NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Dissemination and Implementation in Embedded Pragmatic Trials:

Science-Powered Strategies to Sustain and Spread Effective Interventions

Participant Guide

18th Annual Conference on the Science of Dissemination and Implementation in Health

December 14, 2025

NIH PRAGMATIC TRIALS COLLABORATORY

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Table of Contents

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Dissemination and Implementation in Embedded Pragmatic Trials: Science-Powered Strategies to Sustain and Spread Effective Interventions

18th Annual Conference on the Science of Dissemination and Implementation in Health
Hosted by AcademyHealth and the National Institutes of Health
"Realizing the Benefits of Dissemination & Implementation Science"

Gaylord National, National Harbor, Maryland
December 14, 2025

Time	Topic	Speakers	Goals
10:00-10:10 am	**Welcome and Opening Remarks**	Emily O'Brien	• Review agenda, objectives, and the Living Textbook
10:10-10:40 am	**Embedded Pragmatic Clinical Trials (ePCTs) and Hybrid Effectiveness-Implementation Trials: Similarities and Differences**	Hayden Bosworth	• Consider the importance of ePCTs, implementation science, and learning health system principles • Identify key similarities and differences between ePCTs and hybrid trials • Discuss advantages and disadvantages of ePCTs and hybrid trials and when they can be used to answer research questions
10:40-11:10 am	**Design and Analysis Considerations**	Qilu Yu	• Identify common experimental designs and randomization schemes in pragmatic trials • Discuss design and analytic considerations for trials with both effectiveness and implementation outcomes • Understand the importance of monitoring adherence and fidelity
11:10 am-12:00 pm	**Measuring Effectiveness and Implementation Outcomes**	Angelo Volandes	• Describe methods for measuring outcomes using sources such as electronic health records and patient-reported outcomes • Identify considerations for defining and measuring implementation outcomes
12:00-1:00 pm	**ePCTs in Context: Small Group Work Followed by Panel Discussion With NIH Collaboratory Trial PIs**	**Moderator**: Emily O'Brien **Panelists**: Diana Burgess Julie Fritz Vince Mor David Wetter	• Hear from PIs of NIH Collaboratory Trials about their studies • Work in groups to discuss design considerations faced by these ePCTs • Discuss how PIs handled challenges from attendees' discussion, reflect on the morning topics, and discuss lessons learned

Time	Topic	Speakers	Goals
1:00-1:45 pm	**Lunch**		• Network with attendees and presenters
1:45-2:15 pm	**Pilot and Feasibility Testing**	Lanay Mudd	• Identify approaches to evaluating the capabilities of partnering health systems and testing key elements of various types of interventions
2:15-2:45 pm	**Ethical and Regulatory Considerations and Posttrial Obligations**	Stephanie Morain	• Learn about recurring and emerging ethical and regulatory issues in ePCTs • Understand posttrial obligations related to dissemination, sustainment, and deimplementation • Discuss ethical considerations for sharing aggregate results
2:45-2:55 pm	**Break**		• Network with attendees and presenters
2:55-3:25 pm	**Engaging and Aligning With Health System and Community Partners**	Hayden Bosworth	• Consider the breadth of individuals to engage as partners and approaches for engaging them throughout the study • Discuss the importance of working with partners to identify and plan for posttrial activities
3:25-3:55 pm	**Posttrial Sustainment or Deimplementation of Study Interventions**	Vince Mor	• Identify factors influencing sustainment and deimplementation of study interventions • Discuss strategies to assist investigators and research partners with posttrial interpretation and sustainment/deimplementation considerations
3:55-4:55 pm	**ePCTs in Context: Small Group Work Followed by Panel Discussion With NIH Collaboratory Trial PIs**	**Moderator**: Stephanie Morain **Panelists**: Diana Burgess Julie Fritz Angelo Volandes David Wetter	• Work in groups to discuss posttrial considerations and dissemination approaches in these ePCTs • Discuss how PIs handled the challenges from attendees' discussion, reflect on the afternoon topics, and discuss lessons learned
4:55-5:25 pm	**Writing a Compelling Grant Application**	Beda Jean-Francois	• Learn how to develop a compelling grant application for ePCTs and hybrid trials • Tips from NIH Collaboratory PIs
5:25-5:30 pm	**Closing Remarks**	Emily O'Brien	• Wrap-up, including identifying resources for further learning

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Speaker Biographies

Hayden B. Bosworth, PhD
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Hayden B. Bosworth, PhD, is a health services researcher and implementation scientist. He is currently a professor of population health sciences, medicine, psychiatry, and nursing at Duke University and the vice chair of research in the Department of Population Health Sciences. He is also the deputy director of the Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT) (COIN) at the Durham Veterans Affairs Medical Center and adjunct professor in the Department of Health Policy and Administration in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. His research interests comprise 3 overarching areas of research: 1) conducting clinical research that improves chronic disease self-management care; 2) implementing research to improve access to quality of care; and 3) eliminating health care disparities. Dr. Bosworth has expertise in developing and implementing scalable/sustainable interventions to improve health behaviors and reduce the burden of chronic diseases. These trials/programs focus on motivating individuals to initiate health behaviors and sustain them long term. He also has ample experience in conducting observational studies examining healthcare use and predictors of medication nonadherence. 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). He is the recipient of a new grant, The Pharmacists for Prevention (P4P) project, funded through the NIH RFA-MH-25-185 mechanism, aims to integrate HIV prevention and implementation science training into pharmacy school curricula across minority-serving institutions in the South to expand access to PrEP and related services.

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 500 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 170 graduate students, postdoctoral fellows, and junior faculty, including 40 career development awardees over the last 10 years. In addition, he was the principal investigator of a K12 National Heart, Lung, and Blood Institute–funded grant to train faculty in dissemination and implementation.

Diana Burgess, PhD
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Diana Burgess, PhD, is a professor in the Department of Medicine at the University of Minnesota and Director of the VA Advanced Fellowship Program in Health Services Research at the Center for Care Delivery and Outcomes Research at the Minneapolis Veterans Affairs Healthcare System. She is also the director of the Complementary and Integrative Health Evaluation Center in the Veterans Affairs Healthcare System. Her research is aimed at increasing the use of non-pharmacological and complementary and integrative health approaches for chronic pain in healthcare systems, with a focus on groups that experience disparities.

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

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

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

Vincent Mor, PhD
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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, MPH
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Stephanie Morain, PhD, MPH is the Dracopoulos Rising Professor of Bioethics in the Berman Institute of Bioethics at Johns Hopkins and Associate Professor in the Department of Health Policy and Management at the Bloomberg School of Public Health. She conducts both empirical and normative research into issues at the intersection of clinical research, public health, and health policy. Dr. Morain's work examines political and ethical issues concerning the scope of government authority in public health and the role of stakeholder opinion in shaping decision-making in public health policy. Dr. Morain's work focuses on two key areas: ethical and practical challenges presented by the integration of research and care, such as occurs in pragmatic clinical trials and in comparative effectiveness research, and issues related to women's reproductive health. Dr. Morain is the Co-Chair of the Ethics & Regulatory Core for the NIH Pragmatic Trials Collaboratory, and Executive Committee Member of the Ethics & Regulation Core for the NIA IMPACT Collaboratory.

Lanay Mudd, PhD
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Lanay M. Mudd, Ph.D., is deputy 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). She joined NCCIH as a program director in 2015. As deputy branch chief, Dr. Mudd assists Dr. Wendy Weber to coordinate NCCIH's Clinical Trial Specific Funding Opportunities. Dr. Mudd also serves as the NCCIH training director and provides oversight and direction for NCCIH's training and career development portfolio. She is the NCCIH co-coordinator for the NIH Common Fund Bridge to Artificial Intelligence program.

At NCCIH, Dr. Mudd oversees a grant portfolio of clinical trials; studies of movement meditation, including yoga, tai chi, and qi gong; research on health promotion, disease prevention, and resilience; and studies of remotely delivered or mHealth interventions. Dr. Mudd's interests include the use of mind and body interventions for perinatal health conditions, mental health conditions, and promoting healthy behaviors.

Dr. Mudd earned a dual-major doctoral degree in kinesiology and epidemiology and completed postdoctoral training in perinatal epidemiology at Michigan State University. Prior to joining NCCIH, she was an assistant professor of kinesiology at Michigan State University, where her research investigated the health benefits of physical activity during pregnancy and the development of interventions to improve health behaviors among pregnant women. She has published in a variety of peer reviewed journals, including *Medicine & Science in Sports & Exercise, Pediatrics, Journal of Physical Activity & Health,* and *Preventive Medicine*. Dr. Mudd is a fellow of the American College of Sports Medicine.

Emily O'Brien, PhD
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Dr. Emily O'Brien is Associate Professor in Population Health Sciences, Associate Professor in Neurology, Core Faculty Member at Duke-Margolis Center for Health Policy, and Co-Director of Population Health Sciences at the Duke Clinical Research Institute. Her research focuses on comparative effectiveness, patient-centered outcomes, and pragmatic health systems research in cardiovascular and pulmonary disease. Her areas of expertise include: Epidemiology, Pragmatic Clinical Trials, and Clinical Decision Sciences. Dr. O'Brien received her PhD in Epidemiology from the University of North Carolina in Chapel Hill. As principal investigator for projects funded by the FDA, NIH, and PCORI, she has extensive experience working with diverse data sources including registries, epidemiologic cohorts, electronic health records, and administrative claims data. Dr. O'Brien teaches Analytic Methods in the Department of Population Health Sciences PhD program and has co-authored over 200 manuscripts in peer-reviewed journals on topics ranging from epidemiologic methods, comparative effectiveness, and pragmatic clinical trials. She is an associate editor for *Circulation: Cardiovascular Quality and Outcomes,* Chair of the AHA QCOR Scientific & Clinical Education Lifelong Learning Committee, social media editor for *the Journal of the American Heart Association*, and a fellow of the American Heart Association.

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

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

David Wetter, PhD, MS
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Dr. Wetter is the Jon M. and Karen Huntsman Presidential Professor at the University of Utah and Huntsman Cancer Institute (HCI). He serves as Director of the Center for HOPE, a Senior Director at HCI, and Director for Community and Stakeholder Engagement for Utah's Clinical and Translational Sciences Institute. Dr. Wetter's work is targeted at reducing health risk behaviors and outcomes through translational research. He has had continuous NIH funding for almost 30 years and has more than 300 publications. His research program has received awards from the Society of Behavioral Medicine, Society for Health Psychology of the American Psychological Association, American Society of Preventive Oncology, and AstraZeneca/Scientific American. Dr. Wetter has extensive leadership experience in team science, including leading numerous large, complex, multi-site, multi-project grants (e.g., center grants). Dr. Wetter's team has developed highly effective healthcare system change and population health management interventions designed to increase utilization of evidence-based interventions, and has also been active in developing and implementing new behavior change approaches including digital health apps and counseling frameworks.

Qilu Yu, PhD
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Qilu Yu, Ph.D., is a statistician in the National Center for Complementary and Integrative Health (NCCIH) Office of Clinical and Regulatory Affairs. She serves as a senior collaborator and expert statistical advisor in areas relating to the development and application of statistical techniques to NCCIH-funded clinical trials. She also provides guidance and consultation on design, implementation, and analysis of extramural and intramural studies.

Dr. Yu has more than 15 years of experience planning and implementing the design and analyses of a broad range of clinical research studies. Areas of particular interest and expertise are leading the design of interventional clinical trials, including comparative effectiveness trials, longitudinal and survival analysis with missing data, as well as developing new structural equation modeling to interpret data. She is experienced with planning and analyses of small- to large-scale randomized trials and pragmatic clinical trials, including presentations on interventional clinical trials and methodology to senior stakeholders and the research community.

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About

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

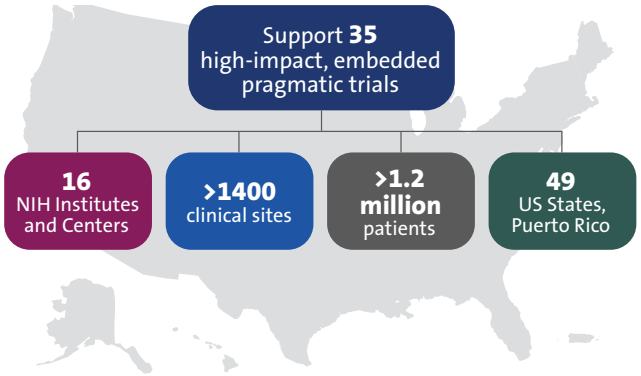
What Are Embedded Pragmatic Clinical Trials?

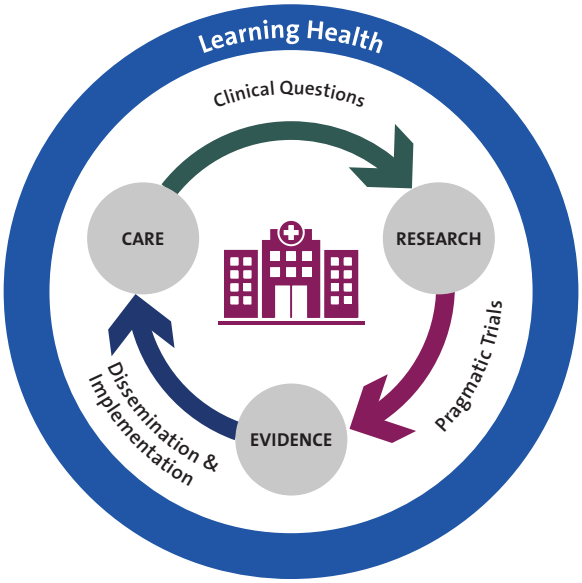
- Conducted in healthcare systems
- Use existing infrastructure and streamlined procedures
- Provide high-quality evidence
- More efficient and cost effective than traditional trials

Our Role

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

Our Reach





NIH Partners, Past and Present

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

Bold denotes current partners (Grant U24AT009676)

Our Impact

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

- **>360** publications*
- Work cited **>11,800** times
- **>245** trial consultations
- **>570** Grand Rounds webinars
- **>100,000** website visitors annually
- **30+** Living Textbook chapters

Wide Influence

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

Our Support

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

Consult and provide guidance on:

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

Offer strategies to:

- Contribute to healthier communities
- Engage health system partners

Assist with:

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

*LAST UPDATED JULY 22, 2025

Why Do an Embedded Pragmatic Clinical Trial? The 5 Rs

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

About NIH Collaboratory Trials

SETTINGS

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

CHARACTERISTICS

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

How We Learn and Share

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

DISSEMINATION

Grand Rounds
Weekly webinar with >90,000 all-time attendees and 53 podcast episodes with >22,000 total plays

Living Textbook
Free online textbook, continually updated and expanded, with 30+ chapters, >1800 pages, and >100 contributors

Resources and Tools
Publications, guidance documents, Quick Start Guides, checklists, etc—over 100 study tools available

Education
Provided >80 hours of presenter-led training at 13 workshops, plus video modules, self-paced learning, fellowships, and more

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

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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

ClinicalTrials.gov Identifier
NCT03609177

Sponsoring Institution
Dana-Farber Cancer Institute

NIH Institutes Providing Oversight
National Institute on Aging

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

DATA AND RESOURCE SHARING

- Data sharing checklist
- Volandes AE, Chang Y, Lakin JR, et al. An intervention to increase advance care planning among older adults with advanced cancer: A randomized clinical trial. *JAMA Netw Open*. 2025 May 1;8(5):e259150. doi: 10.1001/jamanetworkopen.2025.9150. PMID: 40343696.

STUDY AT A GLANCE

STUDY QUESTION AND SIGNIFICANCE

Many older adults with advanced cancer do not discuss treatment preferences or goals of care with their clinicians. Lack of communication about patients' preferences can lead to patients receiving care that does not match their values.

DESIGN AND SETTING

Stepped-wedge, cluster randomized trial testing the delivery of a video decision aid to patients together with goals-of-care communication skills training to oncology clinicians in 29 clinics in 3 healthcare systems in the South, Midwest, and Mid-Atlantic regions from April 1, 2020, to November 30, 2022. The study included 13,800 patients aged 65 years or older. Each clinic was randomly assigned to either the intervention or usual care at the beginning of the study. Due to the stepped-wedge design of the trial, all clinics were exposed to the intervention by the end of the study.

INTERVENTION AND METHODS

The intervention included an evidence-based, patient-facing video decision aid available in 25 languages. It also included a communication training program to improve clinicians' skills in delivering serious news, responding to emotion, and eliciting patients' goals. The primary outcome was documentation of advance care planning in the electronic health record, which could include documentation of a goals-of-care conversation, palliative care, hospice, or limitation of life-sustaining treatments.

FINDINGS

The proportion of patients with documentation of advance care planning was greater with the ACP PEACE intervention than with usual care (adjusted rate difference, 6.8% [95% CI, 2.8%-10.8%]; $P < .001$). The difference was attributable to a greater proportion of patients in the intervention phase having a goals-of-care conversation. There were no significant differences between the intervention and usual care for the documentation of palliative care, hospice, or limitation of life-sustaining treatments.

CONCLUSIONS AND RELEVANCE

A video decision aid for older patients with advanced cancer, coupled with communication skills training for clinicians, led to higher rates of documented advance care planning in oncology clinics. The innovative approach led to a clinically meaningful increase in documentation of advance care planning, a widely used metric that reflects high-quality, patient-centered care delivery.

