIs • Q & A with attendees
10:40 - 11:55 a.m.	**ePCTs in Context: Small Group Work Followed by Panel Discussion with Collaboratory Demonstration Project PIs**	**Moderator:** Vince Mor **Panel:** Margaret Kuklinski Ardith Doorenbos	• Have attendees work in small groups to discuss challenges faced by ongoing ePCTs • Introduce PIs of ongoing ePCTs to discuss how they handled the challenges from attendees' discussion, reflect on the morning topics, and discuss lessons learned • Q & A with attendees
11:55 a.m. - 12:00 p.m.	**Closing Remarks**	Kevin Weinfurt	• Wrap-up including identifying sources for further learning

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Driving Tomorrow's Outcomes Through Clinical Research in Real-World Settings: Essentials of Embedded Pragmatic Clinical Trials Workshop

2023 AcademyHealth Annual Research Meeting
Seattle, WA
June 23-24, 2023

Speaker Biographies

Hayden B. Bosworth, PhD
Duke University
hayden.bosworth@duke.edu

Hayden B. Bosworth, PhD, is a health services researcher and implementation scientist. He is currently a professor of population health sciences, medicine, psychiatry, and nursing at Duke University and the vice chair of education in the Department of Population Health Sciences. He is also the deputy director of the Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT) (COIN) at the Durham Veterans Affairs Medical Center and adjunct professor in the Department of Health Policy and Administration in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. His research interests comprise 3 overarching areas of research: 1) clinical research that provides knowledge for improving self-management in chronic care; 2) implementing research to improve access to quality of care; and 3) eliminating health care disparities. His expertise is in patient-centered, multidisciplinary self-management programs for adults with chronic disease.

Dr. Bosworth also has expertise in developing and implementing scalable/sustainable interventions to improve health behaviors and reduce the burden of chronic diseases. These trials/programs focus on motivating individuals to initiate health behaviors and sustain them long term. He also has ample experience in conducting observational studies examining healthcare use and predictors of medication nonadherence. Current examples of his work include a multisite trial evaluating a nurse-administered intervention to extend the HIV treatment cascade for cardiovascular disease prevention (EXTRA-CVD) and a similar study being conducted in the VA (VA-EXTRA-CVD).

Dr. Bosworth is the recipient of numerous awards, including an American Heart Association Established Investigator award, a VA Senior Career Scientist Award, and the Under Secretary's Award for Outstanding Achievement in Health Services Research. He has been the principal investigator of over 30 trials resulting in over 400 peer-reviewed publications and 4 books. His work has been implemented in Medicaid of North Carolina, the UK National Health System, Kaiser Permanente, the Veterans Health Administration, as well as by a number of health care payers such as Humana.

In addition to his research experience, mentoring is an area to which he has devoted significant effort. He has mentored over 140 graduate students, postdoctoral fellows, and junior faculty, including 28

career development awardees over the last 10 years. In addition, he is the principal investigator of a K12 National Heart, Lung, and Blood Institute–funded grant to train faculty in dissemination and implementation.

Ardith Z. Doorenbos, PhD, RN, FAAN
University of Illinois Chicago
ardith@uic.edu

Ardith Z. Doorenbos, PhD, RN, FAAN is a Professor in the Department of Biobehavioral Nursing Science, College of Nursing at the University of Illinois Chicago. Dr. Doorenbos' research is centered on pain and symptom management. Dr. Doorenbos is a distinguished researcher with a well-funded program of research that has received funding from the National Institute of Health, Congressionally Directed Medical Research Programs, and other professional sources. In 2010, she was named a Fellow of the American Academy of Nursing and in 2018, was inducted into the Sigma Theta Tau, International Nurse Researcher Hall of Fame.

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

Dr. Heagerty is Professor and former Chair of the Department of Biostatistics at the University of Washington. He received a PhD from the Johns Hopkins University, and a BS from Cornell University. He has extensive experience as an educator, independent and collaborative scientist, and administrator. He has developed fundamental methods for longitudinal studies with a focus on prognostic model evaluation and structural longitudinal models, and he has detailed rigorous methods for the design, analysis, and interpretation of cluster-randomized trials conducted within health care delivery systems. Dr. Heagerty has co-authored two leading texts (Analysis of Longitudinal Data, Oxford 2002; Biostatistics: A Methodology for the Health Sciences, Wiley 2004). He is an elected Fellow of the American Statistical Association and has twice been honored by professional societies for specific research contributions (in 2000 as the Snedecor Award winner; and in 2005 by the International Biometrics Society for the best paper published in the society's flagship journal, Biometrics). Dr. Heagerty directs the Center for Biomedical Statistics (CBS), a core partially funded by the NIH Clinical and Translational Science Award (CTSA) with responsibility for coordination of biostatistical collaboration in Seattle and the greater Northwest region (Wyoming, Alaska, Idaho, Montana). The CBS houses the data coordinating centers for several U01 and R01 funded projects including GARNET (Genomics and Randomized Trials), BOLD (Backpain Outcomes using Longitudinal Data), UH3 funded pragmatic trials including LIRE (Lumbar Imaging Reporting with Epidemiology), and PCORI funded trials evaluating surgical interventions and psychiatric treatment strategies. The CBS has previously conducted high-impact multi-site randomized trials including INVEST (Investigational Vertebroplasty Safety and Efficacy Trial, NEJM 2009), the Carpal Tunnel Surgical Trial (Lancet 2009), and LESS (Lumbar Epidural Steroid Injections for Spinal Stenosis, NEJM 2014). Dr. Heagerty is the Director of the Biostatistics and Research Design Core for the NIH Health Care Systems Research Collaboratory, for the NIH Mental Health Research Network, and a member of the Executive Committee for the FDA Sentinel Innovation Center. Dr. Heagerty is also a licensed teacher (NY State: Mathematics, Biology, and Chemistry) and has taught from middle school to graduate school (UW SPH Outstanding Teacher Award, 2009).

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

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

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.

Vincent Mor, PhD
Brown University School of Public Health
vincent_mor@brown.edu

Vincent Mor, PhD, is a professor of health services, policy & practice and Florence Pirce Grant Professor in the Brown University School of Public Health, and has been principal investigator of 40+ NIH-funded grants focusing on use of health services and outcomes of frail and chronically ill people. He has evaluated the impact of programs and policies including Medicare funding of hospice, changes in Medicare nursing home payment, and the introduction of nursing home quality measures. He co-authored the Congressionally-mandated Minimum Data Set (MDS) and was architect of an integrated Medicare claims and clinical assessment data structure used for policy analysis, pharmaco-epidemiology and population outcome measurement. Dr. Mor developed summary measures using MDS data to characterize residents' physical, cognitive and psycho-social functioning. These data resources are the heart of Dr. Mor's NIA- funded Program Project Grant, "Changing Long Term Care in America," which examines the impact of Medicaid and Medicare policies on long-term care. These data are also at the core of a series of large, pragmatic cluster randomized trials of novel nursing home-based interventions led by Dr. Mor.

Dr. Mor is one of the Principal Investigators of the National Institute on Aging (NIA) **IM**bedded **P**ragmatic **A**lzheimer's Disease (AD) and AD-Related Dementias (AD/ADRD) **C**linical **T**rials (IMPACT) Collaboratory which was established in 2019 to meet the urgent public health need to deliver high quality, evidence-based care to people living with dementia (PLWD) and their care partners within the healthcare systems (HCS) that serve them. The Mission of IMPACT is to build the nation's capacity to conduct pragmatic clinical trials of interventions embedded within health care systems for people living with dementia and their care partners.

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

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

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

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

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

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

Michael L. Parchman, MD, MPH
Kaiser Permanente Washington Health Research Institute
Michael.X.Parchman@kp.org

Michael L. Parchman, MD, MPH, is a primary care physician and a senior investigator at the Center for Accelerating Care Transformation within the Kaiser Permanente Washington Health Research Institute. He has over thirty years of primary care clinical experience and work a medical educator. Dr. Parchman's research has examined the effectiveness of strategies to improve primary care for people with chronic illnesses, methods to advance research in primary care settings, and the theoretical underpinnings of the delivery of primary care. His current work focuses on addressing overuse of low-value care services. Building on his work as director of a Robert Wood Johnson Foundation fellowship program to train clinician value champions, he currently serves as Principal Investigator of a two-year IMPACT Collaboratory pragmatic trial to decrease the use of potentially inappropriate medications among patients with dementia across two Accountable Care Organizations.

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)
wendy.weber@nih.gov

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

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

Kevin Weinfurt, PhD
Duke Clinical Research Institute
Duke University School of Medicine
kevin.weinfurt@duke.edu

Kevin P. Weinfurt is Professor and Vice-Chair of Research in the Department of Population Health Sciences at Duke University Medical Center and a faculty member of the Duke Clinical Research Institute. He holds secondary appointments as a Professor of Psychology and Neuroscience, Professor of Psychiatry and Behavioral Sciences, Professor of Biostatistics and Bioinformatics, and as a Faculty Associate of the Trent Center for the Study of Medical Humanities and Bioethics. Dr. Weinfurt also co-directs the Center for Health Measurement at Duke and is co-director of the Clinical Research Training Program (Masters degree offered through the School of

Medicine). Dr. Weinfurt currently works as Special Governmental Employee for the U.S. Food and Drug Administration, helping to create the Patient-Focused Drug Development guidance series. He is also a member of the Secretary's Advisory Committee for Human Research Protections.

Dr. Weinfurt conducts research on measuring patient-reported outcomes, medical decision making, and bioethics. In addition to conducting research, Dr. Weinfurt has taught undergraduate courses in introductory psychology, judgment and decision making, and the psychology of medical decision making, and graduate courses in multivariate statistics, patient-reported outcomes, and research ethics

2023 AcademyHealth Annual Research Meeting

Driving Tomorrow's Outcomes Through Clinical Research in Real-World Settings: Essentials of Embedded Pragmatic Clinical Trials Workshop

June 23-24, 2023

Title: Driving Tomorrow's Outcomes Through Clinical Research in Real-World Settings: Essentials of Embedded Pragmatic Clinical Trials

Program Description

Recent rapid changes in the challenges facing healthcare have made it even more critical to have a highly efficient mechanism for clinical research that can deliver much-needed evidence faster and with minimal additional resources. This workshop introduces concepts in the design, conduct, and implementation of embedded pragmatic clinical trials (ePCTs), with a particular focus on methods relevant to health services researchers. ePCTs are randomized trials conducted within health care systems and use streamlined procedures and existing infrastructure to answer important medical questions for patients, providers, and health system leaders. Such trials have the potential to inform policy and practice with broadly generalizable, high-quality evidence at lower cost and greater efficiency compared with traditional explanatory clinical trials. The workshop will provide an introduction to the investigative opportunities for embedded health systems research, along with strategies for conducting clinical trials that provide real-world evidence necessary to inform both practice and policy. Workshop attendees will have the opportunity to participate in facilitated, hands-on learning activities and to interact with Principal Investigators of current and past ePCTs. Firsthand ePCT experiences and case studies from the NIH Pragmatic Trials Collaboratory will support and illustrate the topics presented and demonstrate how ePCTs in real-world settings are driving tomorrow's outcomes.

Learning Objectives

1. To clarify the definition of ePCTs and explain their utility.
2. To introduce attendees to the unique characteristics and challenges of designing, conducting, and implementing ePCTs within diverse health care systems.
3. To increase the capacity of health services researchers to address important clinical questions with ePCTs in real-world settings, driving tomorrow's research outcomes.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

ACP PEACE

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, MD, MPH (NIA)

Project Scientist
Karen Kehl, PhD, RN, FPCN (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

- Video Interview: Update on the ACP PEACE Demonstration Project (May 2022)
- Publication: Reaching Ambulatory Older Adults with Educational Tools: Comparative Efficacy and Cost of Varied Outreach Modalities in Primary Care
- Publication: Association of an Advance Care Planning Video and Communication Intervention With Documentation of Advance Care Planning Among Older Adults: A Nonrandomized Controlled Trial
- Publication: A Yet Unrealized Promise: Structured Advance Care Planning Elements in the Electronic Health Record
- Publication (Study Design): Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP-PEACE): The Study Protocol for a Pragmatic Stepped-Wedge Trial of Older Patients With Cancer
- Interview: ACP PEACE Trial Moves From Planning to Implementation Phase: An Interview With Dr. Angelo Volandes (July 2019)
- PCT Grand Rounds Webinar: Promoting Effective Advance Care Planning Communication in the Elderly: The ACP-PEACE Trial (February 2019)

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Study design

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Participating healthcare systems

- Duke Health
- Northwell Health
- Mayo Clinic

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

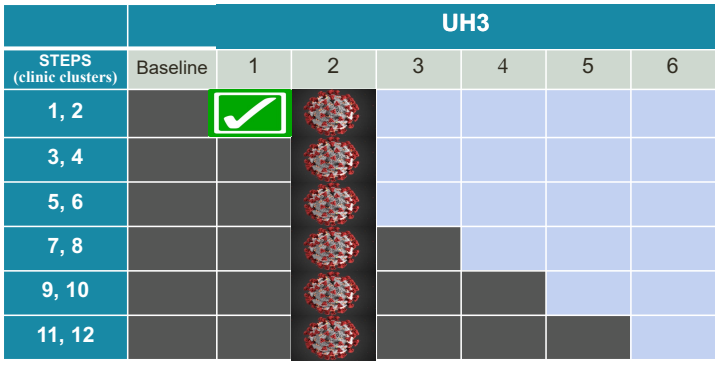
Barriers/challenges

- 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

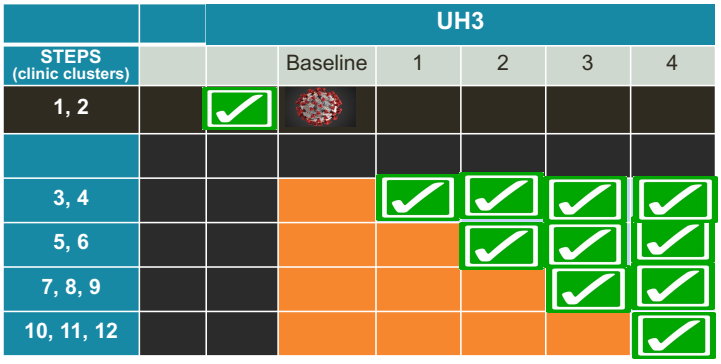
Original Design



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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)**

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

Demonstration Project Snapshot

Can Value Champions Reduce Inappropriate Prescribing for People with Dementia?

