Convergence of Dissemination & Implementation Research Methods and Embedded Pragmatic Trials: Examples from the NIH Health Care Systems Research Collaboratory and NIA IMPACT ADRD Collaboratory

December 13, 2021

Participant Guide

Pre-Conference Workshop
Virtual AcademyHealth Annual Conference on the
Science of Dissemination and Implementation in Health (D&I)

NIH Collaboratory *Rethinking Clinical Trials®*
Health Care Systems Research Collaboratory

NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

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Pre-Conference Workshop
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Virtual AcademyHealth Annual Conference on the
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DURATION	AGENDA TOPIC	SPEAKERS	GOALS
10:30 - 11:00 a.m.	**What Are Embedded Pragmatic Clinical Trials (ePCTs) and How Do They Intersect with D&I Research?**	**Wendy Weber**	• Introduce overall learning objectives of the workshop • Recognize key considerations in the design and conduct of ePCTs • Review relevant concepts and terms in D&I research • Identify key areas of synergy between ePCTs and D&I research

11:00 a.m. - 12:00 p.m.	**Stakeholder Engagement and Planning for D&I From the Beginning**	**Moderator: Kevin Weinfurt**
		
		Devon Check
		
		Case Studies:
		• **Vince Mor** PROVEN
		• **Ariel Green** ALIGN
		• **Ab Brody** HAS-QOL
			• Describe the breadth of stakeholders to engage as partners and approaches for engaging them through all phases of the study
			• Understand the importance of aligning research with the priorities of health system leaders
			• Highlight challenges of partnering with diverse health systems
			• Understand and align with real-world priorities
			
			• **Case studies:**
			  ○ *PRagmatic trial Of Video Education in Nursing Homes (PROVEN)*
			  ○ *Aligning Medications with What Matters Most (ALIGN)*
			  ○ *The Hospice Advanced Dementia Symptom Management and Quality of Life Trial (HAS-QOL)*
			• Q&A

12:00 - 1:00 p.m.	**Lunch**		

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
1:00 - 2:30 p.m.	**Integrating D&I Into ePCT Study Designs & Analysis**	**Moderator: Devon Check** **Geoff Curran** **Case Study:** • **Ellen McCreedy** METRIcAL **Patrick Heagerty**	• Overview of the 3 types of effectiveness-implementation hybrid trial designs and when they may be appropriate for ePCTs • Illustrate with analytic challenges and trade-offs with an example from the IMPACT Collaboratory • **Case study**: ○ *Music & MEmory: A Pragmatic TRial for Nursing Home Residents With ALzheimer's Disease_part1 (METRIcAL)* • Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know highlighting design and analysis considerations/decision points from METRIcAL • Q&A
2:30 - 2:45 p.m.	**Break**		
2:45 - 4:15 p.m.	**Additional Considerations When Conducting ePCTS**	**Moderator: Vince Mor** **Stephanie Morain** **Wendy Weber** **Jonathan Jackson** **Case Studies: IMPACT Pilot Awardees** • **Richard Fortinsky** Pragmatic Clinical Trial to Embed Tele-Savvy into Health Care Systems • **Annette Totten** ADVANCE-PC	• Ethics and Regulatory - Learn about the regulatory and ethical challenges associated with both ePCTs and implementation research studies specifically around consent issues - Understanding considerations for distinguishing QI verses Research • Pilot and Feasibility - Identify approaches to evaluating the capabilities of the partner health system and testing key elements of various types of interventions - Describe the role of implementation readiness assessments in the pilot and feasibility phases of ePCTs • A Framework for Achieving Health Equity in Pragmatic Trials • **Case Studies:** Hear about experiences from the IMPACT pilot awardees ○ *Pilot Pragmatic Clinical Trial to Embed Tele-Savvy into Health Care Systems* ○ *ADVANCE-PC: Testing Critical Components for a Trial of Advance Care Planning in Primary Care for Dementia* • Q&A
4:15 - 4:30 p.m.	**Closing**	**David Chambers**	• Commentary and reflections from NIH

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Speaker Biographies

Abraham Brody, PhD, RN, FAAN
NYU Langone Health
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The Hospice Advanced Dementia Symptom Management and Quality of Life Trial (HAS-QOL)

Ab Brody, PhD, RN, FAAN is associate director of the Hartford Institute for Geriatric Nursing and associate professor of Nursing and Medicine at NYU Meyers College of Nursing. He is also the founder of Aliviado Health and the Pilot Core Lead of the NIA IMPACT Collaboratory. His work focuses on the intersection of geriatrics, palliative care, quality, and equity. The primary goal of his research, clinical, and policy pursuits is to improve the quality of care for older adults with serious illness wherever they reside. His primary mode for doing so is through the development, testing, and dissemination of real-word, technology, and informatics supported quality improvement interventions. He is currently the principal investigator of two NIH-funded large-scale pragmatic clinical trials to improve the quality of care and quality of life for persons living with dementia and their caregivers in the community and a co-investigator on several other pragmatic trials and health services research projects in geriatrics and palliative care. Brody also maintains an active practice in the Geriatric and Palliative Consult Services at NYU Langone Health.

David Chambers, DPhil
National Cancer Institute (NCI)
dchamber@mail.nih.gov

Dr. David Chambers is Deputy Director for Implementation Science in the Office of the Director in the Division of Cancer Control and Population Sciences (DCCPS) at the National Cancer Institute (NCI). Dr. Chambers manages a team focusing on efforts to build and advance the field of Implementation Science (IS) through funding opportunity announcements, training programs, research activities, dissemination platforms, and enhancement of partnerships and networks to integrate research, practice and policy.

From 2008 through the fall of 2014, Dr. Chambers served as Chief of the Services Research and Clinical Epidemiology Branch (SRCEB) of the Division of Services and Intervention Research at the National Institute of Mental Health (NIMH). He arrived at NIMH in 2001, brought to the Institute to run the Dissemination and Implementation Research Program within SRCEB, developing a portfolio of grants to study the integration of scientific findings and effective clinical practices in mental health within real-world service settings. From 2006 to the fall of 2014, Dr. Chambers also served as Associate Director for Dissemination and Implementation Research, leading NIH initiatives around the coordination of dissemination and implementation research in health, including a set of research announcements across 15 of the NIH Institutes and Centers, annual scientific conferences, and a summer training institute.

Prior to his arrival at NIH, Dr. Chambers worked as a member of a research team at Oxford University, where he studied national efforts to implement evidence-based practice within healthcare systems. He publishes on strategic research directions in implementation science and serves as a plenary speaker at numerous scientific conferences. He received his A.B. degree (with Honors) in Economics from Brown University in 1997, and an M.Sc. and D.Phil degree in Management Studies (Organisational Behaviour) in 1998 and 2001, respectively, from Oxford University (UK).

Devon K. Check, PhD
Duke University School of Medicine
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Devon Check, PhD is a health services and implementation researcher. She is an Assistant Professor in the Department of Population Health Sciences at Duke and a member of the Duke Cancer Institute. Her primary research interests are quality of care and implementation of evidence-based practices in oncology. Dr. Check's work combines quantitative and qualitative methods to understand and address barriers to the delivery of high-quality, equitable care during and after cancer treatment. She is a Co-Investigator for the NIH Health Care Systems Research Collaboratory Coordinating Center and leads the implementation science resource efforts for Collaboratory demonstration projects.

Geoffrey M. Curran, PhD
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Dr. Curran is a medical sociologist. He is Professor of Pharmacy Practice and Psychiatry at the University of Arkansas for Medical Sciences (UAMS). His broad research area has been health services research, with focus in the diffusion of innovation in a variety of health care settings (e.g., specialty care, primary care, and community settings). For the past 20 years he has been continually funded by the National Institutes of Health (US), the US Department of Veterans Affairs, and other funders to develop and test a range of facilitation and other implementation strategies designed to support the uptake and sustainment of evidence-based practices. Dr. Curran also has written widely on research design and methodology in implementation science. He is the Director of the Center for Implementation Research at UAMS. The Center is devoted to developing and testing implementation strategies across a wide range of service contexts, assisting with the implementation of practices within UAMS clinics and community practices, and training the next generation of implementation scientists.

Richard Fortinsky, PhD
UConn Center on Aging, University of Connecticut School of Medicine
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Pilot Pragmatic Clinical Trial to Embed Tele-Savvy into Health Care Systems

Richard H. Fortinsky, PhD, is a professor at the University Of Connecticut School Of Medicine, where he is a core faculty member at the UConn Center on Aging and holds the Health Net, Inc. endowed chair in geriatrics and gerontology. For more than 30 years, Dr. Fortinsky has collaborated with colleagues from a wide range of scientific disciplines, and with numerous healthcare system and community-based organization partners, to design and carry out studies intended to improve healthcare and optimize health-related outcomes for community-dwelling older adults living with Alzheimer's disease and AD-related dementia and their families. Presently, he serves as principal investigator for studies funded by the National Institute on Aging (NIA) and the Patient-Centered Outcomes Research Institute designed to test in-home, team-based interventions targeting older adults with cognitive vulnerability due to dementia, depression, and/or a history of delirium.

Ariel Green, MD, MPH, PhD
Johns Hopkins University School of Medicine
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ALIGN: Aligning Medications with What Matters Most

Ariel Green, MD, MPH, PhD is an assistant professor of medicine in the Division of Geriatric Medicine and Gerontology at the Johns Hopkins University School of Medicine. Her research focuses on improving communication between older adults, care partners and health care professionals about unnecessary and potentially harmful interventions, including medication use. As a member of the American Geriatrics Society (AGS) Clinical Practice Committee, Dr. Green co-wrote the Society's recommendations for Choosing Wisely, a national initiative that promotes patient-physician conversations about unnecessary medical tests and procedures. Dr. Green received the AGS Choosing Wisely Champion Award for leading efforts to reduce overuse in medicine. Her research, supported by the NIA, is evaluating the impact on patient and care partner outcomes of pragmatic interventions to optimize prescribing for older adults with dementia in primary care. A former award-winning health journalist, Dr. Green has published personal essays and op-eds in Annals of Internal Medicine, The Washington Post and The New York Times, among other publications.

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

Dr. Patrick Heagerty is Professor and former Chair of the Department of Biostatistics at the University of Washington. He received a PhD from the Johns Hopkins University, and a BS from Cornell University. He has extensive experience as an educator, independent and collaborative scientist, and administrator. He has developed fundamental methods for longitudinal studies with a focus on prognostic

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

Jonathan Jackson, PhD
Instructor in Neurology, Massachusetts General Hospital
Instructor, Harvard Medical School
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Jonathan Jackson, PhD, is the founding director of the Community Access, Recruitment, and Engagement (CARE) Research Center at Massachusetts General Hospital and Harvard Medical School, which investigates the impact of diversity and inclusion on the quality of human subjects research and leverages deep community entrenchment to build trust and overcome barriers to clinical trial participation. Dr. Jackson also works as a cognitive neuroscientist, investigating the early detection of Alzheimer's disease (AD), particularly in the absence of overt memory problems. He specializes in identifying and overcoming barriers to clinical research for people and communities of color. He has become a well-known MGH representative to communities of color and dozens of affiliated organizations, particularly regarding clinical research. Dr. Jackson serves on the leadership team of several organizations focused on community health, as well as local, statewide, and national advisory groups for research recruitment, Alzheimer's disease, and community engagement.

Ellen M. McCreedy, MPH, PhD
Brown University
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Music & MEmory: A Pragmatic TRial for Nursing Home Residents With ALzheimer's Disease_part1 (METRIcAL)

Ellen McCreedy is interested in improving the quality of life for people with dementia. Her research goals are to help people living with dementia receive the care they desire at the end of life; and to provide comfort, meaning, and moments of joy to people living with dementia and their families. Professor McCreedy received her MPH in Global Health and Epidemiology from the University of South Florida, her PhD in Health Services Research from the University of Minnesota, and completed a postdoctoral research fellowship at Brown University, Center for Gerontology and Healthcare Research. Dr. McCreedy is directing a pragmatic trial of a personalized music intervention to reduce agitation and isolation in nursing home residents with dementia. She is also leading a pragmatic trial focused on helping people living with dementia in assisted living centers have better advance care planning conversations with their providers.

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

https://impactcollaboratory.org/business-directory/1943/mor-vincent-phd/

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

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

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

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

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

Annette Totten, PhD
Oregon Health & Science University
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ADVANCE-PC: Testing Critical Components for a Trial of Advance Care Planning in Primary Care for Dementia

Annette Totten, PhD, MPA, is an associate professor in the Department of Medical Informatics & Clinical Epidemiology at the OHSU School of Medicine and teaches in Public Health Practice program in the OHSU-PSU School of Public Health. Her research interests include aging, chronic disease, long-term services and supports, shared decision making, and research methods. Dr. Totten conducts primary research in related to serious illness, advance care planning, and aging in a network of US and Canadian primary care Practice Based Research Networks (PBRNs) and directs systematic reviews and projects to develop clinical practice guides for a range of topics at the Pacific Northwest Evidence based Practice Center.

Wendy J. Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH), NIH
wendy.weber@nih.gov

Dr. Weber is the Branch Chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH) at NIH. She joined NCCIH as a program director in 2009. The Clinical Research Branch is responsible for the oversight of all NCCIH-supported clinical trials. Dr. Weber is coordinator for NCCIH's Clinical Trial

Specific Funding Opportunity Announcements (FOAs) and point-of-contact for natural product-related clinical trial FOAs. She is a member of the NIH Common Fund-supported Health Care Systems Research Collaboratory and the program officer for the Coordinating Center. Dr. Weber is also a member of the planning and oversight team for the NIH-DoD-VA Nonpharmacologic Approaches to Pain Management Collaboratory and project scientist for its Coordinating Center.