GENERALIZABLE LESSONS

Challenge	Solution
Fixed variable data fields were unavailable for advance care planning	Shifted to using natural language processing
Interruption of the study by the COVID-19 public health emergency created an important secular trend for which the study team had to account	Established a new baseline after the interruption and shortened the stepped-wedge design from 6 steps to 4 steps

"By focusing concurrently on both clinicians and patients—giving clinicians the skills to have these difficult conversations and preparing patients to engage with them—we were able to increase the number of documented goals-of-care conversations." — Dr. James Tulsky

"What made it work was a shared commitment—from frontline clinicians to healthcare system leaders—to ensure that older adults with advanced cancer had the opportunity to reflect on their values and have those conversations documented. This trial wasn't just about changing documentation rates, it was about changing the culture of communication, at scale." — Dr. Angelo Volandes

ADDITIONAL RESOURCES

- *Rethinking Clinical Trials* Grand Rounds Presentation: A Cluster Randomized, Stepped-Wedge Pragmatic Trial to Enhance Goals-of-Care Communication for Older Adults With Cancer (ACP-PEACE) (2025)
- *Rethinking Clinical Trials* Podcast: ACP-PEACE (2025)
- Article: Structural Barriers to Well-Grounded Advance Care Planning for the Seriously Ill: A Qualitative Study of Clinicians' and Administrators' Experiences During a Pragmatic Trial (2023)
- Article: Association of an Advance Care Planning Video and Communication Intervention With Documentation of Advance Care Planning Among Older Adults: A Nonrandomized Controlled Trial (2022)

Access the complete set of ACP PEACE resources.

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

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

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Disclosures

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

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Objective

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

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Study design

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

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Outcomes

- Advance care plan completion
- Medical orders for resuscitation preferences
- Palliative care consultations
- Hospice use
- Detailed patient-centered outcomes in a subgroup of 450 patients, including video declarations of individual preferences

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Participating healthcare systems

- Duke Health
- Northwell Health
- Mayo Clinic

DukeHealth

Northwell Health℠

MAYO CLINIC

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Barriers/challenges

- Incomplete and variable content of structured data in 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 study design

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Original design

ACP PEACE

		UH3					
STEPS (clinic clusters)	Baseline	1	2	3	4	5	6
1, 2		✓					
3, 4							
5, 6							
7, 8							
9, 10							
11, 12							

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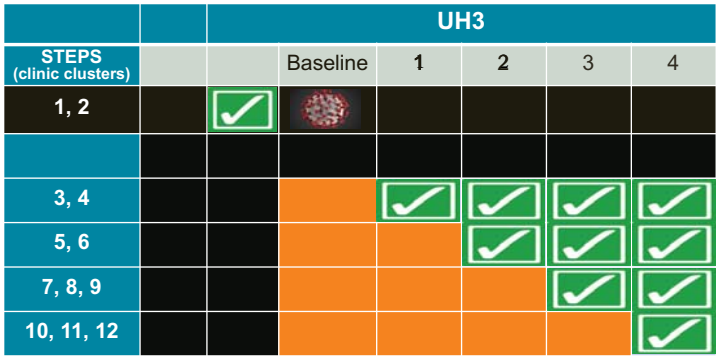
Revised design



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

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

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)**

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 (2018)

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
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BEATPAIN Utah

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

Principal Investigator
Julie Fritz, PhD, PT

Sponsoring Institution
University of Utah

Collaborator
Association for Utah Community Health

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

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

Project Scientist
Lanay Mudd, PhD (National Center for Complementary and Integrative Health)

ClinicalTrials.gov Identifier
NCT04923334

ABSTRACT

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

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

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

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

WHAT WE'VE LEARNED SO FAR

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

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

PRESENTATIONS & ABSTRACTS

- PCT Grand Rounds Presentation: BeatPain Utah: Partnering With Community Health Centers Within a Socio-Technical Framework (2023)
- Presentation: Presentation to the NIH Pragmatic Trials Collaboratory Steering Committee (2023)
- Article (Study Design): BeatPain Utah: Study Protocol for a Pragmatic Randomised Trial Examining Telehealth Strategies to Provide Non-pharmacologic Pain Care for Persons With Chronic Low Back Pain Receiving Care in Federally Qualified Health Centers (2022)
- Article: Use of Implementation Mapping in the Planning of a Hybrid Type 1 Pragmatic Clinical Trial: The BeatPain Utah Study (2024)

Access the complete set of BeatPain Utah resources.

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

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

BEATPAIN Utah

NIH PRAGMATIC TRIALS COLLABORATORY
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Objectives

- Compare effectiveness of nonpharmacologic interventions for patients with back pain seeking care in FQHCs in Utah
  - Telehealth strategy: Brief pain consult with telehealth physical therapy
  - Adaptive strategy: Brief pain consult, followed by telehealth physical therapy for nonresponders
- Strategies designed to overcome barriers specific to rural and lower-income communities served by FQHC clinics
- Study also evaluates implementation outcomes to inform future efforts to scale effective strategies into other settings

NIH PRAGMATIC TRIALS COLLABORATORY
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Goal and strategy

- Improve pain management and reduce reliance on opioids for patients with chronic back pain in FQHCs in Utah
- Hybrid type 1 effectiveness-implementation trial
  - Compare effectiveness of first-line nonpharmacologic pain treatments using telehealth to overcome access barriers, improve patient-centered outcomes, reduce opioid use
  - Collect implementation outcomes for EHR-based e-referral process and telehealth care

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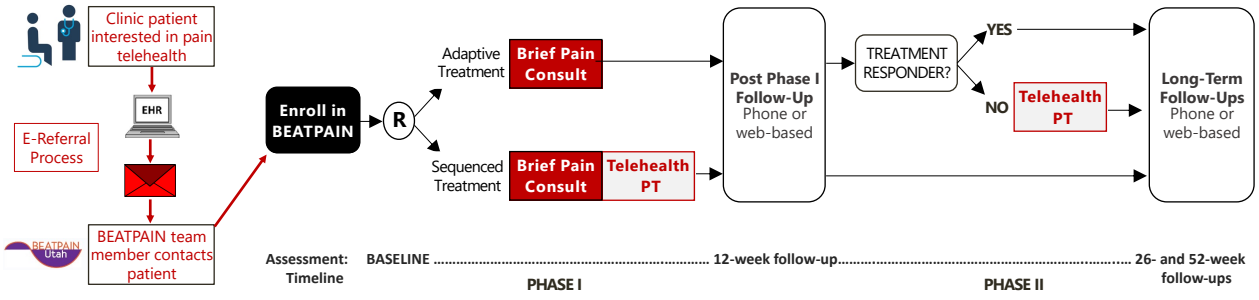
Study design



NIH PRAGMATIC TRIALS COLLABORATORY
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Study aims

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

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Interventions

Brief pain consult

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

Telehealth physical therapy

- 10 weekly sessions
- Provided in Phase I or Phase II (nonresponders) for enrolled participants
- Builds on brief pain consult, exercise program, goal setting, motivation and problem-solving approach

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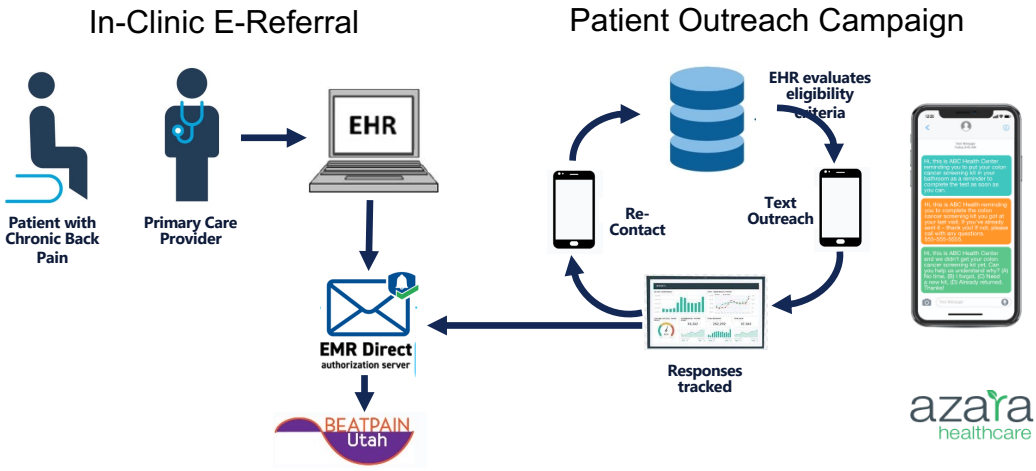
Implementation strategies



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

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Participating healthcare systems

AUCH
ASSOCIATION FOR UTAH COMMUNITY HEALTH

HEALTH
UNIVERSITY OF UTAH

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

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Barriers/challenges

- Slower than anticipated start due to COVID-19
- Staffing challenges for providers and support personnel
- “Research fatigue” in FQHC settings
- Challenges in using text messaging to inform patients
- Building trust between the academic medical center and FQHC leadership, staff, and communities served
- Bringing in new FQHCs from surrounding states through the NIH CARE for Health™ program

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Solutions/lessons learned

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

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Population Health Management Approaches to Increase Lung Cancer Screening in Community Health Centers (LungSMART)

Principal Investigators
David Wetter, PhD, MS; Guilherme Del Fiol, MD, PhD; and Kensaku (Ken) Kawamoto, MD, PhD

Sponsoring Institution
University of Utah

Collaborators
- Community health centers in Utah
- Association for Utah Community Health

NIH Institute Providing Oversight
National Cancer Institute (NCI)

Program Official
Sallie J. Weaver, PhD, MHS (NCI)

Project Scientist
Paul Han, MD, MA, MPH (NCI)

ABSTRACT

Annual lung cancer screening by low-dose computed tomography is recommended by the US Preventive Services Task Force. Despite evidence of effectiveness and the USPSTF recommendations, implementation of lung cancer screening in clinical practice has been exceedingly limited, with only 6.5% of eligible individuals screened in 2020, and there are significant disparities in screening related to race/ethnicity and socioeconomic status. The LungSMART study team plans to conduct a 2-phase trial with a sequential, multiple assignment, randomized trial (SMART) design in community health centers in Utah. Utah has 14 community health center systems with approximately 50 primary care clinics. Each of the Utah community health centers is a federally qualified health center providing comprehensive primary care to more than 160,000 patients annually. Patients in Utah community health centers are 52% Latino, 8% Native American, 40% best served in a language other than English, 55% below the federal poverty level, and 43% uninsured, and 41% of the clinics are in rural areas. Phase 1 of LungSMART will compare a variety of text messaging strategies to increase patients' completion of an eligibility assessment for lung cancer screening. Phase 2 of LungSMART will test telehealth interventions designed to address logistical barriers and hesitancy around completing lung cancer screening among referred patients. LungSMART leverages smartphone/internet technologies when available, and also supports patients whose only telehealth connectivity is a cellphone. A centralized "hub" enables eligibility assessment, shared decision-making with clinical decision support, screening referral, and screening logistics assistance at scale to address numerous social determinants of health that affect low-resource settings and historically marginalized populations. All study procedures and interventions will be conducted in English or Spanish based on the patient's preferred language. In sum, LungSMART will be conducted in a real-world context across multiple independent healthcare delivery systems and will provide a critical evidence base for the large-scale implementation of interventions designed to reduce disparities in lung cancer screening in community health centers and other low-resource settings nationwide.

SELECTED PUBLICATIONS & PRESENTATIONS

- Presentation: NIH Collaboratory Onboarding Presentation (2024)

See the complete set of LungSMART resources.

LungSMART Utah: Population Health Management Approaches to Increase Lung Cancer Screening in Community Health Centers

David W. Wetter, PhD, MS
Jon M. and Karen Huntsman Presidential Professor
Director, Center for HOPE
Senior Director, Huntsman Cancer Institute
Director, Community and Stakeholder Engagement for the Clinical and Translational Sciences Institute
University of Utah and Huntsman Cancer Institute

NIH PRAGMATIC TRIALS COLLABORATORY
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Objective

- To increase the reach and uptake of USPSTF-recommended lung cancer screening (LCS) at scale among patients in Community Health Centers

We will test strategies to:

Assess LCS eligibility via digital tools

Offer access to, and facilitate, Shared Decision Making (SDM)

Enhance LCS completion

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Study Population and Setting

- Study population
  - All patients aged 50 to 80 years who are smokers or former smokers and who had a visit to a participating community health center in the previous 3 years
- Study setting
  - ~9-14 community health center systems with approximately 40-60 primary care clinics in Utah

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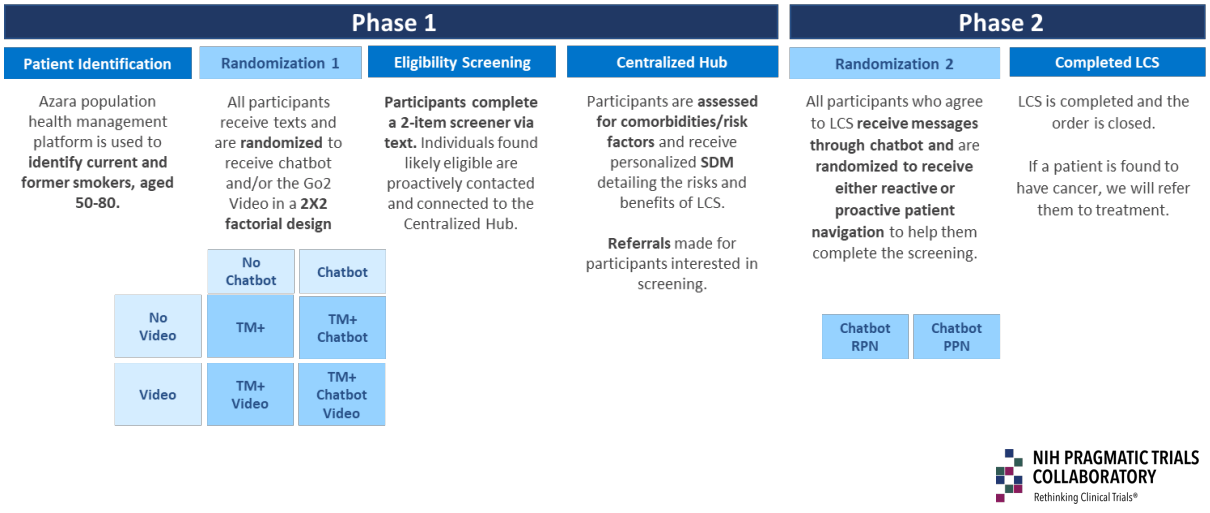
Sequential Multiple Assignment Randomized Trial (SMART) With 2 Phases



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Outcomes

Phase 1:

- Completed eligibility assessments for lung cancer screening among randomized patients
- Completed SDM among patients initially eligible for LCS

Phase 2:

- Completed LCS among patients randomized in phase 2

Partners

Utah Community Health Centers operate ~50 primary care clinics and serve > 161,000 individuals

Multiple Population Groups
- 52% Hispanic/Latino Ethnicity
- 8% American Indian/Alaska Native
- 40% Best served in a language other than English

Low Socioeconomic Status
- 55% < Federal Poverty Level
- 43% Uninsured

Rural/Frontier
- 41% of clinics in rural/frontier areas (RUCC ≥4)

CENTER FOR HOPE
HEALTH OUTCOMES & POPULATION EQUITY

AUCH
ASSOCIATION FOR UTAH COMMUNITY HEALTH

14
Community Health Centers

Utah Department of Health & Human Services

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PROVEN

PRagmatic Trial of Video Education in Nursing Homes

Pragmatic Trial of Video Education in Nursing Homes (PROVEN)

Principal Investigators
Susan Mitchell, MD, MPH; Angelo Volandes, MD, MPH; Vincent Mor, PhD

ClinicalTrials.gov Identifier
NCT02612688

Sponsoring Institution
Brown University

NIH Institute Providing Oversight
National Institute on Aging (NIA)

DATA AND RESOURCE SHARING

- Data sharing checklist
- **Primary study results:** Mitchell SL, Volandes AE, Gutman R, et al. Advance care planning video intervention among long-stay nursing home residents: a pragmatic cluster randomized clinical trial. *JAMA Intern Med*. 2020;180(8):1070-1078. PMID: 32628258.

STUDY AT A GLANCE

STUDY QUESTION AND SIGNIFICANCE

Nursing homes are often charged with guiding patients through decisions about the direction of their treatment. Identifying effective approaches that nursing homes can use to better promote goal-directed care within existing resources is a research, public health, and clinical priority. Yet, evidenced-based approaches to advance care planning in nursing homes are lacking. The objective of the study was to test the effect of an advance care planning video program on hospital transfers, burdensome treatments, and hospice enrollment among long-stay nursing home residents.

DESIGN AND SETTING

Cluster randomized trial with 197,692 residents in 360 nursing homes in 32 states owned by 2 for-profit corporations, of which 241 facilities were randomly assigned to the control group and 119 facilities were randomly assigned to the intervention.

INTERVENTION AND METHODS

The intervention involved 5 short advance care planning videos made available on tablet computers or online. Designated champions in the intervention facilities were instructed to offer residents or their proxies the opportunity to view a video on admission and every 6 months. Control facilities used usual advance care planning practices. The primary outcome was hospital transfers per 1000 person-days alive among residents with advanced illness. Secondary outcomes included the proportion of residents with or without advanced illness experiencing 1 or more hospital transfer, 1 or more burdensome treatment, and hospice enrollment. The analyses followed the intention-to-treat principle.

FINDINGS

There was no significant reduction in hospital transfers per 1000 person-days alive in the intervention vs control groups. Secondary outcomes did not significantly differ between groups among residents with and without advanced illness. Only 912 of 4171 residents with advanced illness viewed the advance care planning videos. Facility-level rates of showing the videos ranged from 0% to more than 40%.

CONCLUSIONS AND RELEVANCE

The advance care planning video program was not effective in reducing hospital transfers, decreasing burdensome treatment use, or increasing hospice enrollment among long-stay nursing home residents with or without advanced illness. The low level of intervention fidelity highlights the challenges of implementing new programs in nursing homes.

GENERALIZABLE LESSONS

Challenge	Solution
Low implementation fidelity	High level of buy-in from frontline staff responsible for implementing the program, and strong endorsement from healthcare system leadership
Healthcare system interactions	Strong relationships with healthcare systems before the study; study-specific project manager in each healthcare system to oversee the project and serve as liaison between research team and healthcare system

"Becoming integrated into the NIH Collaboratory scientific community was an exceptional experience for all 3 of the PROVEN PIs. Learning from the other investigators and Collaboratory leaders was the definitive highlight. We learned so much, and the experience of PROVEN will lead the way for future pragmatic trials in the nursing home setting." — Susan Mitchell

ADDITIONAL RESOURCES

- Article: Understanding Implementation Fidelity in a Pragmatic Randomized Clinical Trial in the Nursing Home Setting: A Mixed-Methods Examination (2019)
- Article: Proxies Viewing Decision Support Video in Nursing Home Report Higher Advance Care Planning Engagement (2019)
- Article: Black Nursing Home Residents More Likely to Watch Advance Care Planning Video (2020)
- Article: Barriers and Facilitators to Implementing a Pragmatic Trial to Improve Advance Care Planning in the Nursing Home Setting (2019)

Access the complete set of PROVEN resources.