Principal Investigator

Michael Parchman, MD, MPH
Kaiser Permanente of Washington Health Research Institute

Health Care Systems

- U.S. Medical Management
- Ochsner Health

"Training front-line clinicians to be effective value champions—someone who can serve as an embedded change agent—has great potential to address the over-prescribing of potentially inappropriate medications among people living with dementia."

RATIONALE: Overuse of potentially inappropriate medications among people living with dementia remains a persistent problem. Clinical value champions are front-line clinicians who can advocate for and influence practice-driven change at multiple levels within a health care organization.

OBJECTIVE: To train value champions across two large accountable care organizations to address over-prescribing of potentially inappropriate medications for people living with dementia. This pragmatic randomized clinical trial will examine the impact of this embedded intervention on prescribing outcomes and health care utilization, and assess its appropriateness, feasibility, fidelity, penetration, and equity.

SETTING: Two large accountable care organizations (ACOs) across 14 states.

POPULATION: Medicare patients with a diagnosis of dementia who are seen in primary care clinic settings**.**

INTERVENTION: Clinicians from randomly selected primary care settings in each ACO will participate in a six-month value champions training program and then engage fellow clinicians, staff and patients in efforts to de-implement potentially inappropriate medications for people living with dementia.

OUTCOMES: The primary outcome is a patient-level measure of exposure to one of three classes of potentially inappropriate medications ascertained from Medicare pharmacy claims data. Secondary outcomes include emergency department visits or a hospitalization for a fall, and five intermediate implementation outcomes: appropriateness, feasibility, fidelity, penetration, and equity.

IMPACT: This study will allow health care systems to gain real-world experience integrating this pragmatic intervention in a manner that provides clear information on its effectiveness and will enable them to train others to be value champions to address other overused services across additional clinical sites.

Can Value Champions Reduce Inappropriate Prescribing for People with Dementia?

Michael L. Parchman, MD, MPH
Senior Investigator, Center for Accelerating Care Transformation
Associate Professor, Department of Health Systems Science
Kaiser Permanente Bernard J. Tyson School of Medicine

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Objective

- To train clinician champions across 2 large accountable care organizations to address over-prescribing of potentially inappropriate medications for people living with dementia
- To examine the impact of the embedded intervention on prescribing outcomes and health care utilization, and assess its appropriateness, feasibility, fidelity, penetration, and equity.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Study design

- Pragmatic cluster randomized clinical trial
- 2 large accountable care organizations (ACO) across 14 states
- Primary Care Clinics randomized to intervention or control (matched pairs in each ACO based on number of patients with dementia in each clinic location)
- One clinician from each intervention clinic recruited by ACO leadership to participate.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Participating ACOs (proposed n=30 sites from each)

- U.S. Medical Management (now Harmony Cares)
  - Limited to clinics with 3 or more clinicians
  - Leadership ruled out 6 clinics due to unstable clinician availability
  - n=22 sites randomized (11 primary care clinician champions)
- Ochsner Health
  - Hurricane September 2021 during clinician recruitment (2 clinics damaged, never re-opened)
  - COVID-19 hospitalization peak in Sept-Oct 2021
  - Proposed using clinical pharmacists as champions instead of clinicians
  - n=13 sites randomized (7 clinical pharmacist champions)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Intervention

- January – June 2022: champions participated in training twice monthly webinars
- March 2022-March 2023: champions engage fellow clinicians and patients to decrease prescribing of potentially inappropriate medications for people living with dementia
  - anti-psychotics
  - benzodiazepines
  - hypoglycemics

5

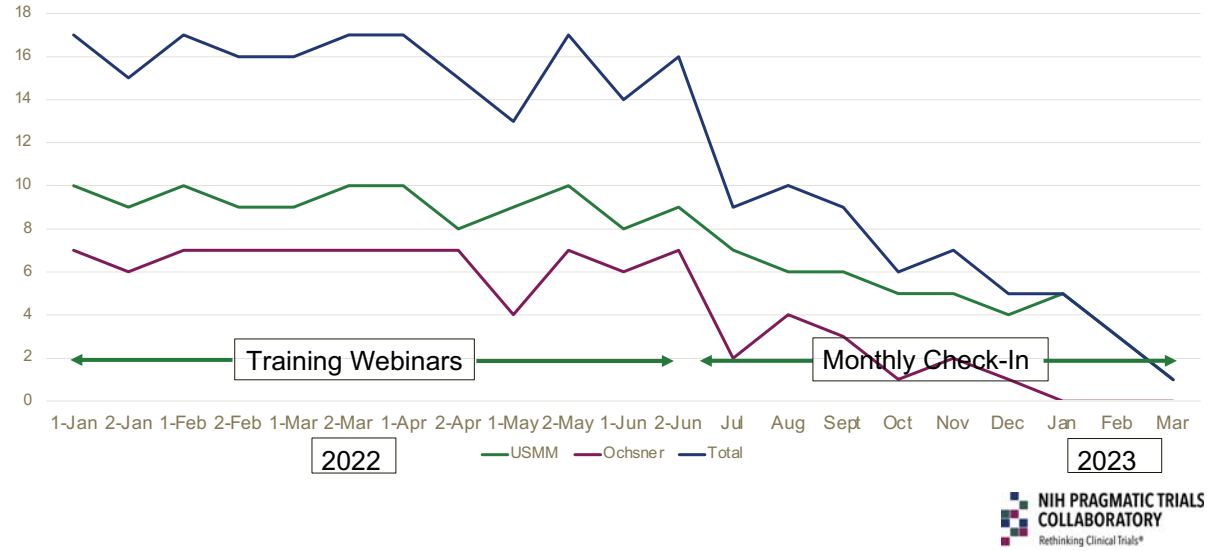
Outcomes

- Primary outcome: patient-level measure of exposure to one of the 3 classes of potentially inappropriate medications ascertained from Part D Medicare pharmacy claims data.
- Secondary outcomes include emergency department visits or a hospitalization for a fall, and 5 intermediate implementation outcomes: appropriateness, feasibility, fidelity, penetration, and equity.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

Outcomes: Clinician Champion Participation



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

Barriers/challenges

- PCT question: should we depend on embedded delivery system employees for the intervention? (impact on PRECIS-2 criteria?
  - Unclear if those selected by ACO leadership had intrinsic motivation to be a clinician champion.
  - ACO leadership assigned a champion as medical director for 2 control clinics after conclusion of training. (Leadership priorities super cede study priorities
- PCT question: should we depend on current IT resources available to clinicians when delivering an intervention? (impact on PRECIS-2 criteria?)
  - Neither ACO was able to provide champions with useful prescribing data in a timely fashion. (One ACO did so 8-9 months after requested)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

Barriers/Challenges

- PCT Question: When does change in contextual factors exceed threshold for ‘pulling the plug’ on a study?
  - Change in study design to use clinical pharmacists in one ACO provides opportunity for unexpected comparison but may adversely impact primary objective of study.
- PCT question: are high “Flexibility” scores in PRECIS-2 criteria detrimental to intervention success?
  - We provided a range of ideas for HOW champions will engage with colleagues to influence prescribing, but champions had little time to act on them.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

Solutions/lessons learned

- Limit dependence on embedded health system employees with delivery of intervention.
- Devote resources to creating the necessary data tools and ‘dashboards’ not currently available in most health systems.
- Expect the unexpected and work with all stakeholders when study design needs to be changed, because it will.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

GUIDING GOOD CHOICES

Guiding Good Choices for Health (GGC4H)

Principal Investigators
Margaret Kuklinski, PhD; and Stacy Sterling, DrPH, MSW

Sponsoring Institution
University of Washington

Collaborators
- Kaiser Permanente
- Henry Ford Health System

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

Program Official
Beda Jean-Francois, PhD (NCCIH)

Project Scientist

Elizabeth Ginexi, PhD (NCCIH)

ClinicalTrials.gov Identifier
NCT04040153

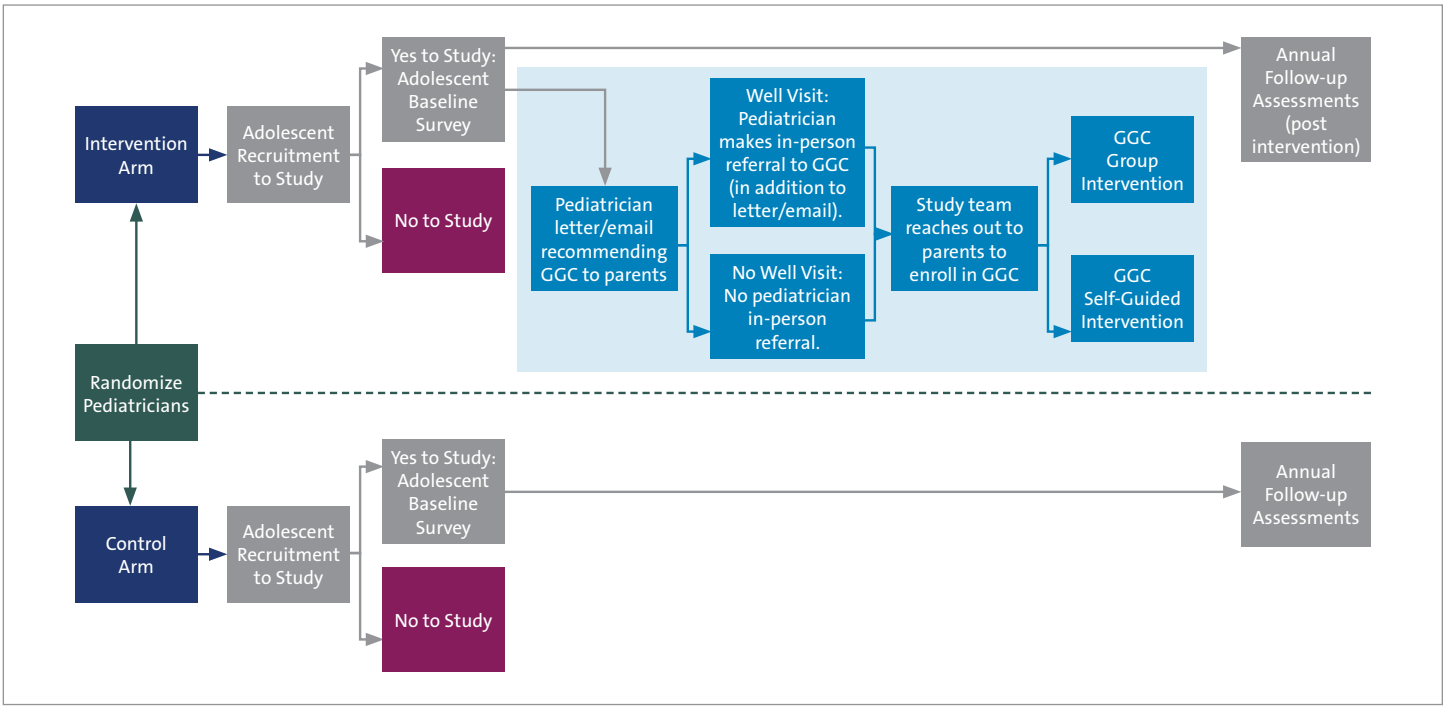
ABSTRACT

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

- Video Interview: Update on the GGC4H Demonstration Project (April 2022)
- Publication (Study Design): Parent-Focused Prevention of Adolescent Health Risk Behavior: Study Protocol for a Multisite Cluster-Randomized Trial Implemented in Pediatric Primary Care
- PCT Grand Rounds Webinar: Guiding Good Choices for Health (GGC4H): Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare Systems (December 2018)

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

Margaret Kuklinski, PhD
Endowed Associate Professor of Prevention in Social Work
Director, Social Development Research Group
Acting Director, Center for Communities That Care
School of Social Work, University of Washington

GUIDING GOOD CHOICES

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Objectives

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Barriers/challenges

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

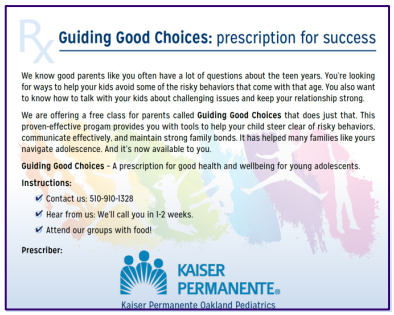
Pragmatic implementation: Key leader support

- 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."

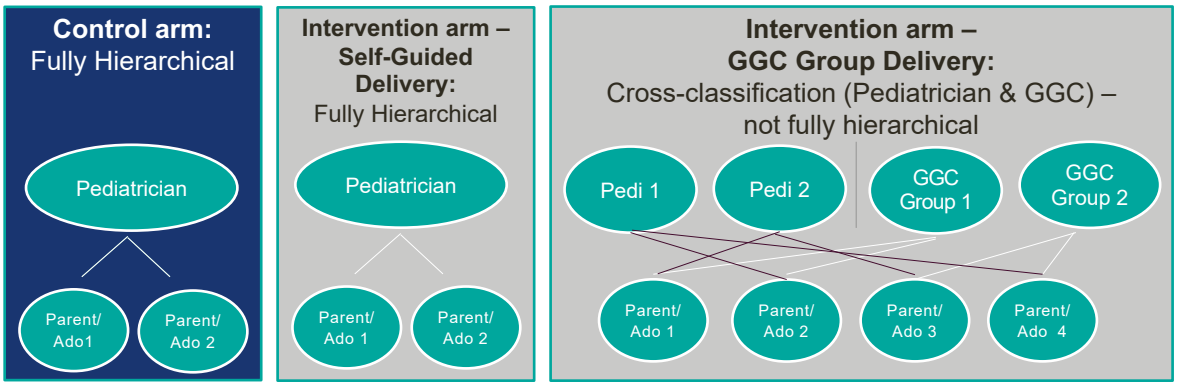
"We're offering a new free class called Guiding Good Choices. It's for parents of children your son's/daughter's age in my practice, to provide you with tools to help your child avoid risky behaviors during the challenging teen years while keeping your relationship strong."



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

Solutions/lessons learned

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

GRACE TRIAL

Hybrid Effectiveness–Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE)

Principal Investigators
Ardith Z. Doorenbos, PhD, RN, FAAN; Judith M. Schlaeger, PhD, CNM, LAc, FAAN; Robert Molokie, MD; Miriam O. Ezenwa, PhD, RN, FAAN; and Nirmish Shah, MD

Sponsoring Institution
University of Illinois Chicago

Collaborators
- University of Illinois Hospital and Health Sciences System
- University of Florida Health
- Duke University Health System

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

Program Official
Beda Jean-Francois, PhD (NCCIH)

Project Scientist
Beda Jean-Francois, PhD (NCCIH)

ClinicalTrials.gov Identifier
NCT04906447

ABSTRACT

Nearly 100 people die every day in the United States from a prescription opioid overdose. This crisis is caused in part by an overreliance on opioids to treat individuals experiencing chronic pain. Acute or chronic pain is a constant companion to more than 100,000 people living with sickle cell disease in the United States and millions more worldwide. Pain is a hallmark of sickle cell disease and results in almost 200,000 annual emergency department admissions and is a leading cause of hospitalization. It is known that the use of complementary and integrative therapies to reduce pain and opioid use has the potential to enable patients with sickle cell disease to better cope with their pain, yet few studies have evaluated the effectiveness of such therapies, and none have assessed how to implement them across multiple healthcare systems and patient populations.