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

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

Dr. Weinfurt is Professor and Vice Chair for Research in the Department of Population Health Sciences in the Duke University School of Medicine. Dr. Weinfurt is also a Professor in the Duke departments of Psychiatry and Behavioral Science, Biostatistics and Bioinformatics, and Psychology and Neuroscience. He is a faculty member of the Duke Clinical Research Institute and Faculty Associate of the Trent Center for the Study of Medical Humanities and Bioethics. Dr. Weinfurt conducts research on measuring patient-reported outcomes, medical decision making, and bioethics.

Dr. Weinfurt was a principal investigator in the NIH PROMIS Network, where he led the development of the SexFS to measure male and female sexual function and satisfaction. Currently, he is co-chair of the coordinating center for the NIH Health Systems Research Collaboratory and served as the former President of the PROMIS Health Organization. As an educator, Dr. Weinfurt co-directs Duke's masters-level Clinical Research Training Program and has taught graduate courses in patient-reported outcomes research and multivariate statistics along with undergraduate courses in introductory psychology, judgment and decision making, and the psychology of medical decision making.

Dr. Weinfurt received his PhD in psychology at Georgetown University and did graduate work in the history of science and philosophy of mind at Linacre College, Oxford.

What Are Embedded Pragmatic Clinical Trials (ePCTs) and How Do They Intersect with D&I Research?

Speaker

Wendy Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH)

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What Are Embedded Pragmatic Clinical Trials (ePCTs) and How do They Intersect With D&I Research?

Wendy Weber, ND, PhD, MPH
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Learning goals

- Recognize key considerations in the design and conduct of ePCTs
- Review relevant concepts and terms in D&I research
- Identify key areas of convergence between ePCTs and D&I research

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ePCTs: 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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ePCT characteristics

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

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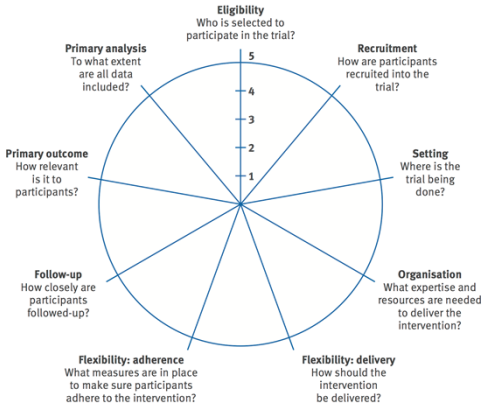
Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) Wheel



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

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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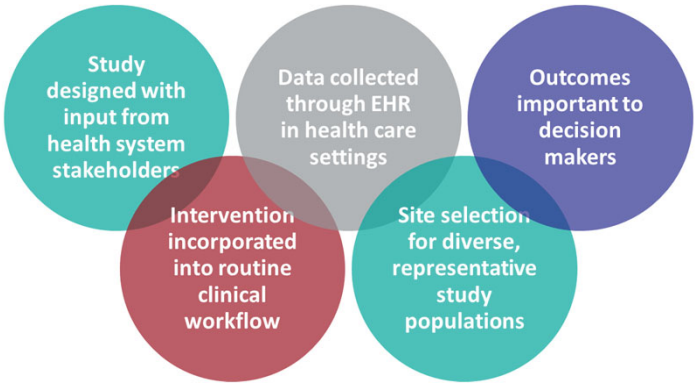
ePCTs bridge clinical care into research



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What is a Pragmatic Clinical Trial?

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

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Relevant D&I concepts: Dissemination Research

- "Scientific study of targeted distribution of information and intervention materials to a specific public health or clinical practice audience. The intent is to understand how best to communicate and integrate knowledge and the associated evidence-based interventions."
- How, when, by whom, and under what circumstances does evidence spread?
- How do we package and share evidence to increase adoption and use?

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Relevant D&I concepts: Implementation Research

- "Scientific study of the use of strategies to adopt and integrate evidence-based health interventions into clinical and community settings in order to improve patient outcomes and benefit population health."
- How do we best implement evidence-based interventions, practices, and programs in routine, real-world settings?
- What approaches are needed to facilitate integration, adaptation, and sustainability of evidence in delivery settings?

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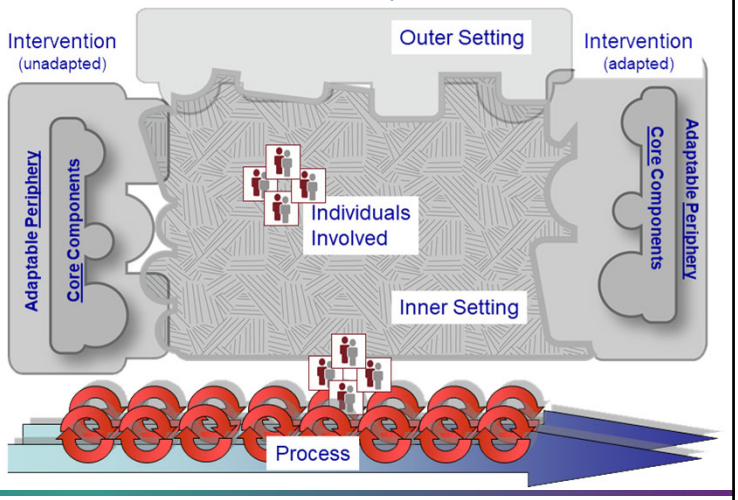
Frameworks



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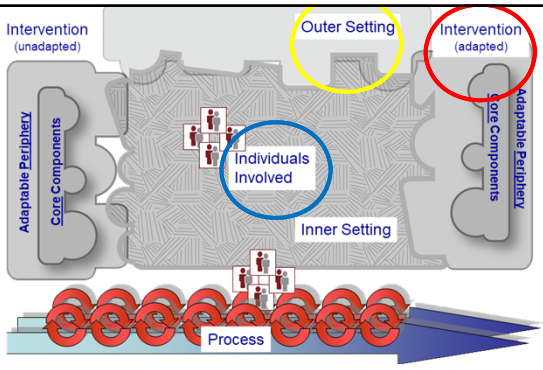
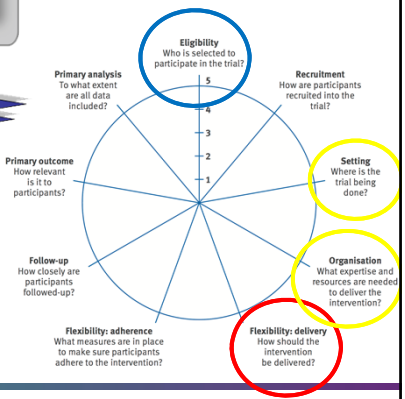
Front. Public Health, 29 March 2019 | https://doi.org/10.3389/fpubh.2019.00064
Front. Public Health, 27 April 2015 | https://doi.org/10.3389/fpubh.2014.00143





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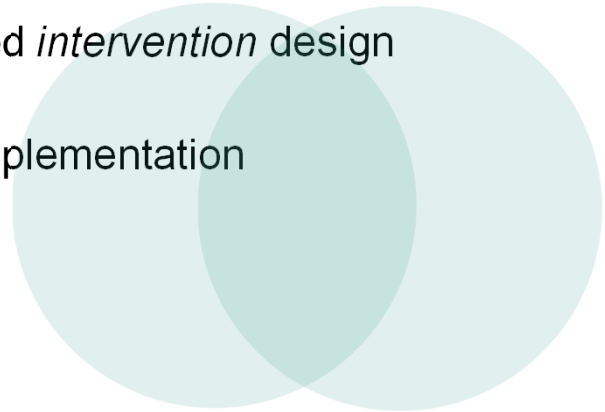
Key areas of convergence with ePCTs

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



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Opportunities

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

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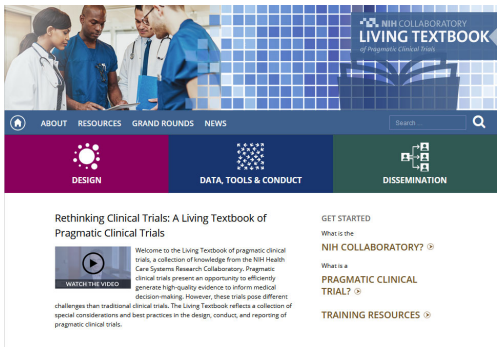
Resources

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



IMPACT Training Modules ePCT Video Learning Library

www.impactcollaboratory.org

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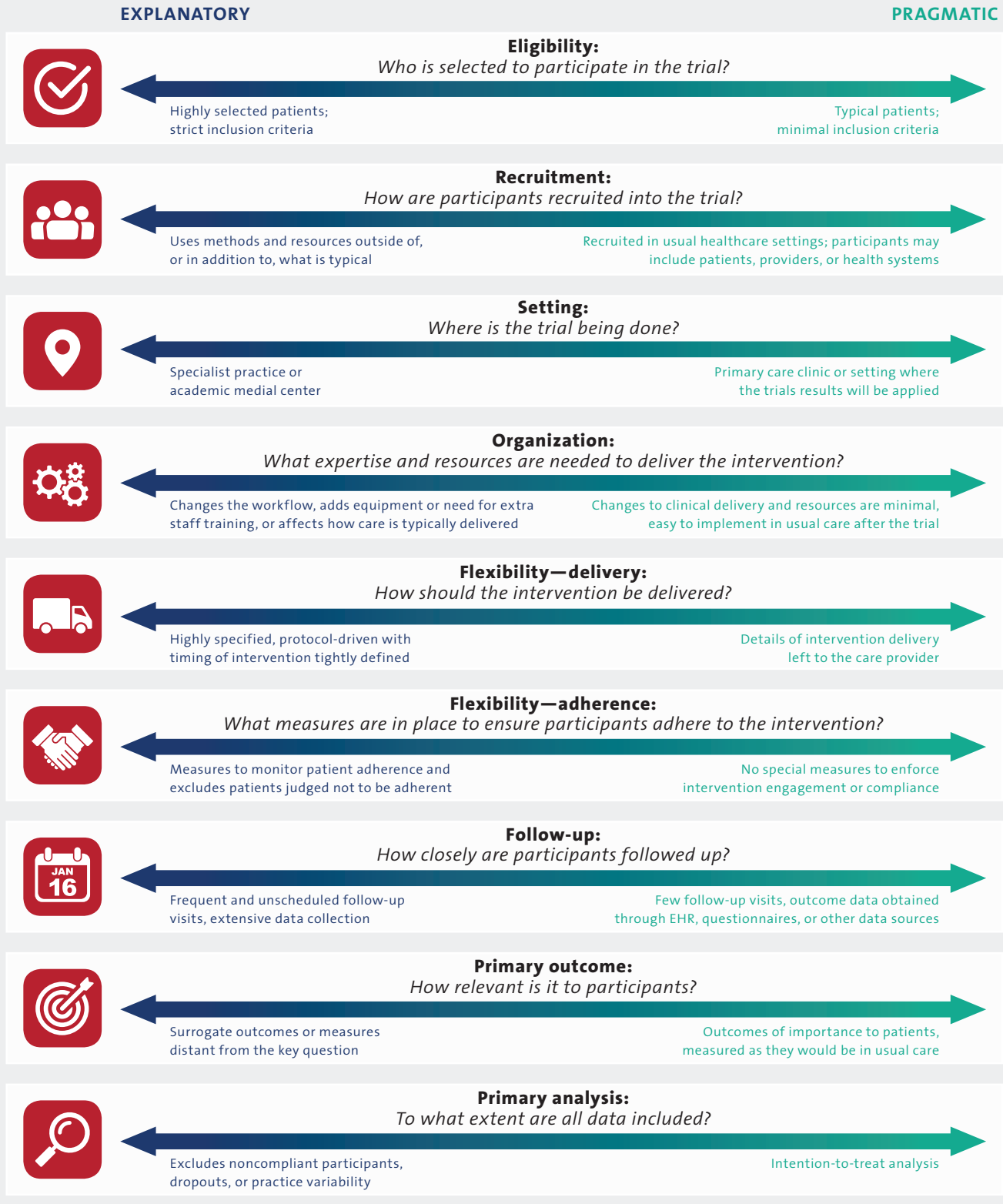
Resource:

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

Resources:
What Are Embedded Pragmatic Clinical Trials and How Do They Intersect with D&I Research?

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

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

Stakeholder Engagement and Planning for D&I From the Beginning

Speakers:

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

Vince Mor, PhD
Brown University School of Public Health

Ariel Green, MD, MPH, PhD
Johns Hopkins University School of Medicine

Abraham Brody, PhD, RN, FAAN
Hartford Institute for Geriatric Nursing
NYU Rory Meyers College of Nursing

Stakeholder Engagement and Planning for Implementation From the Beginning

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

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Learning goals

- Learn why a critical element in the success of an ePCT is engaging health system stakeholders early and often
- Discuss strategies for health system stakeholder engagement
- Understand how health system stakeholders can help to design interventions for real-world implementation and sustainment

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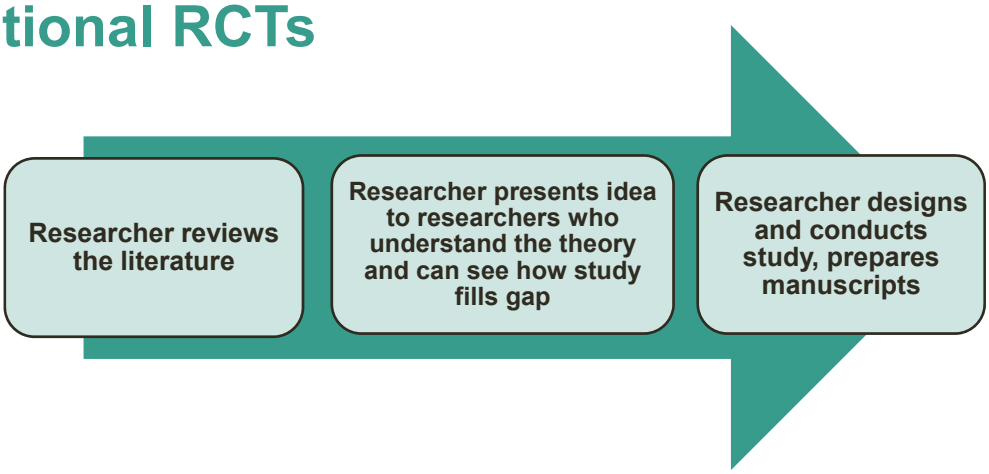
How researchers approach stakeholders in traditional RCTs



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Researchers partner with stakeholders in ePCTs differently.