PROVEN: Pragmatic Trial of Video Education in Nursing Homes

Vincent Mor, PhD
Brown University

PROVEN
PRagmatic Trial of Video Education in Nursing Homes

NIH PRAGMATIC TRIALS COLLABORATORY
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Objective

- To test the effect of an advance care planning video program on hospital transfers, burdensome treatments, and hospice enrollment among long-stay nursing home residents

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Study design

- Cluster randomized trial
- 197,692 residents in 360 nursing homes in 32 states owned by 2 for-profit corporations
- 241 facilities in the control group, 119 facilities in the intervention group

NIH PRAGMATIC TRIALS COLLABORATORY
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Intervention

- 5 short advance care planning videos made available on tablet computers or online
- Designated champions in the intervention facilities offered residents or their proxies the opportunity to view a video on admission and every 6 months
- Control facilities used usual advance care planning practices

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Outcomes

- Primary outcome: Hospital transfers per 1000 person-days alive among residents with advanced illness
- Secondary outcomes: Proportions of residents with or without advanced illness experiencing 1 or more hospital transfer, 1 or more burdensome treatment, and hospice enrollment

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Results

- No significant reduction in hospital transfers per 1000 person-days alive in the intervention vs control groups
- Secondary outcomes did not significantly differ between groups among residents with and without advanced illness
- Only 912 of 4171 residents with advanced illness viewed the advance care planning videos; facility-level rates of showing the videos ranged from 0% to more than 40%

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Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)

Principal Investigators
Diana Burgess, PhD; Roni L. Evans, DC, MS, PhD; Katherine E. Hadlandsmyth, PhD

Sponsoring Institution
Center for Veterans Research and Education

Collaborators
- Minneapolis VA Health Care System
- University of Minnesota
- University of Iowa

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

Program Official
Karen Kehl, PhD, RN (NINR)

Project Scientist
Lanay Mudd, PhD (National Center for Complementary and Integrative Health [NCCIH])

ClinicalTrials.gov Identifier
NCT06568250

ABSTRACT

The Veterans Administration (VA) has become a leader in complementary and integrative health through its Whole Health initiative. Yet there remain many barriers, especially for patients with pain in rural communities. The RAMP trial aims to overcome these barriers. The study team is working with partners in the community and the VA, including rural patients, to develop an innovative, evidence-based telehealth intervention, the RAMP program, that brings together multiple evidence-based complementary and integrative health self-management strategies to address rural veterans' biophysical, psychological, and social needs. The RAMP program consists of 9 weekly group sessions, which include prerecorded, expert-led education videos, mind-body skills training and practice, and group discussions led by a health coach. Program content covers pain education, mindfulness, pain-specific exercises, and cognitive behavioral strategies. In the trial's planning phase, the study team identified and developed new community partnerships and used mixed-methods data collection from patients, community partners, and VA healthcare system leaders and staff, guided by the RE-AIM/PRISM framework, to understand key factors that may affect long-term adoption of the intervention. A pilot study with 40 rural VA patients with chronic pain assessed the feasibility of delivering the RAMP program in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other metrics. The pilot also assessed the extent to which the program met veterans' pain self-management needs, as well as areas for refinement and optimization. In the trial's implementation phase, the study team will conduct a randomized, multicenter, hybrid type 2 effectiveness-implementation pragmatic clinical trial of the RAMP program vs usual care among 500 rural patients in the VA healthcare system. The primary effectiveness outcome is pain interference at 3 and 6 months. Secondary outcomes include opioid use and the NIH HEAL Initiative's core pain domains. The study team will continue to work with patient, community, and healthcare system partners identified during the planning phase to evaluate the implementation strategies used in the trial and adapt these strategies to scale up RAMP within the VA healthcare system. This will include mixed-methods assessments of research partners' and trial participants' views of implementation-related barriers and facilitators, resource needs, and other domains; co-creation of additional plausible strategies for overcoming implementation barriers; and budget impact analyses using models informed by research partners' views to inform future decision-making.

WHAT WE'VE LEARNED SO FAR

Challenge	Solution
Developing relationships with representatives of community organizations on a short, grant-driven timeline	Leveraged networks of existing collaborators, such as veteran patient experts, who were able to facilitate contacts between the study team and community partners

"The big goal is to alleviate suffering for people with chronic pain and to get more tools and resources to rural-dwelling veterans. This is a population that is particularly vulnerable to not having access to pain self-management and complementary and integrative health approaches, and they are at higher risk for potentially risky prescribing around chronic pain." — Dr. Katherine Hadlandsmyth

"Develop strong relationships with your healthcare system partners early. We were fortunate to have longstanding relationships with our healthcare system partners, and we've been working closely with them to understand how we can develop an intervention that is really meaningful to them." — Dr. Diana Burgess

"Really listen to the people you're trying to affect—the patients. We've benefited from previous studies where we collected qualitative data that informed what we're doing now. So listen, but listen in a systematic way. Qualitative research is a great way to do that." — Dr. Roni Evans

SELECTED PUBLICATIONS & PRESENTATIONS

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

See the complete set of RAMP resources.

RAMP: Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention

Diana Burgess, PhD
Professor of Medicine, University of Minnesota
Director, VA Advanced Fellowship Program in Health Services Research,
Minneapolis VA Health Care System Research Service

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Objective

- To test implementation of an evidence-based telehealth intervention to improve chronic pain self-management among rural-dwelling patients in the VA healthcare system

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Study design

- Randomized, multicenter, hybrid type 2 effectiveness-implementation pragmatic clinical trial of the RAMP program vs usual care
- 500 rural patients in the VA healthcare system

NIH PRAGMATIC TRIALS COLLABORATORY
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Intervention

- Group-based telehealth program for rural-dwelling VA patients with chronic pain which integrates multiple complementary and integrative Health (CIH) self-management components (pain education, mindfulness, pain-specific exercises, and cognitive behavioral strategies) delivered using expert-led videos, with sessions led by trained facilitators

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Outcomes

- Primary effectiveness outcome: pain interference at 3 and 6 months
- Secondary effectiveness outcomes: opioid use and other outcomes in the NIH HEAL Initiative–recommended domains
- Mixed-methods assessments of research partners' and trial participants' views of implementation-related barriers and facilitators, resource needs, and other domains
- Co-creation of additional plausible strategies for overcoming implementation barriers
- Budget impact analyses using models informed by research partners' views to inform future decision-making

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Welcome & Opening Remarks

SPEAKER

Emily C. O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Welcome

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

NIH PRAGMATIC TRIALS COLLABORATORY
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Learning objectives

Identify Synergy

Explore how embedded pragmatic clinical trials and implementation research **can amplify each other** to accelerate real-world impact

Demystify Design

Learn the key features, challenges, and opportunities of embedding pragmatic trials into diverse healthcare systems and **how implementation methods can strengthen their success**

Build Capacity

Equip health services researchers with **practical tools and lessons from implementation science** to drive adoption, sustainment, scale-up, and smart deimplementation of effective interventions

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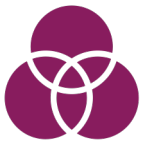
Workshop sessions: Part 1



ePCTs and Hybrid Trials: Similarities and Differences

Hayden Bosworth

Design and Analysis Considerations

Qilu Yu

Measuring Effectiveness and Implementation Outcomes

Angelo Volandes

ePCTs in Context

Diana Burgess, Julie Fritz, Vince Mor, David Wetter

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Workshop sessions: Part 2

Pilot and Feasibility Testing

Lanay Mudd

Ethical and Regulatory Considerations and Posttrial Obligations

Stephanie Morain

Engaging and Aligning With Health System and Community Partners

Hayden Bosworth

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Workshop sessions: Part 2 (continued)

Posttrial Sustainment or Deimplementation of Study Interventions

Vince Mor

ePCTs in Context

Diana Burgess, Julie Fritz, Angelo Volandes, David Wetter

Writing a Compelling Grant Application

Beda Jean-Francois

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Resource: Living Textbook of Pragmatic Clinical Trials

Visit
rethinkingclinicaltrials.org

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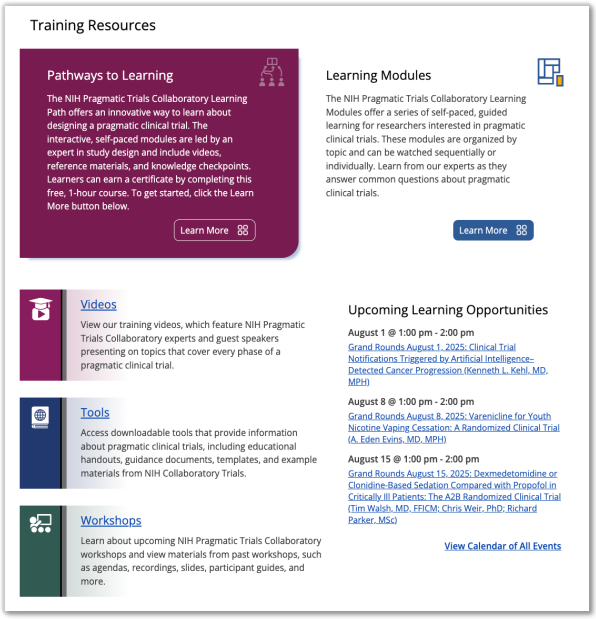
ePCT Training Resources

rethinkingclinicaltrials.org/training-resource/

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



Rethinking Clinical Trials® Grand Rounds

Weekly webinars

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

Learn more:

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https://impactcollaboratory.org

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About you

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

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About you

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

About you

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

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ePCTs and Hybrid Effectiveness-Implementation Trials: Similarities and Differences

SPEAKER

Hayden B. Bosworth, PhD

Professor in Population Health Sciences
Duke University

Embedded Pragmatic Clinical Trials and Hybrid Effectiveness-Implementation Trials: Similarities and Differences

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Disclosures

- Hayden Bosworth reports research funding through his institution from BeBetter Therapeutics, Boehringer Ingelheim, Esperion, Improved Patient Outcomes, Luminate Insights, Merck, Cleery, NHLBI, Novo Nordisk, Otsuka, Sanofi, Veterans Administration, Elton John Foundation, Hilton foundation, Pfizer.
- He also provides consulting services for Boehringer Ingelheim, Esperion, Elevance Health, Sanofi, Walmart, Webmed, Janssen. He was also on the board of directors of Preventric Diagnostics.

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Learning goals

- Consider the importance of ePCTs, implementation science, and learning health system principles
- Identify key similarities and differences between ePCTs and hybrid trials
- Discuss advantages and disadvantages of ePCTs and hybrid trials and when they can be used to answer research questions

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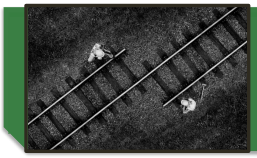
Getting the right evidence to decision-makers

Research timelines vs community needs
- First submission to publication ~6 years at least
- Decisions are made without waiting for research



Mismatched priorities and incentives
- Leaders want specific and timely answers
- Lack of incentives for community engagement

Lack of planning for future scale-up for interventions
- What is the “value proposition”?
- Avoiding “helicopter research”

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Important things to know about ePCTs

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

Broad engagement and support are essential from beginning to end

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

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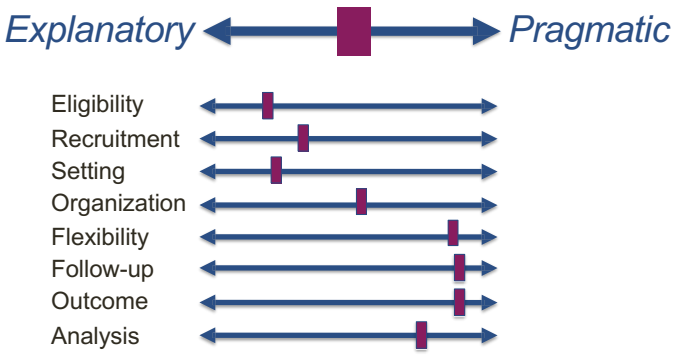
Trials elements vary across a spectrum



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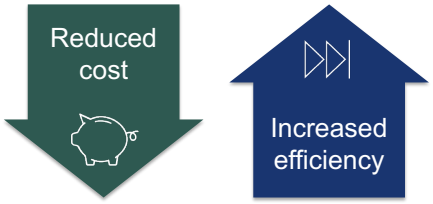
Why conduct ePCTs?

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



vs traditional trials

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ePCT characteristics

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

Why Do an ePCT? The 5 Rs

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

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Why pragmatic implementation trials?

Answering the right questions for decision-makers

An effective treatment or practice is only as good as how and whether…

- It is adopted?
- Practitioners are trained to use it?
- Trained practitioners choose to use it?
- Eligible populations/patients benefit from it?

If we assume 50% threshold for each step…

Even with perfect access, adherence, dosage, and maintenance…

Clinical impact

50% × 50% × 50% × 50% = **6% benefit**

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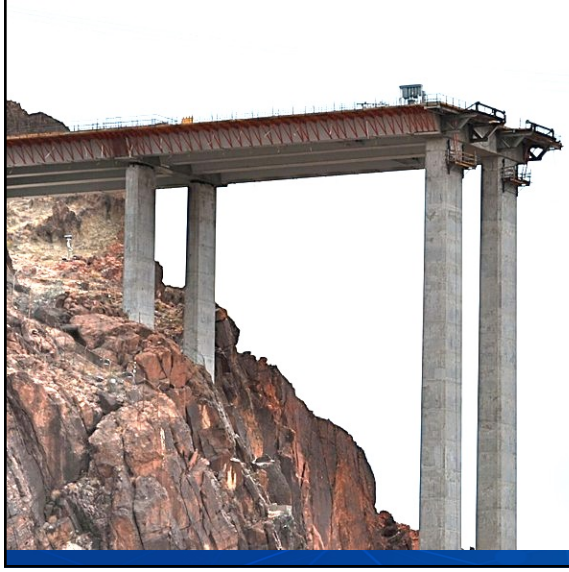
Interventions tested in ePCTs are intentionally designed to align with health system priorities and leverage existing healthcare system infrastructure and resources, with the goals of easing intervention implementation during the trial and increasing the likelihood that effective interventions will be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

Problems



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

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

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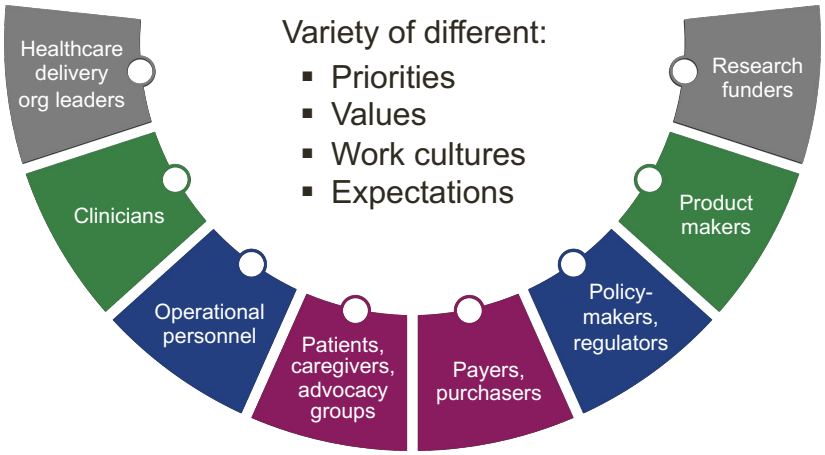
Who is interested and involved?



Variety of different:

- Priorities
- Values
- Work cultures
- Expectations

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Use existing workflows

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

—Vincent Mor, PhD (PROVEN)

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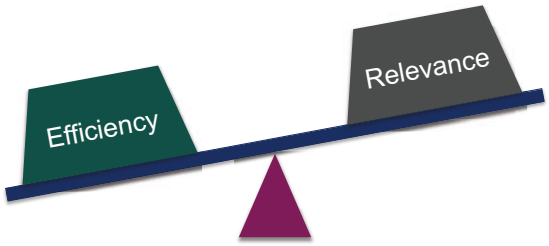
It's a balancing act



ePCTs want to achieve both

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

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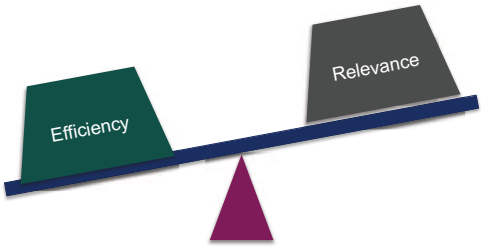
Example



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

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Important things to do

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

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Why the increased focus on implementation science?

- "If you build it, they will come" is no longer effective
- Massive investment in innovations has not translated to expected gains in population health
- Clear performance gaps—innovations are not reaching all intended recipients
- Innovations are also not reaching recipients equitably
- Funders see implementation as important for the "last mile" delivery of innovations

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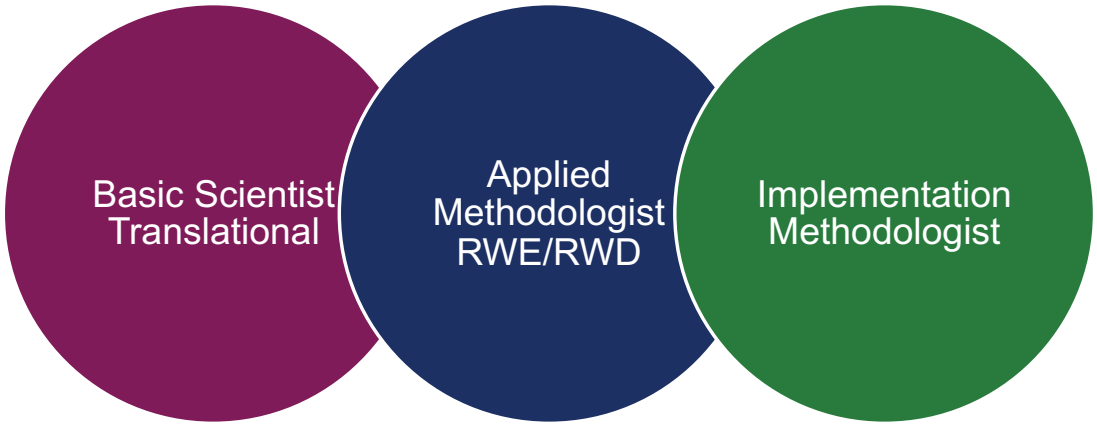
3 types of implementation scientists



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Why hybrid trial designs?

