NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Patient-Centered Research in Real-World Settings: *Essentials of Embedded Pragmatic Clinical Trials Workshop*

Participant Guide

SCT 2024 Annual Meeting

May 19, 2024

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Table of Contents

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Patient-Centered Research in Real-World Settings: Essentials of Embedded Pragmatic Clinical Trials Workshop

SCT 2024 Annual Meeting
Boston, MA
May 19, 2024
8:00 a.m.-12:00 p.m. ET

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
8:00-8:05 a.m.	**Welcome**	Emily O'Brien	• Welcome and introduction to the agenda, objectives, and Living Textbook
8:05-8:30 a.m.	**What Are Embedded Pragmatic Clinical Trials (ePCTs)?**	Wendy Weber	• Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials • Learn about the advantages and disadvantages of ePCTs, and when a pragmatic approach can be used to answer a research question • Q & A with attendees
8:30-9:00 a.m.	**Engaging and Aligning With Health System and Community Partners**	Emily O'Brien	• Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study • Identify skills needed for a strong study team and consider the diversity of the team, including inclusive practices • Understand the real-world priorities and perspectives of healthcare system leaders and how to obtain their support • Identify engagement practices to obtain patient and community perspectives • Q & A with attendees

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
9:00-10:00 a.m.	**ePCT Design and Analysis**	Jonathan Moyer	• Learn about cluster randomized and stepped-wedge study designs • Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what principal investigators (PIs) need to know • Overview of effectiveness-implementation hybrid trial designs • Q & A with attendees
10:00-10:10 a.m.	**Break**		
10:10-10:40 a.m.	**Measuring Outcomes**	Angelo Volandes	• Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs) • Discuss the integration of a health equity lens in evaluating outcomes • Q & A with attendees
10:40-10:50 a.m.	**Overview of NIH Collaboratory Trials** • Pragmatic Trial of Video Education in Nursing Homes (PROVEN) • Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP PEACE)	Vincent Mor Angelo Volandes	• Hear a brief description of the NIH Collaboratory Trials being utilized as case studies for the small group activity
10:50-11:20 a.m.	**ePCTs in Context Part 1: Small Group Work**	Emily O'Brien	• Attendees work in small groups to problem-solve challenges faced by Collaboratory ePCTs • Each group reports out their top 1-2 ideas

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
11:15-11:55 a.m.	**ePCTs in Context Part 2: Panel Discussion with NIH Collaboratory Trial PIs**	**Moderator:** Emily O'Brien **Panel:** Vincent Mor (PROVEN) Angelo Volandes (ACP PEACE)	• Hear how the Collaboratory Trial PIs discuss how they handled the challenges from attendees' discussion, reflect on the workshop topics, and discuss lessons learned • Q & A with attendees
11:55 a.m.-12:00 p.m.	**Closing Remarks**	Emily O'Brien Wendy Weber	• Wrap-up including identifying sources for further learning

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Patient-Centered Research in Real-World Settings:
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SCT 2024 Annual Meeting
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Speaker Biographies

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

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

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

Jonathan Moyer, PhD
NIH Office of Disease Prevention
jonathan.moyer@nih.gov

Jonathan Moyer, PhD, is a statistician with the NIH Office of Disease Prevention and focuses on efforts to enhance the rigor and reproducibility of NIH-funded prevention research by promoting the use of the best available research methods. This includes expanding the resources available on NIH's Research Methods

Resources website, providing guidance on the Methods: Mind the Gap Webinar Series, and collaborating with NIH Institutes and Centers on projects that require group randomization or delivery of interventions to groups.

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

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

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

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

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

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

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

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

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GOAL

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

WHAT ARE EMBEDDED PRAGMATIC CLINICAL TRIALS (EPCTS)?

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

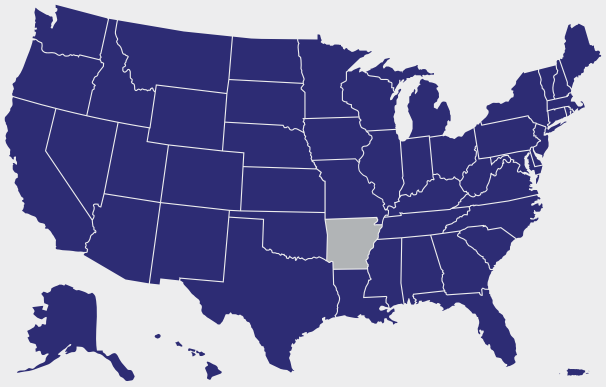
PROGRAM

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

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

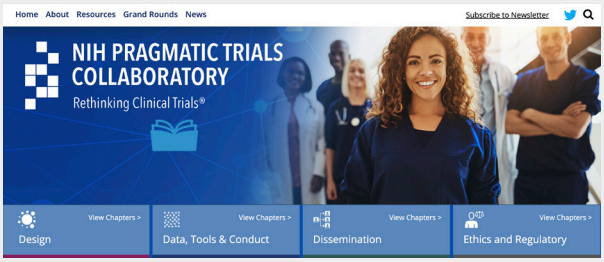
32 NIH COLLABORATORY TRIALS

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



RESOURCES

Living Textbook of Pragmatic Clinical Trials
Comprehensive resource on ePCTs



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

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

DISSEMINATION describes data sharing, dissemination, and implementation approaches

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

Plus:

- Grand Rounds webinars and podcasts
- Monthly NIH Collaboratory newsletter

Visit the Living Textbook:
www.rethinkingclinicaltrials.org

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

HOW IS A CLINICAL TRIAL CONSIDERED PRAGMATIC?

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

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

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

Visit the Living Textbook:
www.rethinkingclinicaltrials.org

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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

Sponsoring Institution
Dana-Farber Cancer Institute

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

NIH Institute Providing Oversight
National Institute on Aging (NIA)

Program Official
Marcel E. Salive, MD, MPH (NIA)

Project Scientist
Karen Kehl, PhD, RN, FPCN (National Institute of Nursing Research [NINR])

ClinicalTrials.gov Identifier
NCT03609177

ABSTRACT

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

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

WHERE CAN ACP VIDEOS BE VIEWED?

View at Home

View in a Clinical Setting

WHAT WE'VE LEARNED SO FAR

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

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

SELECTED PUBLICATIONS & PRESENTATIONS

- Presentation: Presentation to the NIH Pragmatic Trials Collaboratory Steering Committee (2023)
- Article: Reaching Ambulatory Older Adults with Educational Tools: Comparative Efficacy and Cost of Varied Outreach Modalities in Primary Care (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)
- Article: A Yet Unrealized Promise: Structured Advance Care Planning Elements in the Electronic Health Record (2021)
- Article (Study Design): Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP-PEACE): The Study Protocol for a Pragmatic Stepped-Wedge Trial of Older Patients With Cancer (2020)

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
Associate Professor of Medicine
Harvard Medical School and Massachusetts General Hospital

ACP PEACE

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Disclosures

- Dr. Angelo Volandes has a financial interest in ACP Decisions, a non-profit organization developing advance care planning video decision support tools. Dr. Volandes' 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 plans completion
- Medical orders for resuscitation preferences
- Palliative care consultations
- Hospice use
- Will also characterize detailed patient-centered outcomes in a subgroup of 450 patients, including video declarations of individual preferences

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Participating healthcare systems

- Duke Health
- Northwell Health
- Mayo Clinic

DukeHealth

Northwell Health℠

MAYO CLINIC

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Barriers/challenges

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

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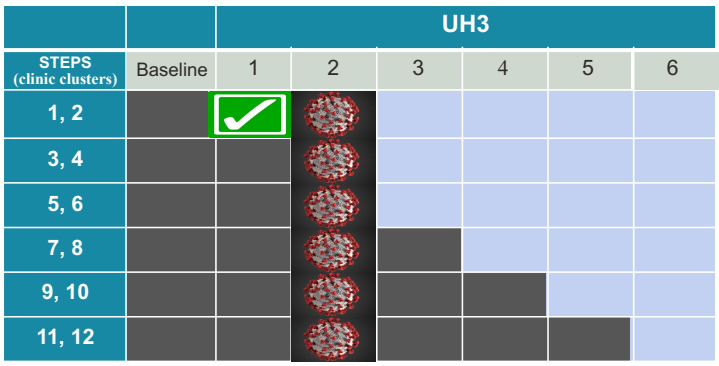
ACP PEACE

Original Design



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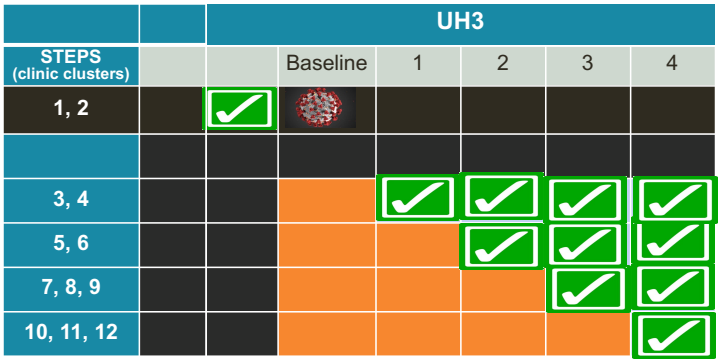
Revised Design



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

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

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Data Challenges

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

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

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Solutions/lessons learned

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

Ellenberg SS. The Stepped-Wedge Clinical Trial: Evaluation by Rolling Deployment. JAMA. 2018 Feb 13;319(6):607-608. doi: 10.1001/jama.2017.21993.

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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 Assisted Advance Care Planning in Nursing Homes

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

PROVEN
PRagmatic Trial of Video Education in Nursing Homes

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Disclosures

- Dr. Vincent Mor has no disclosures to report.

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Objectives

- To conduct a pragmatic cluster RCT of a video assisted advance care planning intervention in nursing home patients with advanced comorbid conditions in 2 nursing home healthcare systems
- To test the impact of video-assisted advance care planning on seriously ill residents' transfer to hospital (inpatient, emergency department, or observational stays)

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Study design

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

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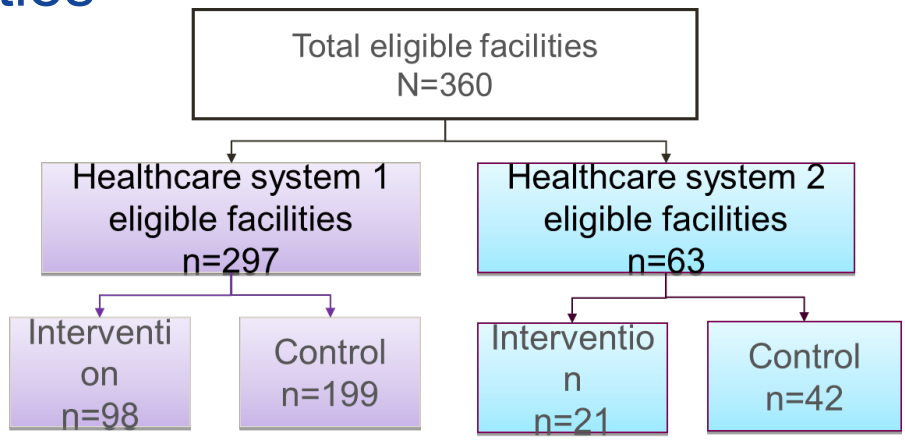
Facilities



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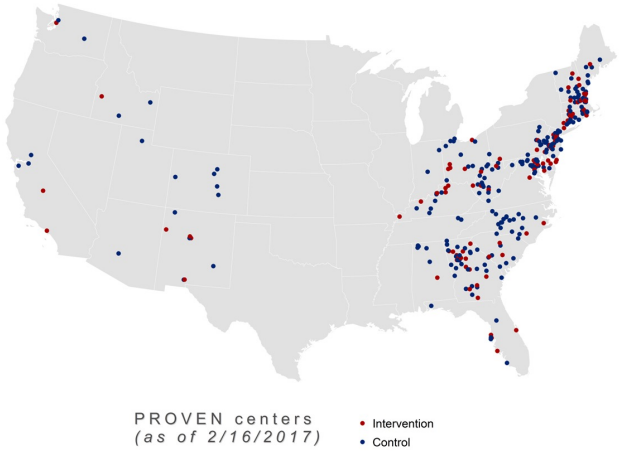
Distribution of PROVEN nursing homes



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Outcomes

- No. hospital transfers/1000 person-days alive among long-stay (> 100 days) Medicare beneficiaries ≥ 65 with advanced dementia, CHF or COPD
- Medicare Claims
- Transfers = admissions, observation stays, emergency room visits
- Up to 12-month follow-up
- Censored on Switch to MA: last date of FFS Medicare coverage

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Intervention

- 24-month accrual; 12-month follow-up
- Suite of 5 advance care planning videos
  - Goals of Care, Advanced Dementia, Hospitalization, Hospice, ACP for Healthy Patients
- Offered facility-wide
  - All new admits, at care-planning meetings for long-stay, readmission
- Flexible (who, how, which video)
- Tablet devices, internet via URL and password
- Training: corporate level, webinars, toolkit

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Why should nursing homes participate?