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

Greg Simon, MD, MPH
SPOT Demonstration Project Principal Investigator

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

For example,

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

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Roles of stakeholders

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

Roles of stakeholders

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

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Choosing a salient question

We want to know what you need.

What research should we be doing?

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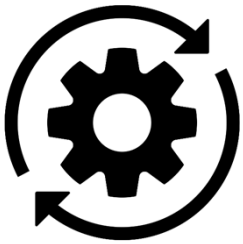
Source: Greg Simon, MD, MPH

Designing the intervention for sustainment



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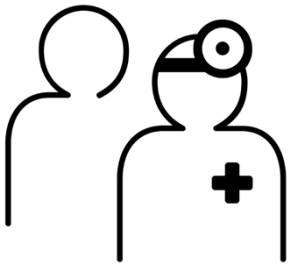
Designing the intervention to minimize burden for patients and clinicians



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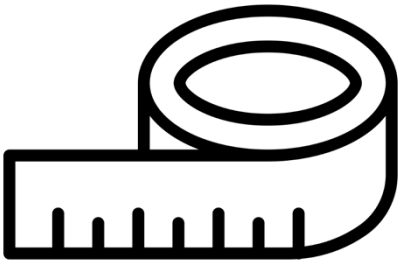
Selecting outcome measures



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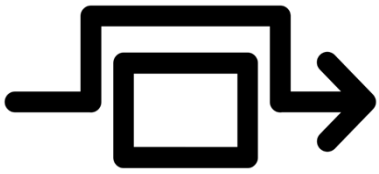
Roles of stakeholders

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

Track challenges and adaptations



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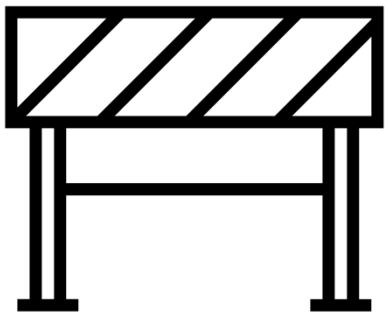
Monitor barriers to real-world implementation



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Interpret study results

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Roles of stakeholders

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

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

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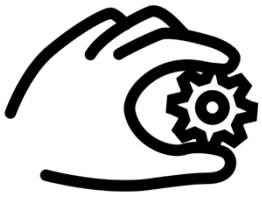
Support implementation or de-implementation



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Roles of stakeholders

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2. Successfully conducting the research
3. Disseminating results

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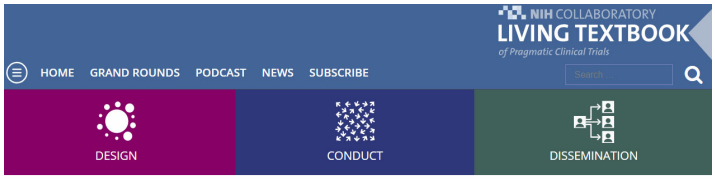
Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

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



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Resources: Journal articles

Concannon TW, et al.
Multi-Group Stakeholder Engagement.
J Gen Intern Med 2019

Whicher DM, et al.
Gatekeepers for pragmatic clinical trials. *Clin Trials.*
12:442–448. 2015

Johnson KE, et al.
A guide to research partnerships for pragmatic clinical trials. *BMJ*. 2014

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Resources

Visit the Living Textbook of Pragmatic Clinical Trials at

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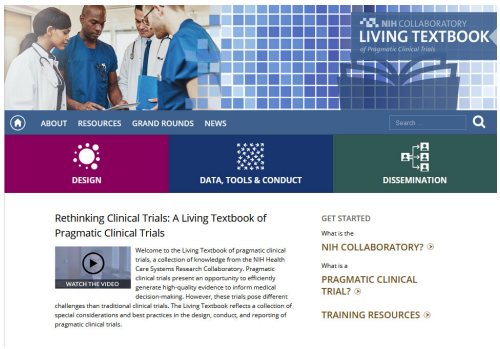

IMPACT Training Modules ePCT Video Learning Library

www.impactcollaboratory.org

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Case Study: Implementing PROVEN

Pragmatic Trial of Video Education in Nursing Homes

Vince Mor, PhD
Brown University School of Public Health

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PROVEN: Objective

- To conduct a pragmatic cluster RCT of an advance care planning video 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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Background: Nursing homes

- Nursing homes are complex healthcare systems
  - 15,000+ nursing homes with ~1.5 million beds
  - 3+ million patients admitted annually
  - Less than 1 million long stay residents
  - Increasingly a site of death
- Patients are medically complex with advanced comorbid illness
- Like hospitals, nursing homes charged with guiding patient decision making by default

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Background: ACP

- Advance care planning
  - Process of communication
  - Align care with preferences
  - Leads to advance directives (e.g., DNR, DNH)
- Better advance care planning associated with improved outcomes
- Advance care planning suboptimal in nursing homes
  - Not standardized
  - Low advance directive completion rates
  - Not reimbursed
  - Regional and racial/ethnic disparities

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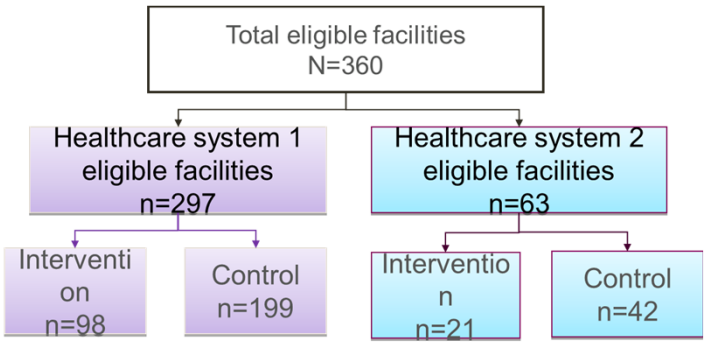
Facilities



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PROVEN: Primary Outcome

- 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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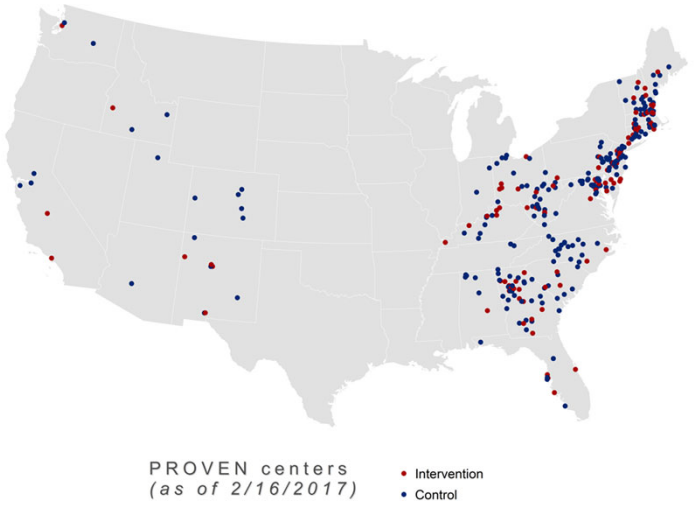
Distribution of PROVEN nursing homes



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PROVEN: 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 home systems want to participate in PROVEN?

- Medicare rehospitalization penalty prompted hospitals to build networks of low rehospitalization providers
- ACOs trying to control post-acute spending
- CMS implementing a re-hospitalization penalty to apply to SNFs in 2018
- Leadership views goal 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
- ACP Implementation viewed as a challenge for both

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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 trainings and orientations with newly-hired implementation liaisons.
  - Began including implementation liaisons on our monthly steering committee calls.

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Healthcare system partners

- CHALLENGE #2: turnover in 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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Health Care System Partners

- 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

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Healthcare system partners

- CHALLENGE #3: 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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Lessons & implications 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 advance directives
- 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 still a challenge even if MDs & NPs can be reimbursed

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Lessons and implications for PCTs

- 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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Case Study: ALIGN

Aligning Medications with What Matters Most

Ariel Green, MD, MPH, PhD
Johns Hopkins University School of Medicine

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ALIGN objective

- To **refine and pilot** a workflow in which an embedded clinical pharmacist makes deprescribing recommendations to the primary care provider (PCP) to reduce medication regimen complexity for people living with dementia (PLWD) and their care partners

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ALIGN aims

1) Assess the feasibility and acceptability of ALIGN in two different health care systems.

2) Determine the feasibility of the primary and secondary outcome measures for the subsequent ePCT:

- Primary outcome: Medication Regimen Complexity Index (MRCI)
- Secondary outcome: Family Caregiver Medication Administration Hassles Scale (FCMAHS)

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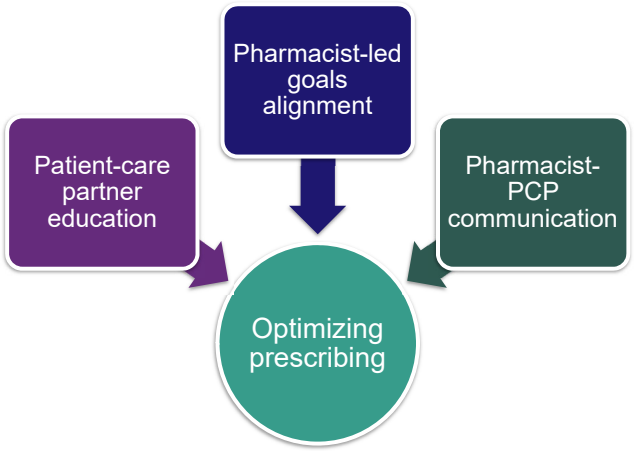
ALIGN intervention



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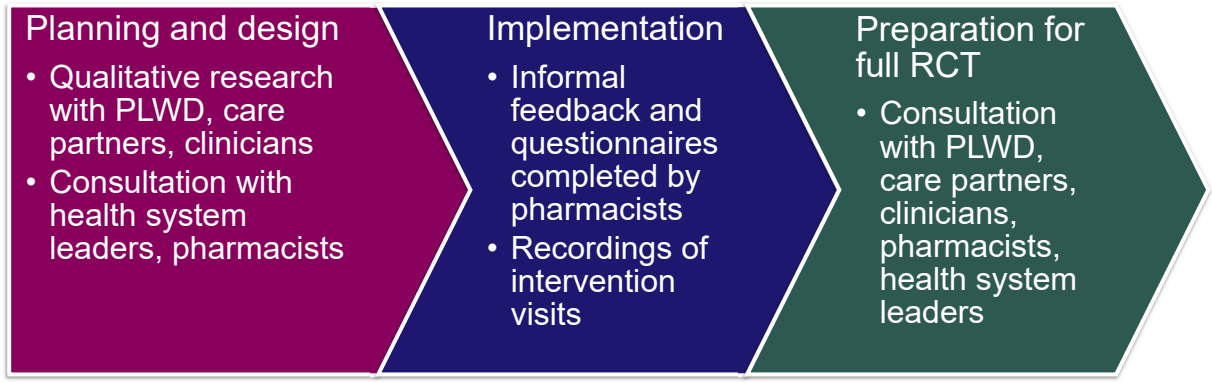
Methods of engaging stakeholders in ALIGN



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Laying the groundwork: Lessons from qualitative research

- Observational study (N=93)
  - Primary care encounters of older adults with cognitive impairment in SAME Page trial
- In-depth individual interviews (N=49)
  - Older adults with cognitive impairment, caregivers and primary care clinicians (PCPs) in OPTIMIZE trial

Green, et al. J Gen Intern Med. 2020 Jan;35(1):237-246.2020 and Dec;35(12):3556-3563.

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Laying the groundwork

Frame deprescribing as routine and positive

"[The doctor] would say, 'At your age, you probably have lived a good, long life.' I didn't like that because I would like to preserve her forever." (Caregiver)

"These medications take years or decades to have an effect. And I think that we should focus on what can help you right now." (Clinician)

Align deprescribing with goals

"What medications do they really need? … It's not going to make things better." (Caregiver)

"I fought for the Ativan because… I know what we go through… I hear what they are saying but I will take that chance." (Caregiver)

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Laying the groundwork

Engage entire health care team

"We rely on [clinical pharmacists]... We need their help sorting through it [or] giving us guidance on... the best plan to wean [a medication]." (Clinician)

Provide direct-to-patient educational materials and suggested language for clinicians

"[The brochure] is a good conversation starter [for older adults who may be accustomed to a time when] you did not question the doctor." (Caregiver)

"It's not an easy conversation to say, 'I think your life expectancy is about 3 years and this statin is not going to benefit you.'" (Clinician)

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ALIGN brochure

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Engagement during planning phase

- Medical director and Director of Ambulatory Pharmacy Services:
  - Identified existing staff that can deliver intervention as part of existing initiatives for high-risk Medicare beneficiaries
  - Minimized impact of research process on clinical operations

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Engagement during planning phase

- Clinical pharmacists
  - Modified existing comprehensive medication management templates to add focus on goals of care and deprescribing
  - Edited language in templates to be more natural and concise
  - Developed Epic smartphrases and drop-down menus to make templates easy to use
  - Developed workflow for communication with PCPs
  - Served as champions within clinics

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Excerpt from pharmacist template

- What are your most important goals for [patient]'s health care for the next 6 months to a year?
- Some people say they want to do everything they can to prevent future illness, such as heart attacks and strokes, even if it means taking additional medicines or experiencing side effects. Others say they want to focus more on comfort than prevention of things that may happen down the road. In general, which would you say is more important for [patient] now?
- If we changed [patient]'s medicines, what do you wish we could help with?