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

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Important things to know about hybrid trials

Hybrid trial designs focus on both clinical effectiveness and implementation outcomes

ePCTs are usually type 1 or type 2 hybrid trials

Choosing the right design balances understanding effectiveness and optimizing implementation strategies

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Types of hybrid designs

Clinical Effectiveness Research → **Implementation Research**

Hybrid Type 1

Test a clinical intervention, observe or gather information on implementation

Hybrid Type 2

Test a clinical intervention, test or study an implementation strategy

Hybrid Type 3

Test an implementation strategy, observe or gather information on intervention's effectiveness

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Hybrid type 1

1

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

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Hybrid type 1 example: PPACT

1

Contemporary Clinical Trials 67 (2018) 91–99

Contents lists available at ScienceDirect

Contemporary Clinical Trials

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

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

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

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Hybrid type 1 example: PPACT

1

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

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Hybrid type 2

2

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

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Hybrid type 2 example: STOP CRC

2

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

Implementation Science

METHODOLOGY Open Access

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

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

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Hybrid type 2 example: STOP CRC

2

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

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Hybrid type 3

3

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

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Hybrid type 3 example: ENABLE

3

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

Implementation Science

STUDY PROTOCOL Open Access

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

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

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Concluding points

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

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Learn more

- Curran et al. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. 2012 Mar;50(3):217-26. PMID: 22310560.
- Landes et al. An introduction to effectiveness-implementation hybrid designs. *Psychiatry Res*. 2019 Oct;280:112513. PMID: 31434011.

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Question & Answer

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Knowledge Checkpoint

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

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Knowledge Checkpoint

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

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Knowledge Checkpoint

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

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Resources

Embedded Pragmatic Clinical Trials (ePCTs) and Hybrid Effectiveness-Implementation Trials

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

- Pragmatic and Explanatory Attitudes to RCTs: Using the PRECIS-2 Tool to Describe the Design of the MyTEMP Trial (Ahmed Al-Jaishi, PhD; Amit Garg, MD, PhD, Merrick Zwarenstein, MBBCh, MSc, PhD)
- Trauma Survivors Outcomes & Support (TSOS) Pragmatic Trial: Revisiting Effectiveness & Implementation Aims (Doug Zatzick, MD)

Key Journal Articles

- Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. 2012 Mar;50(3):217-26. PMID: 22310560.
- Gordon KS, Peduzzi P, Kerns RD. Designing trials with purpose: Pragmatic clinical trials of nonpharmacological approaches for pain management. *Pain Med*. 2020 Dec 12;21(Suppl 2):S7-S12. PMID: 33313727.
- Johnson KE, Neta G, Dember LM, et al. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. *Trials*. 2016 Jan 16;17:32. PMID: 26772801.

- Weinfurt KP, Hernandez AF, Coronado GD, et al. Pragmatic clinical trials embedded in healthcare systems: Generalizable lessons from the NIH Collaboratory. *BMC Med Res Methodol*. 2017 Sep 18;17(1):144. PMID: 28923013.
- Landes SJ, McBain SA, Curran GM. An introduction to effectiveness-implementation hybrid designs. *Psychiatry Res*. 2019 Oct;280:112513. PMID: 31434011.
- Cocoros NM, Gurwitz JH, Cziraky MJ, et al. Pragmatic guidance for embedding pragmatic clinical trials in health plans: Large simple trials aren't so simple. *Clin Trials*. 2023 Aug;20(4):416-424. PMID: 37322894.
- Green T, Bosworth HB, Coronado GD, et al. Factors affecting post-trial sustainment or de-implementation of study interventions: A narrative review. *J Gen Intern Med*. 2024 May;39(6):1029-1036. PMID: 38216853.
- Gaugler JE, Baier RR, Baker ZG, et al. Using hybrid effectiveness studies to facilitate implementation in community-based settings: Three case studies in dementia care research. *J Am Med Dir Assoc*. 2024 Jan;25(1):27-33. PMID: 37643720.
- Fortney JC, Curran GM, Lyon AR, Check DK, Flum DR. Similarities and differences between pragmatic trials and hybrid effectiveness-implementation trials. *J Gen Intern Med*. 2024 Jul;39(9):1735-1743. PMID: 38627320.

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Design and Analysis Considerations

SPEAKER

Qilu Yu, PhD

Statistician, Office of Clinical and Regulatory Affairs
National Center for Complementary and Integrative Health (NCCIH)

Design & Analysis Considerations

Qilu Yu, PhD
Statistician, Office of Clinical and Regulatory Affairs
National Center for Complementary and Integrative Health (NCCIH)

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Learning goals

- Identify common experimental designs and randomization schemes pragmatic trials
- Discuss design and analytic considerations for trials with both effectiveness and implementation outcomes
- Understand the importance of monitoring adherence and fidelity

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Design Considerations

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Three kinds of randomized trials

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

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Methods for pragmatic trials

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

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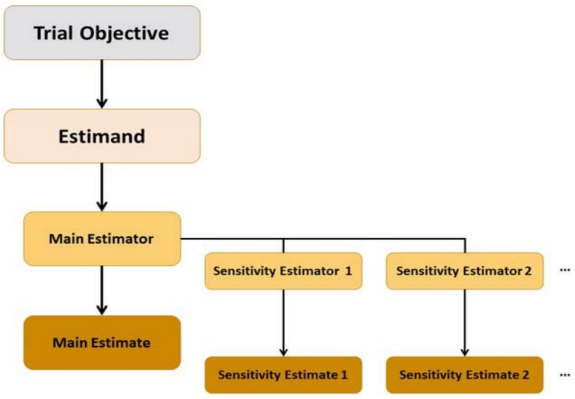
Start with a clear research question

Elements of a research question:

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



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

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Important things to know

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

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

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

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OPTIMUM, an NIH Collaboratory Trial

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

Optimizing Pain Treatment In Medical Settings Using Mindfulness (OPTIMUM)

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

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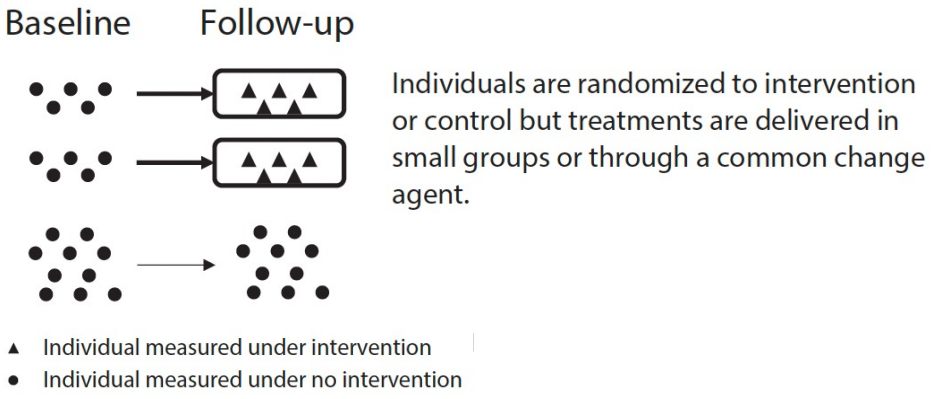
IRGT trial design in OPTIMUM



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

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Three kinds of randomized trials

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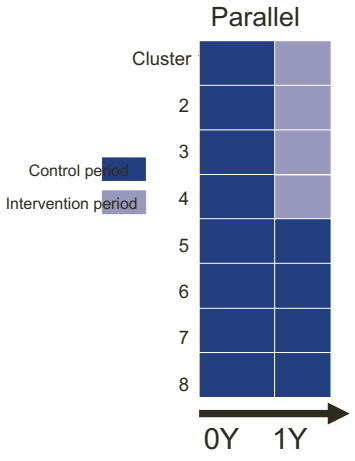
In this example:
- 8 clusters
- 1-year intervention



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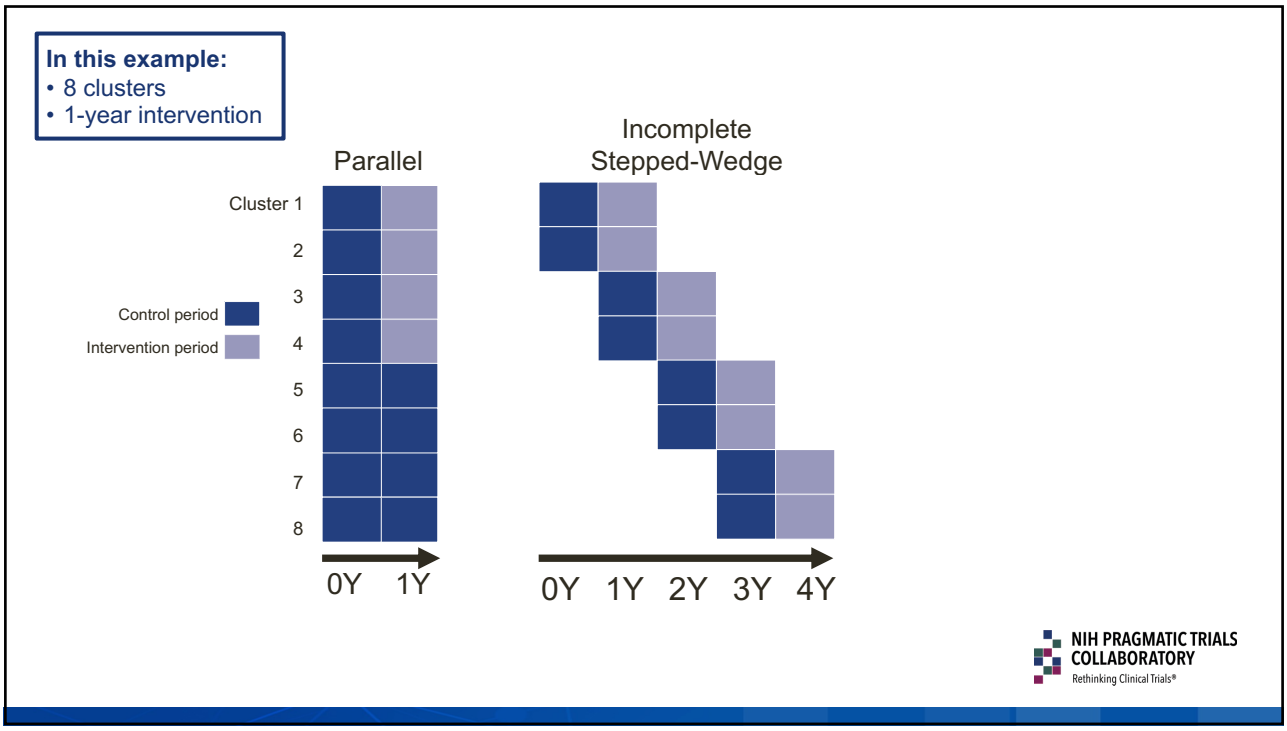
In this example:
• 8 clusters
• 1-year intervention
Parallel
Incomplete Stepped-Wedge
Cluster 1
2
3
4
5
6
7
8
Control period
Intervention period
0Y 1Y
0Y 1Y 2Y 3Y 4Y
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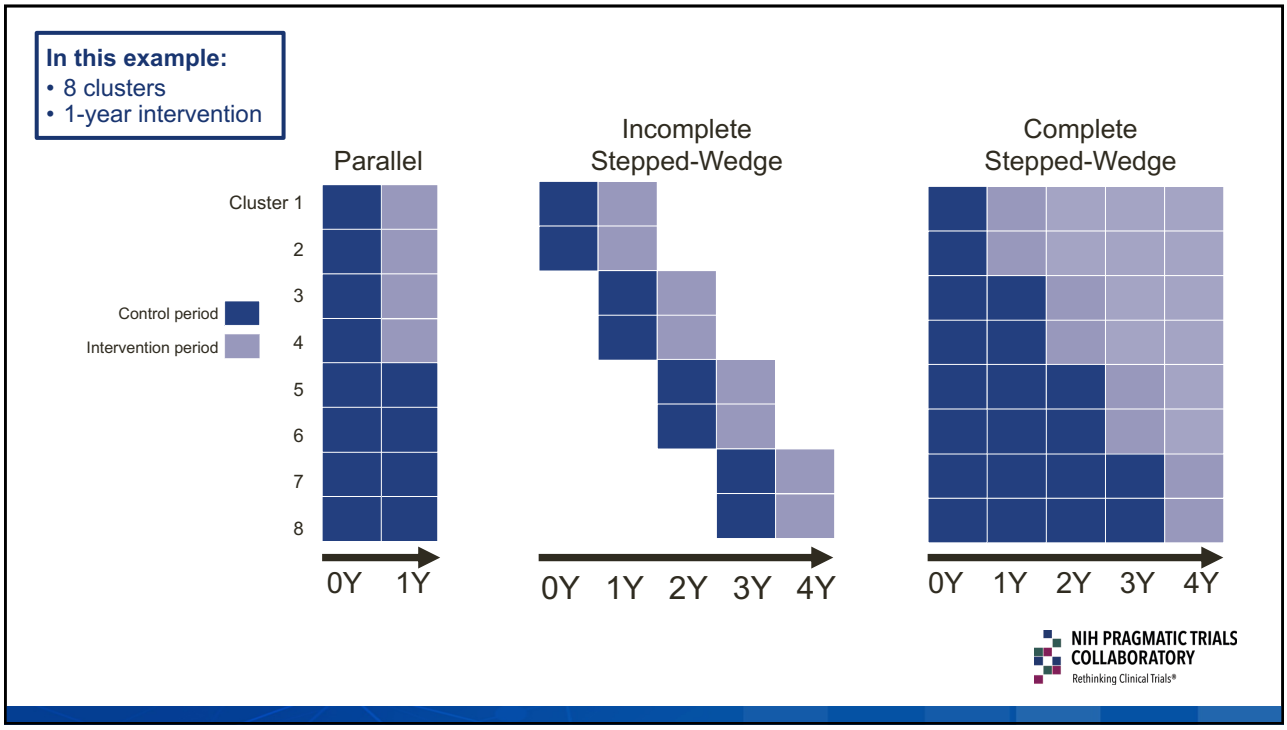
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Parallel
Incomplete Stepped-Wedge
Complete Stepped-Wedge
Cluster 1
2
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4
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6
7
8
Control period
Intervention period
0Y 1Y
0Y 1Y 2Y 3Y 4Y
0Y 1Y 2Y 3Y 4Y
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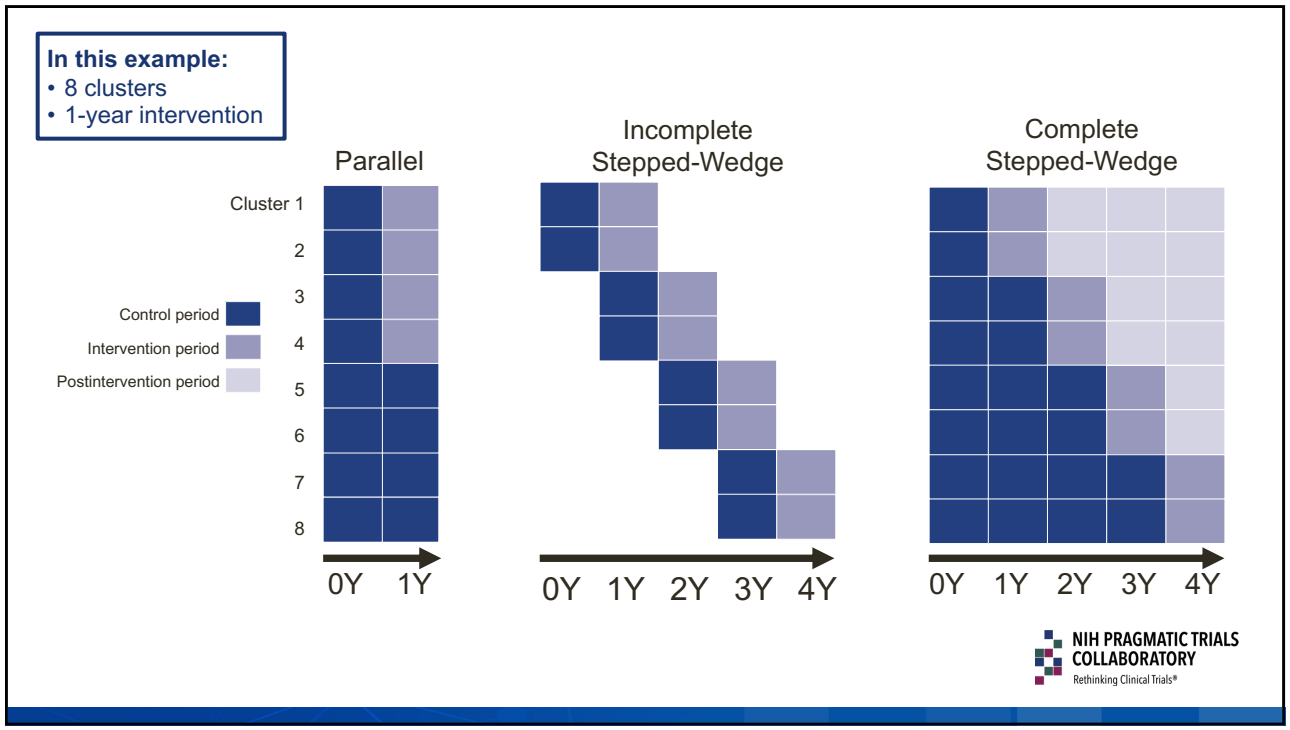