- Medicare rehospitalization penalty prompted hospitals to build networks of NHs with low rehospitalization rates
- ACOs committed to controlling post-acute spending
- CMS planning a re-hospitalization penalty that was applied to SNFs in 2018
- NH leadership views goal of care to reduce transfers that are inconsistent with patient preferences

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Longer-term rationale

- One NH company was developing an ACO;
  - Financially and clinically accountable for long stay patients
- Another NH company was developing an Institutional Special Needs Plan (HMO)
  - Financially and clinically accountable for long stay patients
- Implementing an ACP Program viewed as a challenge for both

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Barriers/challenges during implementation

- Changes at healthcare system partners
  - Changes in corporate office
  - Changes in participating facilities
- Changes in health care policy environment
- Changes in regulatory environment

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Healthcare system partners

- CHALLENGE #1: Turnover in key partner staff
  - Both of our healthcare system partners experienced turnover (twice) in the system implementation liaison role.
- SOLUTIONS:
  - Kept engaged with senior leadership in our healthcare system partners.
  - Provided one-on-one orientation with newly-hired system liaison staff.
  - Began including implementation liaison on our monthly steering committee calls which included CMO and/or System Level Director of Nursing.

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Healthcare system partners

- CHALLENGE #2: Turnover in Facility Specific ACP Champion staff
  - More than half of nursing home had at least 1 Champion turnover.

	# of NHs	% of NHs
No turnover in ACPCs	55	46.22%
1 ACPC loss	39	32.77%
2 ACPC losses	22	18.49%
3 ACPC losses	2	1.68%
5 ACPC losses	1	0.84%
Total intervention NHs	**119**	

Data as of 2/15/2017

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Healthcare system partners

- CHALLENGE #3: Changing Environment
- Changes in Health Care Policy Environment
  - New Option to pay MDs/NPs for ACP conversation
  - Declining Length of Stay with Medicare Advantage growth
  - Planning for new SNF payment system
- More intensive Quality Inspection Schedule
- A policy environment where nothing stands still!

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Healthcare system partners

- CHALLENGE #4: Divestitures
  - At one partner, a total of 12 nursing homes were divested after they were randomized to the study sample.
  - These divestitures occurred after the ACP Video Program had launched.

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Solutions/lessons learned for ACP

- Videos selected because standardized and ready for broad implementation
- Unanticipated complications in the “mechanics” of introducing videos into daily operations—seemed so simple!
- Just showing video doesn’t mean going to next step of signing advance directive
- Lots of anecdotal stories of families’ resistance to discuss advance directives
- Since MDs & NPs can now bill for advance care planning, perhaps that is best strategy. -- BUT, even now very low use of these extra visits
- But still a challenge even if MDs & NPs can be reimbursed

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Solutions/lessons learned for ePCTs

- Integrating interventions into health care systems means changing standard operating procedures
- Implies a mandate from management, not a research project
- Continuum of intervention complexity; easy to substitute one thing for another, hard to change clinical guidelines and practices
- Even corporate buy-in may not be enough; essential to have fully engaged local and regional managers

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Welcome

Speaker

Emily O'Brien, PhD

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

Welcome

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

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Workshop learning objectives

1. Clarify the definition of ePCTs and explain their utility.
2. Introduce attendees to the unique characteristics and challenges of designing, conducting, and implementing ePCTs within diverse healthcare systems.
3. Increase the capacity to address important patient-centered questions with ePCTs in real-world settings.

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Workshop sessions

- What Are Embedded Pragmatic Clinical Trials?
  - Wendy Weber
- Engaging & Aligning With Health System and Community Partners
  - Emily O'Brien
- ePCT Design and Analysis
  - Jonathan Moyer
- Measuring Outcomes
  - Angelo Volandes

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Workshop sessions - continued

- Overview of NIH Collaboratory Trials
  - Vincent Mor
  - Angelo Volandes
- ePCTs in Context Part 1: Small Group Work
  - Emily O'Brien
- ePCTs in Context Part 2: Panel Discussion with Collaboratory Trial PIs
  - Emily O'Brien
  - Vincent Mor
  - Angelo Volandes
- Closing Remarks
  - Emily O'Brien

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Resource: The Living Textbook

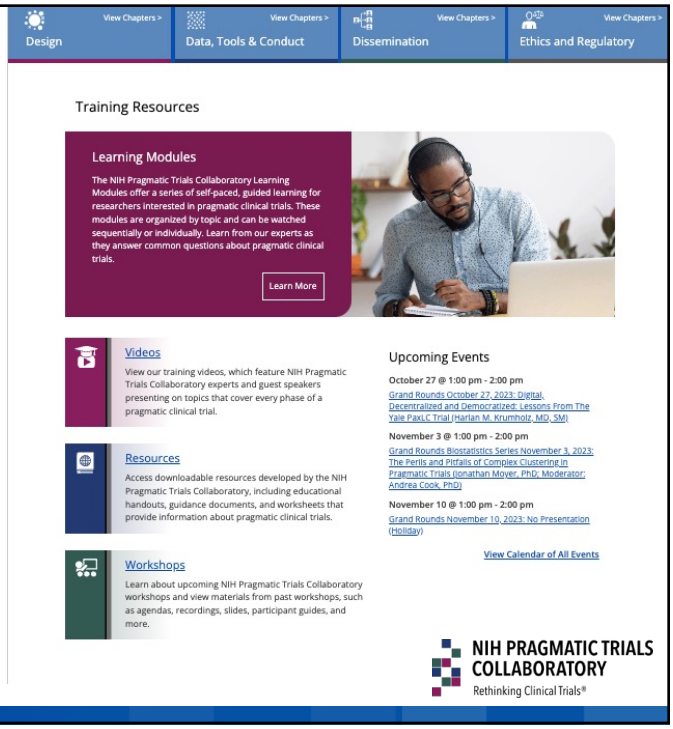
Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

New Training Resources
rethinkingclinicaltrials.org

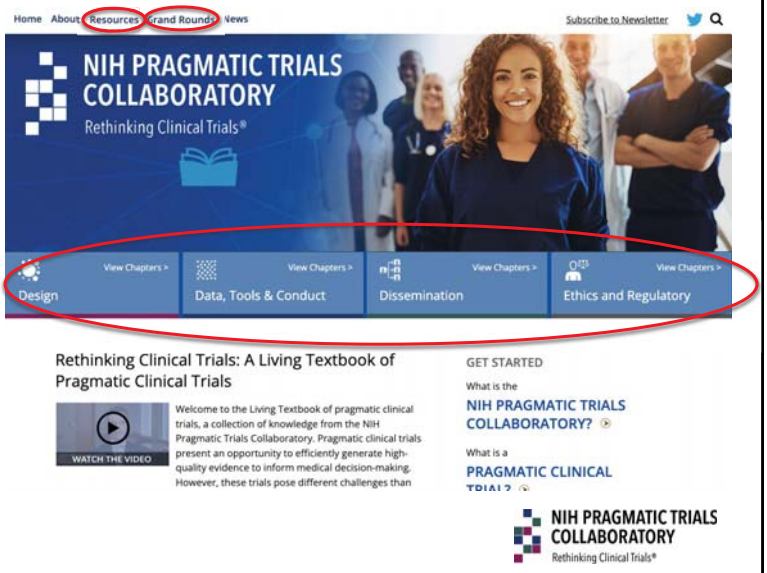
Website Features Include:

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



Key Resources

- Living Textbook
- Grand Rounds Hub
- Training Resources



Best Practices for Integrating Health Equity in ePCTs

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 Health Care systems Leadership
  - Research Support Staff
  - Student or Trainee
  - Other

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About you

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

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About you

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

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What Are Embedded PCTs?

Speaker

Wendy J. Weber, ND, PhD, MPH

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

What Are Embedded PCTs?

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

- Dr. Wendy Weber has no financial disclosures to report. The views expressed in this presentation are those of the speaker and do not necessarily reflect the position or policy of the NIH or the U.S. government.

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Learning goals

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

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Important things to know

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

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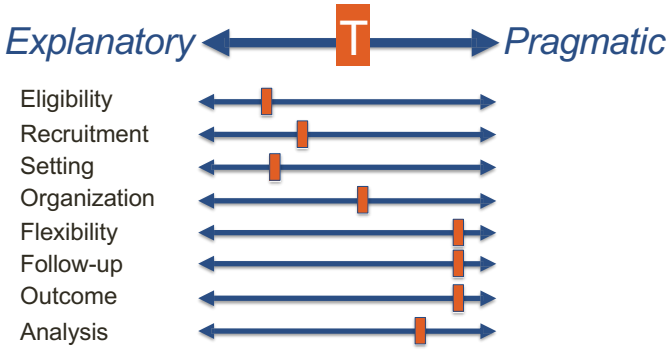
Trials vary across a spectrum of explanatory and pragmatic elements

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



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Why conduct ePCTs?

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

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ePCT characteristics

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

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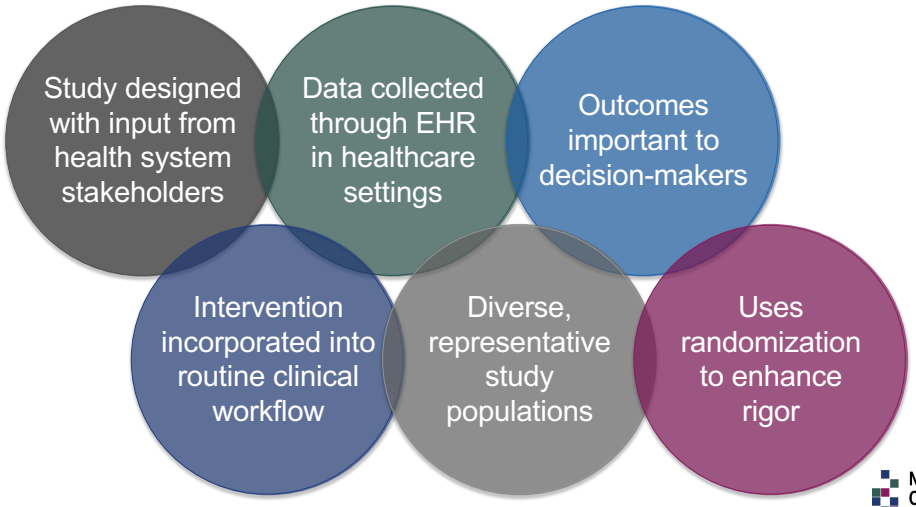
ePCTs bridge clinical care into research



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Who are your stakeholders?

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

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

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Integrating health equity into ePCTs

6 Best Practices for Getting Started

- Consider health equity in all domains of ePCT design
- Select a research question that matters to health disparity populations
- Collaborate with community members to ensure relevant, respectful, and inclusive research
- Allocate sufficient resources to ensure appropriate and inclusive engagement of health disparity populations
- Build a research team that is diverse and knowledgeable about health equity issues
- Design with health equity monitoring and reporting in mind

Listen to the frontline

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

– Greg Simon, MD, MPH (SPOT)

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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

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

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

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Important things to do

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

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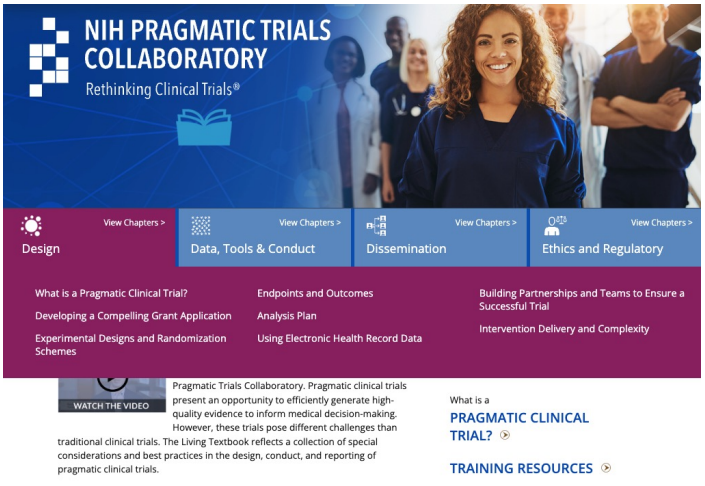
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



Question & Answer

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Resources:

What Are Embedded PCTs (ePCTs)?