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Pharmacist feedback during implementation

- "I have a routine...so [the script] will take some getting used to."
- "Any adjustments have to be made in partnership with the specialist...Time-consuming in terms of coordinating that everyone is in agreement."
- "Many of these patients are on so many medications and I don't know them...It has been taking me ~2-3 hours per patient...Phone call, chart review, follow-up phone call and then follow-up materials sent to them."
- "I was pleased with how appreciative [the] care partners [were]. I think they appreciated having someone ask what's important to them and what their concerns are."

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Preparing for full RCT

- Creating advisory panels of care partners, clinicians, pharmacists, health system leaders to provide advice on:
  - Patient identification and recruitment
  - Language for goals elicitation
  - Core components of intervention for scaling
  - Relevance of patient and care partner-centered outcome measures

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Conclusion

- Importance of understanding and aligning with real-world priorities
  - Patients and care partners: Understanding needs, tailoring language
  - Primary care clinicians: Embracing expertise of multidisciplinary team to relieve time pressures
  - Health system leaders: Aligning intervention with existing health system priorities and clinical workflows
  - Pharmacists: Building on existing workflows and templates, adapting to challenges encountered during implementation
- ALIGN is benefiting from strong partnerships and champions, identification of priorities and perspectives

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Case Study: HAS-QOL

The Hospice Advanced Dementia Symptom Management and Quality of Life Trial

Abraham Brody, PhD, RN, FAAN
Hartford Institute for Geriatric Nursing
NYU Rory Meyers College of Nursing

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Acknowledgement

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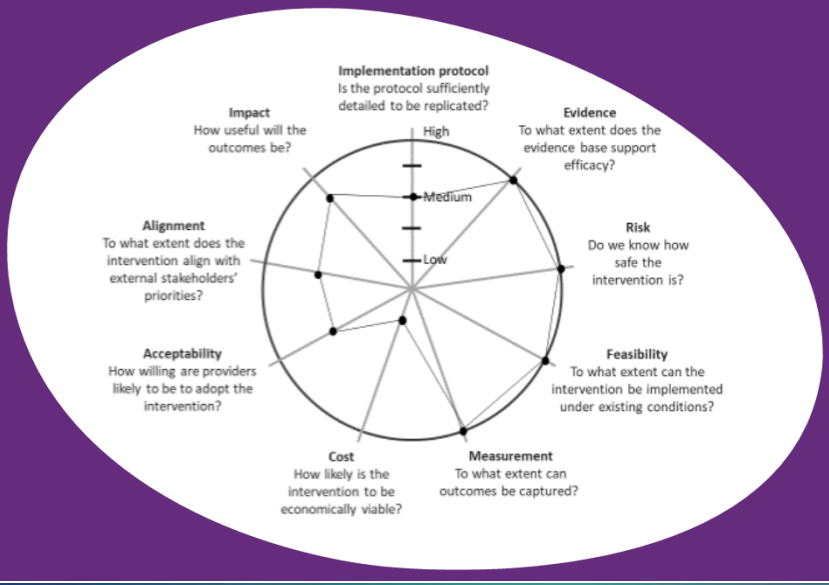

Pre-Pilot Readiness Assessment for Pragmatic Trials (RAPT) Diagram

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Baier, Jutkowitz, Mitchell, McCreedy & Mor, 2019
DOI: 10.1186/s12874-019-0794-9

R61 Purpose

- To sequentially test and adapt Aliviado Dementia Care for use by the hospice interdisciplinary team through stakeholder input

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R61 Aims

01

Establish the infrastructure necessary for implementing a pragmatic clinical trial of Aliviado Dementia Care.

02

Further tailor the Aliviado program specifically for hospice IDT members caring for PLWD receiving end of life care and adapt for wide-scale implementation in hospice.

03

Pilot test the complete protocol in 2 hospice agencies and refine the protocol further based on feedback from the pilot agencies.

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R61 Methods of Engaging Staff

- Pre-Implementation huddles with executive Leadership and data managers at each hospice
- Post-champion training focus group with champions
- Post-online training program evaluations
- Follow up telephone calls with champions at 1-week, 1 month

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R61 Milestones

- 1) Feasibility. Milestone: completion of all required education and training by at least 80% of eligible hospice IDT members
- 2) Applicability. Milestone: post-implementation surveys indicating 80% of IDT members feel the program is applicable to their work and that they will implement changes in their practice
- 3) Fidelity. Milestone: at least 75% of advanced dementia patients receiving home hospice having at least 1 care plan or assessment instrument utilized within the month following implementation.

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R61 Methods

Modify Intervention	Pilot Test Hospice 1	Update Intervention	Pilot Test Hospice 2
Update tools and begin process of developing additional tools	Single east coast hospice; learn about EHR integration, available resources, data	Develop MD/NP Modules, HHA Videos, Update existing content, begin developing mobile app	Test for milestones, data collection, EHR integration, Outcome measures

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Stakeholder Engagement Led to:

- Flexibility in how we collect data because of the limited flexibility of hospice EHRs
- Creation of a mobile health app with access to the tools and tracking of results over time***
- Spanish language tools, home health aide training requested by sites
- Modification of social work and chaplain tools to even further de-medicalize

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Stakeholder Engagement Led to:

- Substantial Implementation Enhancements
  - Creation of QAPI templated plans for champions
  - Continuing monthly champion calls beyond 6 months
  - Implementing automated, personalized, nudge push notifications and emails that are discipline specific and thematic

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Sample Email

ALIVIADO
DEMENTIA CARE

Hey Ab,

Wow, how time flies! Aliviado Test is in full swing of implementing Aliviado Dementia Care. This is the week where everyone should be completing their training if they haven't already. At this point you should be implementing the Aliviado tools in real-world care if you haven't been already.

You did it! Congratulations on completing all your training. Now is the time to focus on putting what you learned into practice.

Tool of the week

Communication with Persons Living With Dementia is HARD! The Communication tip sheet in the Aliviado mobile app focuses on how you can better communicate how you are trying to help them, and also better understand their needs. This can reduce agitation and make it easier to perform care tasks.

We noticed you haven't logged into the Aliviado mobile app yet. If you need help accessing, please reply to this email and we'll get you all setup.

Thanks for reading!

The Aliviado Team

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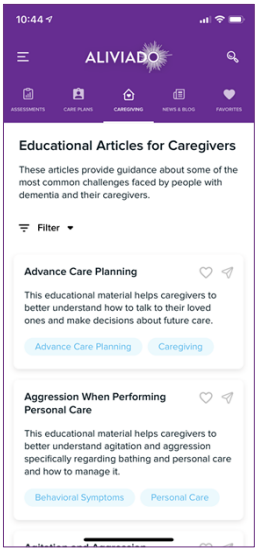
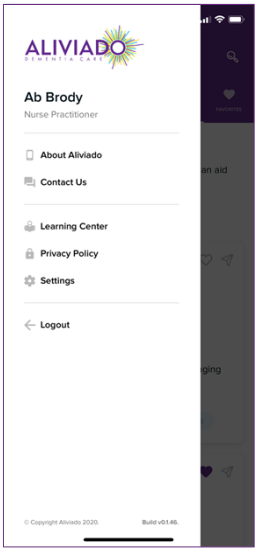
Mobile App





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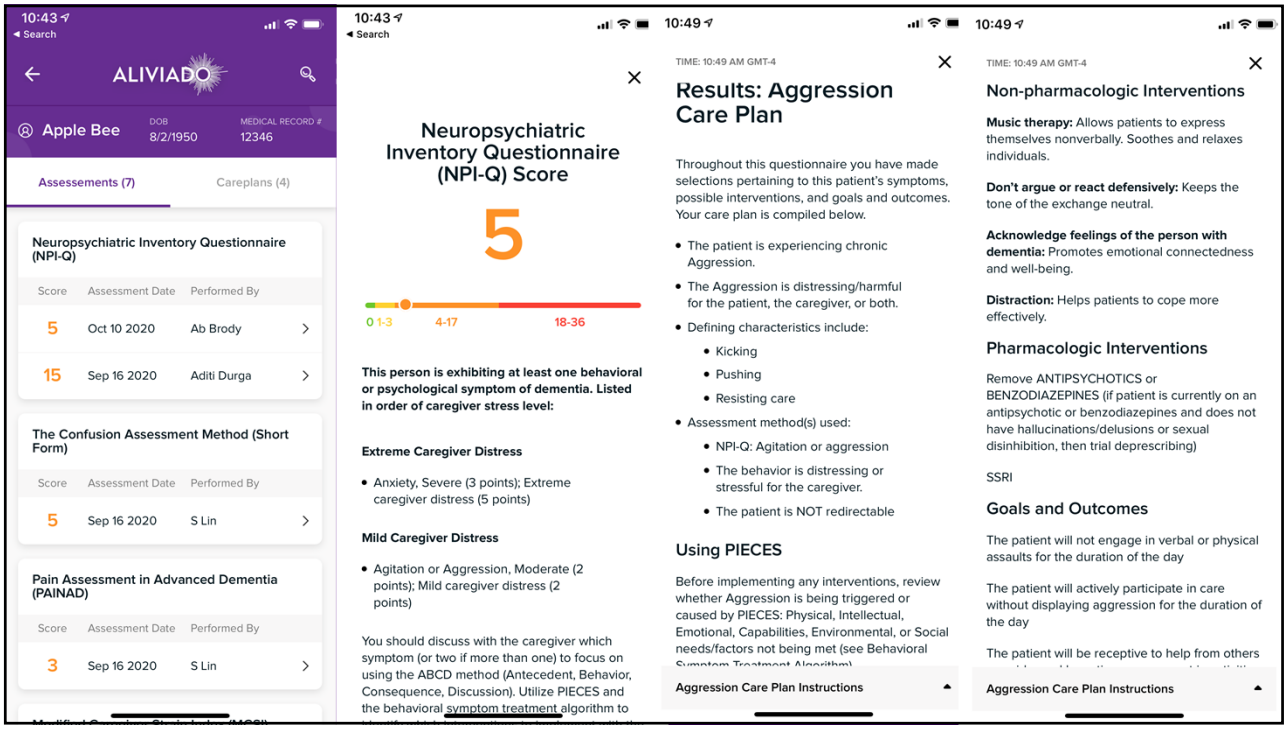
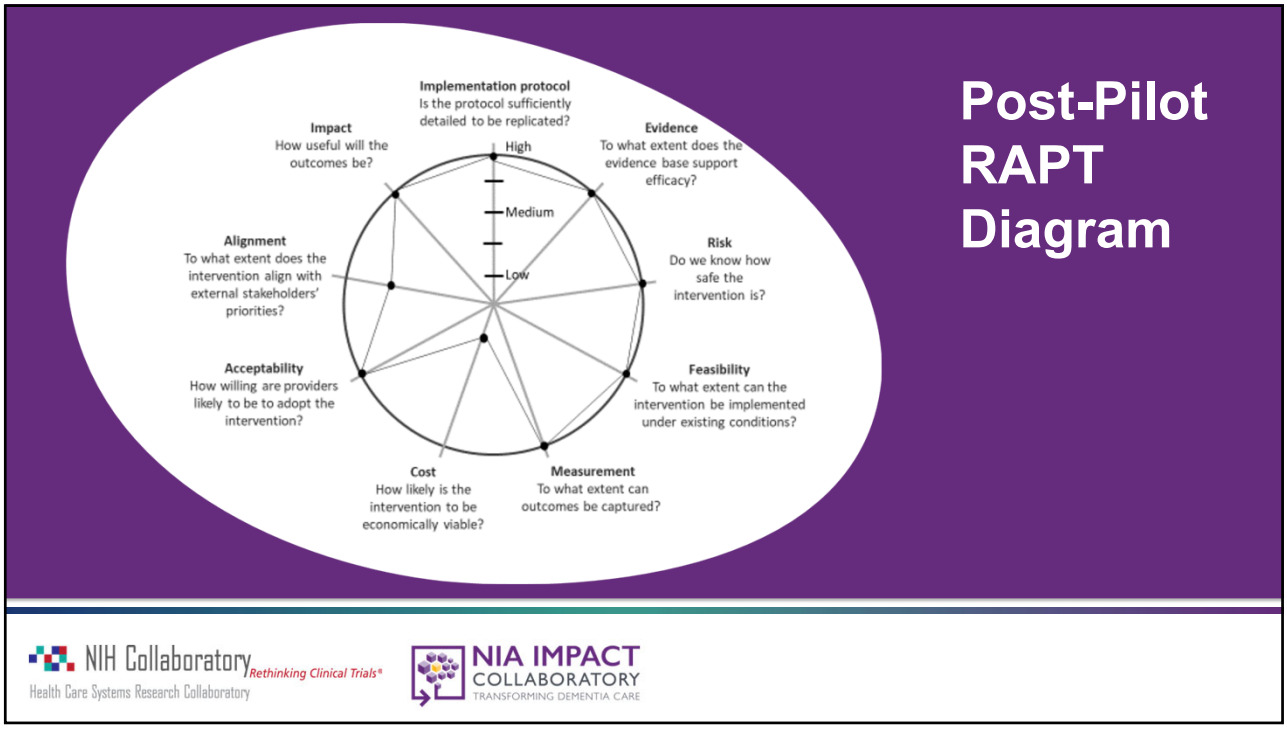