To address this gap, GRACE is a pragmatic trial conducted across 3 large healthcare systems that will assess the effects of guided relaxation and acupuncture treatments for people with sickle cell disease. GRACE has 3 priorities:

- Evaluate the effectiveness of guided relaxation and acupuncture to improve pain control.
- Determine the most appropriate and effective treatment sequence for any given patient based on their unique characteristics.
- Describe the processes and structures required to implement guided relaxation and acupuncture within healthcare systems.

The intervention phase will involve 3 arms (guided relaxation, acupuncture, and usual care) and will follow a quantitative adaptive design that responds to patients' characteristics and evolving pain status. GRACE will use the Consolidated Framework for Implementation Research to plan, execute, and evaluate the associated implementation processes.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Potential responses to the Patient Health Questionnaire (PHQ)-9 item about suicidal ideation	The study now makes support available for any patients who may report having suicidal thoughts.
Change in study design due to patient stakeholder input	The study team consulted with the NIH Collaboratory's Biostatistics and Study Design Core Working Group to come up with new design and power considerations.

"If we can better manage pain, we can impact the quality of life and change the possibilities for patients with sickle cell disease. They can have a plan for activities and have a more productive work situation. Pain management can change so many things in their lives." — Dr. Ardith Doorenbos.

"I think we will get the most realistic findings of how these therapeutic interventions work, whereas in more classic trials they're going to end up with such a group of selected patients that it may not be as generalizable as a pragmatic clinical trial." — Dr. Robert Molokie

PRESENTATIONS & ABSTRACTS

- Presentation: Presentation to the NIH Collaboratory Steering Committee (May 2023)
- Publication: Developing an Implementation Blueprint for the NIH HEAL Initiative GRACE Trial: Perspectives on Acupuncture and Guided Relaxation for Chronic Sickle Cell Disease Pain
- Publication (Study Design): Hybrid Effectiveness-Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE): A Protocol
- Publication: Acupuncture for Chronic Pain in Adults With Sickle Cell Disease: A Mixed-Methods Pilot Study
- Video Interview: GRACE Trial Seeks More Options for Sickle Cell Pain (August 2021)

GRACE: Hybrid Effectiveness-Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain

Ardith Z. Doorenbos, PhD, RN, FAAN
Nursing Collegiate Professor
Department of Biobehavioral Nursing Science
University of Illinois Chicago

GRACE TRIAL

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Objective

- Evaluate the effectiveness of guided relaxation and acupuncture to improve pain control
- Determine the most appropriate and effective treatment sequence for any given patient based on their unique characteristics
- Describe the processes and structure required to implement guided relaxation and acupuncture within healthcare systems

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Study design

- Pragmatic trial that follows a quantitative adaptive design that responds to patients' characteristics and evolving pain status
- Randomized to 3 arms (guided relaxation, acupuncture, and usual care)
- 3 healthcare systems (soon adding 2 more)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Participating healthcare systems

- Duke Health
- University of Florida Health
- University of Illinois Hospital and Health Sciences System
- New: Johns Hopkins University
- New: Emory University

DukeHealth

UFHealth
UNIVERSITY OF FLORIDA HEALTH

UI Health | UIC

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Outcomes

- **Aim 1**: Determine the effectiveness of guided relaxation and acupuncture as compared to usual care in decreasing pain and opioid use for SCD patients. **Hypothesis**: At 6 weeks, SCD patients randomized to either CIH intervention will have a greater decrease in pain, opioid use, sleep, anxiety, depressive symptoms, and pain catastrophizing compared to SCD patients randomized to usual care.
- **Aim 2**: Identify the best adaptive intervention for improved outcomes by documenting outcomes among adaptive intervention sequences: (1) initiate guided relaxation and switch to acupuncture for non-responders at midpoint; (2) initiate guided relaxation and continue with guided relaxation for non-responders at midpoint; (3) initiate acupuncture and switch to guided relaxation for non-responders at midpoint or (4) initiate acupuncture and continue with acupuncture for non-responders at midpoint.
- **Aim 3**: Explore differences in response to the adaptive interventions by age and sex.
- **Aim 4:** Identify implementation facilitators, challenges, and solutions for structures and processes that contribute to the seamless integration of CIH therapies into the health systems by conducting individual interviews with participants in the intervention group who responded to the intervention and those who did not. We will also conduct focus groups with hospital personnel at 4 timepoints.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

Barriers/challenges

- Recruitment
  - Overall: 72% of current expected number of participants
    - Duke: 82%
    - UIC: 93%
    - UF: 45%
- Adherence
  - Each site has struggled with completing a ‘full dose’ of each intervention to varying degrees

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

Solutions/lessons learned

- Recruitment responses
  - Team worked with animators at Duke to create videos that explain acupuncture, guided relaxation, and the study overall
    - Duke sent videos through MyChart
    - UIC and UF showed these in clinic/ texted links to interested patients

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

Solutions/lessons learned

- Recruitment responses
  - UIC ran an ad on Chicago public transportation, and posted new flyers in clinic spaces

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

Solutions/lessons learned

- Recruitment responses
  - UIC and UF sent letters to sickle cell patients about the study
  - Patients were given the opportunity to 'opt out' of the study
  - Research staff are contacting those who did not opt out

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

Solutions/lessons learned

- Recruitment responses
  - Adding additional recruitment sites
    - Emory University in Atlanta
    - Johns Hopkins in Baltimore

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

Solutions/lessons learned

- Adherence
  - Set up automatic weekly text reminders to guided relaxation participants
  - Increased travel compensation for those in the acupuncture arm
  - UIC hired racially concordant acupuncturists

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Welcome

Speaker

Kevin P. Weinfurt, PhD

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

Welcome

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Workshop learning objectives

- Clarify the definition of ePCTs and explain their utility
- Introduce attendees to the unique characteristics and challenges of designing, conducting, and implementing ePCTs within diverse healthcare systems
- Increase the capacity of health services researchers to address important clinical questions with ePCTs in real-world settings, driving tomorrow's research outcomes.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Workshop sessions – Day 1

- 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 (Hayden Bosworth)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Workshop sessions (Day 1 continued)

- Measuring Outcomes (Emily O'Brien)
- ePCT Design and Analysis (Patrick Heagerty)
- ePCTs in Context: Small Group Work and Panel Discussion with Collaboratory Demonstration Project PIs

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Workshop sessions – Day 2

- Pilot & Feasibility Testing (Wendy Weber)
- Ethical & Regulatory Oversight (Stephanie Morain)
- Writing a Compelling Grant Application (Beda Jean-Francois)
- ePCTs in Context: Small Group Work and Panel Discussion with Collaboratory Demonstration Project PIs
- Next Steps (Kevin Weinfurt)

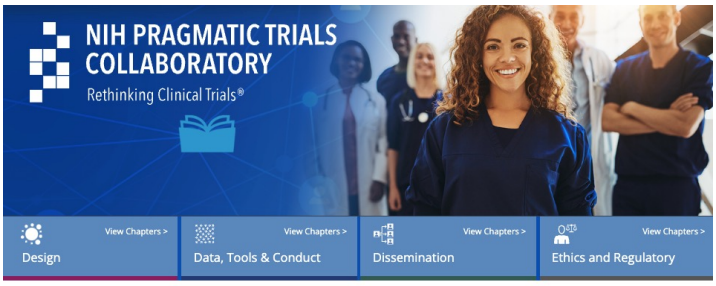
NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials

WATCH THE VIDEO

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

GET STARTED

What is the NIH PRAGMATIC TRIALS COLLABORATORY?

What is a PRAGMATIC CLINICAL TRIAL?

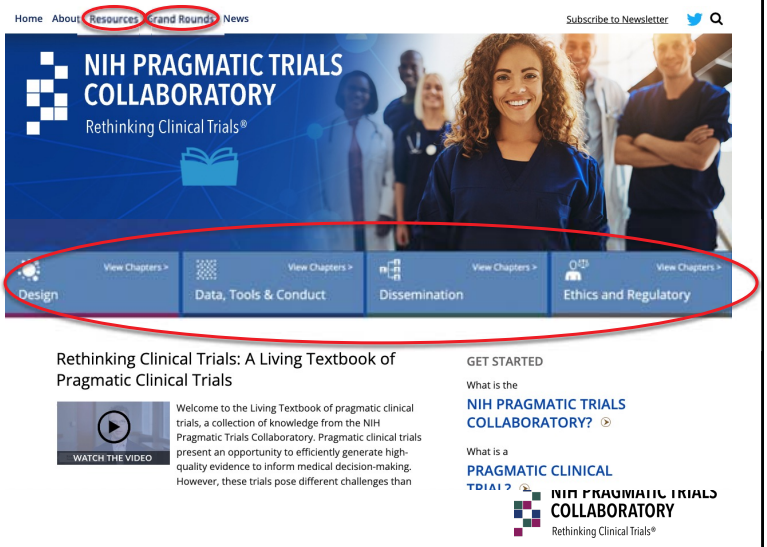
TRAINING RESOURCES

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

Key Resources

- Living Textbook
- Grand Rounds Hub
- Training Resources



7

slido

What best matches your professional position?

ⓘ Start presenting to display the poll results on this slide.

8

slido

Where are you in your career track?

ⓘ Start presenting to display the poll results on this slide.

9

slido

What is your experience conducting pragmatic trials in health care systems?

ⓘ Start presenting to display the poll results on this slide.

10

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

What are Embedded Pragmatic Clinical Trials (ePCTs)?

Speaker

Wendy 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Important things to know

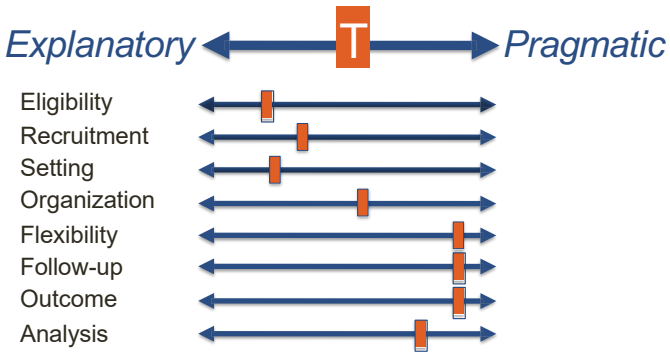
- ePCTs are designed to answer important, real-world clinical questions
- Broad stakeholder engagement and support are essential from beginning to end
- Trade-offs in flexibility, adherence, and generalizability are inevitable

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Trials vary across a spectrum of explanatory and pragmatic elements

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



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

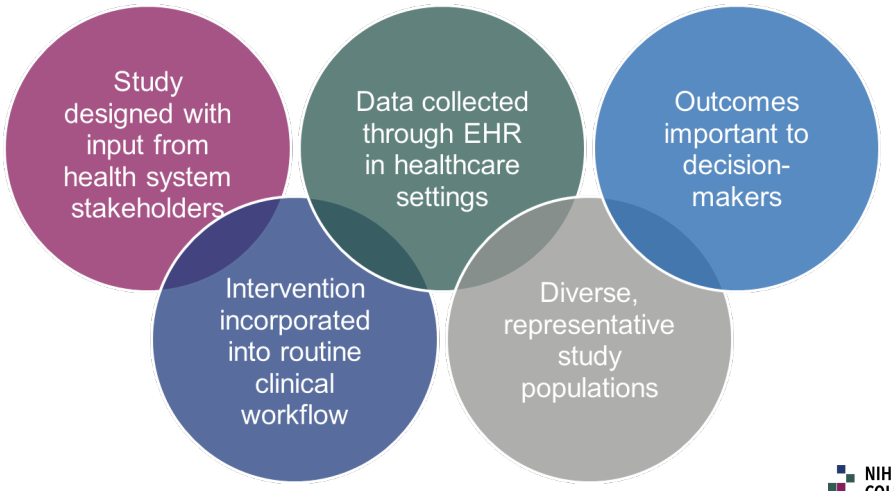
ePCT characteristics

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

ePCTs bridge clinical care into research



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Engaging Stakeholders & Aligning with Health System Partners

Speaker

Emily O'Brien, PhD

Associate Professor in 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

***New*: Group Activity!**

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

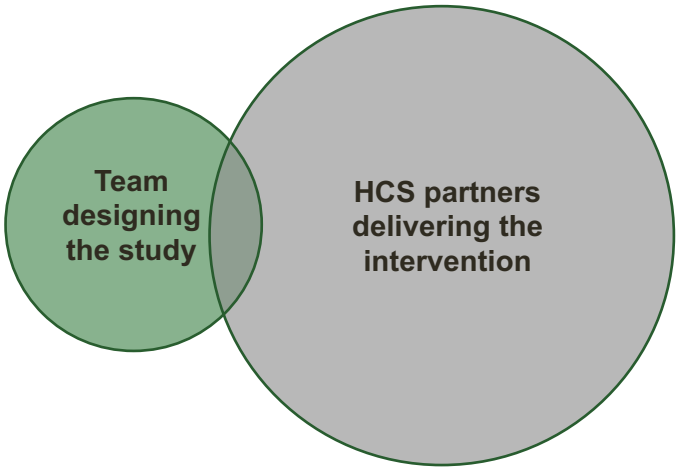
Important things to know

- 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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Who is involved?