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Engaging and Aligning with Health System and Community Partners

Speaker

Emily O'Brien, PhD

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

Engaging and Aligning with Health System and Community Partners

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

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Learning goals

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

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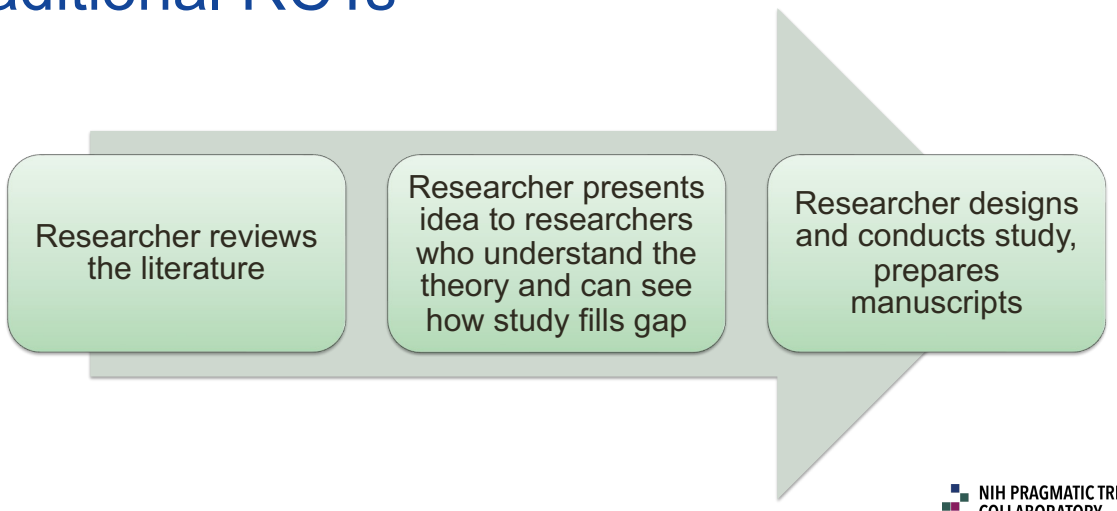
How researchers approach partners in traditional RCTs



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ePCTs work differently.

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

– Greg Simon, MD, MPH (SPOT)

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Important things to know

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

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Who will be impacted? Who are the decision makers?

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

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

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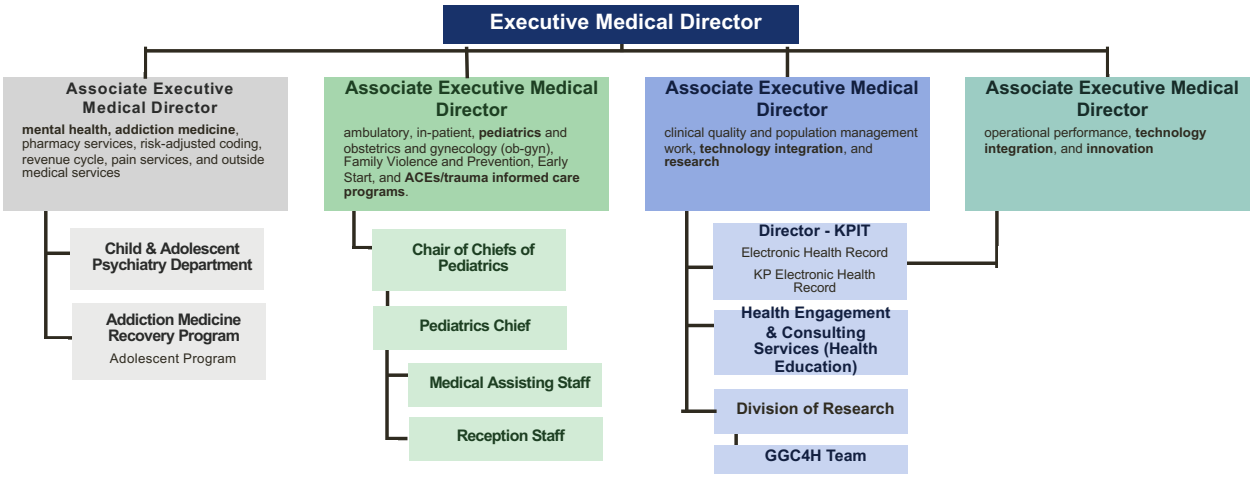
Kaiser Permanente Northern California



Guiding Good Choices for Health: **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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Choosing a salient question

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

Source: Greg Simon, MD, MPH

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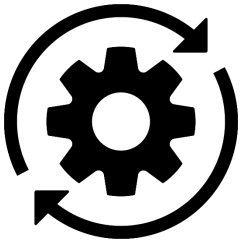
Designing the intervention for sustainment



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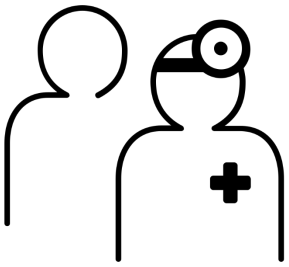
Designing the intervention to minimize burden for patients and clinicians



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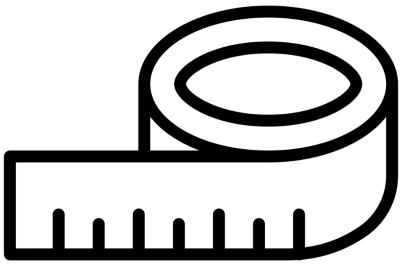
Selecting outcome measures



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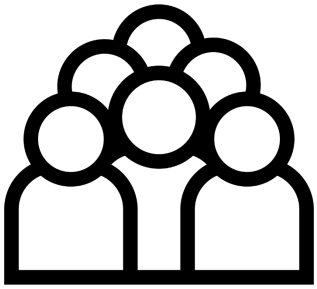
Determining inclusion and exclusion criteria



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Roles of partners

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

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Develop recruitment strategies

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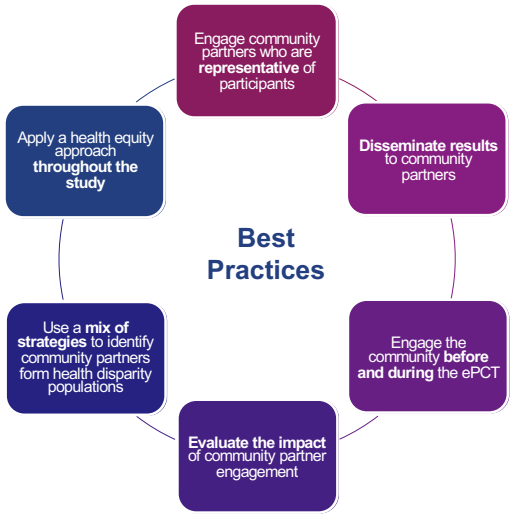
Integrating health equity in engagement



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https://impactcollaboratory.org/new-guidance-document-offers-best-practices-for-incorporating-health-equity-concerns-into-embedded-pragmatic-clinical-trials-for-dementia/

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Example: Community Advisory Board

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

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Example: Patient Advisory Panel

- Old name
  - LS7 Bot and Backup: Using artificially intelligent text messaging technology to improve American Heart Association's Life's Simple 7 Health Behaviors
- New name, suggested name by patient
  - Chat 4 Heart Health

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Serve as study champions

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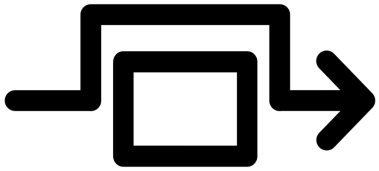
Track challenges and adaptations



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Interpret study results

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Roles of partners

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

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Determine key messages for different groups and

identify avenues for dissemination

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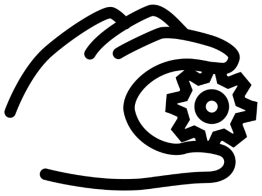
Support implementation or de-implementation



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Consider changes to policies and guidelines

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Roles of ePCT partners

1. Design
- Question
- Intervention
- Outcomes
- Population

2. Conduct
- Recruitment
- Advocacy
- Challenges
- Interpretation

3. Dissemination
- Messaging
- Venues
- Implementation
- Guidelines

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Important things to do

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

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Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

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Question & Answer

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Resources:

Engaging With Health System and Community Partners

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

Other

- Health Care Services Research Network website

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ePCT Experimental Design and Analysis

Speaker

Jonathan Moyer, PhD

Statistician, National Institutes of Health
Office of Disease Prevention

ePCT Experimental Design and Analysis

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

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Disclosures

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Learning goals

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

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Important things to know

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

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Design Considerations

Embedded Pragmatic Clinical Trials

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

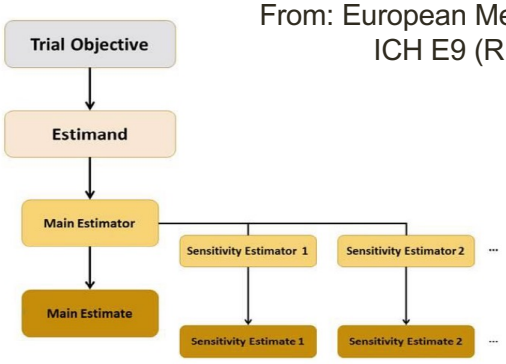

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Methods for pragmatic trials

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

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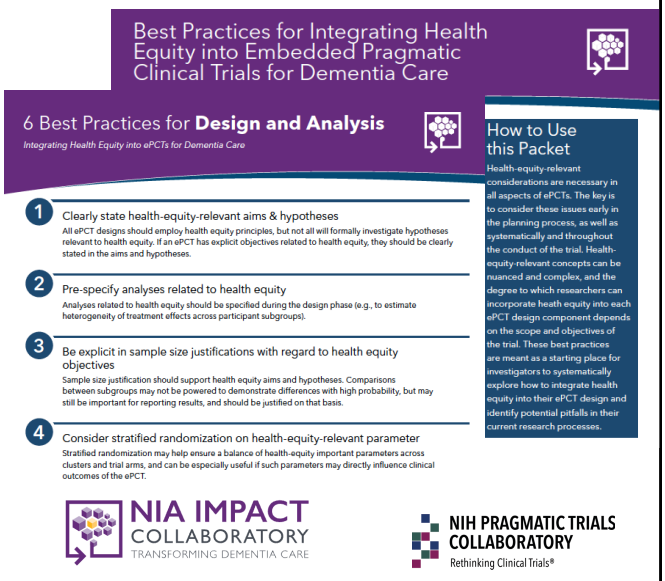
Integrating health equity in design & analysis

- Clearly state health-equity-relevant aims & hypotheses
- Pre-specify analyses related to health equity
- Be explicit in sample size justifications with regard to health equity objectives
- Consider stratified randomization on health-equity-relevant participant characteristics
- Collect data to allow description and reporting of health-equity-relevant participant characteristics
- Be aware of, monitor, and report differential risk-benefit across health equity-relevant groups



NIH Collaboratory ePCT: STOP CRC

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

stop screen to prevent colon cancer

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

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Reasons to randomize clusters instead of individuals

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

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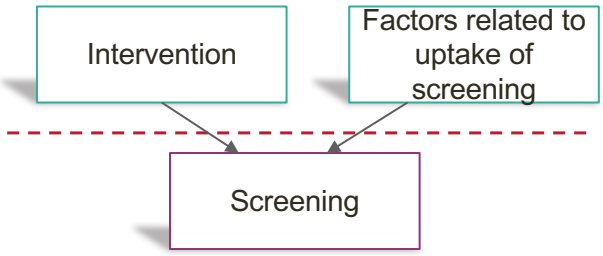
STOP CRC cluster randomization

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



Level 1: Individual-level outcomes nested within clinics

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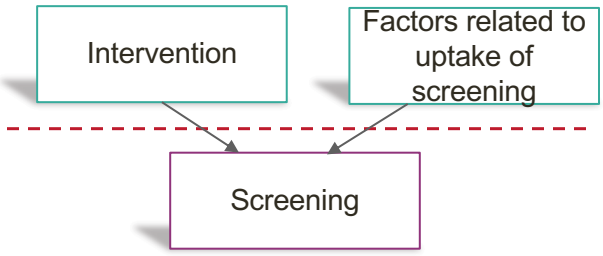
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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Understanding outcome clustering