10:43
Search
ALIVIADO
Apple Bee
DOB
8/2/1950
MEDICAL RECORD #
12346
Assessements (7)
Careplans (4)
Neuropsychiatric Inventory Questionnaire (NPI-Q)
Score
Assessment Date
Performed By
5
Oct 10 2020
Ab Brody
15
Sep 16 2020
Aditi Durga
The Confusion Assessment Method (Short Form)
Score
Assessment Date
Performed By
5
Sep 16 2020
S Lin
Pain Assessment in Advanced Dementia (PAINAD)
Score
Assessment Date
Performed By
3
Sep 16 2020
S Lin
10:43
Search
Neuropsychiatric Inventory Questionnaire (NPI-Q) Score
5
0 1-3
4-17
18-36
This person is exhibiting at least one behavioral or psychological symptom of dementia. Listed in order of caregiver stress level:
Extreme Caregiver Distress
Anxiety, Severe (3 points); Extreme caregiver distress (5 points)
Mild Caregiver Distress
Agitation or Aggression, Moderate (2 points); Mild caregiver distress (2 points)
You should discuss with the caregiver which symptom (or two if more than one) to focus on using the ABCD method (Antecedent, Behavior, Consequence, Discussion). Utilize PIECES and the behavioral symptom treatment algorithm to
10:49
TIME: 10:49 AM GMT-4
Results: Aggression Care Plan
Throughout this questionnaire you have made selections pertaining to this patient's symptoms, possible interventions, and goals and outcomes. Your care plan is compiled below.
The patient is experiencing chronic Aggression.
The Aggression is distressing/harmful for the patient, the caregiver, or both.
Defining characteristics include:
Kicking
Pushing
Resisting care
Assessment method(s) used:
NPI-Q: Agitation or aggression
The behavior is distressing or stressful for the caregiver.
The patient is NOT redirectable
Using PIECES
Before implementing any interventions, review whether Aggression is being triggered or caused by PIECES: Physical, Intellectual, Emotional, Capabilities, Environmental, or Social needs/factors not being met (see Behavioral
Aggression Care Plan Instructions
10:49
TIME: 10:49 AM GMT-4
Non-pharmacologic Interventions
Music therapy: Allows patients to express themselves nonverbally. Soothes and relaxes individuals.
Don't argue or react defensively: Keeps the tone of the exchange neutral.
Acknowledge feelings of the person with dementia: Promotes emotional connectedness and well-being.
Distraction: Helps patients to cope more effectively.
Pharmacologic Interventions
Remove ANTIPSYCHOTICS or BENZODIAZEPINES (if patient is currently on an antipsychotic or benzodiazepines and does not have hallucinations/delusions or sexual disinhibition, then trial deprescribing)
SSRI
Goals and Outcomes
The patient will not engage in verbal or physical assaults for the duration of the day
The patient will actively participate in care without displaying aggression for the duration of the day
The patient will be receptive to help from others
Aggression Care Plan Instructions


Implementation protocol
Is the protocol sufficiently detailed to be replicated?
Impact
How useful will the outcomes be?
Evidence
To what extent does the evidence base support efficacy?
High
Medium
Low
Alignment
To what extent does the intervention align with external stakeholders' priorities?
Risk
Do we know how safe the intervention is?
Acceptability
How willing are providers likely to be to adopt the intervention?
Feasibility
To what extent can the intervention be implemented under existing conditions?
Cost
How likely is the intervention to be economically viable?
Measurement
To what extent can outcomes be captured?
Post-Pilot RAPT Diagram
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Resources:
Stakeholders Engagement and Planning for D&I From the Beginning

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

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

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

Integrating D&I Into ePCT Study Designs & Analysis

Speakers:

Geoffrey Curran, PhD
Director, Center for Implementation Research
Professor, Pharmacy Practice & Psychiatry
University of Arkansas for Medical Sciences
Research Health Scientist
Central Arkansas Veterans Healthcare System

Ellen McCreedy, MPH, PhD
School of Public Health Brown University

Patrick Heagerty, PhD
Professor, Biostatistics
University of Washington
School of Public Health

An Overview of Hybrid Designs

Geoffrey Curran, PhD
Director, Center for Implementation Research
Professor, Pharmacy Practice & Psychiatry
University of Arkansas for Medical Sciences
Research Health Scientist
Central Arkansas Veterans Healthcare System

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Learning goals

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

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Hybrid trial design

Trials with a focus on both patient and implementation outcomes

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Why Hybrid Trial Designs?

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

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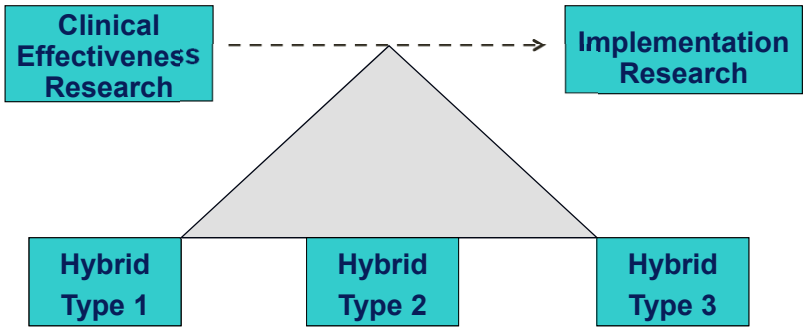
Types of Hybrids



Hybrid Type 1: test a clinical intervention, observe/gather information on implementation

Hybrid Type 2: test a clinical intervention, test/study an implementation strategy

Hybrid Type 3: test an implementation strategy, observe/ gather information on intervention's effectiveness

Type 1

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

Type 2

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

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Type 3

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

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Concluding points

- 1 This was a VERY brief summary!
- 2 ePCTs would usually be type 1 or 2, depending on
  - How ready you are to "test" an implementation strategy or strategies on "summative" implementation outcomes
    - "Just" want to describe implementation during the trial and prepare for more work later on "real world" implementation strategies = 1
    - Ready to test the impact of "real world" strategies on implementation outcomes like adoption or fidelity = 2

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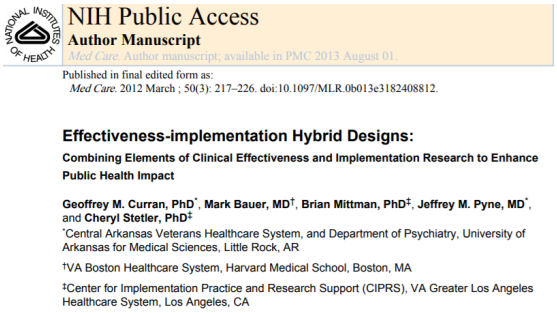
Concluding points

- 3 If you want to learn more…



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

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

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Contents lists available at ScienceDirect

Psychiatry Research

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

An introduction to effectiveness-implementation hybrid designs

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What about METRicAL?

- Consistent with hybrid type 2 (pilot version)
- Trial of competing music therapy approaches
  - Personalized music selections (favorite songs)
  - Preferred genre music selection
- Consistent use of 3 implementation strategies
  - Training(s)
  - Implementation guide
  - coaching

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Resources

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

IMPACT Training Modules ePCT Video Learning Library

www.impactcollaboratory.org

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Case Study: METRIcAL

Music & MEmory: A Pragmatic TRIal for Nursing Home Residents with ALzheimer's Disease

Ellen McCreedy, MPH, PhD
School of Public Health
Brown University

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Acknowledgements

- METRIcAL: Music & MEmory: A Pragmatic TRIal for Nursing Home Residents with ALzheimer's Disease
  - NIA R21AG057451 (PI: Vincent Mor)
  - NIA R33AG057451 (PI: Vincent Mor)
- METRIcAL Team: Rosa Baier, James Rudolph, Kali Thomas, Roee Gutman, Renee Shield, Tingting Zhang, Jeff Hiris, Jessica Ogarek, Faye Dvorchak, Rebecca Uth, Laura Dionne, Esme Zediker, Miranda Olson, Natalie Davoodi, Ennie Zhu, Angelina Ossimetha
- The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of the funder.

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Background

- Drugs used to manage agitated behaviors in nursing home residents with dementia increase the risk of falls and death
- Reminiscence therapies may reduce agitated behaviors resulting from boredom, social isolation, or sensory deprivation by eliciting long-stored memories
- In Music & Memory, the music a resident preferred when s/he was young is put on a personalized music device (mp3 player) and played at early signs of agitation
- Effectiveness evidence for Music & Memory and other nonpharmacological approaches for managing behaviors is lacking

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Research Study

- Music & MEmory: A Pragmatic TRIal for Nursing Home Residents with ALzheimer's Disease (METRIcAL) – R21 / R33 Mechanism
- The purpose of the trial is to assess the real-world effectiveness of a personalized music intervention for management of agitated behaviors in nursing home residents with dementia.
- Examine factors associated with variation in providers' adherence to the implementation of intervention.

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Hybrid Design? (A Disclaimer)

- This session focuses on effectiveness-implementation hybrid designs
- This trial was not designed using the hybrid definitions presented, but, rather, using the NIH Stage Model for Behavioral Intervention Development
- However, the trial meets many of the criteria of a pilot hybrid type 2

Landes SJ, McBain SA, Curran GM. An introduction to effectiveness-implementation hybrid designs. Psychiatry Res. 2019 Oct;280:112513.

Outline

- Study overview
- Highlight key design features
- Discuss points of alignment with hybrid type 2 trial

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METRIcAL

- Conducting two cluster-randomized, parallel trials evaluating the effectiveness of a personalized music intervention for agitated behaviors in nursing home residents with dementia
- Each trial enrolled 54 nursing homes (27 treatment, 27 control); ~800 residents per trial
- Both trials have the same primary and secondary outcomes
- Both trials have the same implementation evaluation metrics
- However, the intervention differs between the two trials

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Original Trial Design

- Stepped-wedge design with primary outcome measured in the first year in a subset of facilities (parallel design)

	Period 1 (June, 2019 - January, 2020)	**Period 2** (April, 2020 - November, 2020)	**Period 3** (February 2021 - September, 2021)
Sequence 1 (27 Nursing Homes)	Intervention*† (405 residents)	Intervention* (405 residents)	Intervention* (405 residents)
Sequence 2 (27 Nursing Homes)	Control*† (405 residents)	Intervention* (405 residents)	Intervention* (405 residents)
Sequence 3 (27 Nursing Homes)	Control* (405 residents)	Control* (405 residents)	Intervention* (405 residents)

*Administrative data (MDS, EHR) used to evaluate secondary study outcomes in all periods for all sequences

†Primary outcome data (CMAI) collected in Sequence 1 and Sequence 2 during Period 1 only

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The Striking Racial Divide in How Covid-19 Has Hit Nursing Homes

Homes with a significant number of black and Latino residents have been twice as likely to be hit by the coronavirus as those where the population is overwhelmingly white.

Exclusive: Nearly Half of U.S. Nursing Homes Have Staff Infected With COVID-19

An AARP analysis also finds a quarter of facilities are short on workers and PPE

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Effect of the pandemic on study design

- We chose the stepped-wedge design because…
  - Need for sequential rollout
  - Desire for all clusters to receive the intervention
  - Likely to be an efficient design for anticipated intra-cluster correlation and cluster size
- BUT… stepped-wedge design is sensitive to confounding by time, particularly when time is correlated with the study outcome due to a secular trend (like increased agitation during a national pandemic)
- LUCKILY…we chose the CMAI as our primary study outcome and we were powered for a stand alone parallel trial (Period 1 Only)

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FOR RATIONALE FOR USING STEPPED WEDGE: Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. Bmj. 2015 Feb 6;350:h391.

Stepped-Wedge Interrupted by Pandemic

	Period 1 (June, 2019 - January, 2020)	**Period 2** (April, 2020 - November, 2020)	**Period 3** (February 2021 - September, 2021)
Sequence 1 (27 Nursing Homes)	Intervention*† (405 residents)	Coronavirus pandemic*	Intervention* (405 residents)
Sequence 2 (27 Nursing Homes)	Control*† (405 residents)	Coronavirus pandemic*	Intervention* (405 residents)
Sequence 3 (27 Nursing Homes)	Control* (405 residents)	Coronavirus pandemic*	Intervention* (405 residents)

*Administrative data (MDS, EHR) used to evaluate study outcomes in all periods for all sequences

†Primary data (CMAI) collected in Sequence 1 and Sequence 2 during Period 1 only

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Conduct a second parallel trial

	Period 1 (June, 2019 - January, 2020)	**Period 2** (April, 2020 - November, 2020)	**Period 3** (February 2021 - September, 2021)
Sequence 1 (27 Nursing Homes)	Intervention*† (405 residents)	Coronavirus pandemic*	Intervention* (405 residents)
Sequence 2 (27 Nursing Homes)	Control*† (405 residents)	Coronavirus pandemic*	Intervention*† (405 residents)
Sequence 3 (27 Nursing Homes)	Control* (405 residents)	Coronavirus pandemic*	Control*† (405 residents)

*Administrative data (MDS, EHR) used to evaluate study outcomes in all periods for all sequences

†Primary data (CMAI) collected in Sequence 1 and Sequence 2 during Period 1 only

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Second parallel trial

- Already completed recruitment and enrollment
- Sequence 2 & 3 were already balanced at baseline (post-randomization)
- **Opportunity to learn from first trial**
- Cluster-randomized adaptive trial (see protocol)

McCreedy EM, Gutman R, Baier R, Rudolph JL, Thomas KS, Dvorchak F, Uth R, Ogarek J, Mor V. Measuring the effects of a personalized music intervention on agitated behaviors among nursing home residents with dementia: design features for cluster-randomized adaptive trial. Trials. 2021 Oct 7;22(1):681. doi: 10.1186/s13063-021-05620-y. PMID: 34620193; PMCID: PMC8496617.