Three kinds of randomized trials

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STOP CRC, an NIH Collaboratory Trial

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

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

Reasons to randomize clusters instead of individuals

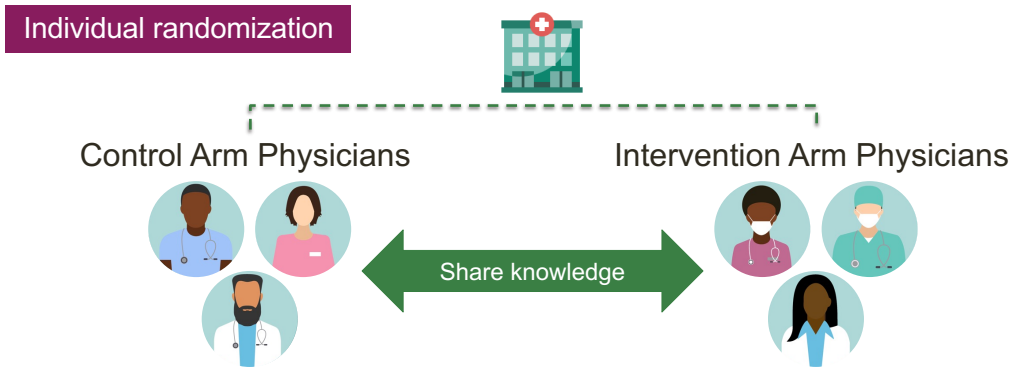
- The intervention targets healthcare units rather than individuals

Healthcare Units

Individuals

Reasons to randomize clusters instead of individuals

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



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Reasons to randomize clusters instead of individuals

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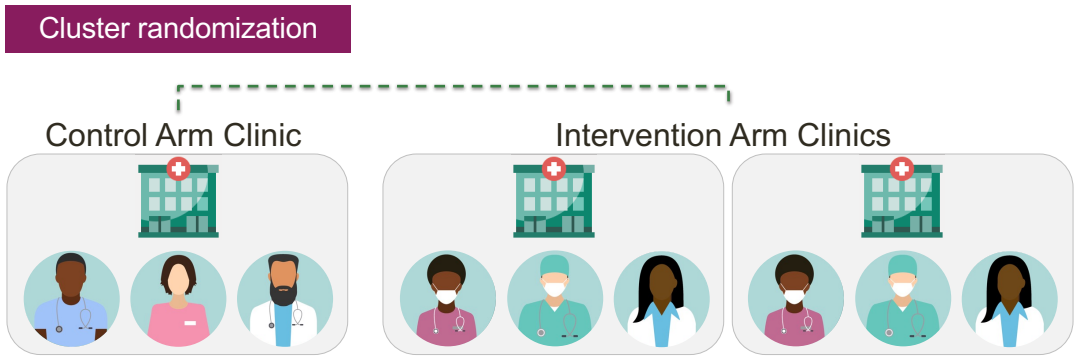

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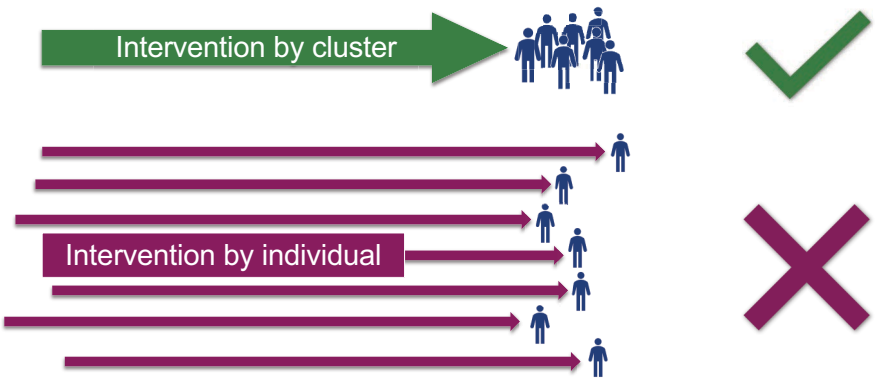
Reasons to randomize clusters instead of individuals

- Logistically easier to implement the intervention by cluster



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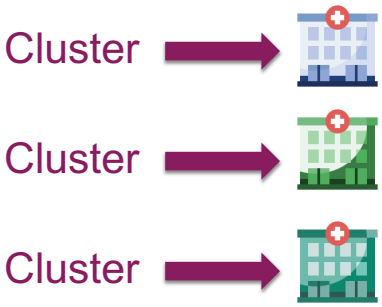
Cluster randomization in the STOP CRC trial

stop screen to prevent colon cancer

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



Level 2

Randomize at the level of the clinic

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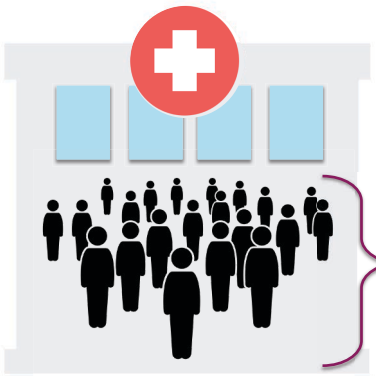
Cluster randomization in the STOP CRC trial

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



Level 1

Patient-level outcomes are nested within the clinic

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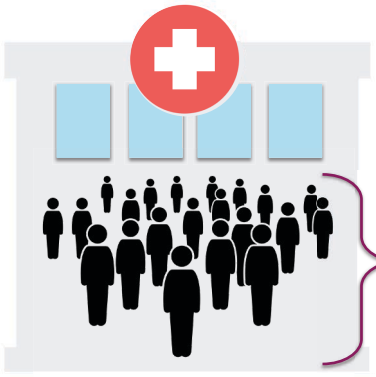
Cluster randomization in the STOP CRC trial

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



STOP CRC outcomes

Did the patients agree to be screened for colorectal cancer?

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stop screen to prevent colon cancer

Individual outcomes within the same clinic are expected to be correlated

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stop screen to prevent colon cancer

Clustering = Outcome Clustering


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes


Outcomes

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stop screen to prevent colon cancer

STOP CRC outcomes

Did the patient agree to be screened for colorectal cancer?

Binary outcome → Yes No

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Three kinds of randomized trials

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

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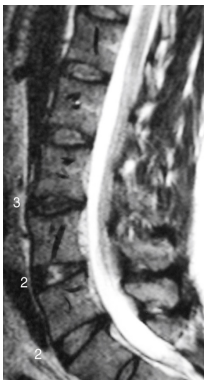
LIRE, an NIH Collaboratory Trial

Lumbar Imaging With Reporting of Epidemiology (LIRE)



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

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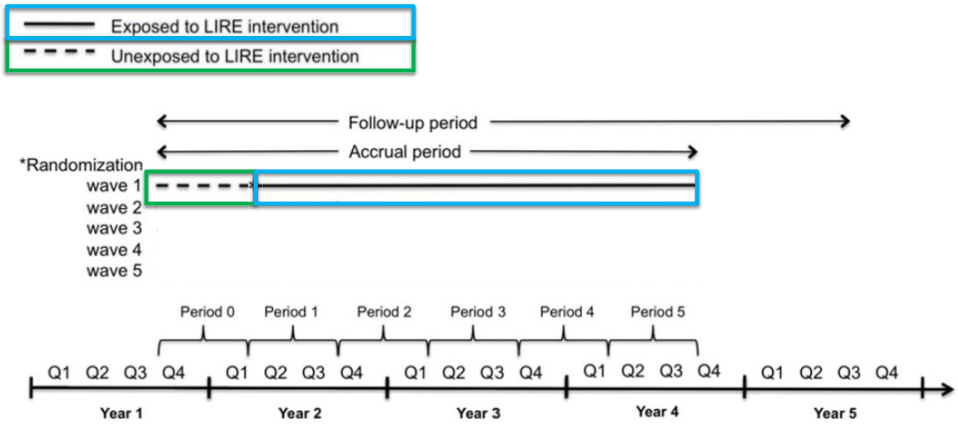
Design of LIRE trial



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

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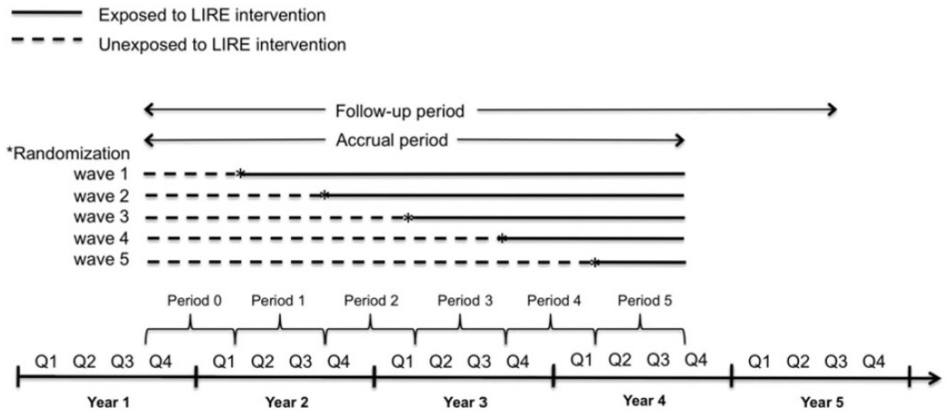
Design of LIRE trial



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

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Analysis Considerations

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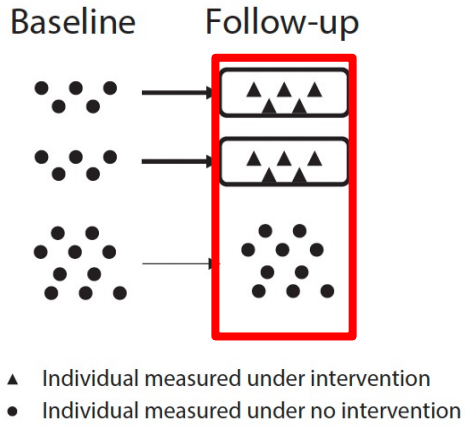
Analysis of IRGT trials



Parallel design

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

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

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Analysis of IRGT trials

- Analyze individual-level data accounting for clustering
  - Random effects or mixed effects models
  - Generalized estimating equations (GEE)
- Considerations on clustering
  - Clustering in both arms: if both conditions group-based and may need different degree of clustering in 2 arms
  - Clustering in intervention arm only: if intervention group-based but control condition not
  - Clustering due to shared agents or group-based intervention delivery often overlooked

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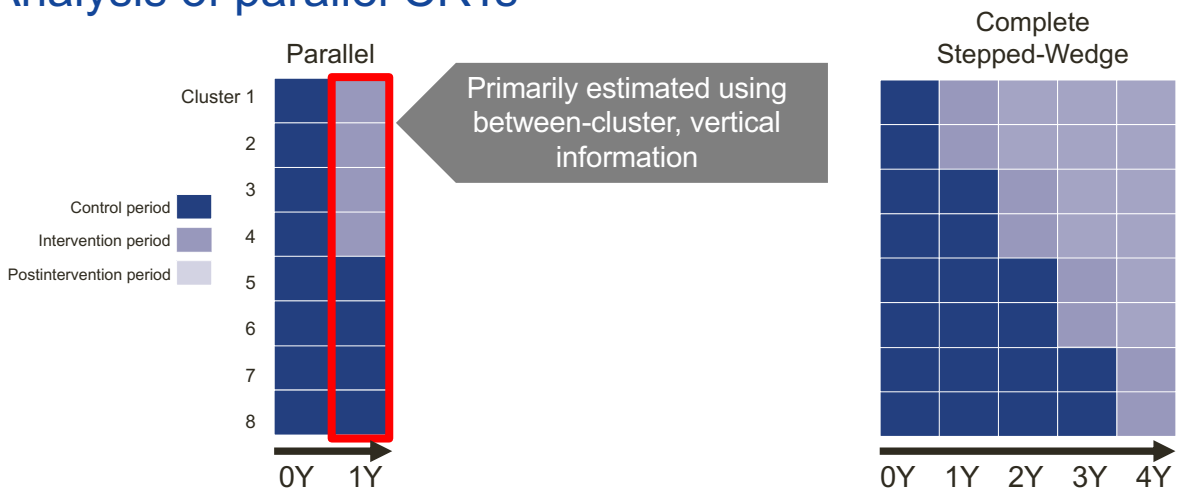
Analysis of parallel CRTs



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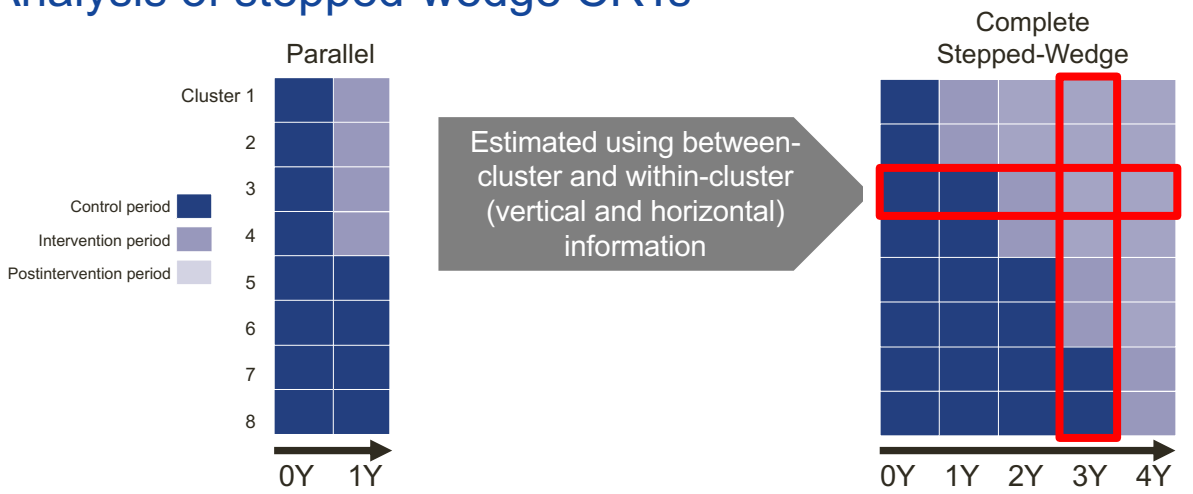
Analysis of stepped-wedge CRTs



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Analysis of IRGT trials and CRTs

- Clustering must be accounted for in analysis
  - Ignoring can lead to inflated Type I error, even with low outcome clustering
    - Type I error rate may be 30%-50% in a CRT
    - Type I error rate may be 15%-25% in an IRGT
- Challenges in “small” trials (fewer than 50 clusters)
  - Intervention effect SE may be underestimated
    - Mixed models: degree of freedom & use of t-test for inference
    - GEE: small sample corrections of SE & use of t-test for inference

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Analytic challenges and trade-offs

- Stepped-wedge designs “roll out” over time and are more susceptible to disruption, and confounding of time and intervention must be accounted for in analysis
- Parallel CRTs are simple and powerful, but still need to address clustering for design and analysis
- IRGT trials designs have benefits of individual-level randomization but still need to address clustering due to shared agents or group-based interventions in design and analysis

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Important things to know about many pragmatic and implementation trials

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

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

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

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Q&A

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Resources

Design and Analysis Considerations

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

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

Key Journal Articles

- Cook AJ, Delong E, Murray DM, Vollmer WM, Heagerty PJ. Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core. *Clin Trials*. 2016 Oct;13(5):504-12. PMID: 27179253.
- Murray DM, Taljaard M, Turner EL, George SM. Essential ingredients and innovations in the design and analysis of group-randomized trials. *Annu Rev Public Health*. 2020 Apr 2;41:1-19. PMID: 31869281.
- Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. *Stat Methods Med Res*. 2021 Feb;30(2):612-639. PMID: 32631142.

- Federico CA, Heagerty PJ, Lantos J, et al. Ethical and epistemic issues in the design and conduct of pragmatic stepped-wedge cluster randomized clinical trials. *Contemp Clin Trials*. 2022 Apr;115:106703. PMID: 35176501.
- Wang X, Turner EL, Li F, et al. Two weights make a wrong: Cluster randomized trials with variable cluster sizes and heterogeneous treatment effects. *Contemp Clin Trials*. 2022 Mar;114:106702. PMID: 35123029.
- Kenny A, Voldal EC, Xia F, Heagerty PJ, Hughes JP. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. *Stat Med*. 2022 Sep 30;41(22):4311-4339. PMID: 35774016.
- Kahan BC, Li F, Copas AJ, Harhay MO. Estimands in cluster-randomized trials: Choosing analyses that answer the right question. *Int J Epidemiol*. 2023 Feb 8;52(1):107-118. PMID: 35834775.
- Brown CH, Hedeker D, Gibbons RD, et al. Accounting for context in randomized trials after assignment. *Prev Sci*. 2022 Nov;23(8):1321-1332. PMID: 36083435.
- Wang X, Turner EL, Li F. Designing individually randomized group treatment trials with repeated outcome measurements using generalized estimating equations. *Stat Med*. 2024 Jan 30;43(2):358-378. PMID: 38009329.

Other Resources

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

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Measuring Effectiveness and Implementation Outcomes

SPEAKER

Angelo Volandes, MD, MPH

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

Measuring Effectiveness and Implementation Outcomes

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Disclosures

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

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Learning goals

- Describe methods for measuring outcomes using real-world data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
- Identify outcomes commonly used in implementation research
- Learn about key issues in measurement of implementation outcomes

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Outcome, measure, endpoint

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

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Types of measures

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

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Outcome, measure, endpoint

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

Examples:

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

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Important things to know

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

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

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

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Choosing and specifying endpoints in ePCTs

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

- Acute myocardial infarction
- Broken bone
- Hospitalization

- Suicide attempts
- Gout flares
- Silent myocardial infarction
- Early miscarriage

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Key questions for choosing endpoints

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

- Does it require hospitalization?
- Is treatment provided in inpatient or outpatient settings?
- Will the event be medically attended?