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

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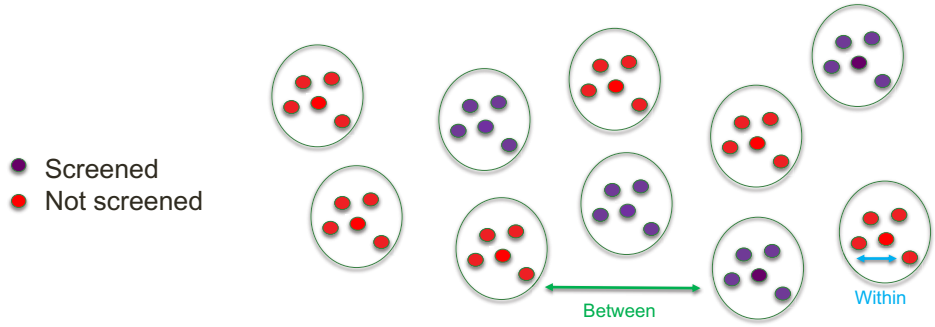
Understanding outcome clustering: complete clustering (ICC =1)



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

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

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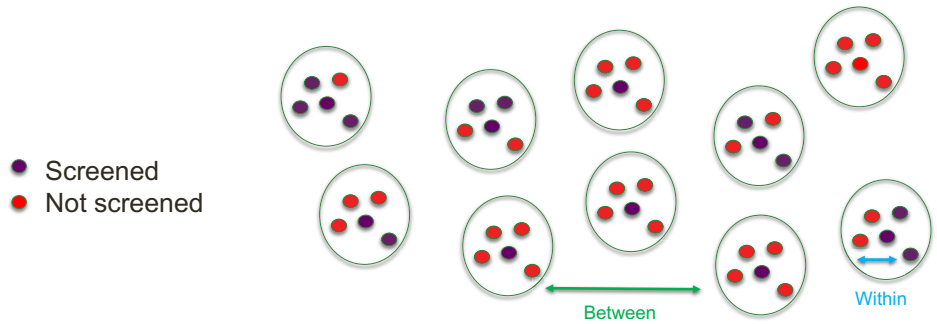
Understanding outcome clustering: some clustering (0 < ICC < 1)



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

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

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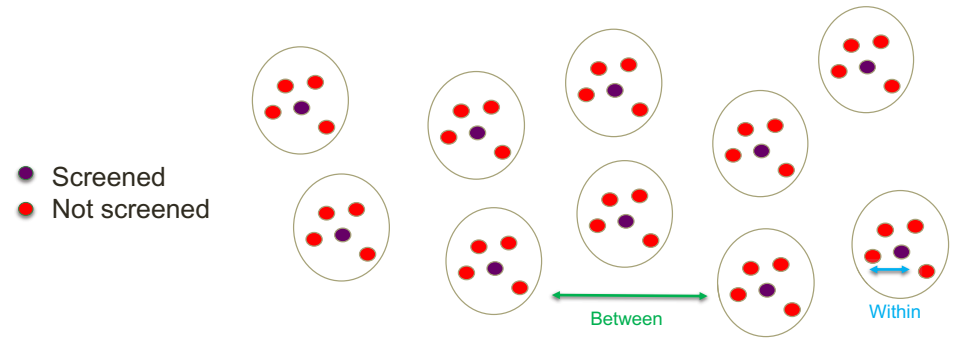
Understanding outcome clustering: no clustering (ICC=0)



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

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

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Summary of design issues for CRTs

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

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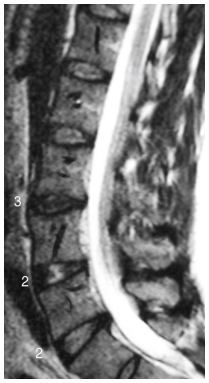
NIH Collaboratory ePCT: LIRE



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

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

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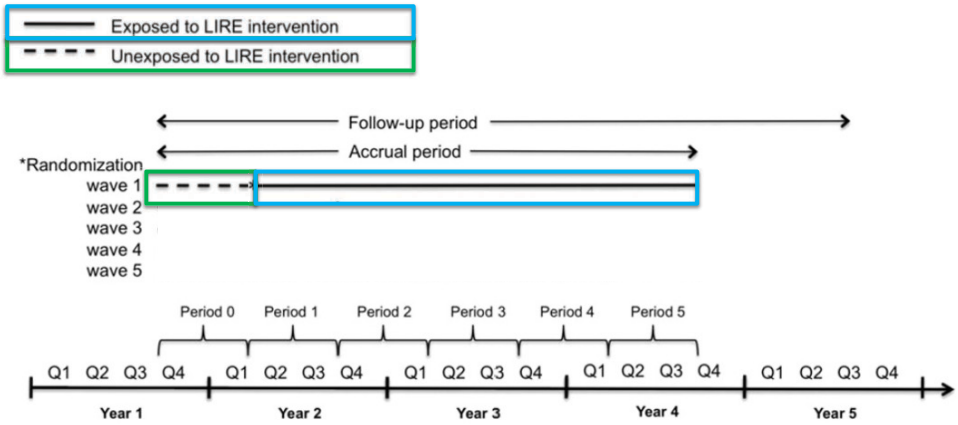
NIH Collaboratory ePCT: LIRE



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

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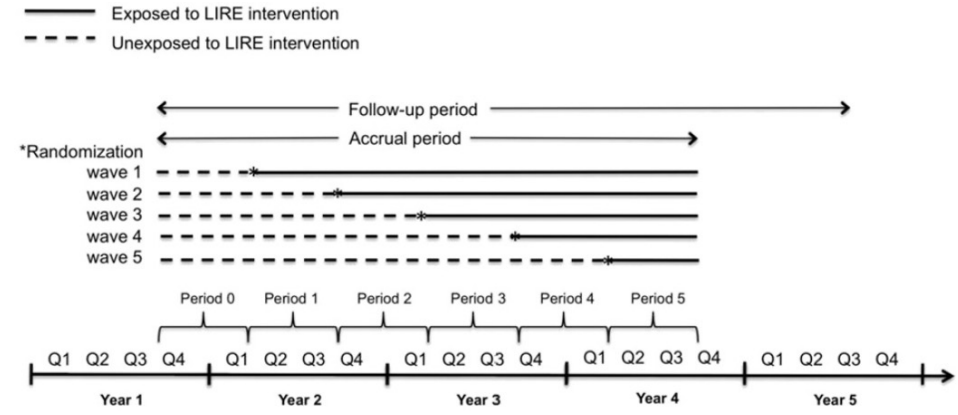
NIH Collaboratory ePCT: LIRE



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

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Summary of design issues for SW-CRTs

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

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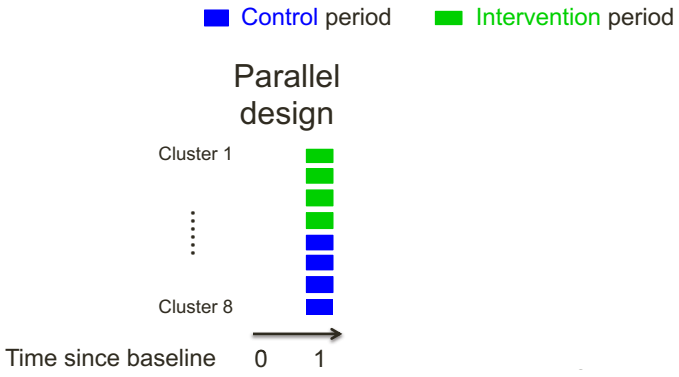
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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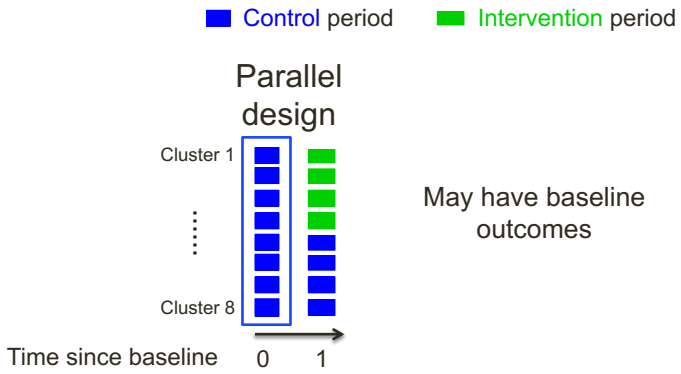
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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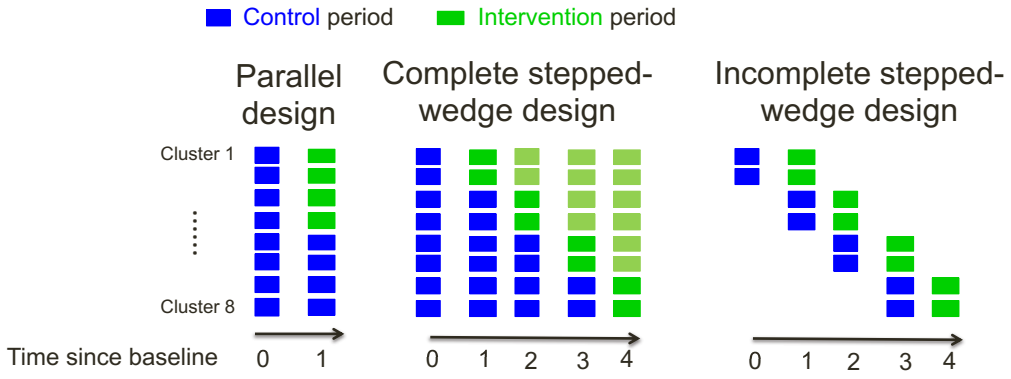
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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

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NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

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

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

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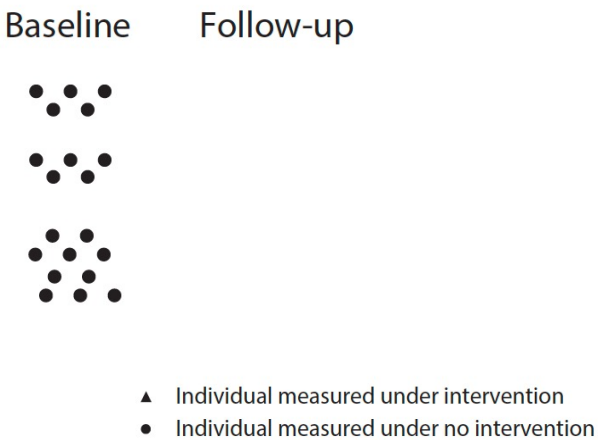
NIH Collaboratory ePCT: OPTIMUM



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

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Summary of design issues for IRGT trials

- Many design features common to RCTs are available to IRGT trials:
  - Cohort, but not easy to conceive of a cross-sectional design
  - Single-comparison designs and factorial designs
  - Restricted randomization procedures
- Clustering emerges post randomization
  - Could be due to a shared agent, participation in a group-based intervention, etc.
  - Clustering can be in both arms or in just one
  - Individual randomization, but ICC has a similar impact as it does for CRTs
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity

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Clustering: Impact on power

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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Clustering: Impact on power in STOP CRC

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

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

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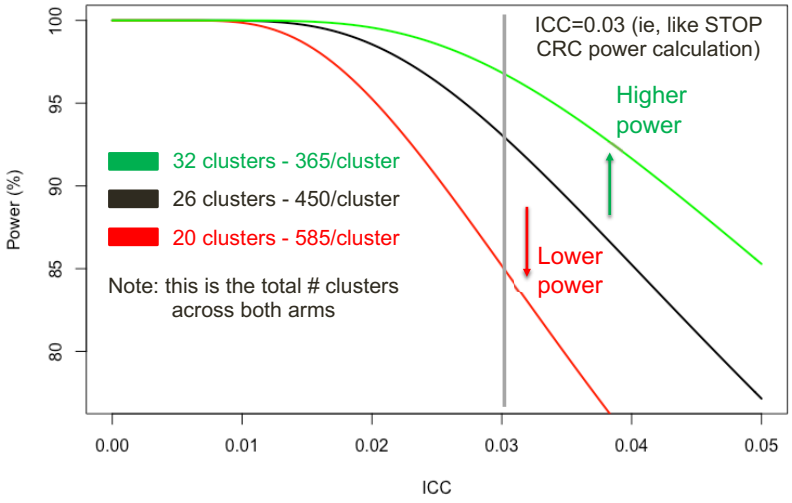
Clustering: Impact on power in STOP CRC