Trial 1

- 8-month intervention (June, 2019 – January, 2020)
- Researchers conducted on-site data collection in 54 nursing homes (27 treatment & 27 control)
- Data were collected at three site visits:
  - Pre-intervention (Baseline)
  - Mid-intervention (4-months)
  - End of intervention (8-months)
- Administrative (MDS and EMR) data was transferred monthly

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Trial 1 - Effectiveness

- No effect of the intervention on frequency of agitated behaviors

	Total, n=976	Intervention, n=483	Control, n=493	AME (SE) [95% CI]
Total **CMAI** score, Mean (SE) Source: Staff Interview Primary outcome	49.65 (1.64) [46.44 , 52.86]	50.67 (1.94) [46.87 , 54.47]	49.34 (1.68) [46.05 , 52.63]	1.33 (1.38) [-1.37 , 4.03]
Total **ARBS** score, Mean (SE) Source: Minimum Data Set Secondary outcome	0.43 (0.11) [0.22 , 0.64]	0.35 (0.13) [0.10 , 0.60]	0.46 (0.11) [0.25 , 0.67]	-0.11 (0.10) [-0.30,0.08]

Abbreviations: CMAI, Cohen-Mansfield Agitation Inventory; ARBS, Agitated and Reactive Behavior Scale; SE, standard error; AME, average marginal effect

Trial 1 - Effectiveness

- No statistically significant effects of the intervention on medication use, but near significant findings for antipsychotics

	Total, n=976	Intervention, n=483	Control, n=493	AME (SE) [95% CI]
Proportion of residents with any **antipsychotic** use in the past week, Mean (SE)	28.1 (1.0) [26.2 , 30.0]	26.2 (1.4) [23.4 , 29.0]	29.6 (1.3) [27.2 , 32.3]	-3.61 (1.85) [-7.22, 0.00]
Proportion of residents with any **antidepressant** use in the past week, Mean (SE)	58.1 (1.1) [56.0 , 60.3]	57.5 (1.5) [54.6 , 60.5]	58.8 (1.5) [55.8 , 61.7]	-1.26 (2.05) [-5.28, 2.76]
Proportion of residents with any **antianxietal** use in the past week, Mean (SE)	22.6 (1.2) [20.2 , 25.0]	20.8 (1.5) [17.8 , 23.8]	24.3 (1.7) [20.9 , 27.6]	-3.47 (2.08) [-7.55, 0.06]

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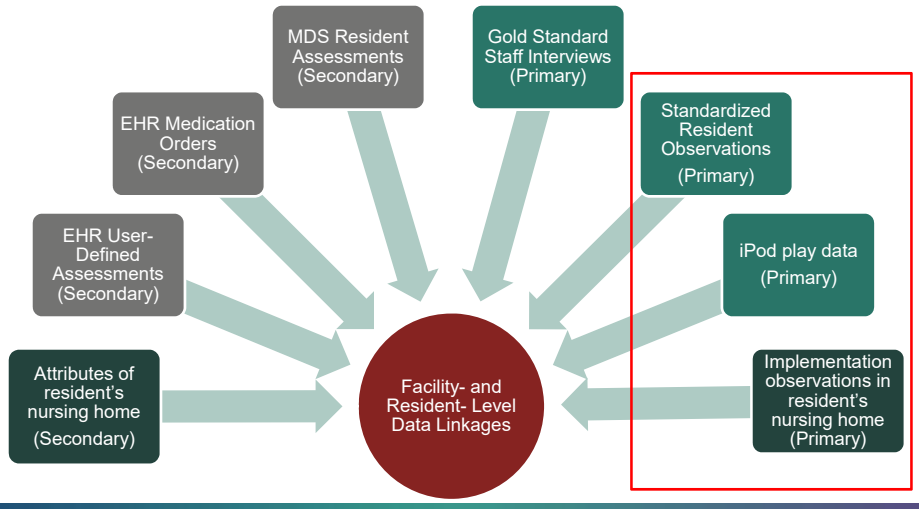
Trial 1 – Implementation Data



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Trial 1 - Implementation data

- **iPod play data**
  - Degree of playlist personalization
  - Dose (minutes per day exposed)
- **Structured observations**
  - Complete labeling of individual headphones / iPods
  - Accessibility of iPods by nursing staff
- **Initial use forms**
  - Date music started with resident (used for dose)
  - Reason music used with resident
  - Method and time spent identifying resident preferred music
- **Staff interview**
  - Frequency of nursing staff use of music with resident

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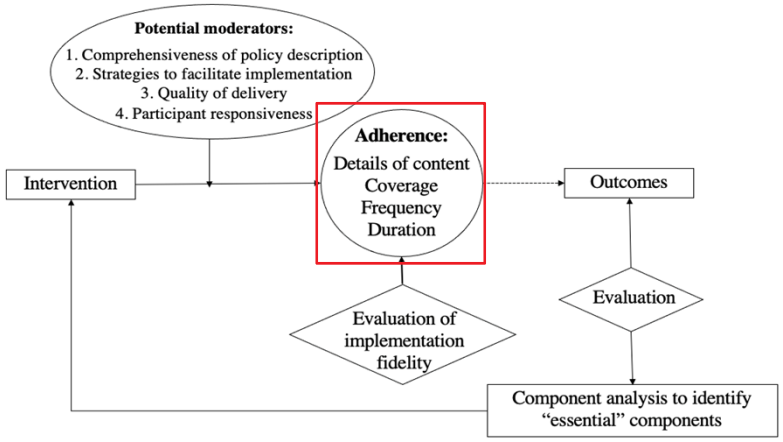
Trial 1 – Implementation Fidelity



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Reference: Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation science. 2007 Dec;2(1):1-9.

Trial 1 – Implementation Fidelity

FIF Adherence Dimension	Definition	Distribution
1. **Details of content**	Adherence to core components of intervention protocol: personalization of playlists, processes for labeling, storing and charging equipment, engaging multidisciplinary team	Range: 7.0–14.0 Mean (SD): 9.6 (2.0)
2. **Coverage**	Total number of residents exposed intervention	Range: 5.0–19.0 Mean (SD): 13.5 (3.7)
3. **Frequency**	Proportion of targeted residents with nurses administering the music at least once per week	Range: 0.0–1.0 Mean (SD): 0.4 (0.3)
4. **Duration**	Median minutes of music per resident exposed day	Range: 0.0–86.9 Mean (SD): 28.5 (23.4)

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Trial 1 Learnings

- Process for identifying and loading preferred music for residents with dementia was time consuming and affected coverage
- Music identification process completed by activities staff, intervention never "owned" by nursing
- Intervention being used but lack of clinical targeting
- If want music to be substitute for PRN medication use, need a solution that can be owned by nursing staff from the beginning

McCreedy E, Sisti A, Gutman R, Dionne L, Rudolph J, Baier R, Thomas K, Olson M, Zediker E, Uth R, Shield R, Mor V. Pragmatic Trial of Personalized Music for Agitation and Antipsychotic Use in Nursing Home Residents with Dementia. (Revise and Resubmit)

Olson M, McCreedy E, Baier R, Shield R, Zediker E, Uth R, Thomas K, Mor V, Gutman R, Rudolph J. Measuring Implementation Fidelity in a Cluster-Randomized Embedded Pragmatic Clinical Trial (ePCT): A Complex Intervention Used in US Nursing Homes. (Submitted)

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Modifications

	Trial 1	Trial 2
Intervention	• Resident preferred music identified by activities staff through trial-and-error process • Activities staff load music on iPods	• Resident "preferred" music predicted using play data from first trial • Research staff load music on iPods before sending to nursing homes
Implementation	• Study consultants and corporate representatives co-lead training for participating nursing homes • Study consultants and corporate representatives co-lead monthly coaching calls	• Corporate representatives lead training (no study consultant participation) • Corporate representatives lead monthly coaching calls (no study consultant participation)

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Other features of adaptive design

- **Increasing enroll residents who are likely to benefit from the program**
  - Identify resident and clinical characteristics associated with more play time
  - Examine midpoint selection from the first trial
- **Equilibrate researcher-collected measure of agitation to administrative measure**
  - Administrative data subject to under-detection
  - Collecting gold standard measure allows for more complete representation of outcomes, but resource intensive
  - Collecting both types of data in the current study allows us to create an imputation model that may be used in future studies to reduce data collection burden