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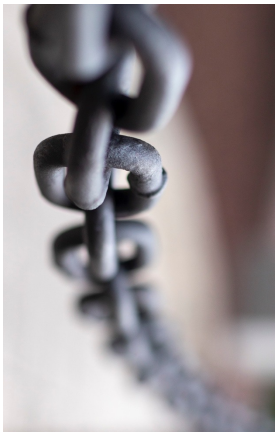
Data sources for endpoints in ePCTs

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



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

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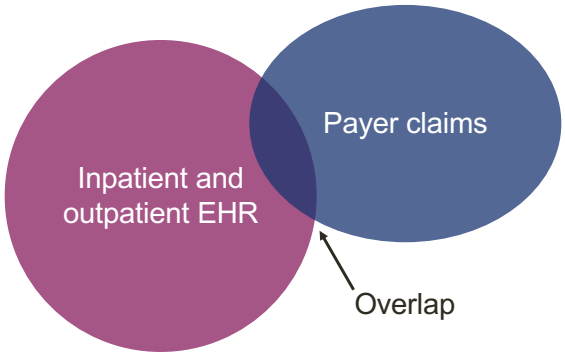
Where is the signal?

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



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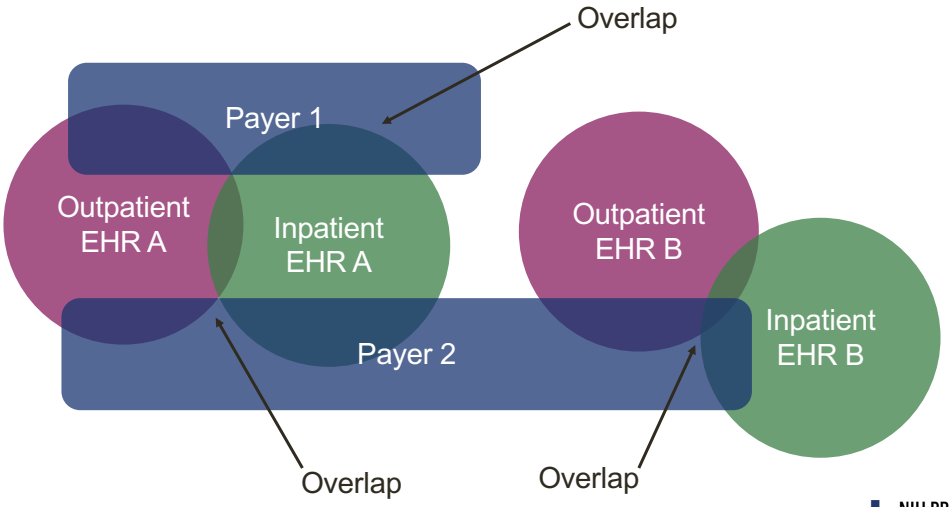
Reality is not straightforward



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Longitudinal data linkage

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

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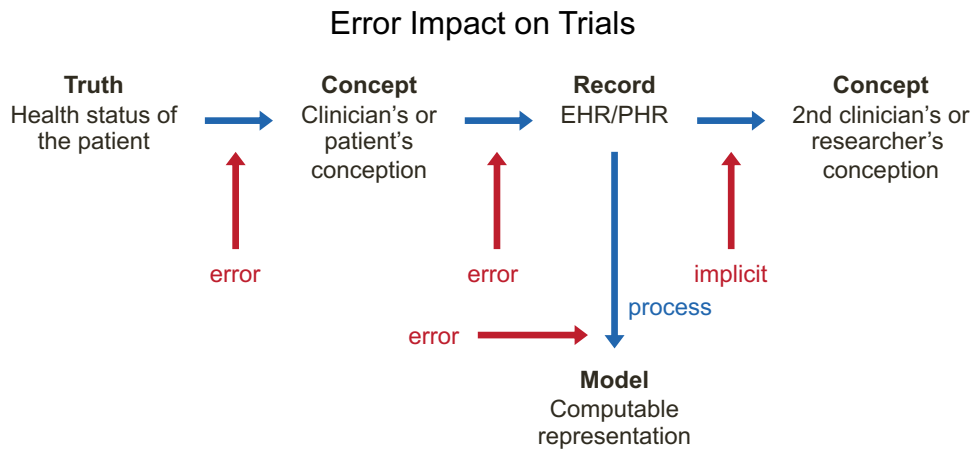
Data is a surrogate for clinical phenomena



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

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Data sources for endpoints in ePCTs

Traditional

- EHR or ancillary health information systems

Complementary

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

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It's a balancing act

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

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

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Outcomes measured via direct patient report

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

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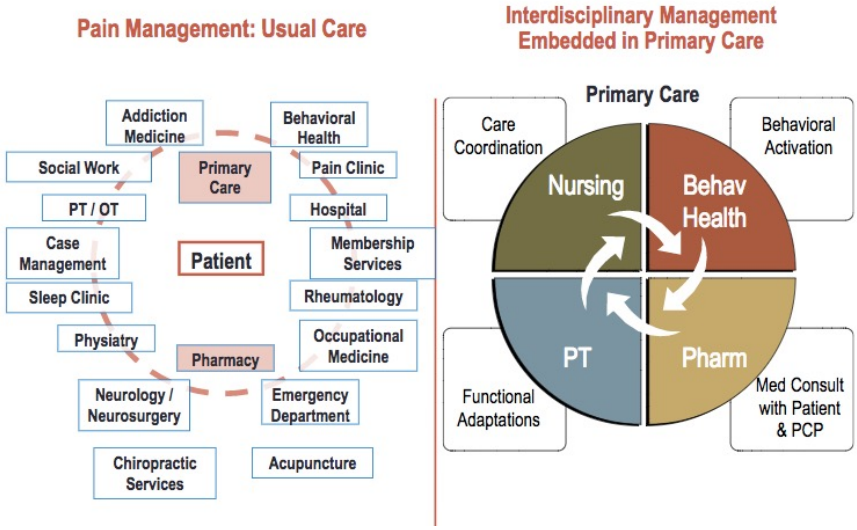
Example: PPACT Trial



Source: Lynn DeBar, Kaiser Permanente Washington Health Research Institute

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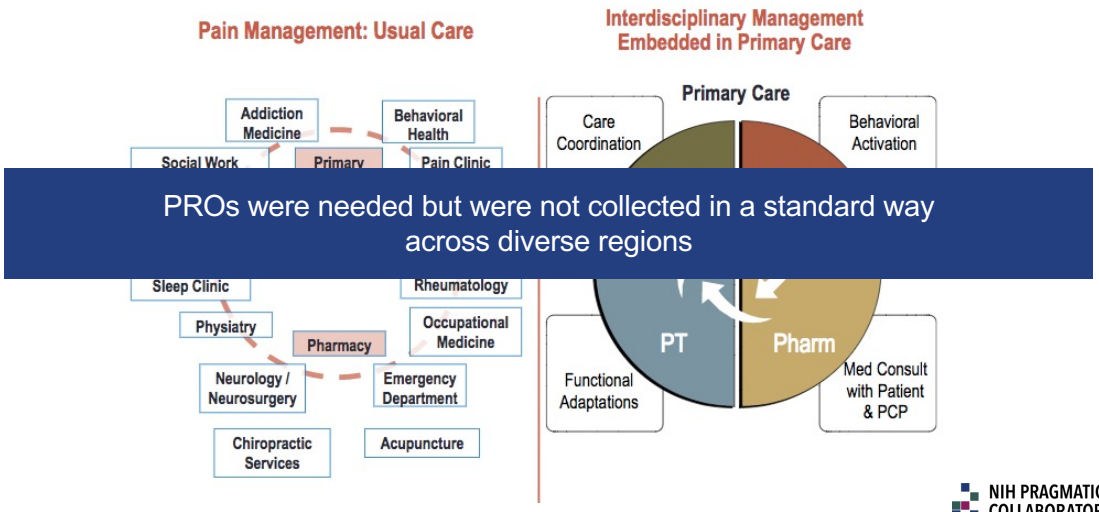
Example: PPACT Trial



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

Source: Lynn DeBar, Kaiser Permanente Washington Health Research Institute

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Example: PPACT Trial

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

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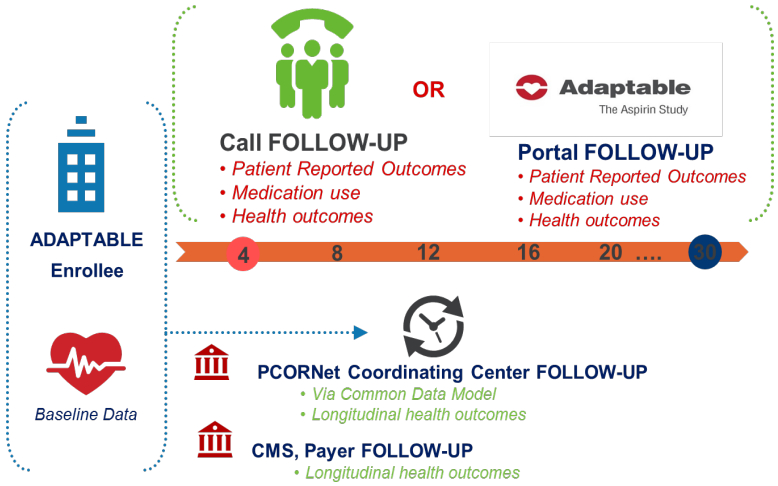
Enabling pragmatic research

E-screening, e-enrollment, and e-follow-up



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Mobile devices for outcome measurement

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

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Data quality assessment

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

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Important things to do

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

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Outcomes and Measurement in Implementation Science

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Implementation science in simpler terms…

- The intervention, practice, or innovation is **the thing**
- Effectiveness research looks at whether **the thing** works
- Implementation research looks at how best to help people/places **do the thing**
- Implementation strategies are the stuff we do to help people/places **do the thing**
- Main implementation outcomes are **how much** and **how well** they **do the thing**

Curran, *Implementation Science Communications*, 2020

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Implementation outcomes

- "The effects of deliberate and purposive actions to implement new treatments, practices, and services."

Proctor, *Adm Policy Ment Health*, 2011

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Implementation outcomes

- "The effects of deliberate and purposive actions to implement new treatments, practices, and services." (implementation strategies)

Proctor, *Adm Policy Ment Health*, 2011

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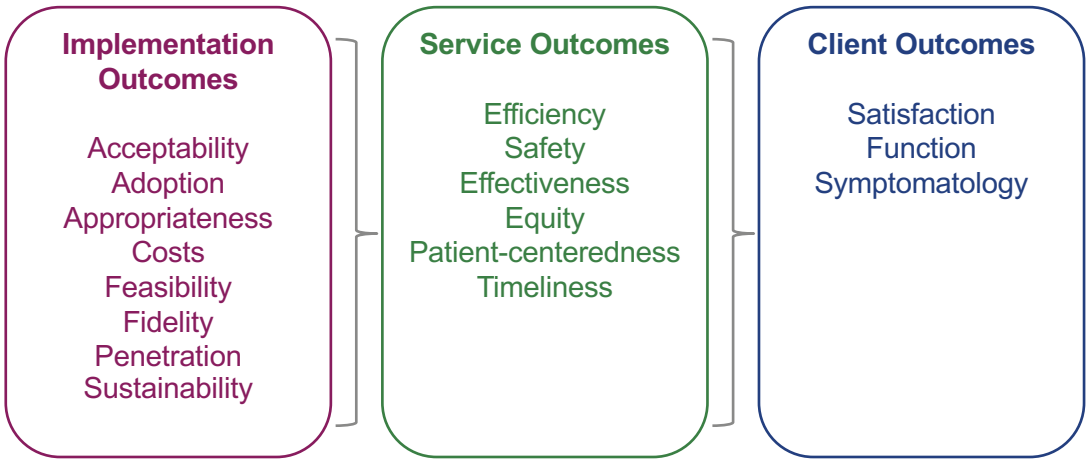
Proctor taxonomy of implementation outcomes



Adapted from Proctor, *Adm Policy Ment Health*, 2011

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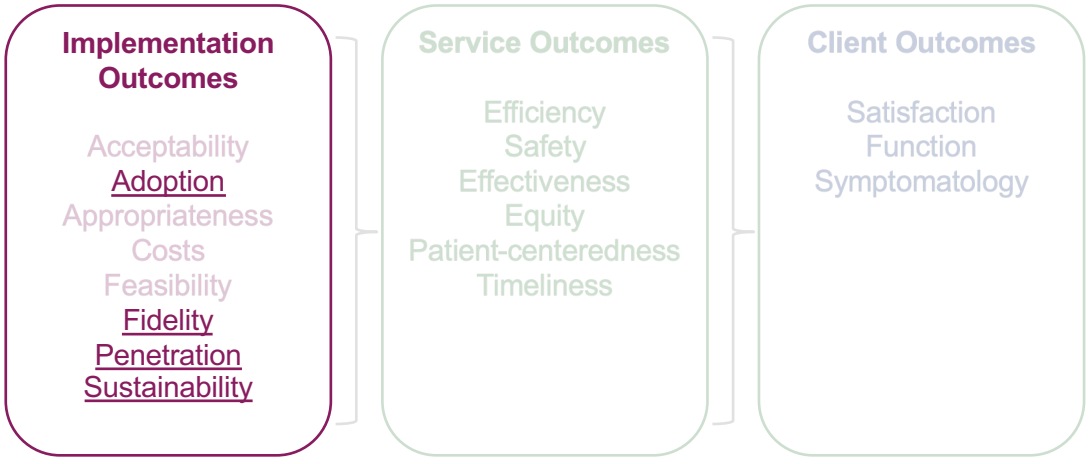

Adapted from Proctor, *Adm Policy Ment Health*, 2011

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Definitions

- **Adoption**: "The intention, initial decision, or action to try or employ an innovation or evidence-based practice."
- **Fidelity**: "The degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the program developers."
- **Penetration**: "Integration of a practice within a service setting and its subsystems. Penetration…can be calculated in terms of the number of providers who deliver a given service or treatment, divided by the total number of providers trained in or expected to deliver the service."
- **Sustainability***: "The extent to which a newly implemented treatment is maintained or institutionalized within a service setting's ongoing, stable operations."

Proctor, *Adm Policy Ment Health*, 2011

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Proctor taxonomy of implementation outcomes

Outcome	Level	Theory	Other terms	Stage	Measurement
Acceptability	Individual provider, patient	"Complexity" from Rogers	Satisfaction	Early	Surveys, interviews
Adoption	Individual provider, org	"Adoption" from RE-AIM	Uptake; utilization; intention to try	Early to mid	Observation, surveys, interviews
Appropriateness	Individual provider, patient, org	"Compatibility" from Rogers	Perceived fit; relevance	Early	Surveys, interviews, focus groups
Feasibility	Individual provider, org	"Compatibility" and "trialability" from Rogers	Practicability	Early	Survey; admin data
Fidelity	Individual provider	"Implementation" from RE-AIM	Delivered as intended; adherence, integrity	Early to mid	Observation; checklist; self-report, admin data
Implementation cost	Provider or org	"Costs" and "resources" from TCU Program Change Model	Marginal cost, cost-effectiveness	Early	Admin data
Penetration	Org	"Reach" from RE-AIM	Spread	Mid to late	Case audit; checklist
Sustainability	Org	"Maintenance" from RE-AIM	Maintenance; integration; institutionalization	Late	Surveys, interviews, checklists

Proctor, *Adm Policy Ment Health*, 2011

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Outcome	Level	Theory	Other terms	Stage	Measurement
Acceptability	Individual provider, patient	"Complexity" from Rogers	Satisfaction	Early	Surveys, interviews
Adoption	Individual provider, org	"Adoption" from RE-AIM	Uptake; utilization; intention to try	Early to mid	Observation, surveys, interviews
Appropriateness	Individual provider, patient, org	"Compatibility" from Rogers	Perceived fit; relevance	Early	Surveys, interviews, focus groups
Feasibility	Individual provider, org	"Compatibility" and "trialability" from Rogers	Practicability	Early	Survey; admin data
Fidelity	Individual provider	"Implementation" from RE-AIM	Delivered as intended; adherence, integrity	Early to mid	Observation; checklist; self-report, admin data
Implementation cost	Provider or org	"Costs" and "resources" from TCU Program Change Model	Marginal cost, cost-effectiveness	Early	Admin data
Penetration	Org	"Reach" from RE-AIM	Spread	Mid to late	Case audit; checklist
Sustainability	Org	"Maintenance" from RE-AIM	Maintenance; integration; institutionalization	Late	Surveys, interviews, checklists

Proctor, *Adm Policy Ment Health*, 2011

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Lewis *et al. Implementation Science* (2015) 10:155
DOI 10.1186/s13012-015-0342-x

IMPLEMENTATION SCIENCE

SYSTEMATIC REVIEW Open Access

Outcomes for implementation science: an enhanced systematic review of instruments using evidence-based rating criteria

Cara C. Lewis[1,2*], Sarah Fischer[1], Bryan J. Weiner[3], Cameo Stanick[4], Mimi Kim[5,6] and Ruben G. Martinez[7]

Evidence-Based Assessment (EBA) rating criteria

- **Reliability (or Internal Consistency)**: Extent to which an instrument consistently measures what it is meant to measure
- **Structural (or Construct) Validity**: Extent to which instrument accurately measures what it is meant to measure
- **Predictive (or Criterion) Validity**: Extent to which a measure is related to an outcome
- **Norms**: An estimate of the position of the tested individual in a predefined population, with respect to construct being measured
- **Responsiveness**: Ability of instrument to detect change over time
- **Usability**: Ease with which instrument can be administered

Lewis, *Implementation Science*, 2015

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Fidelity measures

- Extent to which an intervention is delivered as intended
  - Core intervention components or functions
- Checklists
- Direct observation
- Questionnaires

Lewis, *Implementation Science*, 2015

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Cost

- Costs to deliver an intervention and implementation strategy (direct and/or indirect)
- Cost-effectiveness of an intervention: costs relative to a health outcome (eg, quality-adjusted life years)
- Return on investment: value for money
- Specific algorithms (eg, substance use treatment programs)*

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Penetration

- % of “eligible” or target clinicians who deliver the intervention
- Questionnaires: for example, level of institutionalization scale for health promotion programs

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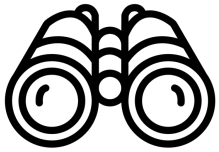
Instrumentation issues revealed



- Minimal psychometric testing, reporting, and strength
- Non-use of theories and frameworks
- Frequent use of home-grown, use-once measures
- Redundant development across teams
- Lack of attention to pragmatic relevance (usability)

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Important things to do

- Look to implementation science protocol papers to see which measures are commonly used
- Increase availability of instruments with promising psychometric properties to further establish their quality
- Work to establish psychometrics of underdeveloped measures
- Engage key partners

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Q&A

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Resources

Measuring Effectiveness and Implementation Outcomes

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

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

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

Key Journal Articles

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

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ePCTs in Context

MODERATOR

Emily C. O'Brien, PhD

Duke University

PANELISTS

Diana Burgess, PhD
Julie M. Fritz, PhD, PT
Vince Mor, PhD
David W. Wetter, PhD, MS

ePCTs in Context

Small Group Work and Panel Discussion With NIH Collaboratory Trial Investigators

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

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Learning goals

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

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NIH Collaboratory Trial panelists

- Diana Burgess, PhD — RAMP
- Julie Fritz, PT, PhD, ATC — BeatPain Utah
- Vince Mor, PhD — PROVEN
- David W. Wetter, PhD — LungSMART

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Small group discussion

- **BeatPain Utah**
  - During pilot phase, COVID-19 pandemic made in-person meetings at partnering clinics impossible and limited the availability of staff to participate in training. How would you implement the e-referral process and ensure the project could reach enough potential participants?
- **LungSMART**
  - Trial requires new practice model for primary care association and community health centers, with liability insurance to be covered by the association and access to EHRs by the registered nurse across multiple community health center systems. How would you overcome this problem?
- **PROVEN**
  - Because of inadequate compliance in the intervention facilities, study team added “personal touch” with monthly calls. Even so, only 30% to 40% of facilities engaged, 30% intermittently engaged, and 20% were noncompliant. How would you address this challenge?
- **RAMP**
  - Changes in partnering healthcare system environment will create challenges in working with stakeholders to cocreate strategies to overcome barriers to national implementation. How would you approach this problem?