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

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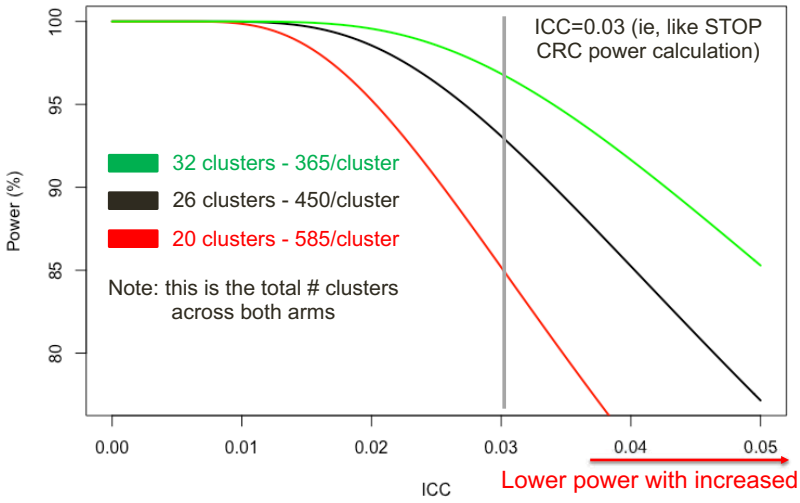
Clustering: Impact on power in STOP CRC



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Question & Answer

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Analysis Considerations

Embedded Pragmatic Clinical Trials

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Learning goals

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

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Two example CRTs inspired by STOP CRC

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

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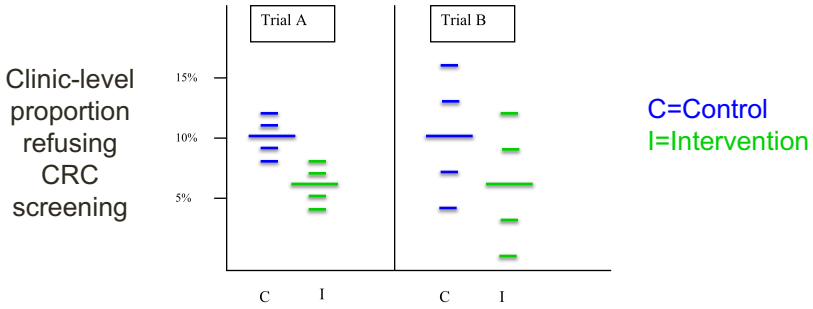
Clustering in CRTs: Implications for analysis



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

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

Adapted from Hayes & Moulton (2009)

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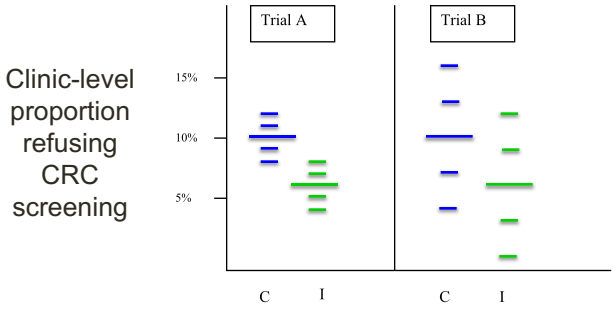
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

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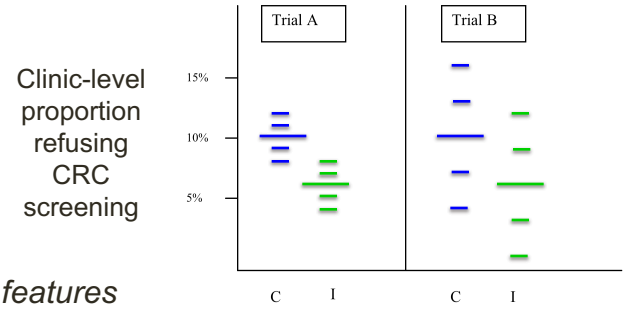
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

Study features

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

Adapted from Hayes & Moulton (2009)

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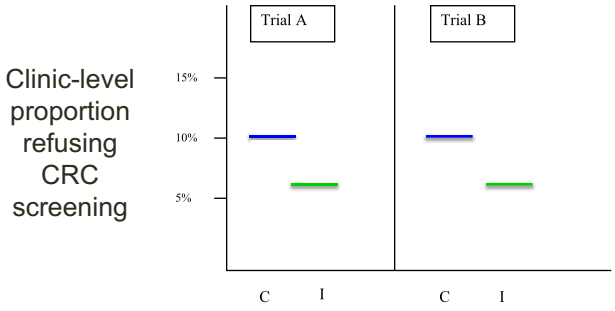
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

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

Adapted from Hayes & Moulton (2009)

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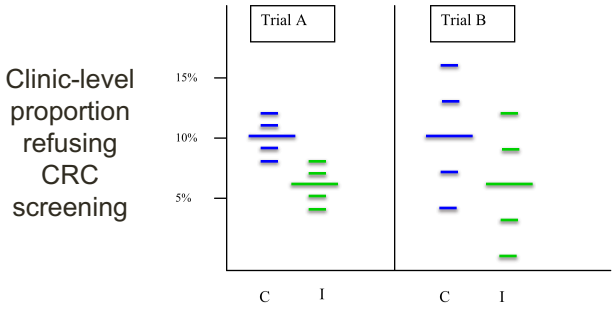
Clustering in CRTs: Implications for analysis



C=Control
I=Intervention

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

Adapted from Hayes & Moulton (2009)

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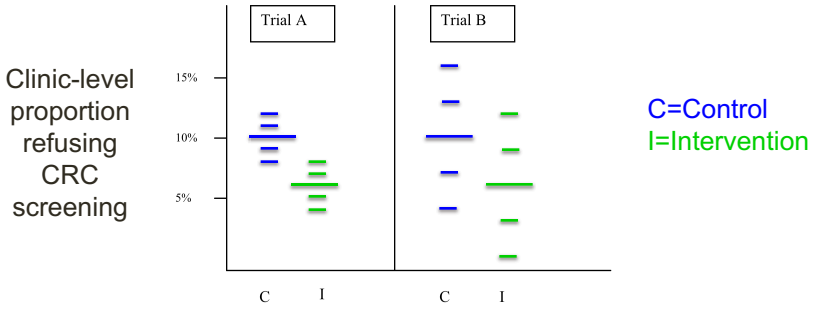
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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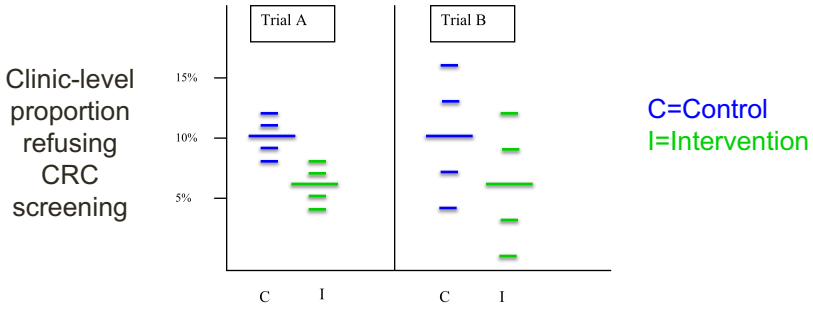
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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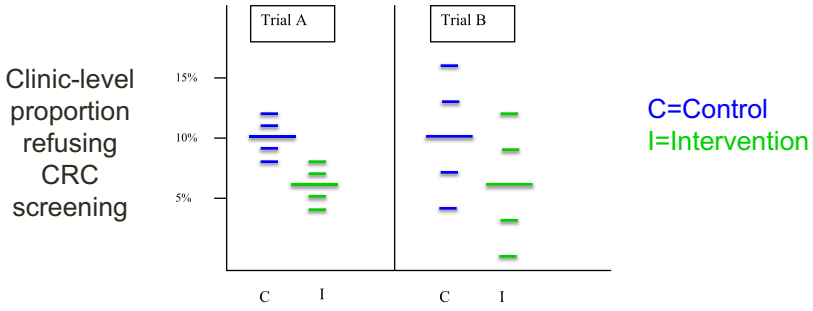
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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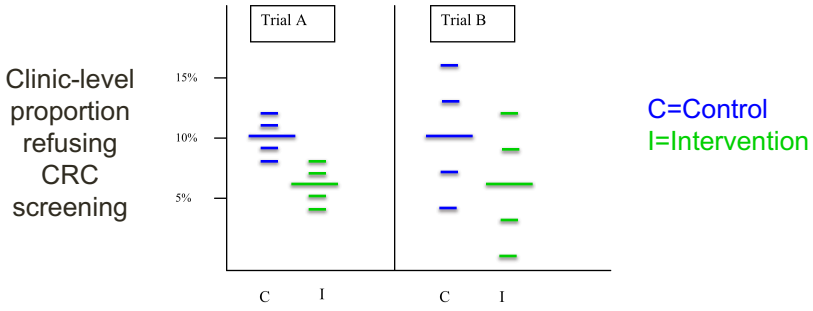
Clustering in CRTs: Implications for analysis



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

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

Adapted from Hayes & Moulton (2009)

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Summary: Analysis of two example CRTs

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

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Analysis of CRTs, including SW-CRTs

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

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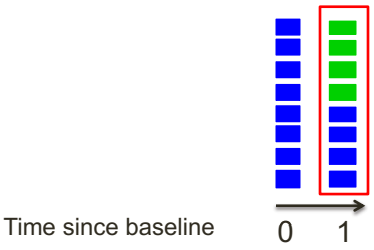
Analysis of CRTs, including SW-CRTs

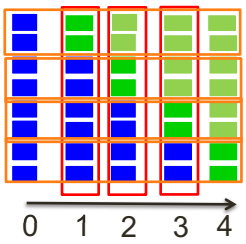
Parallel design

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



Complete SW design

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



Control period Intervention period

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

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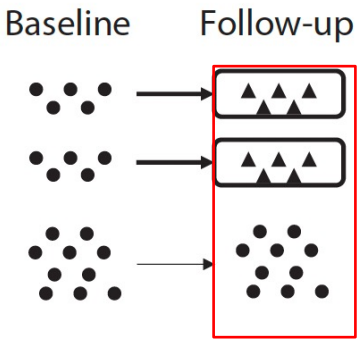
Analysis of IRGT trials



Parallel design

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

▲ Individual measured under intervention
● Individual measured under no intervention

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

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Analysis of IRGT trials

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

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Analysis of CRTs, SW-CRTs, and IRGTs

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

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Strategies to protect the analysis

Avoid model misspecification

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

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Strategies to protect the analysis

Avoid low power

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

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NIH Collaboratory: examples of analytic challenges and trade-offs

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

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Effectiveness-Implementation Hybrid Trial Designs

Embedded Pragmatic Clinical Trials

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

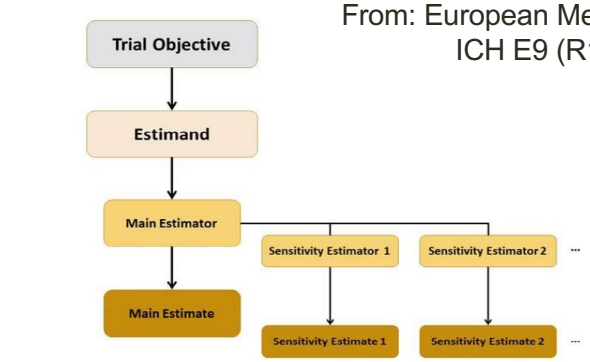

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Effectiveness and Implementation

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

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Hybrid Designs

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

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Hybrid Studies

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

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Hybrid Study Design Prototypes

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

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Other Issues in Hybrid Studies

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

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Resource: The Living Textbook

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

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Summary: Important things to know

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

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NIH resources

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

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Recommended reading

- Murray DM et al. Essential ingredients and innovations in the design and analysis of group-randomized trials. Ann Rev Public Health. 2020;41:1-19
- Hemming K, Taljaard M. Reflection on modern methods: When is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol. 2020. PMID: 32386407.
- Hemming K, Taljaard M. Key considerations for designing, conducting and analysing a cluster randomized trial. Int J Epidemiol. 2023. PMID: 37203433.
- Hughes JP et al. Sample size calculations for stepped wedge designs with treatment effects that may change with the duration of time under intervention. Prev Sci. 2023. PMID: 37728810.
- Kenny A et al. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. Stat Med. 2022. PMID: 35774016.
- Kahan BC et al. Estimands in cluster-randomized trials: Choosing analyses that answer the right question. Int J Epidemiol. 2022. PMID: 35834775.
- Brown CH et al. Accounting for context in randomized trials after assignment. Prev Sci. 2022. PMID: 36083435.
- Curran GM et al. Reflections on 10 years of effectiveness-implementation hybrid studies. Front Health Serv. 2022. PMID: 36925811.
- Stevens J et al. Design of a dual randomized trial in a type 2 hybrid effectiveness-implementation study. Implement Sci. 2023. PMID: 37996884.