Hybrid type 2

- Dual focus on the clinical intervention and implementation related factors
- Explicit measurement of implementation outcome (e.g., adoption, fidelity)
- Pilot test an implementation strategy aimed at increasing use and fidelity of the intervention

~~~~~~

- Conducted process evaluation during R21 pilot phase (Type 1)
- NOT primarily focused on implementation outcomes or directly comparing strategies (Type 3)

Landes SJ, McBain SA, Curran GM. An introduction to effectiveness-implementation hybrid designs. Psychiatry Res. 2019 Oct;280:112513.

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Conclusions

- Rigorous measurement of fidelity guided modifications in intervention and implementation strategies
- Hybrid and adaptive designs may shorten the time to useable evidence
- Don’t retrofit -- Plan to use hybrid and/or adaptive designs as part of your next submission!

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Integrating D&I Into ePCT Study Designs & Analysis

Patrick Heagerty, PhD
Professor, Biostatistics
University of Washington
School of Public Health

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Learning goals

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

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Important things to know

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

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NIH Collaboratory ePCT: STOP CRC

stop screen to prevent colon cancer

- 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 rates
  - Applied to clinical site → cluster randomization
- Unit of randomization: clinical site
- Two-arm cluster randomized trial (CRT)
  - Also referred to as a group-randomized or community randomized trial

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

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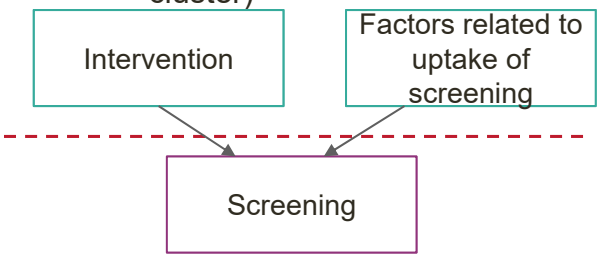
Reasons to randomize clusters instead of individuals

- 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

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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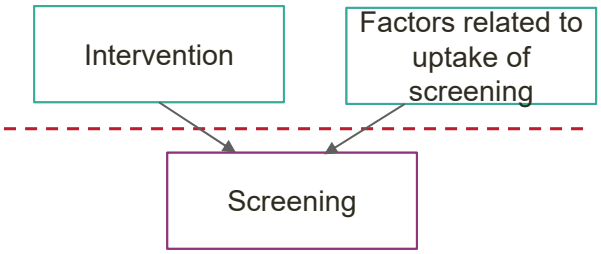
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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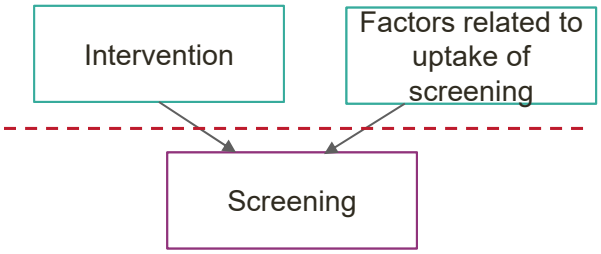
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (ie, 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 (ie, clusters)
- Each with 5 age-eligible patients: ie, who are not up to date with colorectal cancer (CRC) screening
- Binary outcome: refused screening (Y/N)

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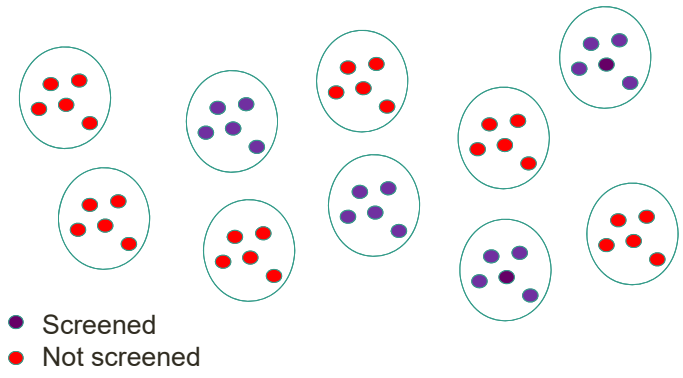
Understanding outcome clustering: complete clustering



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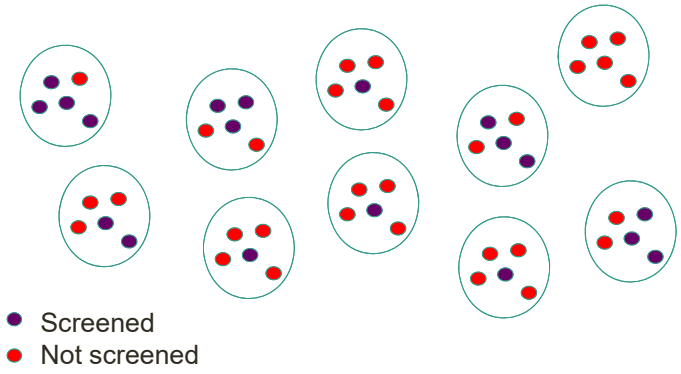
Understanding outcome clustering: some clustering



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Methods for pragmatic trials

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

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Summary of design issues

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

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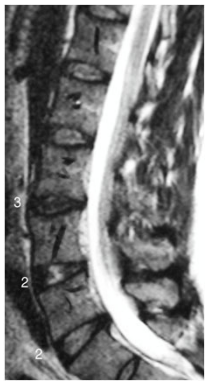
NIH Collaboratory ePCT: LIRE



- 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

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

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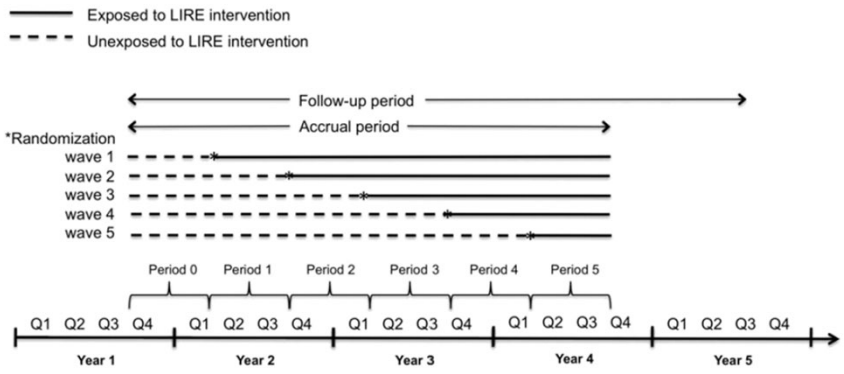
NIH Collaboratory ePCT: LIRE



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

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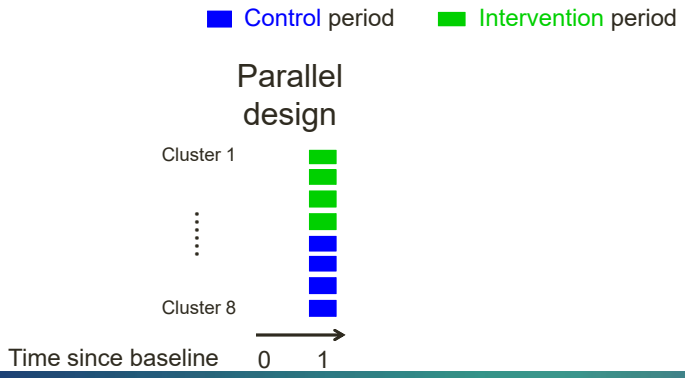
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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Based on: Hemming K, Lilford R, Girling AJ. 2015. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Stat Med. 34:181-196. doi:10.1002/sim.6325. PMID: 25346484

Types of CRT designs

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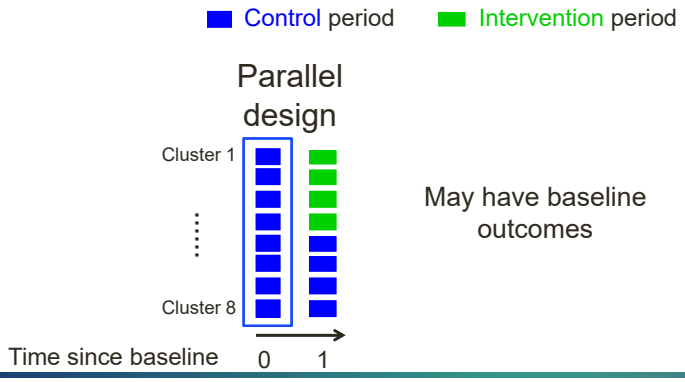

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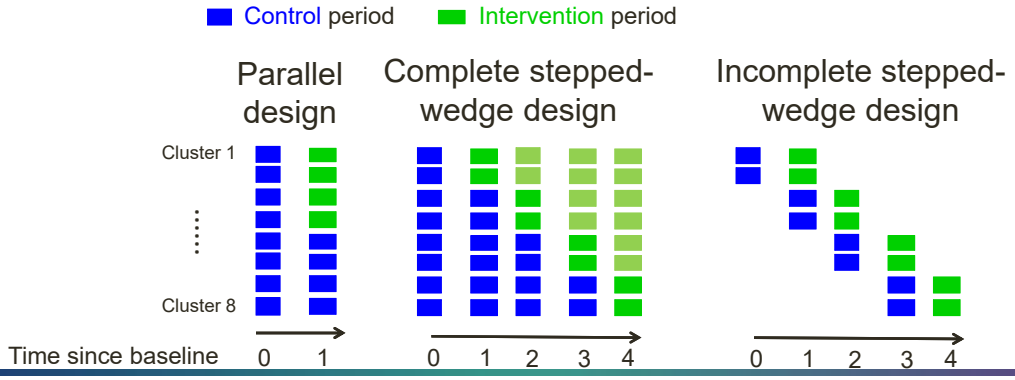

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  - A priori matching, stratification, or constrained randomization to create comparable sequences.
- The primary threats to internal and statistical validity are well known, and defenses are available.
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Challenges of pragmatic study design

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

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IMPACT Collaboratory: examples of analytic challenges and trade-offs

- Stepped wedge designs "roll out" over time and are more susceptible to disruption!
- Parallel group randomized designs are simple and powerful, but still need to address "clustering" for design and analysis.

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Resources

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

IMPACT Training Modules ePCT Video Learning Library

www.impactcollaboratory.org

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Resources:
Integrating D&I Into ePCT
Study Design and Analysis

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

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

- 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

Additional resources

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

Additional Considerations When Conducting ePCTS

Speakers:

Stephanie Morain, PhD, MPH
Johns Hopkins Berman Institute of Bioethics

Wendy Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH)

Jonathan Jackson, PhD
Executive Director, CARE Research Center, Massachusetts General Hospital Assistant Professor in Neurology, Harvard Medical School

Richard H. Fortinsky, PhD
UConn Center on Aging
University of Connecticut School of Medicine

Annette M. Totten, PhD
Oregon Health & Science University
Meta-LARC (a consortium of PBRNs)

Additional Considerations When Conducting ePCTS: Ethical and Regulatory

Stephanie Morain, PhD, MPH
Johns Hopkins Berman Institute of Bioethics

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Ethical and regulatory considerations: learning goals

- Learn about the regulatory and ethical challenges associated with both ePCTs and implementation research studies
- Understanding considerations for distinguishing QI versus research

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Important things to know

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

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ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions

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Evolving understanding of unique ethical/regulatory issues for ePCTs

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

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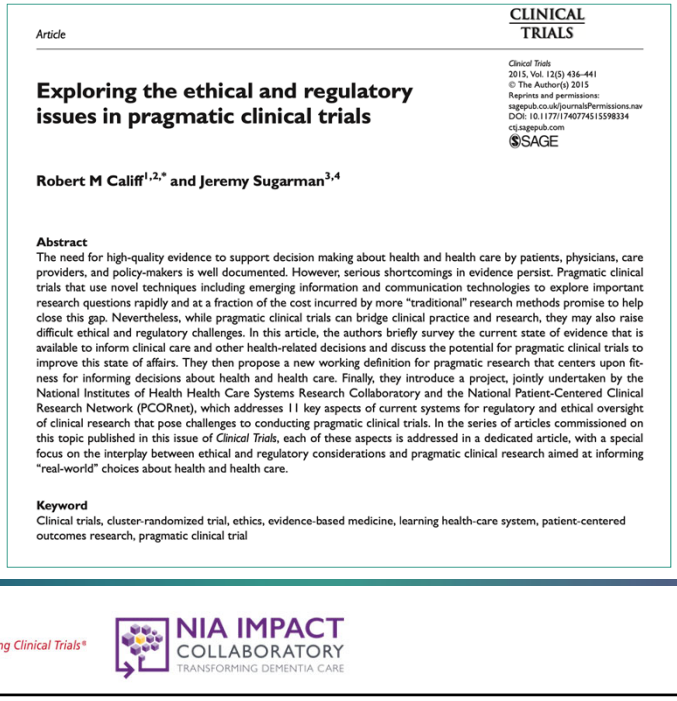

Article

CLINICAL TRIALS

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Exploring the ethical and regulatory issues in pragmatic clinical trials

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

Abstract

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

Keyword

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

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Current ethics/regulatory in flux

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Determining if the Common Rule applies

- ✓ The activity is conducted or supported by HHS
- ✓ The activity is non-exempt human subjects research

To determine whether the activity is non-exempt human subjects research, **ask these questions:**

1) Does the activity involve **research**?
2) Does the research involve **human subjects**?
3) Is the human subjects research **exempt**?

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Does the ePCT involve a research intervention?

Definition of research:

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

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Distinguishing QI versus research

- Quality Improvement activities are not subject to the Common Rule
- Quality Improvement activities are intended to improve the quality of a health care delivery locally
- Quality Improvement activities are not intended to contribute to generalizable knowledge

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Regulatory perspective: *Who are the subjects in ePCTs?*

Definition of human subject:

Human subject means a living individual about whom an investigator conducting research:

- obtains **information or biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

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Regulatory perspective: *Who are the subjects in ePCTs?*

Test Case:

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

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

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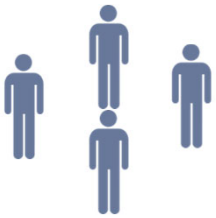
Regulatory & ethical challenges of ePCTs



Ethical, not regulatory, question:

Whose rights and welfare need to be protected?

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Types of participants in an ePCT

Direct Indirect

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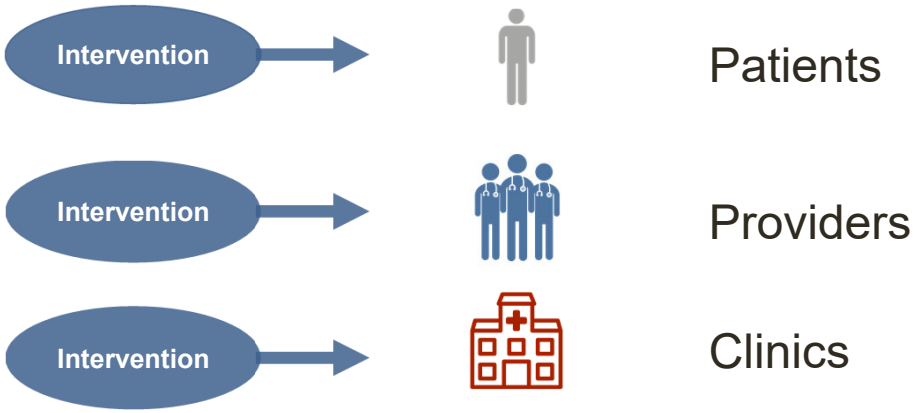
Direct participants

Immediate or mediated targets of the intervention



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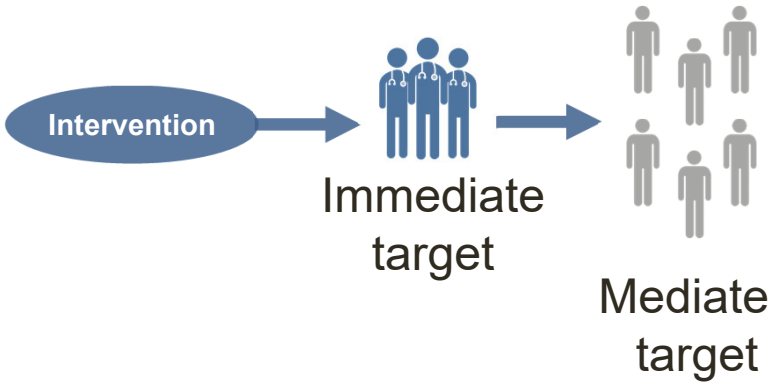
Direct participant



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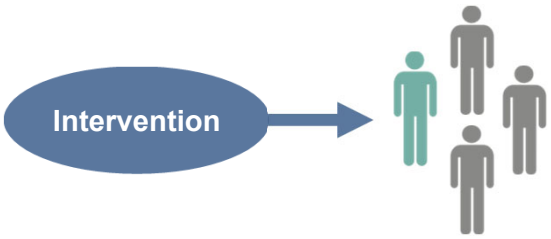
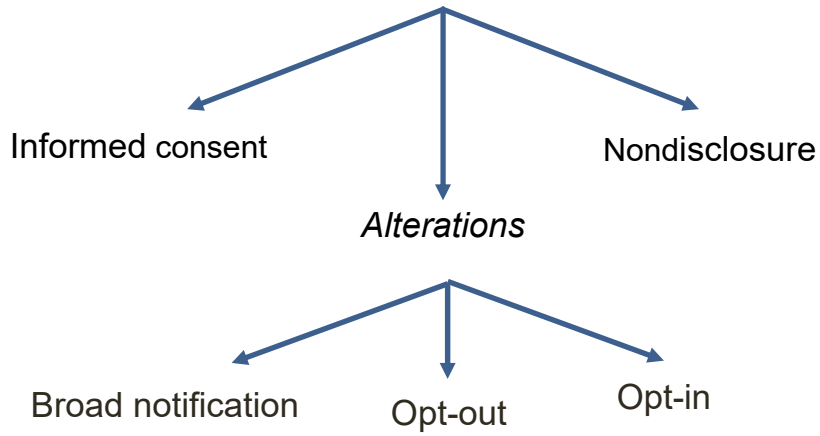
Indirect participants

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



Approaches to notification & authorization



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Criteria for Waiver/Alteration of Informed Consent

- The research involves no more than minimal risk
- The research could not be carried out practicably without the waiver or alteration
- The waiver or alteration will not adversely affect the rights & welfare of the subject, and
- Where appropriate, the subjects will be provided with additional information about their participation

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Working with human subjects oversight bodies

- Institutional review boards (IRBs)
- Data monitoring committees (DMCs) or data and safety monitoring boards (DSMBs)

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Requirement for single IRB review

Applicability

- US institutions engaged in cooperative research for the portion of the research conducted in the United States

- Does not apply:
  - When more than single IRB review is required by law (including tribal law)