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Reflection on today's topics

- ePCTs and hybrid effectiveness-implementation trials
- Design, analysis, and monitoring considerations
- Measuring effectiveness and implementation outcomes

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Resources

ePCTs in Context

- ACP PEACE: Improving Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly
- BeatPain Utah: Nonpharmacologic Pain Management in Federally Qualified Health Centers Primary Care Clinics
- LungSMART: Population Health Management Approaches to Increase Lung Cancer Screening in Community Health Centers
- PROVEN: Pragmatic Trial of Video Education in Nursing Homes
- RAMP: Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole HealthzTelehealth Intervention

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Pilot and Feasibility Testing

SPEAKER

Lanay M. Mudd, PhD

Acting Branch Chief, Clinical Research in Complementary and Integrative Health
Program Director, Division of Extramural Research
National Center for Complementary and Integrative Health (NCCIH)

Pilot & Feasibility Testing

Lanay M. Mudd, PhD
Acting Branch Chief, Clinical Research in Complementary & Integrative Health
Program Director, Division of Extramural Research
National Center for Complementary and Integrative Health (NCCIH)

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Learning goals

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

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Important things to know

Pilot testing the methods increases the likelihood of completing the trial and can prevent silly mistakes

You need a biostatistician in the pilot/feasibility stage

Use the pilot to maximize acceptability, maintain affordability, and consider the scalability of the intervention

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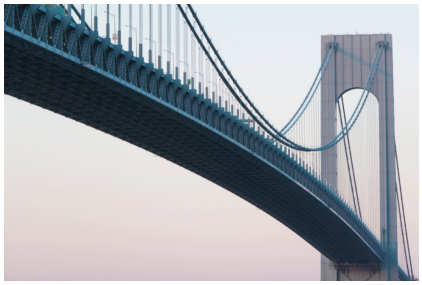
ePCTs are not efficacy trials

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



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During the pilot phase

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

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Build partnerships

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

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Aspects of feasibility that can be piloted

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

Use what you learn to design the ePCT

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Evaluate power calculations

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

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Quantify feasibility for pilot study aims

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

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

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Quantifying example 1

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

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

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Quantifying example 2

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

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

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Quantifying example 3

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

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

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Ensuring trial readiness

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

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Readiness checklist

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

Implementation Readiness Checklist available on the Living Textbook

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In the end, good planning will help

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

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Important things to do

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

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Q&A

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Resources

Pilot and Feasibility Testing

Living Textbook Readings

- Assessing Feasibility
- Implementation Readiness Checklist

Rethinking Clinical Trials Grand Rounds Webinars

- ICD-Pieces: From Planning to Performance (Miguel A. Vazquez, MD)
- Who to Include in a Pragmatic Trial? It Depends (Greg Simon, MD, MPH; Laura Dember, MD)

Key Journal Articles

- Tuzzio L, Meyers CM, Dember LM, et al. Accounting for quality improvement during the conduct of embedded pragmatic clinical trials within healthcare systems: NIH Collaboratory case studies. *Healthc (Amst)*. 2021 Jun;8 Suppl 1(Suppl 1):100432. PMID: 34175091.
- Hubbard G, O'Carroll R, Munro J, et al. 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: Findings from a pilot trial of cardiac rehabilitation versus usual care (no rehabilitation) with an embedded qualitative study. *Pilot Feasibility Stud*. 2016 Aug 24;2:51. PMID: 27965868.
- Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res*. 2011 May;45(5):626-9. PMID: 21035130.

Other Resources

- Pilot and Feasibility Testing: The LIRE Example

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Ethical and Regulatory Considerations and Posttrial Obligations

SPEAKER

Stephanie R. Morain, PhD

PhD Program Director and Dracopoulos Rising Professor in Bioethics
Johns Hopkins Berman Institute of Bioethics

Ethical & Regulatory Considerations and Posttrial Obligations

Stephanie Morain, PhD, MPH
PhD Program Director and Dracopoulos Rising Professor in Bioethics
Johns Hopkins Berman Institute of Bioethics

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Learning goals

- Learn about recurring and emerging ethical and regulatory issues in ePCTs
- Understand posttrial obligations related to dissemination, sustainment, and deimplementation
- Discuss ethical considerations for sharing aggregate results

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Important things to know

Ethical analysis for ePCTs is (still) a work in progress

Federal and local policies and their operationalization regarding oversight of ePCTs are in flux

There is often confusion and misunderstanding about ePCTs on the part of patient-subjects, providers, IRBs, and DSMBs

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ePCTs are motivated by ethical imperatives

They also raise interesting ethical and regulatory questions

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Evolving understanding of ethical and regulatory issues

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

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Article

CLINICAL TRIALS

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Exploring the ethical and regulatory issues in pragmatic clinical trials

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

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

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

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Evolving understanding of ethical and regulatory issues

- **Informed consent**
- Data monitoring
- Defining minimal risk
- Distinction between research and quality improvement
- Vulnerable subjects
- IRB harmonization
- **Data sharing**
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
- Management of collateral findings
- **Posttrial obligations**
- ….

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Informed Consent, Waivers & Alterations

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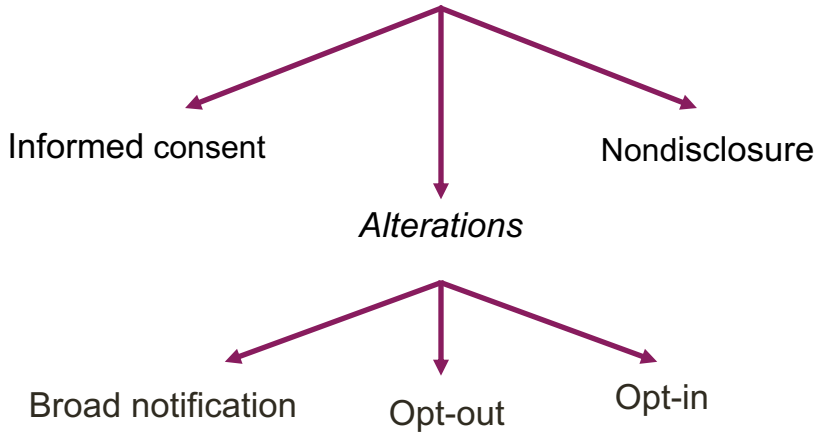
Approaches to notification and authorization



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Knowledge checkpoint

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

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Knowledge checkpoint

- Which of the following is NOT an acceptable justification for waiving or altering informed consent?
  a. Research involves no more than minimal risk
  b. Research could not practicably be carried out without the waiver or alteration
  c. Refusals to participate could bias the study results
  d. Waiver or alteration will not adversely affect the rights and welfare of the subject

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Criteria for waiver or 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/alteration will not adversely affect rights and welfare of subject
- Where appropriate, subjects will be provided with additional information about their participation

Common Rule: 45 CFR 46.116(f)

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Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

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

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Distinguishing research risks

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

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Regulatory permissible ≠ ethically optimal

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

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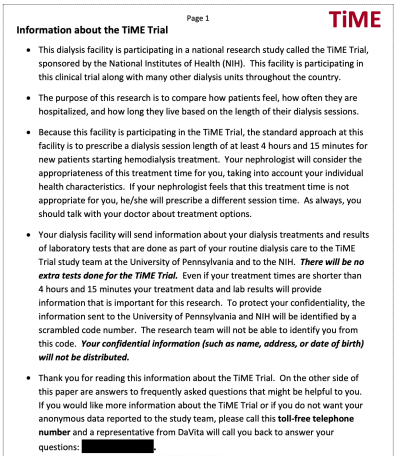
Examples: Information sheets or flyers

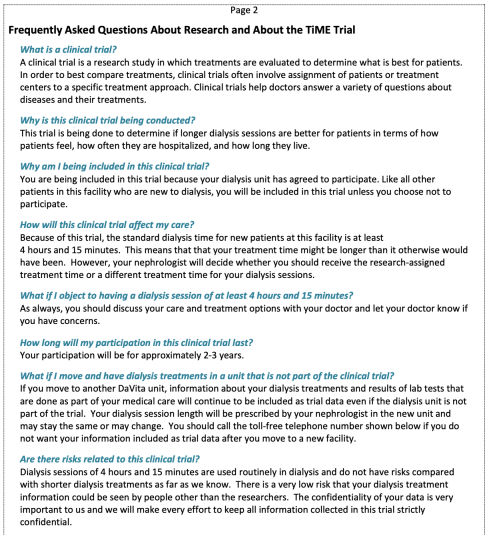


Page 1

TiME

Information about the TiME Trial

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



Page 2

Frequently Asked Questions About Research and About the TiME Trial

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

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

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

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

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

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

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

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

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Knowledge checkpoint

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

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Data Sharing & PCTs

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Increasing expectation for sharing clinical trials data

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Challenges for sharing PCT data

Often conducted with waivers or alterations of informed consent

Use of extant data (eg, EHR, claims)

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If PCT uses a waiver or alteration of consent…

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

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

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Implications of embeddedness for PCT data sharing

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

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Recommendations for PCT data sharing

- Consider interests of those beyond patient-subjects
- Proactively engage health system partners, other data partners & funders in decision-making about data sharing

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Sharing Aggregate Results

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Ethical arguments for sharing aggregate results

- Respect and reciprocity
- Promoting participant trust and research(er) trustworthiness

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Countervailing considerations

- Lesser risks/burdens of research → reduced obligations to share?
- Consequentialist-based considerations
- Logistical and practical barriers to sharing
- Privacy and confidentiality considerations

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Recommendations for sharing aggregate results

- Sharing aggregate results should be the presumptive default
- Planning for aggregate results sharing should begin at the earliest phases of research and be incorporated into study protocols, funding applications, IRB applications, and, where appropriate, informed consent processes
- Healthcare system partners have a key role in decision-making about and implementation of sharing aggregate results
- PCTs conducted with a waiver of consent involve special considerations

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Posttrial Obligations in PCTs

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Posttrial obligations in explanatory clinical trials

- Existing scholarship and research ethics guidelines are largely focused on posttrial access to study medications or interventions

Declaration of Helsinki

"Sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial."

Council for International Organizations of Medical Sciences (CIOMS)

Researchers and sponsors should make plans for "providing continued access to study interventions that have demonstrated significant benefit."

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Ethical arguments for posttrial obligations

- Avoid exploitation
- Respect and reciprocity
- Preventing harm
- Social value

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Considerations for posttrial obligations in PCTs

- Lower-risk interventions, fewer (individual-level) burdens – but potentially obligations owed to those beyond individual participants?
- Interventions delivered by and within healthcare delivery systems—healthcare systems must be key partners in fulfilling post-trial obligations
- Ethical presumption that practice/operations should change in light of PCT results
- Existing guidance focuses on successful interventions, but should also address *de*implementation

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Q&A

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Resources

Ethical and Regulatory Considerations and Posttrial Obligations

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

- Data and Safety Monitoring in Pragmatic Clinical Trials (Greg Simon, MD, MPH)
- The DSMB Role in Pragmatic Trials: NIMH Progress and Challenges (Galia Siegel, PhD; Anna Ordonez, MD, MAS; Scott Kim, MD, PhD; Kate Comtois, PhD, MPH)
- A Tentative Introduction to the Revised Common Rule for the Protection of Human Subjects (Jeremy Sugarman, MD, MPH, MA)
- Comparison of Different Approaches for Notification and Authorization in Pragmatic Clinical Research Evaluating Commonly Used Medical Practices (Kevin P. Weinfurt, PhD)
- Recommendations From the Clinical Trials Transformation Initiative's Data Monitoring Committee ProjectMonitoring Committee Project (Karim Anton Calis, PharmD, MPH; Ray Bain, PhD; Dave DeMets, PhD)
- Research on Medical Practices (Benjamin Wilfond, MD; David Magnus, PhD)
- Privacy and Confidentiality in Pragmatic Clinical Trials (Alan Rubel, PhD, JD)
- FDA and Pragmatic Clinical Trials of Marketed Medical Products (Monique Anderson, MD, MHS)
- Oversight on the Borderline (Jonathan Finkelstein, MD, MPH)

- Altered Informed Consent in Pragmatic Clinical Trials (Ross McKinney Jr, MD)
- Considerations in the Evaluation and Determination of Minimal Risk in Research Studies (John Lantos, MD)
- Ethical Responsibilities Toward Indirect and Collateral Participants in Pragmatic Clinical Trials (PCTs) (Jaye Bea Smalley, MPA)

Key Journal Articles

- Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. *JAMA*. 2014 Jun 18;311(23):2381-2. PMID: 24810723.
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Engaging and Aligning With Health System and Community Partners

SPEAKER

Hayden B. Bosworth, PhD

Professor in Population Health Sciences
Duke University

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Disclosures

- Hayden Bosworth reports research funding through his institution from BeBetter Therapeutics, Boehringer Ingelheim, Esperion, Improved Patient Outcomes, Luminate Insights, Merck, Cleery, NHLBI, Novo Nordisk, Otsuka, Sanofi, Veterans Administration, Elton John Foundation, Hilton foundation, Pfizer.
- He also provides consulting services for Boehringer Ingelheim, Esperion, Elevance Health, Sanofi, Walmart, Webmed, Janssen. He was also on the board of directors of Preventric Diagnostics.

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Learning goals

- Describe individuals to engage as partners and approaches for engaging them through all phases of the study
- Identify the skills and qualities of a strong study team
- Understand the priorities of healthcare system leaders and how to obtain their support
- Identify engagement practices to obtain patient and community perspectives

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Approaching partners in traditional clinical trials

Researcher reviews the literature

↓

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

↓

Researcher designs and conducts study, prepares manuscripts

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ePCTs work differently.