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

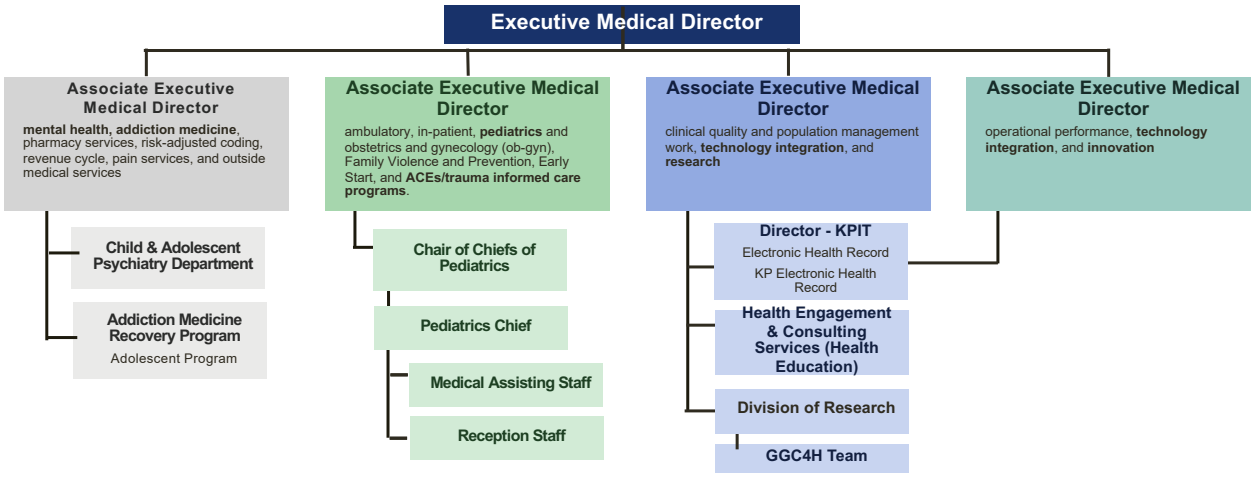
What skills will be needed?

- 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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

Kaiser Permanente Northern California



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

8

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

EPCT QUICK START GUIDE FOR RESEARCHER AND HEALTHCARE SYSTEMS LEADER PARTNERSHIPS

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

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,*]

journal

Review article

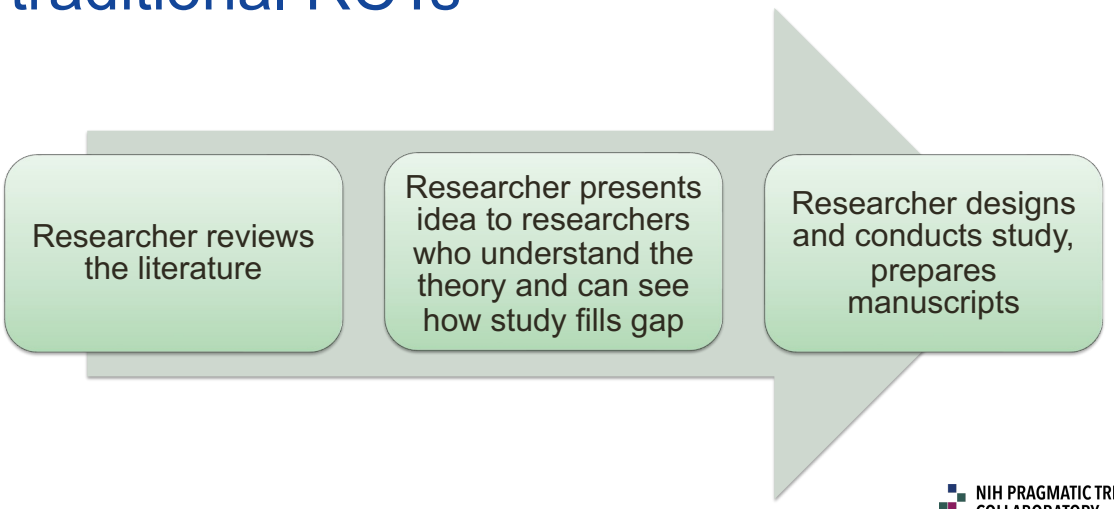
Pragmatic clinical trials offer unique opportunities for disseminating, implementing, and sustaining evidence-based practices into clinical care: Proceedings of a workshop

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

How researchers approach stakeholders in traditional RCTs



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

Researchers partner with stakeholders in ePCTs differently.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

Roles of stakeholders

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

Roles of stakeholders

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

16

Choosing a salient question

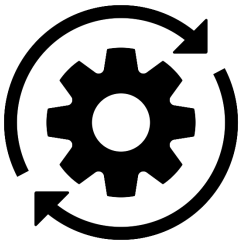
We want to know what you need.
What research should we be doing?

Source: Greg Simon, MD, MPH

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

17

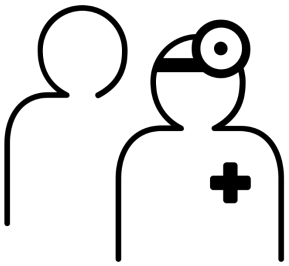
Designing the intervention for sustainment



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

18

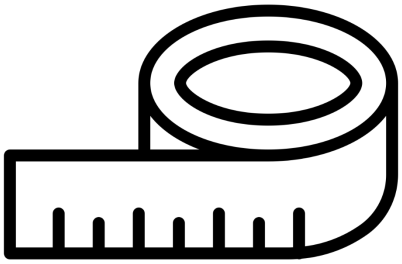
Designing the intervention to minimize burden for patients and clinicians



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

19

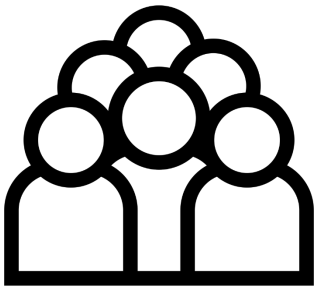
Selecting outcome measures



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

20

Determining inclusion and exclusion criteria



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

21

Roles of stakeholders

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

22

Develop recruitment strategies

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

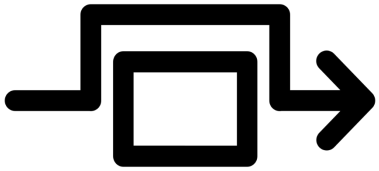
23

Serve as study champions

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

24

Track challenges and adaptations



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

25

Interpret study results

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

26

Roles of stakeholders

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

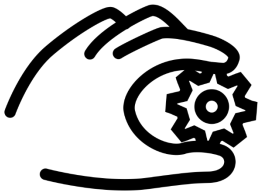
27

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

28

Support implementation or de-implementation



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

29

Consider changes to policies and guidelines

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

30

Roles of stakeholders

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

31

Engaging Stakeholders Group Activity

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

32

Group Activity Instructions

- Look at the **assigned letter (A, B, or C)** on your engagement activity sheet and find your small group
- Spend **5 minutes on your own** reading the prompt and jotting down some thoughts about the questions
- Spend **10 minutes as a group** discussing responses
- **Report back** to the large group

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

33

A Stakeholder Engagement Success Story: STOP CRC

- **Goal**: STOP CRC aims to improve rates of colorectal cancer screening in patients at Federally Qualified Health Centers
- **Problem**: Some patients lacked health insurance coverage to pay for follow-up colonoscopy after a positive fecal test.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

34

A Stakeholder Engagement Success Story: STOP CRC

- The advisory board included legislators who changed state law to require commercial insurance plans to cover follow-up diagnostic colonoscopy with no patient out-of-pocket costs
- Local community organizations provided free colonoscopy through a network of donated care
- Medicaid expansion resulted in higher insurance coverage rates

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

35

Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

36

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

37

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

38

Questions?

Stakeholder roles in:

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

39

Ancillary slides

- Additional slides with ancillary content

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

40

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

41

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

42

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

43

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

44

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Objectives and Trial Design: An Overview of Hybrid Designs

Speaker

Hayden Bosworth, PhD

Professor, Population Health Sciences
Duke University

Trial Objectives and Design: An Overview of Hybrid Designs

Hayden Bosworth, PhD
Professor, Population Health Sciences
Duke University

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Hybrid trial designs

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

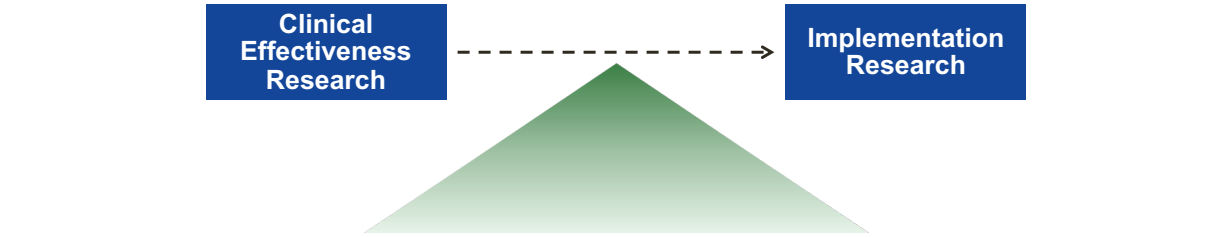
Why hybrid trial designs?

- 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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

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…)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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]

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

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]

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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†]

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

Concluding points

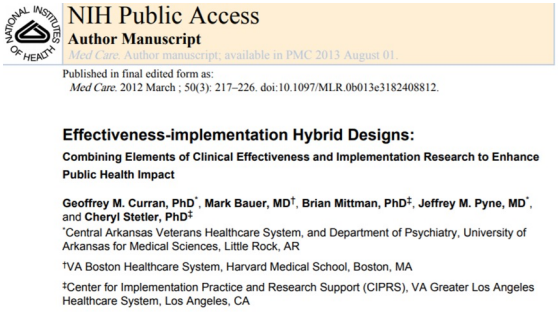
- This was a very brief summary!
- ePCTs are usually type 1 or 2, depending on how ready you are to test an implementation strategy on summative implementation outcomes
  - To describe implementation during the trial and prepare for later work on real-world implementation strategies = 1
  - To test the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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

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*

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

Resources:

Objectives and Trial Design: An Overview of Hybrid Designs

Key journal articles

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

Additional resources

- Designing With Implementation and Dissemination in Mind: Hybrid Designs

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Measuring Outcomes

Speaker

Emily O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Measuring Outcomes

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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."

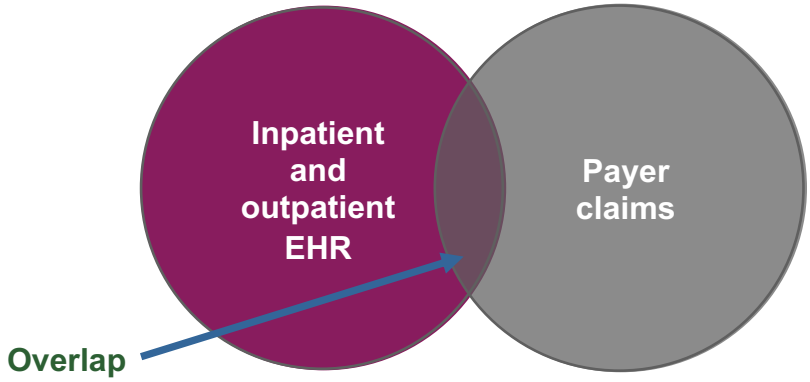
Weber GM et al. JAMA. 2014;311(24):2479-2480.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

Where is the signal?

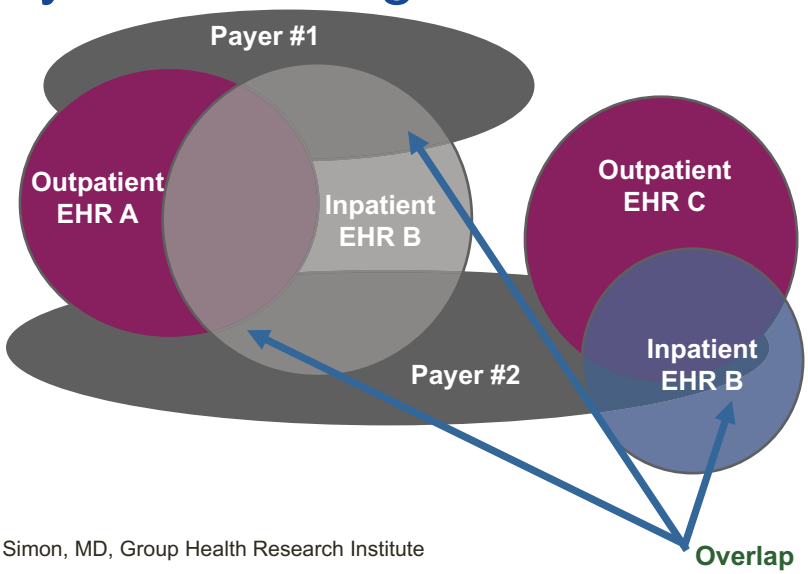
- EHR (laboratory values, treatments, etc)
- Claims data (does the event generate a bill?)



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

Reality is not straightforward



Source: Greg Simon, MD, Group Health Research Institute

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

Data sources for endpoints in ePCTs

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

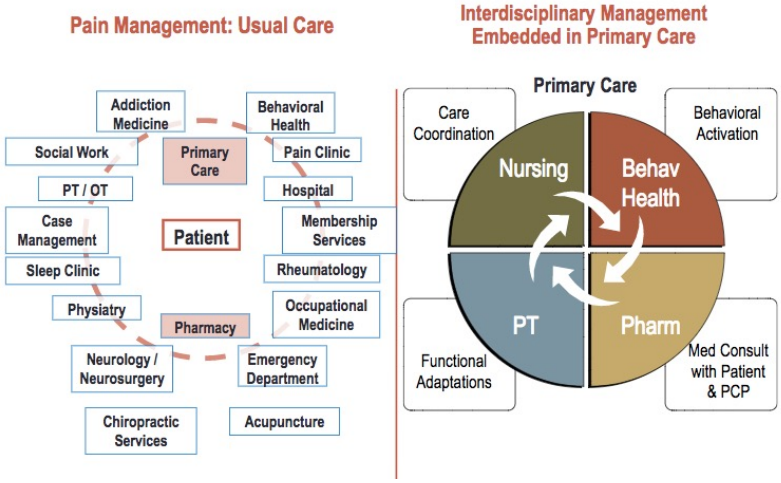
Outcomes measured via direct patient report

- 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

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

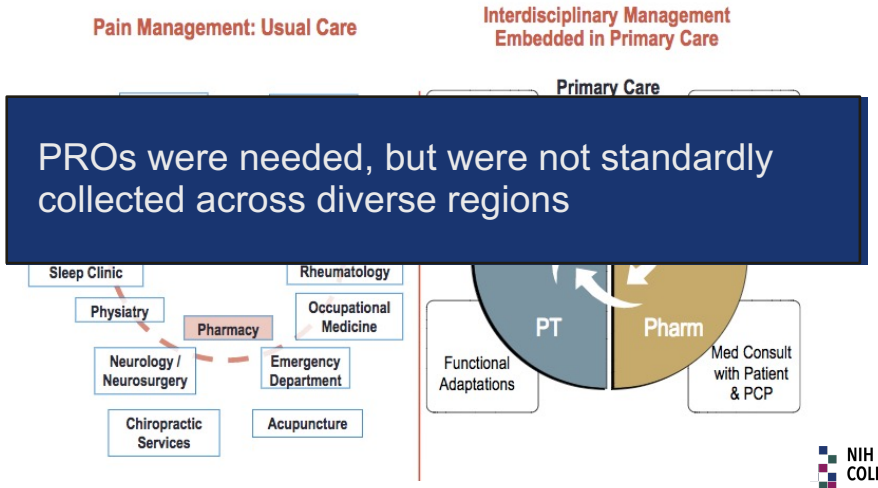


Source: Lynn DeBar, PhD, MPH, Kaiser Permanente Washington Health Research Institute