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Question & Answer

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Resources:

ePCT Experimental Design & Analysis

Living Textbook readings

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

NIH Research Methods

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

Collaboratory Grand Rounds webinar recordings & slides

- Lessons Learned from the NIH Collaboratory Biostatistics and Design Core

Key journal articles

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

Additional resources

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

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Measuring Outcomes

Speaker

Angelo Volandes, MD, MPH

Associate Professor of Medicine
Harvard Medical School and Massachusetts General Hospital

Measuring Outcomes

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

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Disclosures

- Dr. Angelo Volandes has a financial interest in ACP Decisions, a non-profit organization developing advance care planning video decision support tools. Dr. Volandes' 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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Learning goals

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

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Outcome, Measure, Endpoint

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

- A measure usually refers to a specific and standardized process to obtain information on an outcome.
  - Includes: instructions, administration materials, content, formatting, and scoring rules.

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Types of measures

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

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Outcome, Measure, Endpoint

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

Example:

- Change from baseline at 6 weeks in mean PROMIS Fatigue score.
- Mean differences in PROMIS Fatigue scores between patients in treatment and standard of care groups, after controlling for baseline status.

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Important things to know

- Outcomes and their related endpoints should be meaningful to providers and patients
- Outcomes and related measures should be relatively easy to collect (i.e., pragmatic)
- Researchers do not control the design or data collected in EHR systems

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Choosing and specifying ePCT endpoints

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

- Acute MI
- Broken bone
- Hospitalization

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

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Key questions for choosing endpoints

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

Does it require hospitalization?

Will the event be medically attended?

Is the treatment generally provided in inpatient or outpatient settings?

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Data sources for endpoints in ePCTs

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

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

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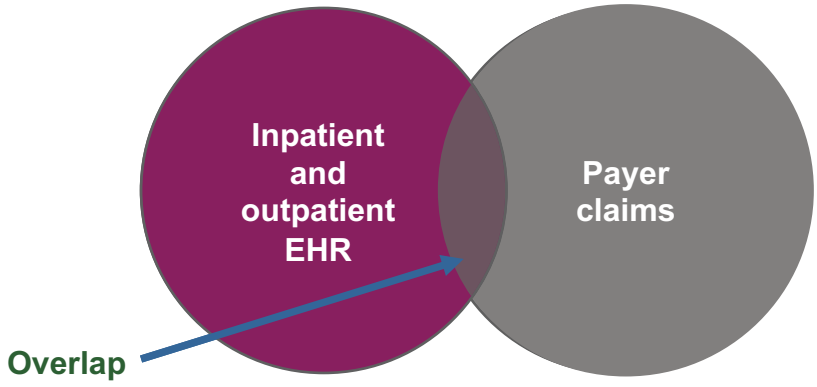
Where is the signal?

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



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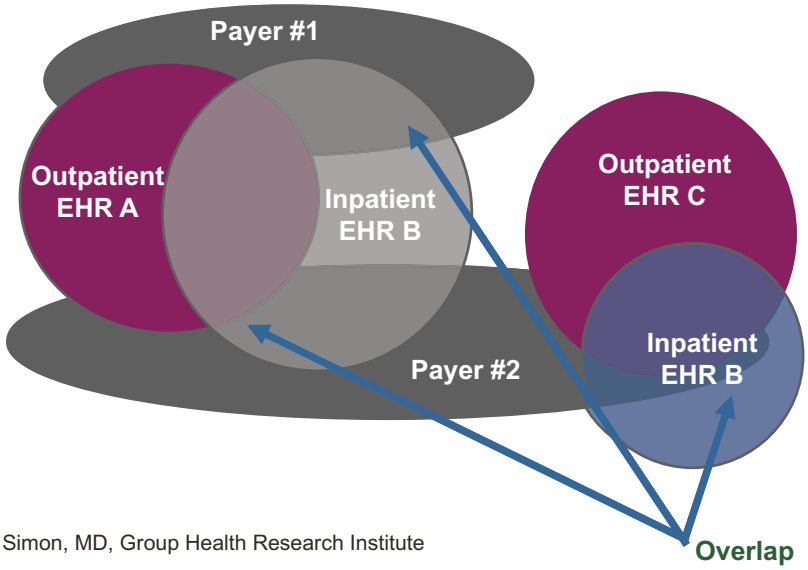
Reality is not straightforward



Source: Greg Simon, MD, Group Health Research Institute

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Longitudinal data linkage

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

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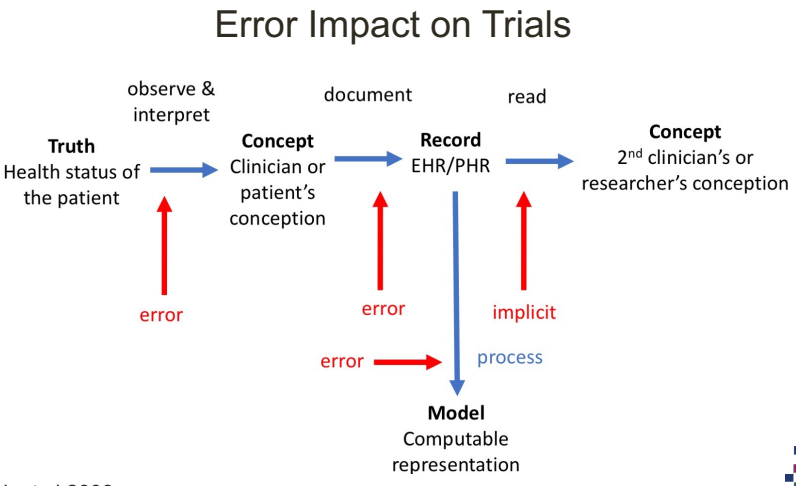
Data is a surrogate for clinical phenomena



Adapted from Hripcsak et al 2009

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Data sources for endpoints in ePCTs

Traditional:

- EHR or ancillary health information systems

Complementary:

Other types of health data not routinely collected outside of standard clinical practice:

- Patient reported data

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It's a balancing act

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

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

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Outcomes measured via direct patient report

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

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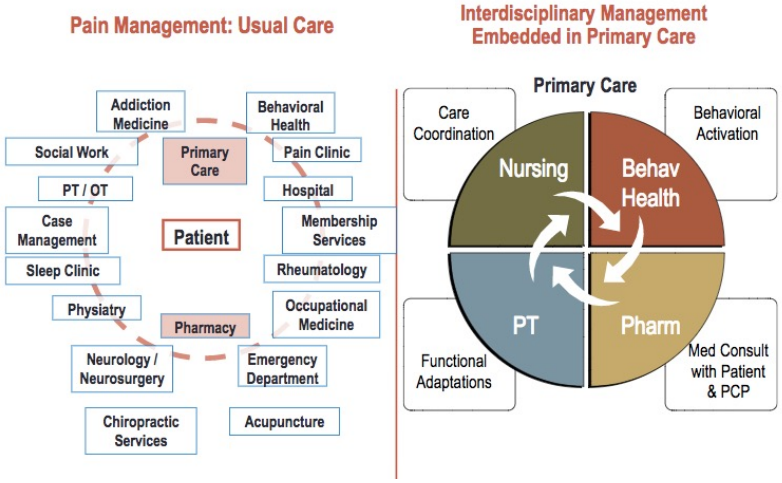
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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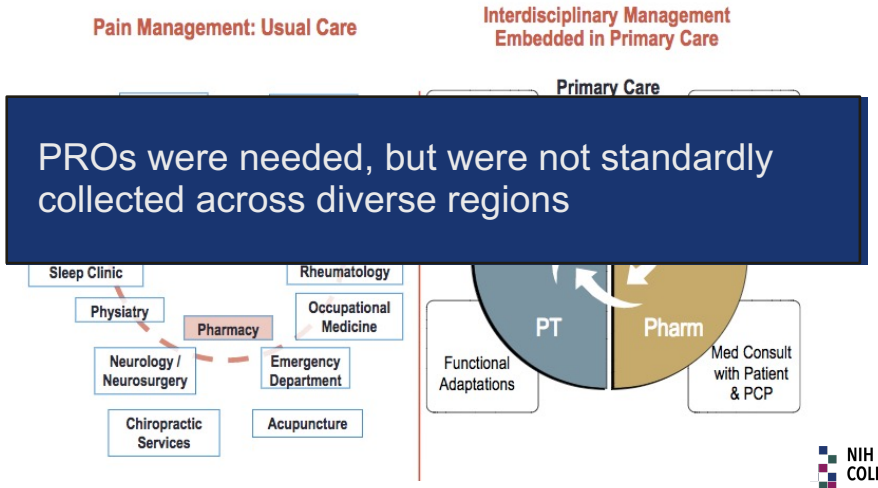
Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)



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

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Case example: PPACT

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

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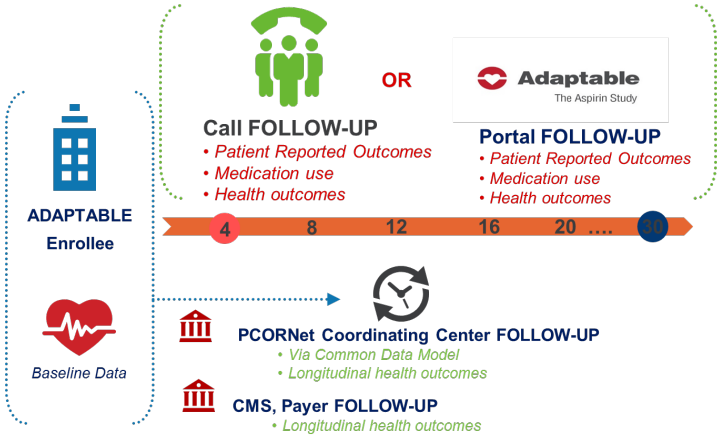
Enabling pragmatic research: e-screening, e-enrollment & e-follow-up



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Mobile devices for outcome measurement

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

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A Health Equity Lens

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

Incomplete and variable capture of data on social determinants of health

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

Data loss due to variable use of technology

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JAMIA Journal of the American Medical Informatics Association

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

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

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

J Am Med Inform

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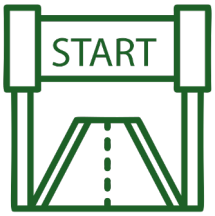
A Health Equity Lens

Recommendations to reduce bias:

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



ELSEVIER
Contemporary Clinical Trials
Volume 130, July 2023, 107238

Short Communication

Equity and bias in electronic health records data

Andrew D. Boyd, Rosa Gonzalez-Guarda, Katharine Lawrence,

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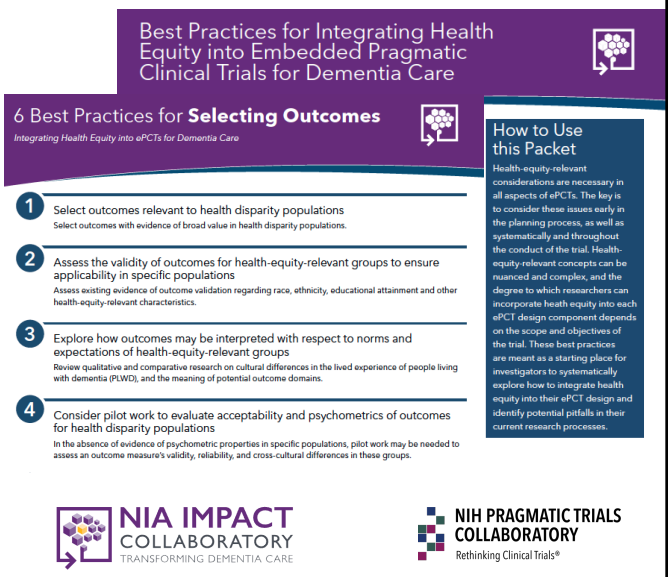
Integrating health equity in outcomes

- Select outcomes relevant to health disparity populations
- Assess the validity of outcomes for health-equity-relevant groups to ensure applicability in specific populations
- Explore how outcomes may be interpreted with respect to norms and expectations of health-equity-relevant groups
- Consider pilot work to evaluate acceptability and psychometrics of outcomes for health disparity populations
- Require linguistic and health literacy accessibility in outcome ascertainment
- Ensure health equity of outcome data capture



Data quality assessment

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

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Important things to do

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

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Concluding points

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

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Resource: The Living Textbook

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Question & Answer

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Resources:

Measuring Outcomes

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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

Speaker

Emily O'Brien, PhD

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

ePCTs in Context

Small Group Work and Panel Discussion With NIH Collaboratory Trial Investigators

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

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Learning goals

- Hear a brief description of the NIH Collaboratory Trials being utilized 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 & lessons learned of the morning topics, to include Q&A.