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Listen to the frontline

> *The purpose of the healthcare system is not to do research, but to provide good healthcare. Researchers often have a tail-wagging-the-dog problem… We need to remember that we're the tail and the healthcare system is the dog.*

—Greg Simon, MD, MPH (SPOT)

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Important things to know

Start engagement early, and engage partners continuously

Be patient: Relationships take time to build and nurture

Expect changes and disruptions

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

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

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

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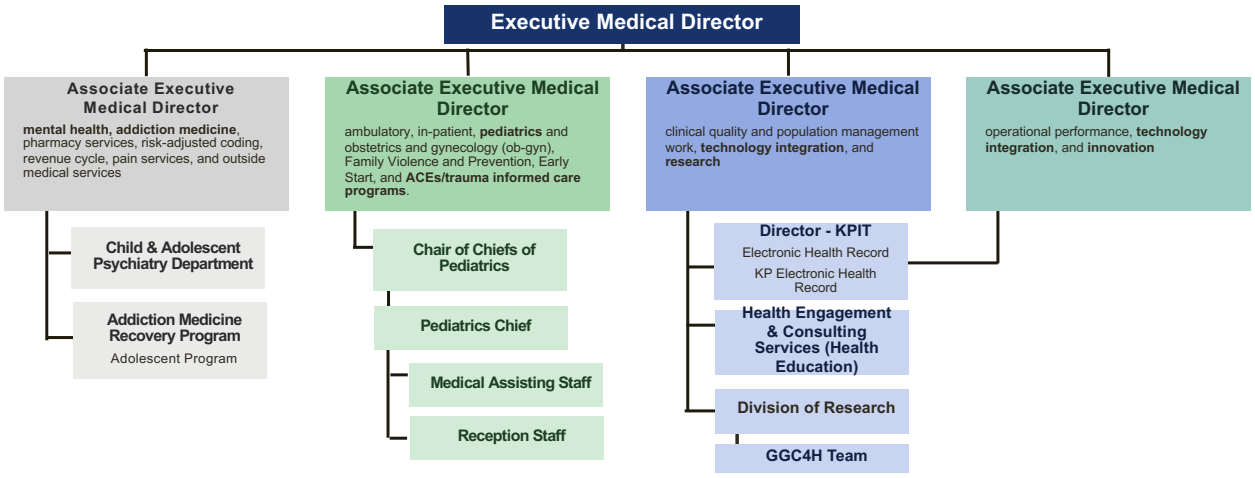
Kaiser Permanente Northern California



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

Roles of partners

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

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Roles of partners

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

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Choose a salient question

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

Source: Greg Simon, MD, MPH

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Design the intervention for sustainment

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Design the intervention to minimize burden for patients and clinicians

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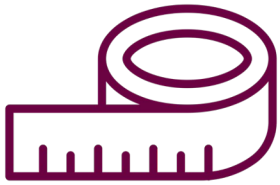
Select outcome measures



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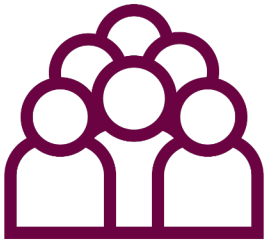
Determine inclusion and exclusion criteria



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Roles of partners

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

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Develop recruitment strategies

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Example: Community advisory board

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

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Example: Patient advisory panel

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

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Serve as study champions

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Track challenges and adaptations

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Interpret study results

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Roles of partners

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

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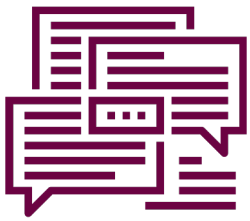
Determine key messages for different groups and identify avenues for dissemination



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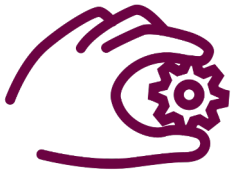
Support implementation or deimplementation



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Consider changes to policies and guidelines

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Important things to do

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

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Q&A

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Knowledge checkpoint

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

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Resources

Engaging and Aligning With Health System and Community Partners

Living Textbook Readings

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

Rethinking Clinical Trials Grand Rounds Webinars

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

Key Journal Articles

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Other Resources

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

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Posttrial Sustainment or Deimplementation of Study Interventions

SPEAKER

Vince Mor, PhD

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

Posttrial Sustainment or Deimplementation of Study Interventions

Vincent Mor, PhD
Brown University

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Learning goals

- Identify factors influencing sustainment and deimplementation of study interventions
- Discuss strategies to assist investigators and research partners with posttrial interpretation and sustainment/deimplementation considerations

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Sustainment factors for pragmatic trial interventions

Factors Affecting Post-trial Sustainment or De-implementation of Study Interventions: A Narrative Review

Terren Green, BA[1], Hayden B. Bosworth, PhD[1,2,3,4], Gloria D. Coronado, PhD[5], Lynn DeBar, PhD, MPH[6], Beverly B. Green, MD, MPH[6], Susan S. Huang, MD, MPH[7], Jeffrey G. Jarvik, MD, MPH[8], Vincent Mor, PhD[9], Douglas Zatzick, MD[10], Kevin P. Weinfurt, PhD[1,2], and Devon K. Check, PhD[2]

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ABSTRACT

In contrast to traditional randomized controlled trials, embedded pragmatic clinical trials (ePCTs) are conducted within healthcare settings with real-world patient populations. ePCTs are intentionally designed to align with health system priorities leveraging existing healthcare system infrastructure and resources to ease intervention implementation and increase the likelihood that effective interventions translate into routine practice following the trial. The NIH Pragmatic Trials Collaboratory, funded by the National Institutes of Health (NIH), supports the conduct of large-scale ePCT Demonstration Projects that address major public health issues within healthcare systems. The Collaboratory has a unique opportunity to draw on the Demonstration Project experiences to generate lessons learned related to ePCTs and the dissemination and implementation of interventions tested in ePCTs. In this article, we use case studies from six completed Demonstration Projects to summarize the Collaboratory's experience with post-trial interpretation of results, and implications for sustainment (or de-implementation) of tested interventions. We highlight three key lessons learned. First, ineffective interventions (i.e., ePCT is null for the primary outcome) may be sustained if they have other measured benefits (e.g., secondary outcome or ePCTs: (1) include secondary outcome measures that are salient to health system partners; (2) collect all appropriate data to allow for post hoc analysis of subgroups; (3) collect experience data from clinicians and staff; (4) engage policymakers before starting the trial.

KEY WORDS: embedded pragmatic clinical trials; de-implementation; implementation; post-trial decisions

J Gen Intern Med
DOI: 10.1007/s11606-023-08593-7

INTRODUCTION

Traditional randomized controlled trials (RCTs) are conducted outside of standard patient care. This separation of research from clinical practice slows the translation of effective research-tested interventions into real-world practice settings.[1] The time lag between RCT completion and implementation of an effective intervention averages 17 years.[2]

In contrast to traditional or explanatory RCTs, embedded pragmatic clinical trials (ePCTs) are conducted with real-world patient populations and within healthcare settings.

Evaluated experiences in 6 diverse NIH Collaboratory Trials

Green et al. J Gen Intern Med 2024

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Trials overview

Trial name	Focus	Results	Intervention status posttrial
ABATE Infection	Evaluate chlorhexidine bathing + mupirocin vs regular soap to reduce bloodstream infection in hospitalized patients	**Null**	**Sustained** for those with medical devices in HCA **Spread** to other systems via partnership with AHRQ
LIRE	Evaluate impact of including standard epidemiologic information in lumbar spine imaging reports to reduce spine-related healthcare utilization after imaging	**Null**	**Sustained** in 2 of 4 health systems
PPACT	Test the use of CBT interventions in primary care settings to improve chronic pain for patients on long-term opioid therapy	**Positive**	**Modified sustainment** of less resource-intense versions of the intervention
PROVEN	Test the effectiveness of an advanced care planning video program to reduce hospital transfers and increase hospice enrollment in nursing home residents	**Null**	**Sustained** in a quarter to a third of facilities with engaged champions and staff members
STOP CRC	Evaluate an EHR-embedded outreach program to improve colorectal cancer screening rates	**Positive**	**Sustained** in 22 of 26 health systems Spread throughout multiple states and hundreds of clinics
TSOS	Test the effectiveness of early interventions for traumatically injured patients with PTSD	**Positive** at 6 but not 12 mos	**Minimal sustainment** in small number of sites **Spread** to other trauma centers via partnership with ACS Committee on Truam

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Sustainment factors in NIH Collaboratory Trials

- Benefits outside of the primary outcome
  - Benefit for a subgroup
  - Benefit for a secondary outcome
  - Benefits for clinicians
- Intervention resource-intensiveness
- Alignment with policy incentives or requirements

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Benefit for a subgroup: ABATE Infection

ABATE Infection Project

- Intervention did not significantly reduce multidrug-resistant bacteria or bloodstream infection in overall study population
- In post hoc subgroup analysis of patients with medical devices, intervention was associated with significant reductions in multidrug-resistant bacteria cultures and bloodstream infections
- **Sustainment factor**: Subgroup represented 10% of study population but accounted for 56% of all bloodstream infections and 37% of multidrug-resistant bacteria cultures
- **Sustainment/spread**: Health system (1) deimplemented protocol as universal practice; (2) sustained protocol for patients with devices in participating hospitals; (3) implemented protocol for patients with devices in all other health system hospitals

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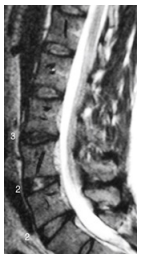
Benefit for a secondary outcome: LIRE



- Intervention did not reduce spine-related healthcare utilization
- In prespecified secondary analysis, intervention slightly reduced subsequent opioid prescriptions
- **Sustainment factors**:
  - Benefit of reduced opioid prescriptions
  - No additional resources required to sustain intervention
  - Clinician feedback suggested other potential benefits (eg, better communication with patients)
- **Sustainment/spread**: After the trial, 2 of the 4 health systems sustained the intervention based in part on its potential to reduce opioid prescriptions

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Benefits for clinicians: PROVEN

PROVEN
PRagmatic Trial of Video Education in Nursing Homes

- Intervention did not significantly reduce hospital transfers from nursing homes or secondary outcomes
- In post hoc analyses, intervention facilities increased documentation of advance directives and reduced burdensome hospital transfers for patients at end of life
- Process evaluations found higher implementation rates at facilities with good staff engagement and personal investment in advance care planning
- **Sustainment factors**: Staff interest, low cost, potential subgroup benefits
- **Sustainment/spread**: Facilities with engaged champions and receptive staff were encouraged by clinic leaders to continue offering intervention videos, leading to adoption into regular practice in one-quarter to one-third of intervention facilities

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Resource-intensiveness: PPACT

- Intervention modestly reduced pain, pain-related disability, and use of benzodiazepines; and reduced healthcare costs overall, cost per QALY, and cost per responder
- **Sustainment factors**: Upfront staffing costs and feasibility; shift in health system priorities; delay in cost-effectiveness analysis outcomes, precluding their consideration at time of sustainment decisions
- **Sustainment/spread**:
  - All health systems adopted pain measure for routine assessment of patients with chronic pain on long-term oxygen therapy
  - One system discontinued intervention entirely
  - Two systems attempted to sustain less intensive versions of intervention; sustainment waned after monthly support calls from study team ended and behavioral health staffing challenges arose

Alignment with policy incentives: STOP CRC

- Intervention clinics had higher proportion of participants who completed fecal immunochemical test (FIT) and any colorectal cancer (CRC) screening
- Higher rates of clinic-level implementation were associated with higher rates of FIT completion
- **Sustainment factors**:
  - Oregon Medicaid adopted CRC screening as incentivized quality metric
  - Commercial insurers began covering recommended follow-up after positive FIT, reducing structural barriers to screening and supporting continued use of FIT as initial screening option
- **Sustainment/spread**:
  - Sustainment in 22 of 26 participating health systems; new uptake by 19 additional sites in these systems
  - State health department contracts with CDC supported spread to 154 clinics in Oregon, Washington, and California
  - CDC funding facilitated dissemination through 2 Medicaid health plans to >500 clinics in Washington and Oregon
  - Intervention has spread to other states through health centers' networks

Alignment with policy incentives: TSOS

- Intervention significantly reduced in PTSD symptoms among trauma patients at 6 months but not 12 months, with greater treatment effects among patients with higher baseline PTSD risk
- **Sustainment factors**: Primary goal of trial was to bring evidence-based recommendations to ACS Committee on Trauma to facilitate guidance development and policy change; investigators presented key partner first-hand accounts and study results to the committee
- **Sustainment/spread**: TSOS results were one element among multiple factors catalyzing the ACS Committee on Trauma to require protocols at all level I and II trauma centers to screen, identify, and refer patients at high risk for PTSD after injury

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Nuanced factors in sustainment

Clinician's Role	Facility-Level Variation	Resource-Intensive	Healthcare Policy	Secondary Analyses
Clinicians' experiences and beliefs impact sustainment decisions Valuable insights, especially in contexts with high burnout	Variation in implementation during trials raises questions about sustainment (complexity a factor) Degree to which intervention fits with the infrastructure of its target setting	Staffing requirements can limit sustainment Cost-effectiveness analysis often completed after sustainment decisions = misalignment	Policy changes external to health systems drove sustainment for some trials Importance of engaging policymakers	Benefits for subgroup of patients or secondary outcomes led to partial sustainment

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Important things to do

- Include secondary outcome measures that are salient to health system partners
- Collect all appropriate data to allow for post hoc analysis of subgroups
- Collect experience data from clinicians and staff
- Engage policy-makers before starting the trial

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Q&A

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Resources

Posttrial Sustainment or Deimplementation of Study Interventions

Living Textbook Readings

- End-of-Trial Decision-Making

Rethinking Clinical Trials Grand Rounds Webinars

- Adoption, Implementation and Sustainment of Family-focused Prevention in Health Care Systems: How Do We Get There? (Margaret Kuklinski, PhD; Stacy Sterling, DrPH, MSW)

Key Journal Articles

- Morain SR, O'Rourke PP, Ali J, et al. Post-trial responsibilities in pragmatic clinical trials: Fulfilling the promise of research to drive real-world change. *Learn Health Syst*. 2024 Mar 6;8(3):e10413. PMID: 39036536.
- Green T, Bosworth HB, Coronado GD, et al. Factors affecting post-trial sustainment or de-implementation of study interventions: A narrative review. *J Gen Intern Med*. 2024 May;39(6):1029-1036. PMID: 38216853.

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ePCTs in Context

MODERATOR

Stephanie R. Morain, PhD

Johns Hopkins University

PANELISTS

Diana Burgess, PhD
Julie M. Fritz, PhD, PT
Angelo Volandes, MD, MPH
David W. Wetter, PhD, MS

ePCTs in Context

Small Group Work and Panel Discussion With NIH Collaboratory Trial Investigators

Moderator:
Stephanie R. Morain, PhD
PhD Program Director and Dracopoulos Rising Professor in Bioethics
Johns Hopkins Berman Institute of Bioethics

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Learning goals

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

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NIH Collaboratory Trial panelists

- Diana Burgess, PhD — RAMP
- Julie Fritz, PT, PhD, ATC — BeatPain Utah
- Angelo Volandes, MD, MPH — ACP PEACE
- David W. Wetter, PhD — LungSMART

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Small group discussion

- **ACP PEACE**
  - Trial revealed some participating health systems have not established a method for patients to opt out of having their deidentified data used for research purposes. How would you approach this problem?
- **BeatPain Utah**
  - Pilot phase showed that patients receiving care in federally qualified health center clinics had less predictable work hours, multigenerational homes or housing instability, and limited technology to use for video visits. What strategies would you use to overcome these obstacles?
- **LungSMART**
  - Project requires data sharing, access to EHRs and e-referral systems, closing the loop between screening facilities and community health centers, and shared understanding and implementation of "patient consent." How would you approach bridging all of these issues and establishing the deep sense of trust needed to make this work?
- **RAMP**
  - Stakeholder engagement revealed contextual factors likely to impact dissemination and implementation, especially those related to changes in VA policies, leadership, and workforce. How would you approach this problem?

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Reflection on today's topics

- Pilot and feasibility testing
- Ethical and regulatory considerations and posttrial obligations
- Engaging with health systems and community partners to plan for dissemination
- Posttrial sustainment or deimplementation of study interventions

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Resources

ePCTs in Context

- ACP PEACE: Improving Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly
- BeatPain Utah: Nonpharmacologic Pain Management in Federally Qualified Health Centers Primary Care Clinics
- LungSMART: Population Health Management Approaches to Increase Lung Cancer Screening in Community Health Centers
- PROVEN: Pragmatic Trial of Video Education in Nursing Homes
- RAMP: Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole HealthzTelehealth Intervention

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Writing a Compelling Grant Application

SPEAKER

Beda Jean-Francois, PhD

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

Writing a Compelling Grant Application

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Learning goals

- Learn how to develop a compelling grant application for a pragmatic trial
- Tips from NIH Collaboratory Trial PIs

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Important things to know

Online resources are available for development of pragmatic trial grant applications

NIH continues to update policies and forms related to clinical trial grant applications

Some things, such as milestones and safety monitoring, may be negotiable around the time of an award

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National Institutes of Health

NIH
National Institutes of Health

- NIH is made up of 27 institutes and centers, or ICs and the Office of the Director (OD)
- ICs award > 80% of the NIH budget each year for research studies
- Each IC has a budget and a director.

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Find the right NIH program official

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

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Matchmaker results (example)

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

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Find the right NOFO

Resource: NIH Guide for Grants and Contracts | Grants & Funding

- Highlighted Topics (HT)
- Types of NOFOs
  - ❑ 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
  - ❑ Program Announcement (PA, PAS, PAR)
    - For an area of scientific interest for one or more ICs where investigator-initiated research is needed

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NIH scientific contacts

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

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Tailor the application

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

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Common application pitfalls

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

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Application dos

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

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Application don’ts

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

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Strategies for success

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

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NIH online resources

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

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

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Design Studies with Generalizability in Mind

- Additional considerations for NIH funded grants:
  - **Inclusion of women and members of minoritized groups as participants is compulsory for NIH-funded clinical research grants.**
  - **Inclusion of participants across the lifespan has been compulsory for NIH-funded clinical research grants since 2019.**

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Important things to do

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

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Tips from NIH Collaboratory Trials

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

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Q&A

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Resources

Writing a Compelling Grant Application

Living Textbook Readings

- Embedded ePCT Team Composition
- Developing a Compelling Grant Application
- Developing the Trial Documentation

Key Journal Articles

- Johnson KE, Tachibana C, Coronado GD, et al. A guide to research partnerships for pragmatic clinical trials. *BMJ*. 2014 Dec 1;349:g6826. PMID: 25446054.
- Dolor RJ, Schmit KM, Graham DG, Fox CH, Baldwin LM. Guidance for researchers developing and conducting clinical trials in practice-based research networks (PBRNs). *J Am Board Fam Med*. 2014 Nov-Dec;27(6):750-8. PMID: 25381071.

Other Resources

- NIH Reporter
- NIH Stage Model for Behavioral Intervention Development
- Health Care Systems Research Network
- Clinical Trial-Specific Funding Opportunities
- Clinical Trial-Specific Review Criteria
- Clinical Research Handbook

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Closing Remarks

SPEAKER

Emily C. O'Brien, PhD

Associate Professor in Population Health Sciences
Duke University

Closing Remarks

Emily C. O'Brien, PhD
Associate Professor in Population Health Sciences
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Considerations for Planning Your Embedded Pragmatic Clinical Trial

1. 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 issue

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 cluster-randomized trial, will your design involve parallel randomization or stepped-wedge randomization?
- 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(6):907-915.
  - 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(7):1078-1086.
  - Hemming K, Taljaard M, McKenzie JE, 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, et al. 2018. Design and analysis of group-randomized trials in cancer: A review of current practices. *Prev Med*. 111:241-247.

5. Pilot and Feasibility Testing

- 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?
- 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

6. 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

7. 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

8. 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

9. Writing the Grant Application

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

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