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

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



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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

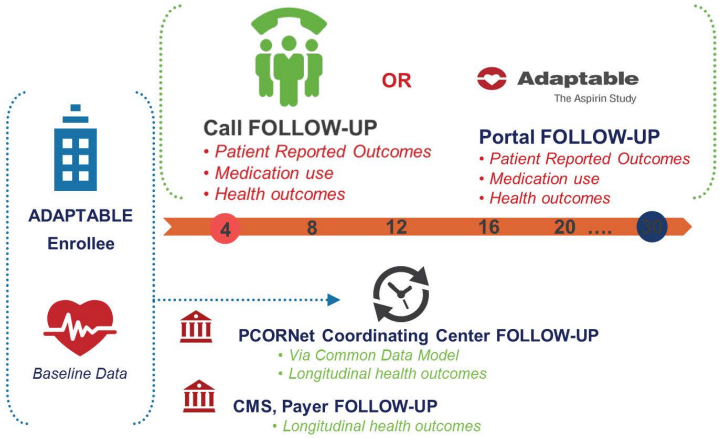
Case example: PPACT

- 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

16

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



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

17

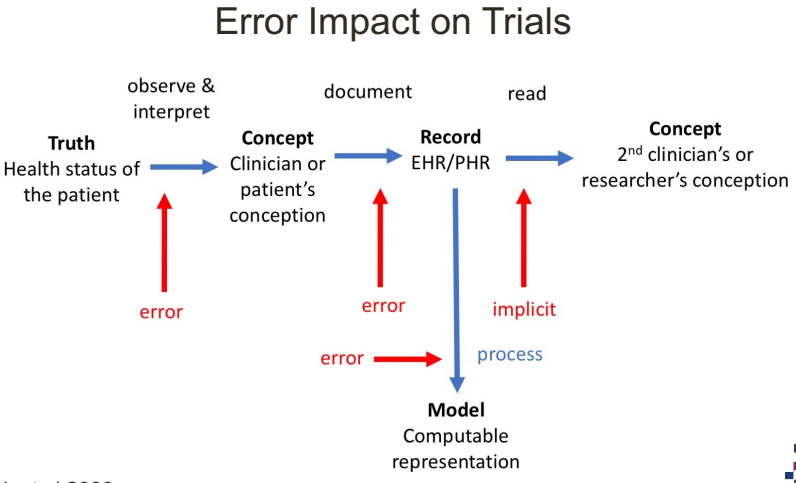
Mobile devices for outcome measurement

- 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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

18

Data is a surrogate for clinical phenomena



Adapted from Hripcsak et al 2009

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

19

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

20

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

21

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

22

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

ePCT Design and Analysis

Speaker

Patrick J. Heagerty, PhD

Professor, Biostatistics
University of Washington

ePCT Experimental Design and Analysis

Patrick J. Heagerty, PhD
Professor, Biostatistics
University of Washington

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

- Learn about cluster randomized and stepped-wedge study designs
- Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know—highlighting design and analysis considerations and key decision points
- Q & A with attendees

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Design Considerations

Embedded Pragmatic Clinical Trials

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Important things to know

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

Reasons to randomize clusters instead of individuals

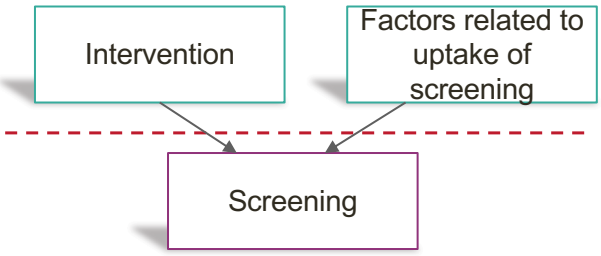
- Intervention targets health care units rather than individuals
  - STOP CRC: clinic-based intervention to improve screening
- Intervention targeted at individual risks "contamination"
  - Intervention spills over to members of control arm
  - For example, physicians randomized to new educational program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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

STOP CRC cluster randomization

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

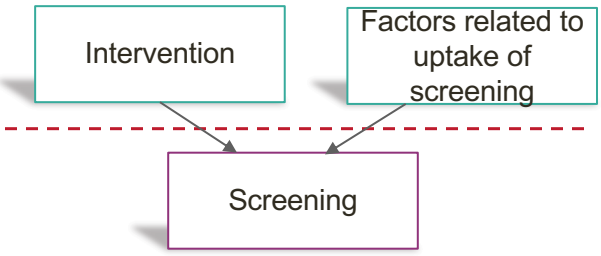


Level 1: Individual-level outcomes nested within clinics

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

STOP CRC cluster randomization



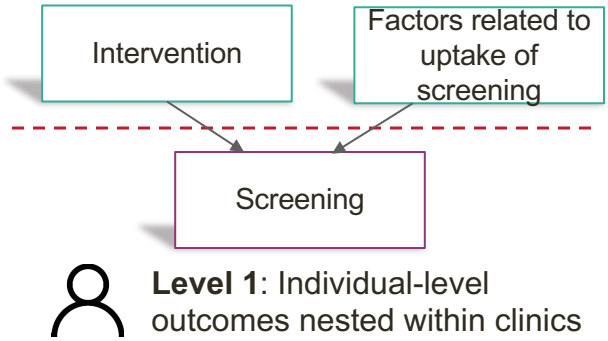
Level 1: Individual-level outcomes nested within clinics

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

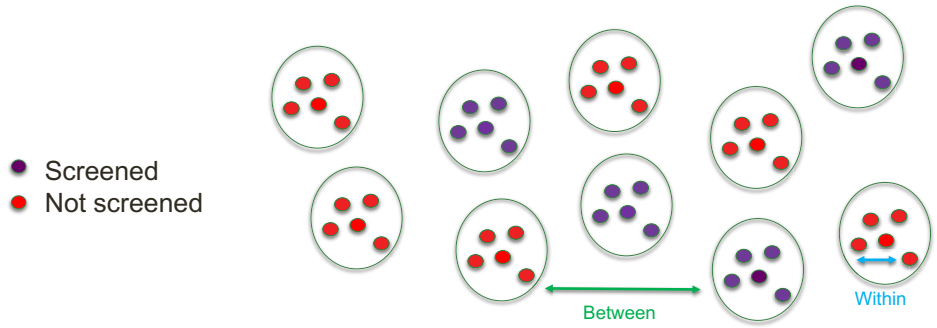
Understanding outcome clustering

- 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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

Understanding outcome clustering: complete clustering (ICC =1)



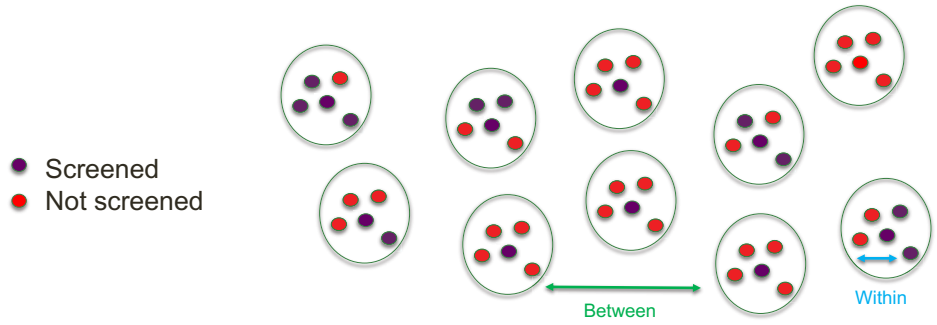
Intracluster correlation coefficient (ICC) = $\frac{\sigma_B^2}{\sigma_{\text{Total}}^2} = \frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2} = \frac{\sigma_B^2}{\sigma_B^2} = 1$, because σ_W^2 =0

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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



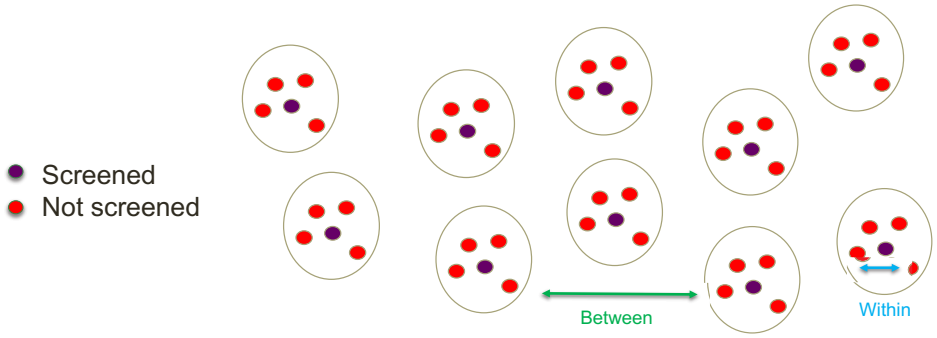
ICC = $\frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2}$; 0 < ICC < 1, because 0< σ_W^2 <1 & 0< σ_B^2 <1

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

Summary of design issues for CRTs

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

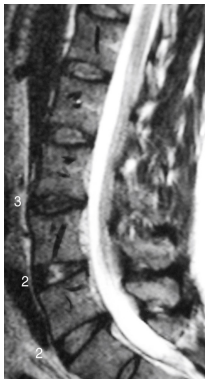
Methods for pragmatic trials

- 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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

NIH Collaboratory ePCT: LIRE



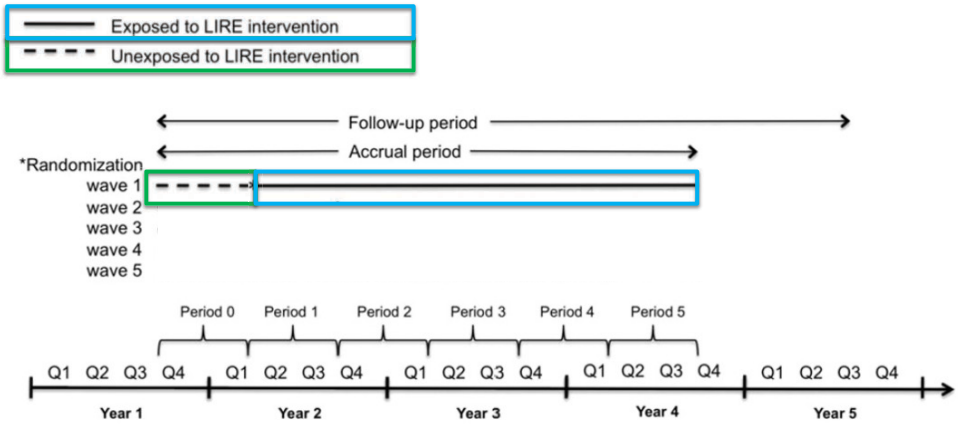
- Lumbar Imaging With Reporting of Epidemiology (LIRE)
- Goal: Reduce unnecessary spine interventions by providing info on prevalence of normal findings
- Patients of 1700 PCPs across 100 clinics
- Clinic-level intervention → cluster randomization
- Unit of randomization: clinic
- Pragmatic trial
  -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

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

16

NIH Collaboratory ePCT: LIRE

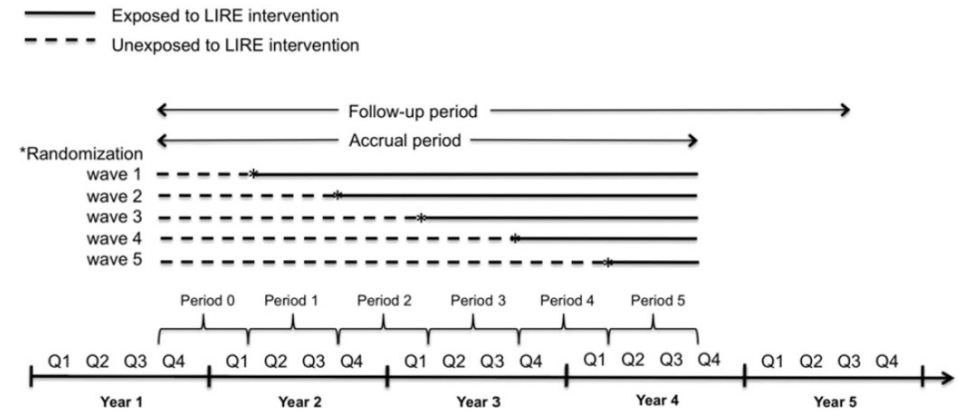


NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

17

NIH Collaboratory ePCT: LIRE



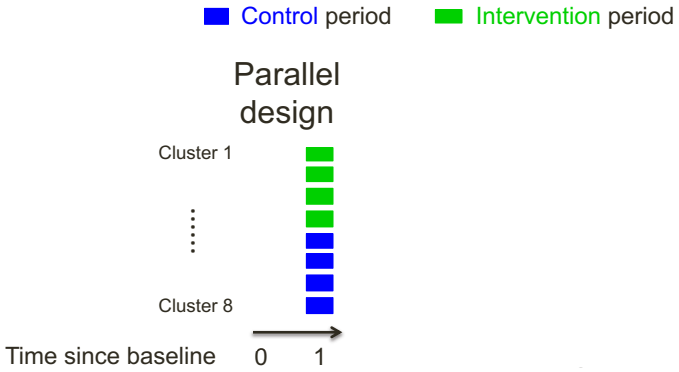
NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

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

18

Types of CRT designs

Examples with 8 clusters: 1-year intervention



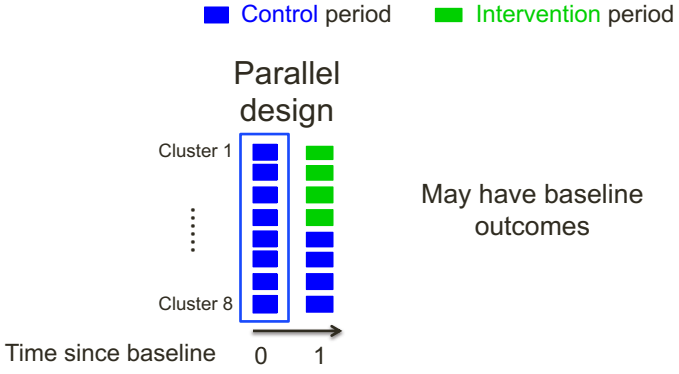
Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