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NIH Collaboratory Trial Panelists

- Vincent Mor, PhD
  - PROVEN
- Angelo Volandes, MD, MPH
  - ACP PEACE

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Small Group Discussion

ACP PEACE: Measuring Outcomes

- The trial's primary outcome was documentation of advanced care planning (ACP), but oncologists rarely use the structured variable in the electronic health record to record ACP. **How would you approach this problem?**

ACP PEACE: Engaging with Health System Partners

- The ACP PEACE trial learned that 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?**

PROVEN: Engaging with Health System Partners

- Experience with PROVEN showed a lack of fidelity to the intervention (a video), that quarterly case conferences are not times to discuss things with patient and caregiver, and that the health care systems and clinicians are overwhelmed with work, so adding a video to the workflow was challenging. **What changes could be made to address these challenges in the next trial?**

PROVEN: Engaging with Health System Partners

- During the PROVEN trial, there was turnover in key roles in the healthcare system and at nursing homes. Both healthcare system partners experienced turnover in the system implementation liaison role, and more than half of nursing homes had at least 1 champion turnover. **How would you approach this problem?**

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Reflection on Today's Topics

- What are embedded pragmatic clinical trials (ePCTs)?
- Engaging and aligning with health system and community partners
- ePCT Design and Analysis
- Measuring Outcomes

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Resources:

ePCTs in Context: Panel Discussion

ACP PEACE

- UH3 Project: Improving Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly (ACP PEACE)

PROVEN

- UH3 Project: Pragmatic Trial of Video Education in Nursing Homes (PROVEN)

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Closing Remarks

Speaker

Emily O'Brien, PhD

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

Closing Remarks: Embedded Pragmatic Clinical Trials

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

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Additional Resources

Resources:

Objectives and Trial Design: An Overview of Hybrid Designs

Key journal articles

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

Additional resources

- Designing With Implementation and Dissemination in Mind: Hybrid Designs

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Resources:

Pilot and Feasibility Testing

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Resources:

Ethical and Regulatory Considerations

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

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Resources:

Writing a Compelling Grant Application

Living Textbook readings

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

Key journal articles

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

Other

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

Best Practices for Integrating Health Equity into Embedded Pragmatic Clinical Trials for Dementia Care

Rationale

The NIH Revitalization Act of 1993 was enacted to compel scientists to design for, and report on, the effectiveness of interventions by gender and racial/ethnic groups, yet the evidence base for underrepresented people living with dementia (PLWD) is sparse. Higher rates of dementia and worse health outcomes have been documented for many minoritized populations relative to PLWD who are non-Hispanic White, yet these populations that experience health disparities are vastly underrepresented in dementia efficacy trials. A concerted effort to integrate health equity into study designs is necessary to ensure researchers are conducting quality science and avoiding harm where evidence gaps exist. However, the efficacy, safety, and tolerability of treatments have not been sufficiently assessed for many groups that experience Alzheimer's disease (AD) and AD-Related Dementias (AD/ADRD), creating critical knowledge gaps at a time when our aging population is becoming increasingly diverse.

The sparse evidence applicable to health disparity populations derived from AD/ADRD efficacy trials extends to pragmatic clinical trial designs embedded in health care systems (ePCTs, HCS). ePCTs aim to evaluate interventions in real-world settings. ePCTs have unique design features that introduce additional novel challenges with respect to health equity, yet to date there is very little guidance on how to integrate health-equity-relevant considerations into the design of impact ePCTs, including those targeting PLWD and their care partners.

How to Use this Packet

Health-equity-relevant considerations are necessary in all aspects of ePCTs. The key is to consider these issues early in the planning process, as well as systematically and throughout the conduct of the trial. Health-equity-relevant concepts can be nuanced and complex, and the degree to which researchers can incorporate heath equity into each ePCT design component depends on the scope and objectives of the trial. These best practices are meant as a starting place for investigators to systematically explore how to integrate health equity into their ePCT design and identify potential pitfalls in their current research processes.

Table of Contents

6 Best Practices for:

Additional Resources

This best practices package includes a glossary of terms and key references for additional resources and publications. The community-based participatory research, implementation science, and cultural adaptation literature offer some additional guidance. We encourage investigators to seek more in-depth guidance incorporating health-equity-relevant features into the ePCT from these resources as well as from methodological and content experts and community partners.

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TRANSFORMING DEMENTIA CARE

This work is supported by grant U54AG063546 from the National Institute on Aging

6 Best Practices for **Getting Started**

Integrating Health Equity into ePCTs for Dementia Care

1 Consider health equity in all domains of ePCT design

There are health equity considerations in all ePCT design domains, as guided by the PRECIS-2 framework. The key is to consider these issues early in the design phase and throughout the trial's conduct.

2 Select a research question that matters to health disparity populations

All trials are ethically required to maximize their social value. One way to achieve this is to prioritize questions that address the needs of health disparity populations including those that are historically disadvantaged, underrepresented, or otherwise underserved.

3 Collaborate with community members to ensure relevant, respectful, and inclusive research

Engage representative partners who are knowledgeable about the community. Keep in mind there are many aspects of diversity (e.g., race/ethnicity, geography, education). Consultation with community members is valuable across the trial lifespan.

4 Allocate sufficient resources to ensure appropriate and inclusive engagement of health disparity populations

Plan for the effort and budget needed to support inclusive participant engagement. Examples include budgeting for: translation or interpretation services, remuneration of research activities for community partners, and project staff diversity training.

5 Build a research team that is diverse and knowledgeable about health equity issues

Your research team should include investigators, consultants, and project staff with the diversity, methodologic expertise, content knowledge, and training to enable rigorous integration of health-equity-relevant issues throughout the ePCT design.

6 Design with health equity monitoring & reporting in mind

When you design an ePCT, keep in mind the health-equity-relevant aspects that need to be monitored and reported. The Consort Equity Extension and Progress-Plus frameworks are useful guidelines.

6 Best Practices for **Community Partner Engagement**

Integrating Health Equity into ePCTs for Dementia Care

1 Apply a health equity approach to community engagement throughout the study

Engage community partners throughout the study lifespan, including: choosing research questions and outcomes that matter, tailoring interventions and protocols, developing appropriate and accessible materials, designing enrollment strategies, interpreting data, and planning for dissemination and implementation.

2 Engage community partners who are representative of the ePCT participants

Consider the racial, social, and cultural backgrounds of potential study participants who will receive and deliver the intervention, including people living with dementia (PLWD), care partners (CP), clinicians, non-clinician medical staff, and community members.

3 Engage the community before and during the ePCT

Include a period of "pre-engagement" to get to know the community, understand their priorities, preferences, and needs, and build relationships and trust. Keep the community informed about the ePCT throughout is progress. Support the community through information, education, and other efforts. Use plain rather than scientific language.

4 Use a mix of strategies to identify community partners from health disparity populations

Partner with community leaders and groups. Go to places that community members frequent such as local businesses, recreation or senior centers, and places of worship. Use culturally-relevant media such as flyers, local radio, social media, and television.

5 Evaluate the impact of community partner engagement

Assess the experiences of community partners related to their involvement with the research. Describe how their contributions had an impact on study design and conduct.

6 Disseminate results to community partners

Plan to deliver presentations (i.e., at community gatherings and settings) of results during and/or upon completion of the study.

6 Best Practices for **Design and Analysis**

Integrating Health Equity into ePCTs for Dementia Care

1 Clearly state health-equity-relevant aims & hypotheses

All ePCT designs should employ health equity principles, but not all will formally investigate hypotheses relevant to health equity. If an ePCT has explicit objectives related to health equity, they should be clearly stated in the aims and hypotheses.

2 Pre-specify analyses related to health equity

Analyses related to health equity should be specified during the design phase (e.g., to estimate heterogeneity of treatment effects across participant subgroups).

3 Be explicit in sample size justifications with regard to health equity objectives

Sample size justification should support health equity aims and hypotheses. Comparisons between subgroups may not be powered to demonstrate differences with high probability, but may still be important for reporting results, and should be justified on that basis.

4 Consider stratified randomization on health-equity-relevant parameter

Stratified randomization may help ensure a balance of health-equity important parameters across clusters and trial arms, and can be especially useful if such parameters may directly influence clinical outcomes of the ePCT.

5 Collect data to allow description and reporting of health-equity-relevant participant characteristics

Design data collection to enable construction of tables and/or flow diagrams to describe participants across equity-relevant groups that were included in the trial, received the intervention, and lost to follow up.

6 Be aware of, monitor, and report differential risk-benefit across health-equity-relevant groups

Adequately protecting the interests of diverse populations requires knowing if/how their risk-benefit balance may differ from that of the general population.

6 Best Practices for **Intervention Design and Implementation**

Integrating Health Equity into ePCTs for Dementia Care

1 Determine who is meant to benefit from the intervention

Consider the racial, social, socioeconomic, linguistic and cultural backgrounds of those who are intended to receive the intervention (providers, people living with dementia (PLWD), care partners (CP) and the healthcare system).

2 Involve community partners and other interested parties in intervention design and implementation

Community partners and other interested parties who represent the backgrounds and interests of the people delivering and receiving the intervention should be involved in its design, content, delivery and adaptations.

3 Adapt interventions for different settings and populations

Most existing interventions for PLWD and their CPs need to be adapted for health disparity populations and implementation in different settings. Take a systematic approach to these adaptations using existing frameworks. Document and report adaptations.

4 Ensure intervention materials are accessible and acceptable to health-equity-relevant populations

Ensure intervention materials are acceptable and accessible with regard to different literacy levels, languages spoken, settings, and cultural practices.

5 Identify and address barriers to equitable implementation

PLWD and CPs	Providers	Healthcare systems
Computer access, transportation, time and cost, acceptability of intervention	Inequitable training, lack of time, discriminatory attitudes, intervention acceptability, incongruence of background with PLWD & CP	• Variable resources • Less attention to sites with underrepresented populations • How programs are marketed and referral pipelines

6 Monitor implementation across health-equity-relevant populations and incorporate corrective adaptations

Plan to monitor implementation (reach, coverage, intensity, uptake) in these groups and take corrective adaptations if inequities occur. Document and report adaptations.

6 Best Practices for **Health Care System and Participant Selection**

Integrating Health Equity into ePCTs for Dementia Care

1 Select health care systems (HCS) that serve populations with the greatest need for improved care

2 Consider health-equity-relevant features of the HCS

Consider features such as: state, rurality of setting, ownership, care model (accountable care organization, integrated delivery system, etc.). Identify existing disparities in the HCS relevant to intervention implementation.

3 HCS and participant selection should support the health equity objectives of the ePCT

The HCS sampling frame and participant eligibility criteria should allow the health equity goals of the ePCT to be met including pre-specified health equity-specific analysis.

4 Consider health-equity-relevant features of the HCS's population and data available to characterize it

Consider characteristics such as: insurance coverage, race, ethnicity, language, nativity/country of origin, sexual/gender identity, disabilities, diagnoses, type of residence, location of residence (rural/suburban/urban), education, and socioeconomic status.

5 Consider the validity and biases of approaches to identify participants

Methods should identify all eligible participants (e.g., people living with dementia, care partners). Consider who may be "missing" (e.g., undiagnosed) from a health equity standpoint. If using an electronic health record-based algorithm, validate it locally by relevant subgroups. Be aware that while an algorithm may not include race, other system-related factors (e.g., access to services) may introduce bias.

6 Consider threats to health equity in the enrollment and recruitment strategy of eligible participants

Once eligible participants are identified, health-equity-relevant factors may impact how they are enrolled such as mode of outreach (e.g., computer access), or recruitment materials (e.g., health literacy, language). If consent is needed, ensure an equitable approach to obtaining it.

6 Best Practices for **Selecting Outcomes**

Integrating Health Equity into ePCTs for Dementia Care

1 Select outcomes relevant to health disparity populations

Select outcomes with evidence of broad value in health disparity populations.

2 Assess the validity of outcomes for health-equity-relevant groups to ensure applicability in specific populations

Assess existing evidence of outcome validation regarding race, ethnicity, educational attainment and other health-equity-relevant characteristics.

3 Explore how outcomes may be interpreted with respect to norms and expectations of health-equity-relevant groups

Review qualitative and comparative research on cultural differences in the lived experience of people living with dementia (PLWD), and the meaning of potential outcome domains.