19

Types of CRT designs

Examples with 8 clusters: 1-year intervention



May have baseline outcomes

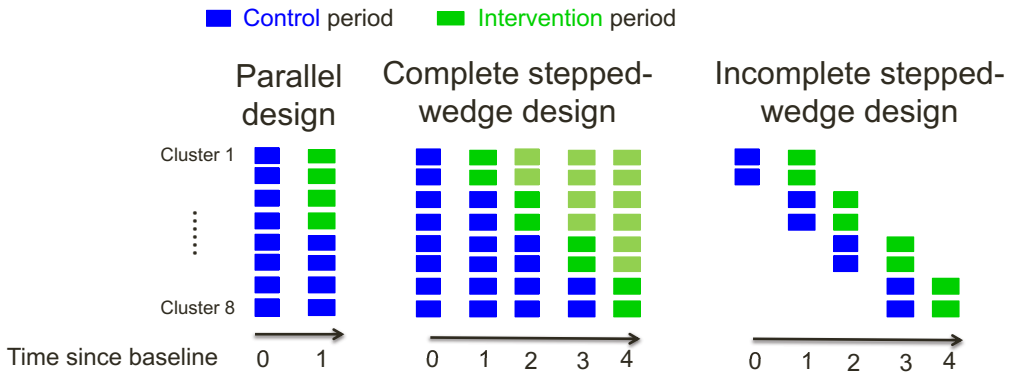
Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

20

Types of CRT designs

Examples with 8 clusters: 1-year intervention



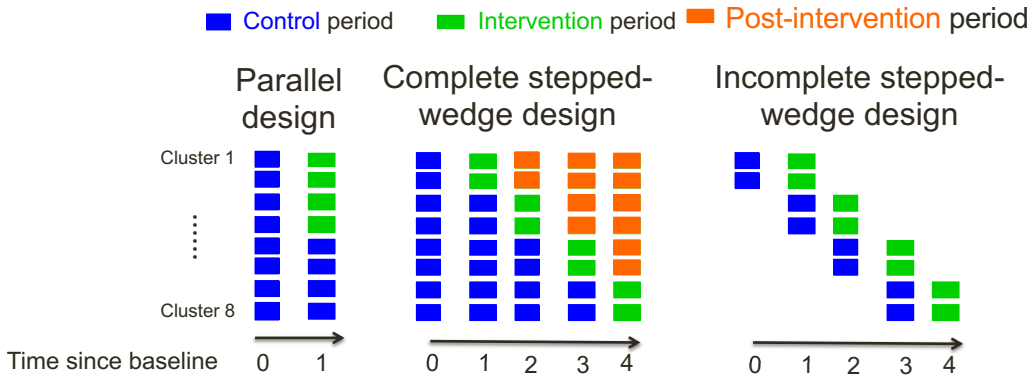
Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

21

Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

22

Summary of design issues

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

23

NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

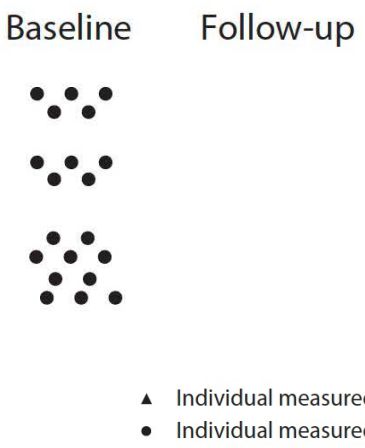
- Optimizing Pain Treatment In Medical settings Using Mindfulness (OPTIMUM)
- Goal: to reduce pain and pharmacologic medications via a group-based mindfulness-based stress reduction (MBSR) program
- Study population: individuals with chronic lower back pain
- Group-based online intervention → groups 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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

24

NIH Collaboratory ePCT: OPTIMUM



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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

25

Summary of design issues

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

26

It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

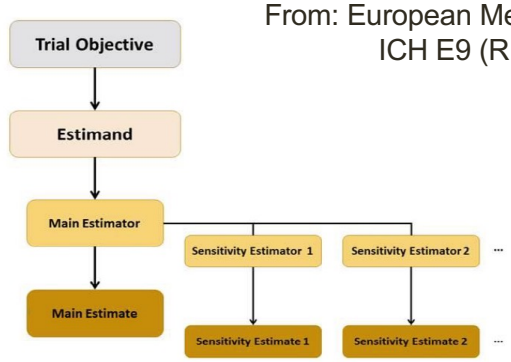


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

27

How to choose the right design?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

28

How to choose the right design?

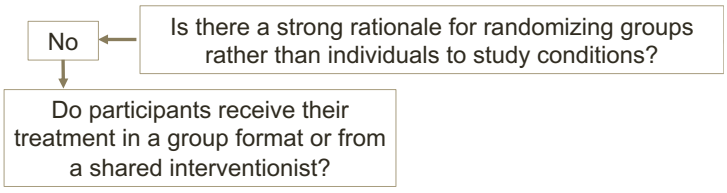
Is there a strong rationale for randomizing groups rather than individuals to study conditions?

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

29

How to choose the right design?

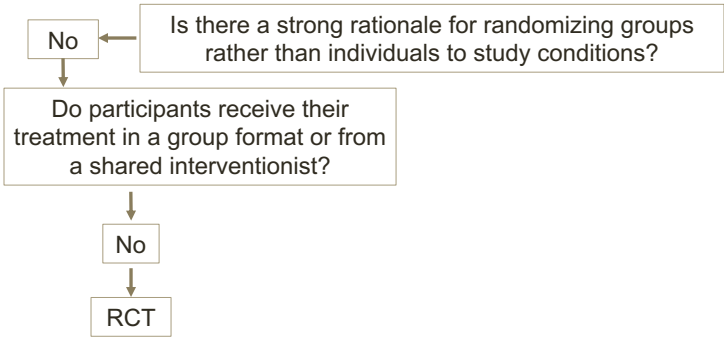


Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

30

How to choose the right design?

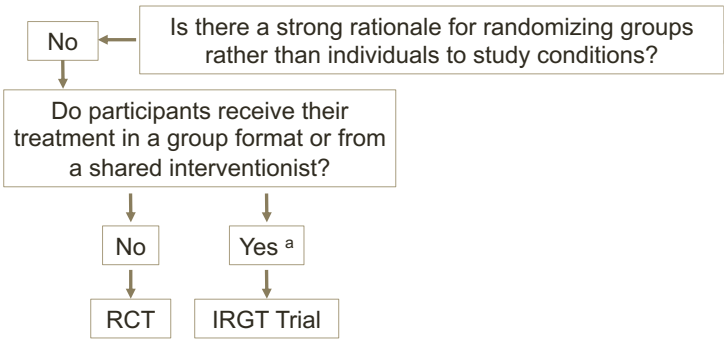


Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

31

How to choose the right design?



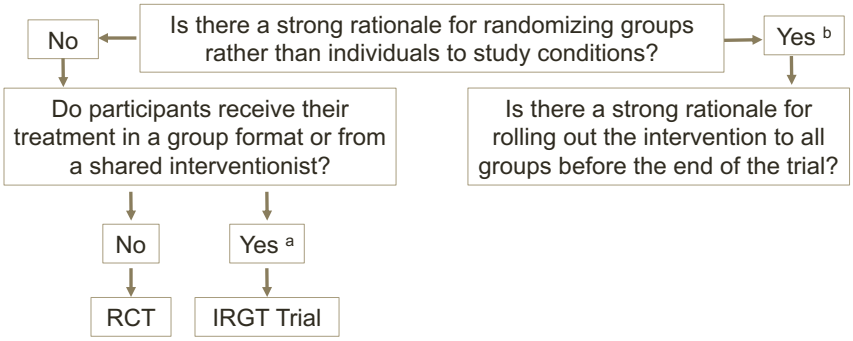
[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

32

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.

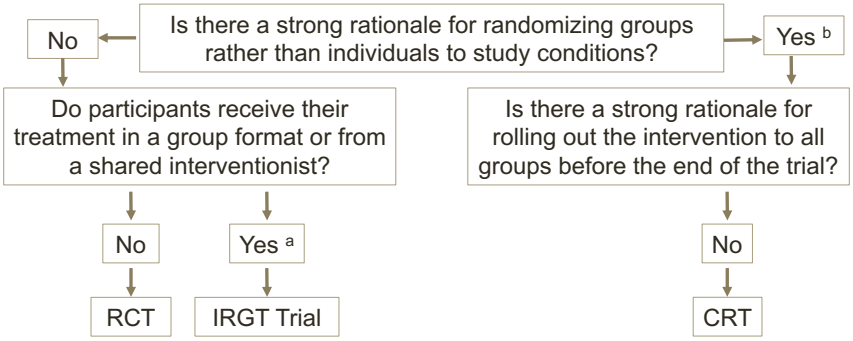
[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

33

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.

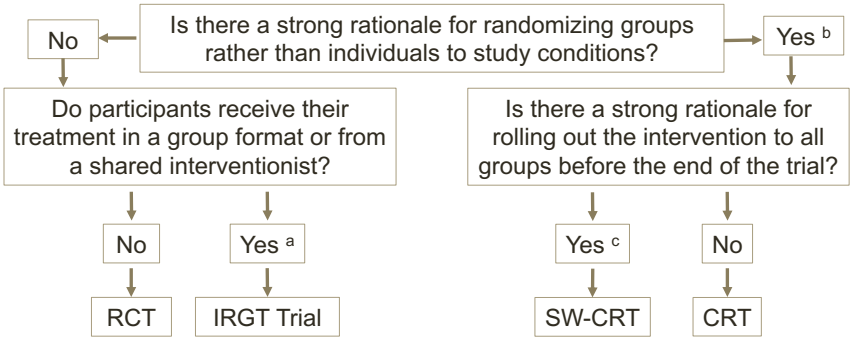
[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

34

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.

[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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

35

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

36

Implications of design choice

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

37

The need for these designs

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

38

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!**

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

39

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

40

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

41

Clustering: Impact on power in STOP CRC

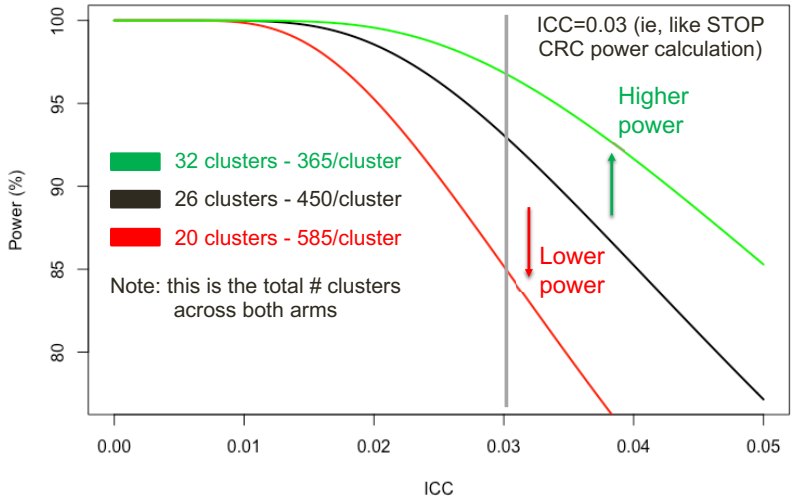
- "Using this figure, we will have **very good power (>91%) to detect absolute differences as small as 10 percentage points** even if the FIT [fecal immunochemical testing] completion rate in the **UC arm is as high as 15%** (fecal testing rates for 2013 for usual care clinics was 10%)."

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

42

Clustering: Impact on power in STOP CRC

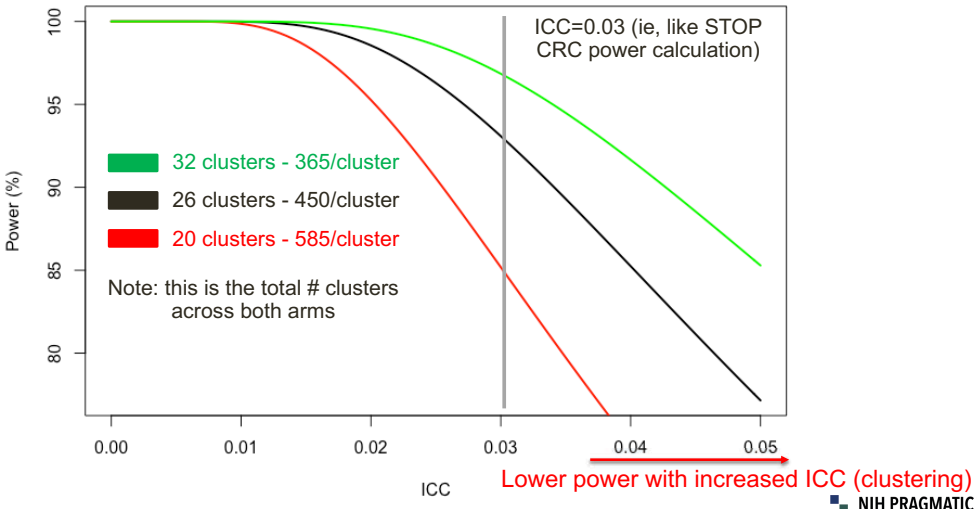


Power for parallel-arm CRT to compare two proportions of 15% vs 25% at two-tailed 5% significance (alpha) for an **overall sample of 11,700** (ie, like STOP CRC CRT)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

43

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

44

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

45

Analysis Considerations

Embedded Pragmatic Clinical Trials

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

46

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

47

Important things to know

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

48

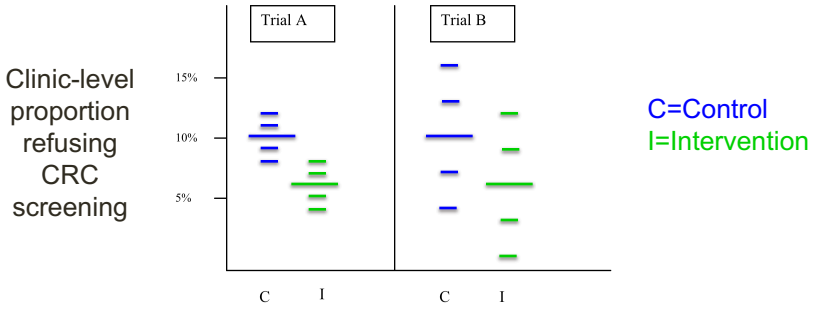
Two example CRTs inspired by STOP CRC

- 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"

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

49

Clustering in CRTs: Implications for analysis



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

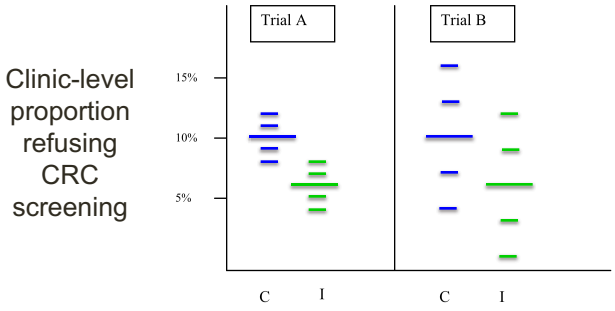
Overall screening refusal proportion in both trials: 10% vs 6%
Question: is intervention effective?