4 Consider pilot work to evaluate acceptability and psychometrics of outcomes for health disparity populations

In the absence of evidence of psychometric properties in specific populations, pilot work may be needed to assess an outcome measure's validity, reliability, and cross-cultural differences in these groups.

5 Require linguistic and health literacy accessibility in outcome ascertainment

For clinically embedded patient/care partner relevant outcomes, ensure forward and back-translation required for linguistic and health literacy accessibility.

6 Ensure health equity of outcome data capture

For PLWD and care partners, assess and adapt for limited computer, internet or smart phone access.
For health care systems, assess the need for enhanced technical assistance for outcome data in populations at risk for health disparities.

Glossary

Community	Social grouping based on individual characteristics and/or geographic location.
Community Engagement	Community engagement is the process of working collaboratively with groups of people who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being and viability. Clinical and Translational Science Awards Consortium, Community Engagement Key Function Committee, Task Force on the Principles of Community Engagement. Principles of Community Engagement, 2nd Edition. 2011. NIH publication. 2011; no. 11-7782. https://www.atsdr.cdc.gov/communityengagement/pdf/PCE_Report_508_FINAL.pdf
Community Health	Community health refers to the wellbeing of a defined group of people and the context, actions, and conditions available to promote, protect, and preserve the community's health. The process of improving community health involves multisectoral and multidisciplinary collaborative efforts in evidence-based science, public health, to engage and work with communities, in a culturally appropriate manner, to optimize the health and quality of life of all people who live, work, or are otherwise active in a defined community or communities." Goodman RA, Bunnell R, Posner SF. What is "community health"? Examining the meaning of an evolving field in public health. Prev Med. 2014;67(Suppl 1):S58-S61. PMID: 25069043. doi: https://doi.org/10.1016/j.ypmed.2014.07.028
Community Leader	Person who is very knowledgeable about the community and takes responsibility for the growth, development, and improvement of the community in a formal or informal way.
Community Members	People who live and interact in any personal or professional way in a specific community. Community Members. County Health Rankings & Roadmaps. https://www.countyhealthrankings.org/take-action-to-improve-health/partner-center/community-members
Community Partner	Any local organization (non-profit, for profit, governmental), groups, or people working together with another team to provide input about interventions or initiatives affecting care. This could include people who represent the backgrounds and interests of the people delivering and receiving the intervention.
Community-Based Participatory Research (CBPR)	Community-based participatory research is a collaborative research approach that is designed to ensure and establish structures for participation by communities affected by the issue being studied, representatives of organizations, and researchers in all aspects of the research process to improve health and well-being through taking action, including social change. AHRQ Activities Using Community-Based Participatory Research to Address Health Care Disparities. Agency for Healthcare Research and Quality. https://www.ahrq.gov/research/findings/factsheets/minority/cbprbrief/index.html
Cultural Adaptation **Cultural Tailoring**	Cultural adaptation and cultural tailoring is a systematic process of modifying an evidence-based intervention to address language and cultural contexts to make them compatible with practices, meanings, and values of those involved. Cultural adaptations are a key aspect of implementation considerations necessary in ePCTs. Barrera M Jr, Castro FG, Strycker LA, Toobert DJ. Cultural adaptations of behavioral health interventions: a progress report. J Consult Clin Psychol. 2013;81(2):196-205. PMID: 22289132. doi: https://doi.org/10.1037/a0027085 Stirman SW, Miller CJ, Toder K, Calloway A. Development of a framework and coding system for modifications and adaptations of evidence-based interventions. Implement Sci. 2013;8:65. PMID: 23758995. doi: https://doi.org/10.1186/1748-5908-8-65 National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care. Think Cultural Health. https://thinkculturalhealth.hhs.gov/clas

Glossary

Cultural Humility	Cultural humility is a position of openness, self-awareness, and incorporation of self-reflection and self-critique when purposefully interacting with diverse communities. Foronda C, Baptiste D-L, Reinholdt MM, Ousman K. Cultural humility: A concept analysis. J Transcult Nurs. 2016;27(3):210-217. PMID: 26122618. doi: https://doi.org/10.1177/1043659615592677 Foronda C. A theory of cultural humility. J Transcult Nurs. 2020;31(1):7-12. PMID: 31516091. doi: https://doi.org/10.1177/1043659619875184
Culturally Appropriate **Culturally Responsive** **Culturally Receptive** **Cultural Competence**	Work (research, intervention, etc.) that is culturally appropriate, responsive, or receptive deliberately and purposefully integrates the values, beliefs, norms, practices, and linguistic needs of those involved. Cultural competence is used to describe the ability to successfully tailor services and programs to meet the diverse values, beliefs and behaviors, social, cultural, and linguistic needs of those involved. There is concern in the field whether cultural competence is attainable when involving individuals from another culture. As a result, the other terms listed may be more appropriate. Betancourt JR, Green AR, Carrillo JE. Cultural competence in health care: emerging frameworks and practical approaches. The Commonwealth Fund, October 2002. Cultural Respect. National Institutes of Health. https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/clear-communication/cultural-respect Kirmayer LJ. Rethinking cultural competence. Transcult Psych. 2012;49(2):149-164. PMID: 22508634. doi: https://doi.org/10.1177/1363461512444673
Culture	Culture is an interpersonal process through which language, customs, values, actions, and institutions influence beliefs, norms, values, and behaviors. Culture is dynamic and shapes individual and/or group behavior. Cultures merge and change in response to population changes. Changes in human diversity assure that different lifestyles and beliefs will persist so that systems of value remain autonomous and distinct. In this sense, culture can be understood as not only habits and beliefs about perceived wellbeing, but also political, economic, legal, ethical, and moral practices and values. Hughes V, Delva S, Nkimbeng M, et al. Not missing the opportunity: strategies to promote cultural humility among future nursing faculty. J Prof Nurs. 2020;36(1):28-33. PMID: 32044049. doi: https://doi.org/10.1016/j.profnurs.2019.06.005 Dilworth-Anderson P, Gibson BE. The cultural influence of values, norms, meanings, and perceptions in understanding dementia in ethnic minorities. Alzheimer Dis Assoc Disord. 2002;16 Suppl 2:S56-63. PMID: 12351916. doi: https://doi.org/10.1097/00002093-200200002-00005 Napier AD, Ancarno C, Butler B, et al. Culture and health. The Lancet. 2014;384(9954):1607-1639. PMID: 25443490. doi: https://doi.org/10.1016/S0140-6736(14)61603-2
Equitable Implementation	Intervention is implemented in such a way as to achieve equal opportunities to engage and access services and resources across health disparities populations.

Glossary

Health Disparities **Health Disparity Populations**	Health disparities refer to unjust health differences with adverse impacts that are closely linked with social, economic, and/or environmental disadvantages. Health disparity populations are defined by the National Institutes of Health as underrepresented racial and ethnic populations, less privileged socioeconomic status populations, underserved rural populations, sexual and gender minorities, and any subpopulations that can be characterized by two or more of these descriptions. US Department of Health and Human Services. Healthy People 2020. Minority Health and Health Disparities: Definitions and Parameters. National Institute of Minority Health and Health Disparities (NIMHD). https://www.nimhd.nih.gov/about/strategic-plan/nih-strategic-plan-definitions-and-parameters.html Duran DG, Pérez-Stable EJ. Novel approaches to advance minority health and health disparities research. Am J Public Health. 2019;109(S1):S8-S10. PMID: 30699017. doi: https://doi.org/10.2105/ajph.2018.304931
Health Equity **Health Inequity**	Health equity is achieved when every person has the opportunity to "attain his or her full health potential" and no one is "disadvantaged from achieving this potential because of social position or other socially determined circumstances." Health inequities are reflected in differences in length of life; quality of life; rates of disease, disability, and death; severity of disease; and access to treatment. Attainment of the highest level of health for all people. Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health disparities. Advancing Health Equity in Chronic Disease Prevention and Management. Centers for Disease Control and Prevention National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP). https://www.cdc.gov/chronicdisease/healthequity/index.htm US Department of Health and Human Services. Healthy People 2020.
Health Literacy	Personal health literacy is the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others. Organizational health literacy is the degree to which organizations equitably enable individuals to find, understand, and use information and services to inform health-related decisions and actions for themselves and others. Health Literacy. Centers for Disease Control and Prevention. https://www.cdc.gov/healthliteracy/index.html

Glossary

Minority **Underserved** **Under-represented** **Minoritized**	A minority or minority group is a subgroup of the population with unique social, religious, ethnic, racial, and/or other characteristics that differ from those of a majority group. The term usually refers to any group that is subjected to oppression and discrimination by those in more powerful social positions, whether or not the group is a numerical minority. Examples of groups that have been labeled minorities include African Americans, women, and immigrants, among others. The general term minorities should be avoided when describing groups or populations; instead, specify with terms such as racial or ethnic minority groups. Other terms such as underserved groups or underrepresented populations may be used provided the categories of individuals included are defined. Marginalized groups can be suitable in certain contexts if the rationale for this designation is provided. Unlike the term minority, minoritized emphasizes that certain groups are rendered into a minority category rather than basing assignment on features of their identity. Perkins K, Wiley S. (2014) Minorities. In: Teo T (eds) Encyclopedia of Critical Psychology. Springer, New York, NY. Flanagin A, Frey T, Christiansen SL, Bauchner H. The reporting of race and ethnicity in medical and science journals: comments invited. JAMA. 2021;325(11):1049-1052. PMID: 33616604. doi: https://doi.org/10.1001/jama.2021.2104 Gilmore-Bykovskyi A, Croff R, Glover CM, Jackson JD, Resendez J, Perez A, Zuelsdorff M, Green-Harris G, Manly JJ. Traversing the aging research and health equity divide: toward intersectional frameworks of research justice and participation, The Gerontologist, 2021. Alvidrez J, Castille D, Laude-Sharp M, Rosario A, and Tabor D, 2019. The National Institute on Minority Health and Health Disparities research framework. American Journal of Public Health 109, S16_S20. PMID: 30699025. doi: https://doi.org/10.2105/ajph.2018.304883
Race and Ethnicity	Race categories generally reflect social definitions in the US and are not an attempt to define race biologically, anthropologically, or genetically. Race categories include social constructs generally based on ancestry, national origins, and sociocultural groups. Although race is a social construct and has very limited utility in understanding biological differences, it is important from a sociopolitical perspective to study racism, discrimination, and inequity. The American Sociological Association defines ethnicity as "shared culture, such as language, ancestry, practices, and beliefs." The Oxford English Dictionary defines ethnicity as "[t]he fact or state of belonging to a social group that has a common national or cultural tradition." In the US, ethnicity may refer, for example, to Hispanic or Latino/a/x people. Ethnicity is also primarily a social construct and some have argued against "arbitrary separation of race and ethnicity, instead of using a mutually exclusive single race/ethnicity variable." Terms used to define and describe race and ethnicity change over time depending on shifts in policy, social norms, and other sociocultural factors. Flanagin A, Frey T, Christiansen SL, Bauchner H. The reporting of race and ethnicity in medical and science journals: comments invited. JAMA. 2021;325(11):1049-1052. PMID: 33616604. doi: https://doi.org/10.1001/jama.2021.2104 Diez Roux AV. Conceptual approaches to the study of health disparities. Annu Rev Public Health. 2012;33:41-58. PMID: 22224879. doi: https://doi.org/10.1146/annurev-publhealth-031811-124534

Glossary

Social Determinants of Health	Social determinants of health are the conditions under which people are born, live, learn, work, play, worship, and age. These conditions affect a wide range of health, functioning, and quality-of-life outcomes. Social Determinants of Health. US Department of Health and Human Services. Healthy People 2030. https://health.gov/healthypeople/objectives-and-data/social-determinants-health
Stakeholders*	Stakeholders are individuals or groups who have an interest or concern in a project, activity, or course of action. *Due to a number of negative historical uses of the word "stakeholder", IMPACT uses alternative terms such as "community partners" or "interested parties" whenever possible. Preferred Terms for Select Population Groups & Communities. Centers for Disease Control and Prevention. Accessed November 3, 2022. https://www.cdc.gov/healthcommunication/Preferred_Terms.html

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Rethinking Clinical Trials®

Considerations for Planning Your Embedded Pragmatic Clinical Trial

1. ePCT Aims and Significance

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

2. Engaging All Stakeholders and Aligning with Healthcare System Partners

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

3. Measuring Outcomes

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

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

4. ePCT Design and Analysis

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

6. Pilot and Feasibility Testing

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

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

7. Ethical and Regulatory Oversight Considerations

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

8. Dissemination and Implementation

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

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

9. Assembling Your ePCT Team

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

10. Writing the Grant Application

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

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