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

50

Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

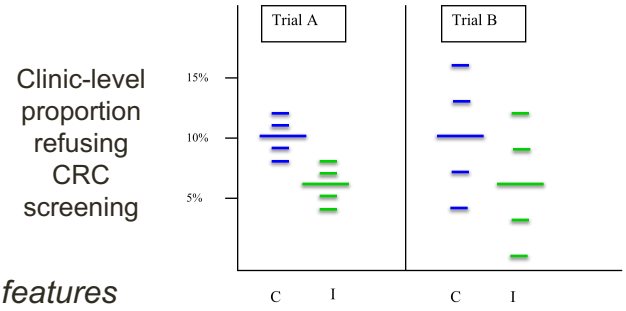
Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

51

Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

Study features

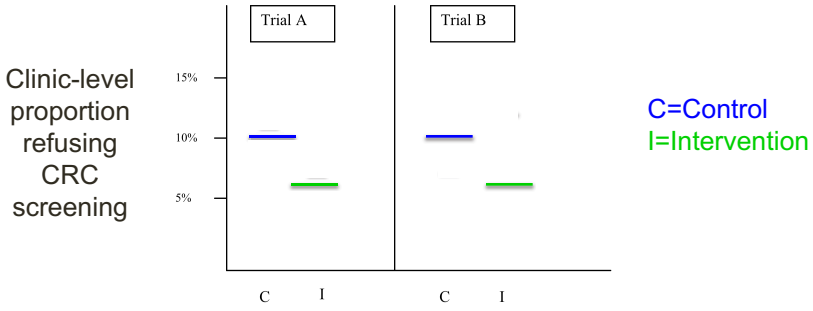
- Trial A:
  - Lower between-clinic variability (ie, less clustering)
  - Little overlap of I & C clinic-level proportions
- Trial B: overlap of intervention (I) & control (C) clinic-level proportions

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

52

Clustering in CRTs: Implications for analysis



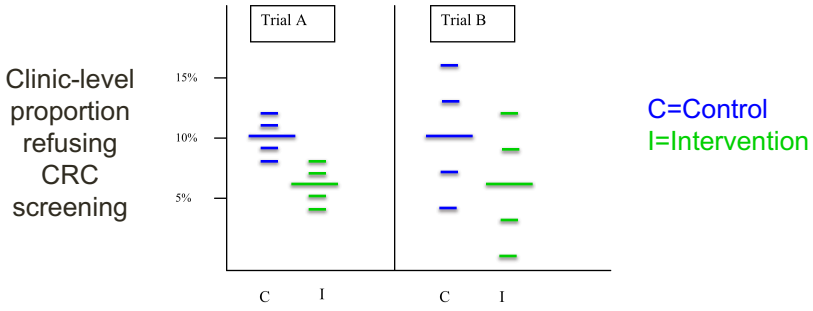
- If ignore clustering: p-value = **0.02** for both trials
- Comparison of 10% (50/500) vs 6% (30/500) by chi-sq. test

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

53

Clustering in CRTs: Implications for analysis



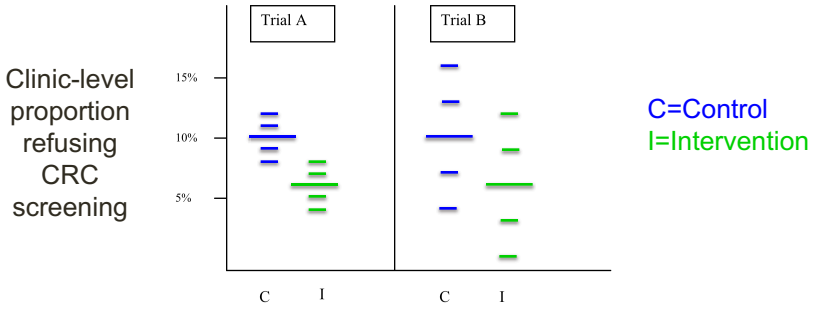
- Trial B p-value accounting for clustered design = ?
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

54

Clustering in CRTs: Implications for analysis



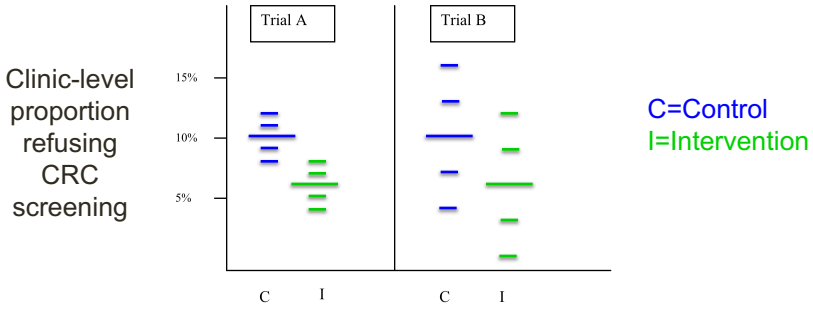
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

55

Clustering in CRTs: Implications for analysis



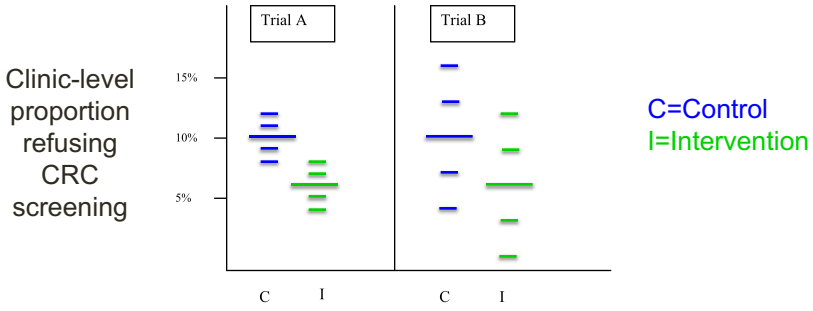
- Trial A p-value accounting for clustered design = **?**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

56

Clustering in CRTs: Implications for analysis



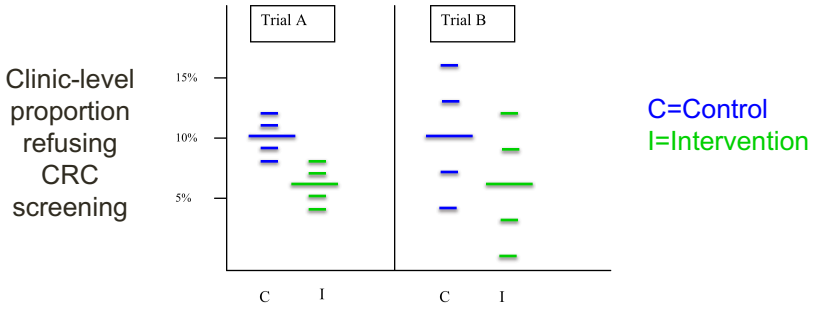
- Trial A p-value accounting for clustered design = **0.01**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

57

Clustering in CRTs: Implications for analysis



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

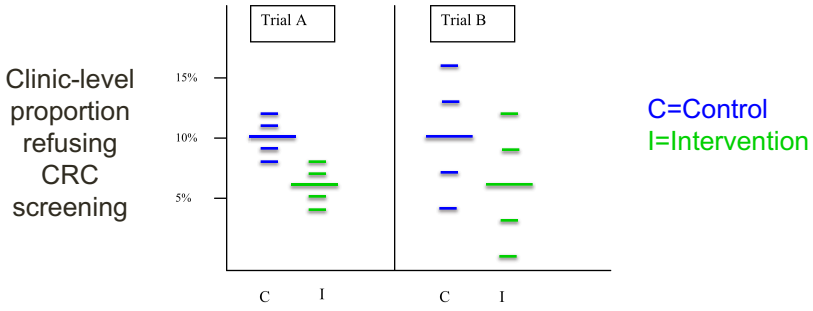
*By using a cluster-level analysis where the 10 cluster-level proportions (5 per arm) are treated as continuous variables and analyzed with Wilcoxon rank sum test

Adapted from Hayes & Moulton (2009)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

58

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

59

Summary: Analysis of two example CRTs

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

60

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

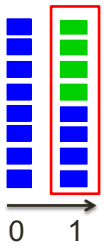
NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

61

Analysis of CRTs, including SW-CRTs

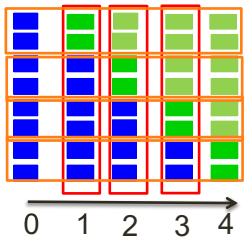
Parallel design

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



Complete SW design

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



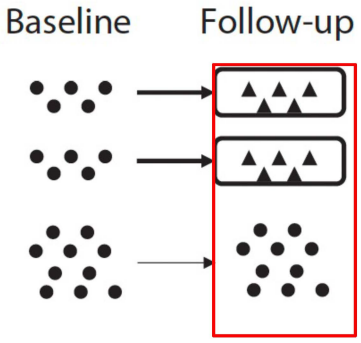
Control period Intervention period

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

62

Analysis of IRGT trials



Parallel design

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

▲ Individual measured under intervention
● Individual measured under no intervention

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

63

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

64

Analysis of CRTs, SW-CRTs, and IRGTTs

- Clustering must be accounted for in analysis
- Challenges in "small" trials (# clusters < 50)
  - Intervention effect SE may be under-estimated
    - Can correct e.g. finite-sample bias corrections for GEE
  - Ignoring can lead to inflated Type I error
    - Type I error rate may be 30-50% in a CRT, even with small ICC
    - Type I error rate may be 15-25% in an IRGTT, even with small ICC
- Work with statistician to ensure properly account for clustering

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

65

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

66

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

67

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.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

68

It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

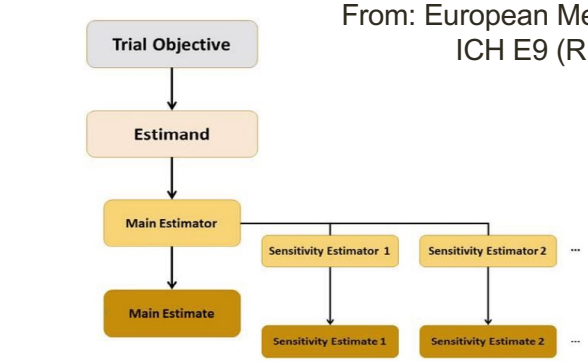


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

69

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

70

NIH resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  - https://prevention.nih.gov/grt
  - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
  - https://prevention.nih.gov/education-training/methods-mind-gap
    - Toward Causal Inference in Cluster Randomized Trials: Estimands and Reflection on Current Practice (Fan Li, November 3, 2022)
    - An Introduction to Cross-classified, Multiple Membership, and Dynamic Group Multilevel Models (Don Hedeker, October 20, 2022)
    - Robust Inference for Stepped Wedge Designs (Jim Hughes, May 17, 2022)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs, IRGTs, SWGRTs and a sample size calculator for each

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

71

Recommended reading

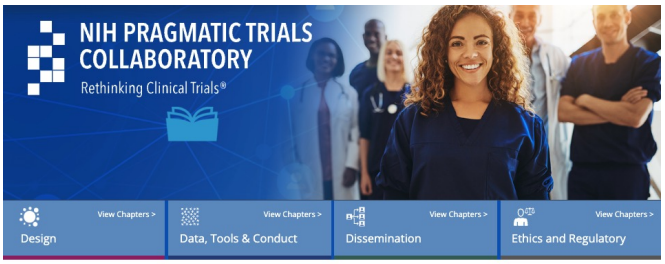
- Murray DM et al. Essential ingredients and innovations in the design and analysis of group-randomized trials. Ann Rev Public Health. 2020;41:1-19
- Kenny A et al. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. Stat Med. 2022. PMID: 35774016.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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

72

Resource: The Living Textbook

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



Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials

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

GET STARTED

What is the
NIH PRAGMATIC TRIALS COLLABORATORY?

What is a
PRAGMATIC CLINICAL TRIAL?

TRAINING RESOURCES

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

73

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Resources:

ePCT Experimental Design & Analysis

Living Textbook readings

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

NIH Research Methods

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

Collaboratory Grand Rounds webinar recordings & slides

- Lessons Learned from the NIH Collaboratory Biostatistics and Design Core

Key journal articles

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

Additional resources

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

ePCTs in Context: Small Group Work Followed by Panel Discussion with Collaboratory Demonstration Project PIs

Moderator

Kevin P. Weinfurt, PhD

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

ePCTs in Context

Small Group Work and Panel Discussion With Demonstration Project Investigators

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Objectives

- Introduction of Demonstration Project Panelists
- Small Group Discussion:
  - Breakout into small groups
  - Report back to the group
  - Panelist discuss how they handled the challenges
- Reflect on the challenges, solutions & lessons learned of the morning topics, to include Q&A.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Demonstration Project Panelist

- Margaret Kuklinski, PhD
  - Guiding Good Choices for Health (GGC4H): Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare Systems
- Angelo Volandes, MD, MPH
  - Improving Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP PEACE)
- Michael Parchman, MD, MPH
  - Can Value Champions Reduce Inappropriate Prescribing for People with Dementia

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Small Group Discussion

GGC4H: Enrollment and Engagement of Subjects

- GGC4H had a few challenges when it came to enrollment: 1) Parents declined virtual groups 2) Parents enrolled but did not attend sessions 3) Did not reach them during the enrollment calls. **How would you approach this problem?**

ACP PEACE: Measuring Outcomes

- The primary outcome was ACP documentation, but oncologists rarely use the structured variable to structure ACP. **How would you approach this problem?**

Can Value Champions Reduce Inappropriate Prescribing for People with Dementia: Enrollment and Engagement of Subjects

- To be pragmatic, the project depended on the embedded delivery system employees to serve as clinic champions, but it is unclear if those selected by ACO leadership had intrinsic motivation to serve as champions. **How would you approach this problem?**

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Reflection on Today's Topics

- Engaging stakeholders and aligning with healthcare system partners
- Objectives and trial design
- Selecting and measuring outcomes
- Design and analysis

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Closing Remarks

Speaker

Kevin P. Weinfurt, PhD

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

Closing Remarks – Day 1

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Challenges, solutions & lessons learned

- Final Thoughts from Panelists
- Final Q & A
- Summary of Day 1
- Roadmap for Day 2

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Workshop sessions – Day 2

- Pilot & Feasibility Testing (Wendy Weber)
- Ethical & Regulatory Oversight (Stephanie Morain)
- Writing a Compelling Grant Application (Beda Jean-Francois)
- ePCTs in Context: Small Group Work and Panel Discussion with Collaboratory Demonstration Project PIs
- Next Steps (Kevin Weinfurt)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Welcome

Speaker

Kevin P. Weinfurt, PhD

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

Welcome

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Workshop learning objectives

- Clarify the definition of ePCTs and explain their utility
- Introduce attendees to the unique characteristics and challenges of designing, conducting, and implementing ePCTs within diverse healthcare systems
- Increase the capacity of health services researchers to address important clinical questions with ePCTs in real-world settings, driving tomorrow's research outcomes

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Workshop sessions – Review of Day 1

- What Are Embedded Pragmatic Clinical Trials?
- Engaging Stakeholders & Aligning With Health System Partners
- Objectives and Trial Design: An Overview of Hybrid Designs
- Measuring Outcomes ePCT Design and Analysis
- ePCTs in Context: Small Group Work and Panel Discussion with Collaboratory Demonstration Project PIs

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Workshop sessions – Day 2

- Pilot & Feasibility Testing (Wendy Weber)
- Ethical & Regulatory Oversight (Stephanie Morain)
- Writing a Compelling Grant Application (Beda Jean-Francois)
- ePCTs in Context: Small Group Work and Panel Discussion with Collaboratory Demonstration Project PIs
- Next Steps (Kevin Weinfurt)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Resource: The Living Textbook

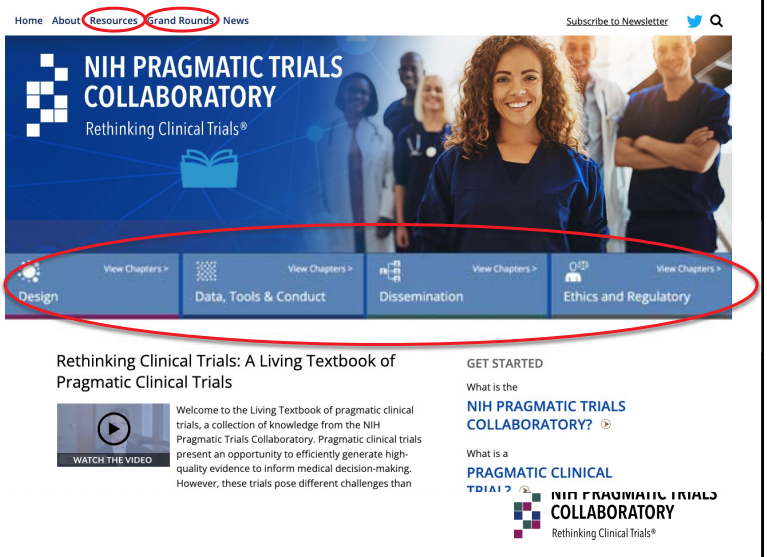
Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

5

Key Resources

- Living Textbook
- Grand Rounds Hub
- Training Resources



6

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Pilot & Feasibility Testing

Speaker

Wendy Weber, ND, PhD, MPH

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

Pilot & Feasibility Testing

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

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?

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

Evaluate power calculations

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

In the end, good planning will help

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

slido

What do you think is the most compelling reason for conducting a pilot/feasibility pragmatic trial?

ⓘ Start presenting to display the poll results on this slide.

16

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

17

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

18

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Ethical & Regulatory Oversight Considerations

Speaker

Stephanie Morain, PhD, MPH

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

Ethical & Regulatory Oversight Considerations

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goals

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

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
- ….

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

Article

CLINICAL TRIALS

Clinical Trials
2015, Vol. 12(5) 436–441
© The Author(s) 2015
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1740774515598334
ctj.sagepub.com
SAGE

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

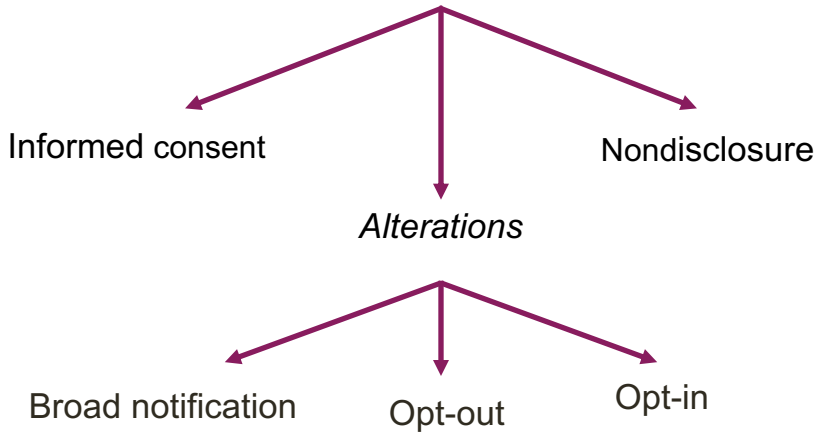
7

Informed Consent, Waivers, and Alterations

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

Approaches to notification & authorization



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

slido

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

ⓘ Start presenting to display the poll results on this slide.

10

slido

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

ⓘ Start presenting to display the poll results on this slide.

11

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

Distinguishing research risks

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

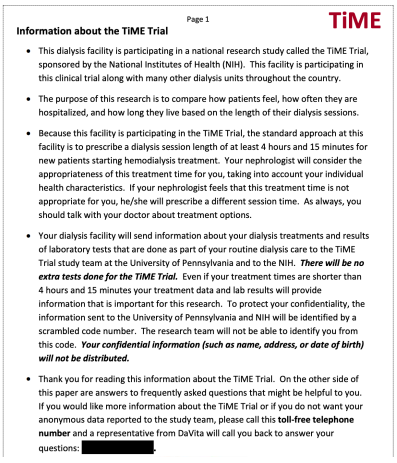
Regulatory permissible ≠ ethically optimal

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

Examples: information sheets or flyers

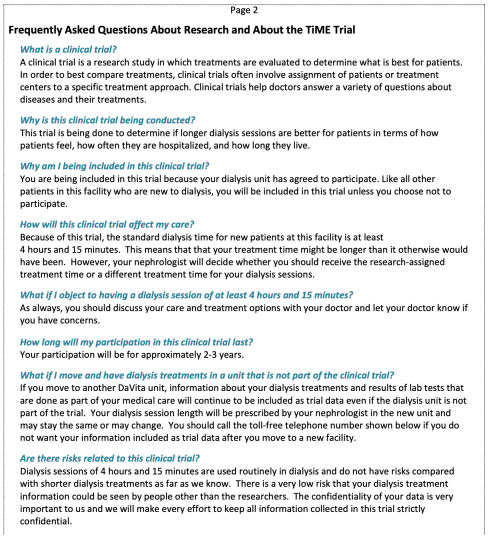


Page 1

Information about the TiME Trial

TiME

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



Page 2

Frequently Asked Questions About Research and About the TiME Trial

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

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

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

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

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

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

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

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

16

Discussion:

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

17

Data and Safety Monitoring

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

18

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

19

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

20

Unique considerations for monitoring ePCTs

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

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

21

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

22

Data Sharing & PCTs

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

23

Increasing expectation for sharing clinical trials data

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

24

Challenges for Sharing PCT Data

Often conducted with waivers or alterations of informed consent

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

25

If PCT uses a waiver/alteration of consent…

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

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

26

Implications of Embeddedness for PCT Data Sharing

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

27

PCTs and Underrepresented Groups

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

28

PCTs, equity, and underrepresented groups

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

29

Promoting equity and representativeness

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

30

POLICY ANALYSES

Learning Health Systems

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

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

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

Special Article | Free Access

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

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

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

31

Important things to do

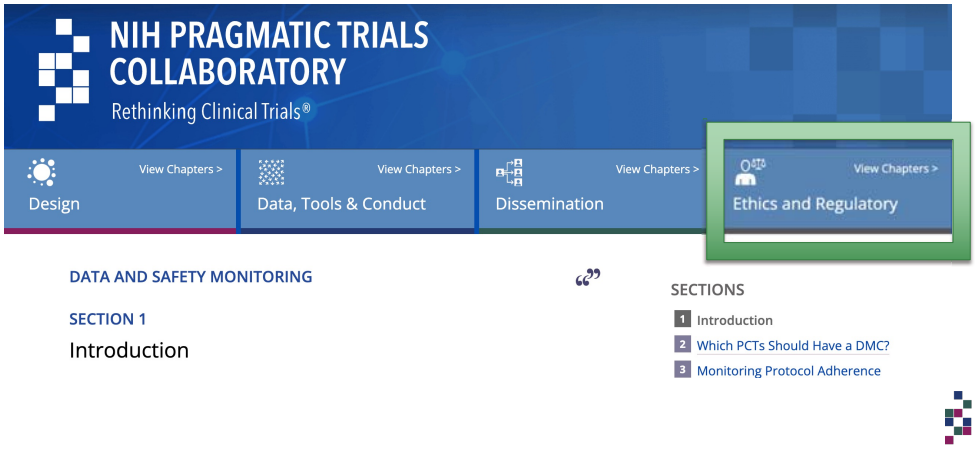
- Designate someone to track local and federal regulatory developments and serve as liaison with regulatory/oversight bodies
- Budget sufficient time for proactive education and negotiations with relevant regulatory/oversight bodies
- Identify all parties who might be affected by the study and its findings;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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

32

Important things to do

- Make use of existing resources!



33

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Writing a Compelling Grant Application

Speaker

Beda Jean-Francois

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

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)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Learning goal

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

National Institutes of Health

NIH
National Institutes of Health

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Find the right NIH program official

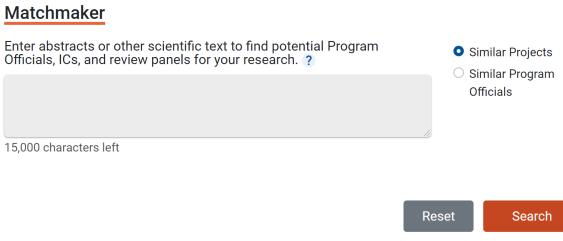
- IC mission and priorities
  - Focus on a specific disease area, organ system, or stage of life
  - Use Matchmaker tool in NIH RePORTER for suggestions
  - Talk to program officials
  - Consult your mentor and colleagues

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

NIH RePORTER matchmaker tool

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



NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

6

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

7

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

8

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		

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

9

Tailor the application

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

10

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

11

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

12

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

13

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

14

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

15

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

16

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

17

Tips from the Demonstration Projects

- What is 1 key tip you would recommend for developing a strong grant proposal?
- Q&A

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

18

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Resources:

Writing a Compelling Grant Application

Living Textbook readings

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

Key journal articles

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

Other

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

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

ePCTs in Context: Small Group Work Followed by Panel Discussion with Collaboratory Demonstration Project PIs

Moderator

Vincent Mor, PhD

Florence Pirce Grant University Professor of Health Services, Policy and Practice
Professor of Health Services, Policy and Practice
Brown University School of Public Health

ePCTs in Context

Small Group Work and Panel Discussion With Demonstration Project Investigators

Moderator:
Vincent Mor, PhD
Florence Pirce Grant University Professor of Health Services, Policy and Practice
Professor of Health Services, Policy and Practice
Brown University School of Public Health

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1

Objectives

- Introduction of Demonstration Project Panelists
- Small Group Discussion:
  - Breakout into small groups
  - Report back to the group
  - Panelist discuss how they handled the challenges
- Reflect on the challenges, solutions & lessons learned of the morning topics, to include Q&A.

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

Demonstration Project Panelist

- Margaret Kuklinski, PhD
  - Guiding Good Choices for Health (GGC4H): Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare Systems
- Ardith Doorenbos, PhD, RN, FAAN
  - Hybrid Effectiveness Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE)

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

Small Group Discussion

GGC4H: Assessing Feasibility

- EHR data did not include all adolescent outcomes and were not consistently available across the sites. **How would you approach this problem?**

GRACE: Assessing Feasibility

- Patient-reported outcomes, such as the Brief Pain Inventory, were not embedded into the EHR system to allow extraction from the record. **How would you approach this problem?**

GGC4H and GRACE: Writing Successful Grant Applications

- Pretend you are a PI for GRACE or GGC4H and see if you can find a good program officer or official for the project using the NIH RePORTER Matchmaker Tool. **To get started, visit: https://reporter.nih.gov/**

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

4

Reflecting on the Morning Topics

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

5

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Closing Remarks

Speaker

Kevin P. Weinfurt, PhD

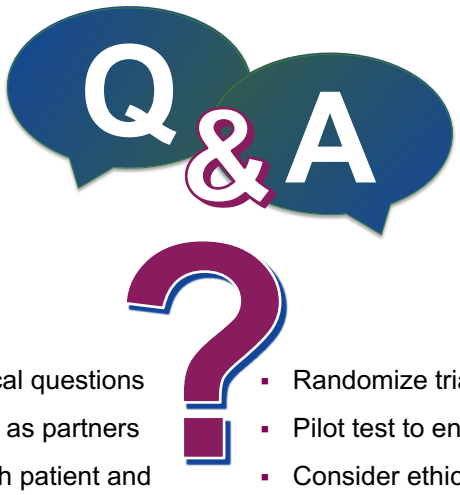
James B. Duke Distinguished Professor and Vice Chair for Research
Department of Population Health Sciences
Duke University School of Medicine

Next Steps: Embedded Pragmatic Clinical Trials

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

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

1



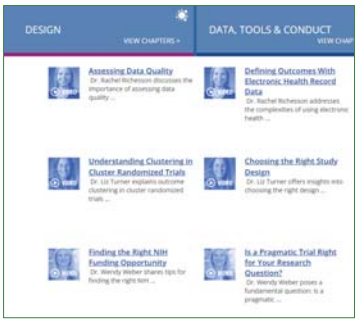
- Answer real-world clinical questions
- Engage health systems as partners
- Design your trial for both patient and implementation outcomes
- Choose meaningful and pragmatic endpoints and outcomes
- Randomize trials for the strongest evidence
- Pilot test to ensure trial readiness
- Consider ethical 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

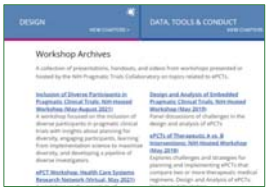
NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

2

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/





NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

3

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

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

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®