  - Whenever any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context

Compliance date for sIRB provision: ***January 20, 2020***

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Data monitoring committee

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

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Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct
- Differential data collection/contact by study arm
- Level of data needed to change practice, especially when studying treatments in wide use?
- Are interim analyses actionable?

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

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Important things to do

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

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Resource: OHRP contacts and resources

- Submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Bookmark this page for quick reference to OHRP resources on the revised Common Rule: www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html

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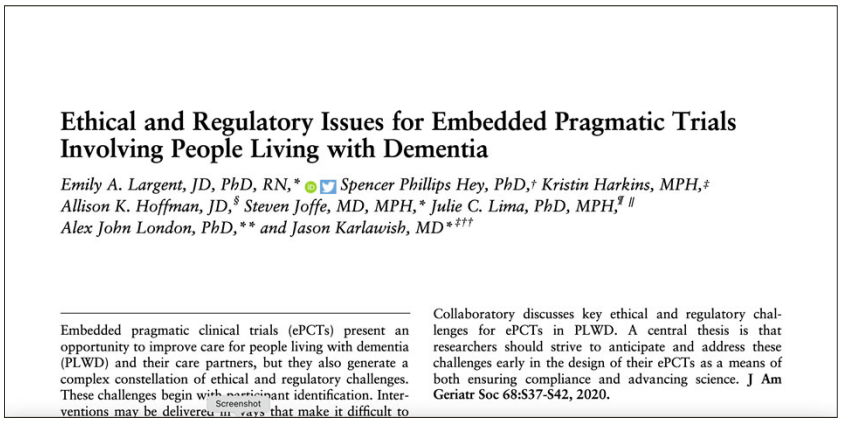
Resource



Ethical and Regulatory Issues for Embedded Pragmatic Trials Involving People Living with Dementia

Emily A. Largent, JD, PhD, RN, Spencer Phillips Hey, PhD,† Kristin Harkins, MPH,‡ Allison K. Hoffman, JD,§ Steven Joffe, MD, MPH,* Julie C. Lima, PhD, MPH,‖ ¶ Alex John London, PhD,** and Jason Karlawish, MD*‡††*

Embedded pragmatic clinical trials (ePCTs) present an opportunity to improve care for people living with dementia (PLWD) and their care partners, but they also generate a complex constellation of ethical and regulatory challenges. These challenges begin with participant identification. Interventions may be delivered in ways that make it difficult to

Collaboratory discusses key ethical and regulatory challenges for ePCTs in PLWD. A central thesis is that researchers should strive to anticipate and address these challenges early in the design of their ePCTs as a means of both ensuring compliance and advancing science. **J Am Geriatr Soc 68:S37-S42, 2020.**

Screenshot

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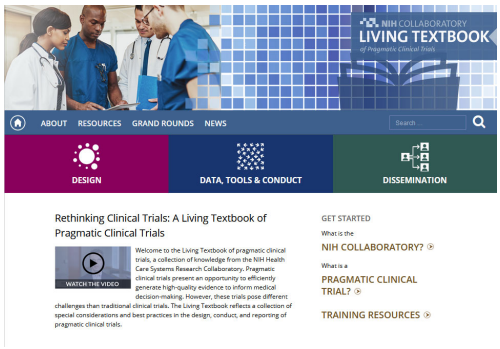
Resources

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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Additional Considerations When Conducting ePCTS: Pilot and Feasibility Testing

Wendy Weber, ND, PhD, MPH
National Center for Complementary and Integrative Health (NCCIH)

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Pilot and feasibility testing considerations: learning goals

- Identify approaches to evaluating the capabilities of the partner healthcare system and testing key elements of various types of interventions
- Describe the role of implementation readiness assessments in the pilot and feasibility phases of ePCTs

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Important things to know

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

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ePCTs are not efficacy trials

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

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During the pilot phase

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

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Build partnerships

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

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Aspects of feasibility that can be piloted

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

Use what you learn to design the ePCT

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Evaluate power calculations

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

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Quantify feasibility for pilot study aims

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

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

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Quantifying example 1

Demonstrate effective recruitment and retention, which we define as the ability to recruit an average of 10 patients per month per site and retain 80% of participants for final data collection at 6 months

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Quantifying example 2

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

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

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Quantifying example 3

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

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

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Ensuring trial readiness

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

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Readiness checklist

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

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In the end, good planning will help

- Avoiding silly mistakes
- Maximizing acceptability
- Maintaining affordability
- Remembering scalability

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Important things to do

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

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Resources

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

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

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Additional Considerations When Conducting ePCTs: A Framework for Achieving Health Equity in Pragmatic Trials

Jonathan Jackson, PhD
Executive Director, CARE Research Center, Massachusetts General Hospital
Assistant Professor in Neurology, Harvard Medical School

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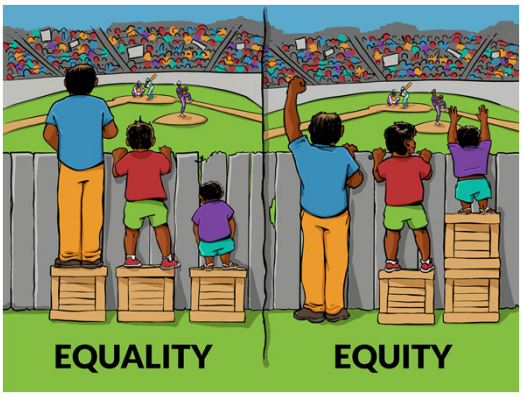
Learning goals

- Understand the meaning and importance of health equity in embedded pragmatic clinical trials (ePCTs)
- Recognize common barriers to ePCT equity using the PRECIS-2 framework



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https://interactioninstitute.org/illustrating-equality-vs-equity/ &
www.madewithangus.com

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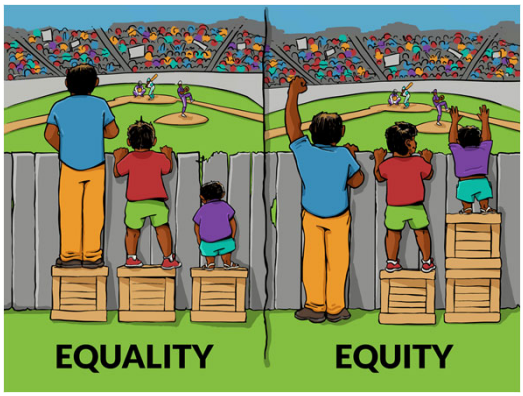
The Necessity of Health Equity in Research

- Helps us “level up” the health of individuals, groups, and communities with greatest need
- Must be front and center as we design and implement studies
- Without health equity, access may be undermined and effectiveness could be misrepresented



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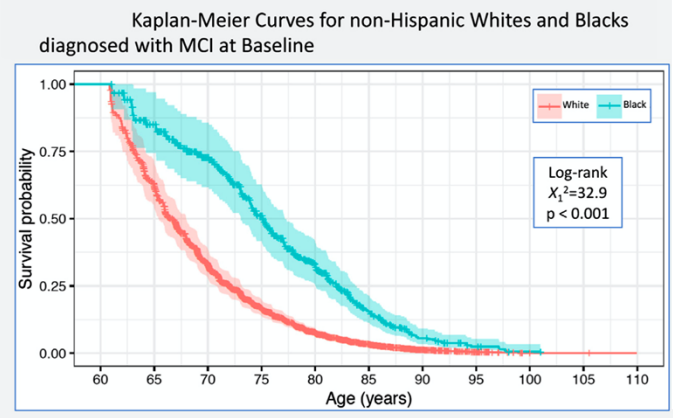

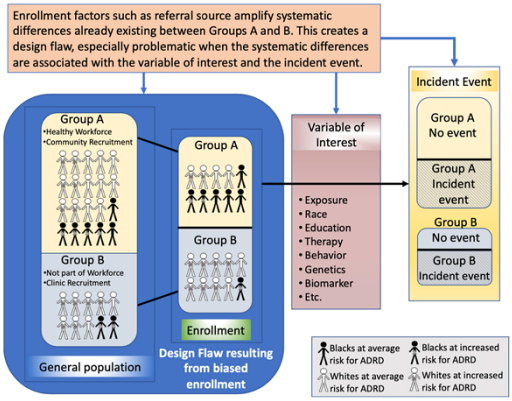

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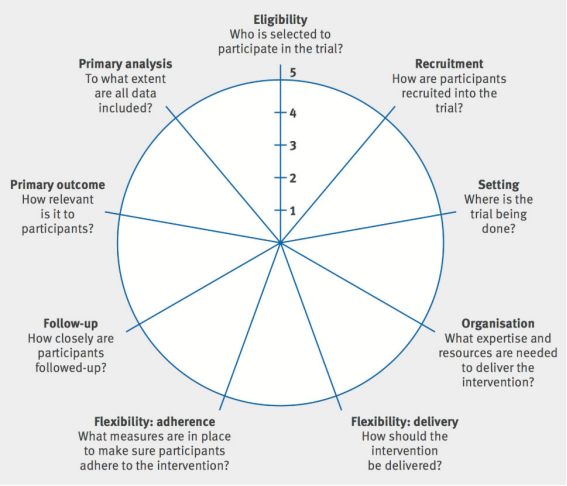
Gleason CE, et al. Association between enrollment factors and incident cognitive impairment in Blacks and Whites: Data from the Alzheimer's Disease Center. Alzheimers Dement. 2019;15(12):1533-45.

Develop and Disseminate Guidance

Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2): *http://www.precis-2.org/*

Enrollment bias occurs at every level of selection

- Not merely at participant level
- "Healthy worker bias" can occur at the level of the HCS too
- ePCT does not sidestep this issue



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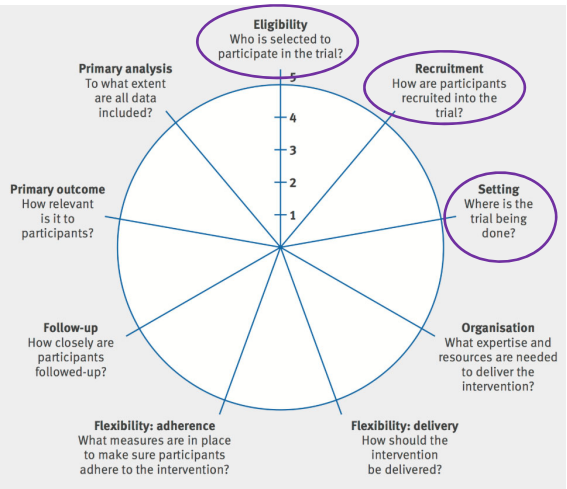
Quiñones AR, et al. Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers. JAGS 2020; 68(Suppl 2):S8-S13.

Health Equity Considerations Using PRECIS-2

Several selection factors in determining who will be involved in an ePCT

- Many healthcare systems (HCS) are segregated
- Willingness to participate may influence HCS selection, particularly HCSs serving minority populations
- Difficult to maintain accurate and complete identification of demographic characteristics in electronic health record (EHRs)



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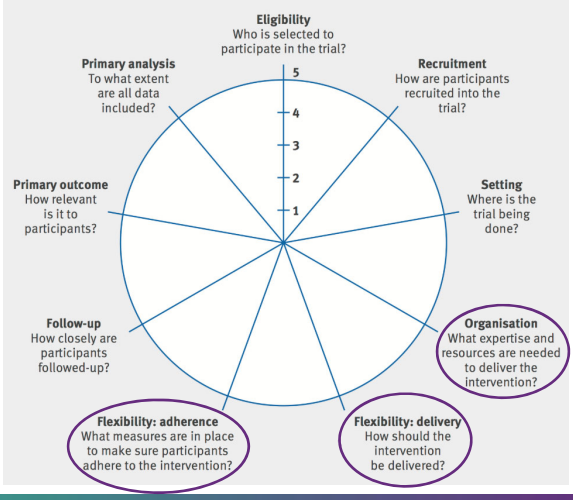
Health Equity Considerations Using PRECIS-2

We may inadvertently perpetuate biases and disparities

- Background and training of providers may impact delivery
- Limitations due to existing language or health literacy barriers
- Flexibly adapting of evidence-based interventions to diverse populations may be ad hoc or may not occur at all
- Adherence to intervention may be uneven or inequitable as a result



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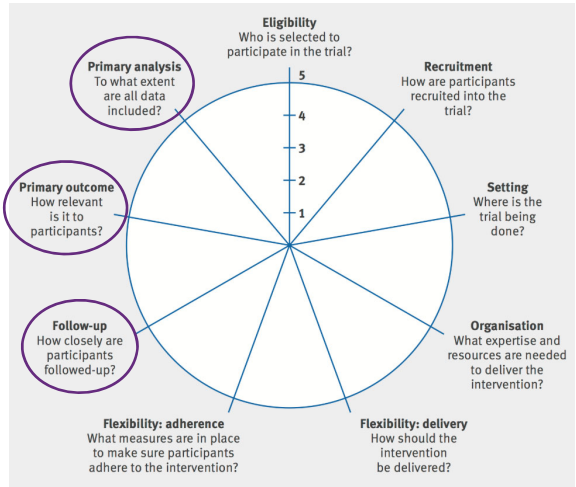
Develop and Disseminate Guidance

Outcomes must be relevant and important to minoritized populations

- Instruments to assess outcomes may not be translated or validated for linguistically and culturally diverse groups
- High risk of differential rates of attrition/retention in standard/usual follow-up care
- Subgroup analyses require sufficient minority participants to enable comparisons, or may falsely suggest lower effectiveness for minorities if there is differential delivery or implementation



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Measures of Equity in Designing ePCTs

HEALTH CARE SYSTEMS	DATA SOURCES	ETHICS/ REG	OUTCOMES	DESIGN/ STATS	IMPLEMENT
Demography (within/among HCS)	Missing-ness & gaps in data sources	Engagement metrics for vulnerable populations	Triangulation and alignment of outcomes across all stakeholder groups	DAGs	GOI Score
Diversity (relative to HCS census, disease burden, community)	Stakeholder outcomes	Consent language & format		Quantitative bias analyses (modified E-value)	CFIR analyses
	Data burden			Floating catchment area metrics	Favorable / unfavorable adaptation

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Summary

- **Health equity is a crucial and unique aspect of ePCTs**
  - Only way to ensure effective and generalizable research
  - Vital to implement PRECIS-2 domains with health equity lens
- **A health equity lens implies limitations in the current use of PRECIS-2 to develop ePCTs**
  - PRECIS-2 only helps us see how *pragmatic* a trial design is
  - Does not inform about study biases

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Key Takeaways

Health equity considerations may be examined by reviewing

- Which HCSes are included
- Bioethical elements of consent
- Data burden
- Calculations to identify selection biases, at multiple levels
- Implementation adaptations

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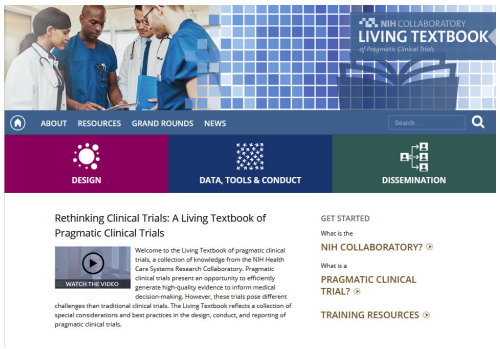

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Case Study:
Pilot Pragmatic Clinical Trial to Embed Tele-Savvy into Health Care Systems

An NIA IMPACT Pilot Study

Richard H. Fortinsky, PhD
UConn Center on Aging
University of Connecticut School of Medicine

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Acknowledgments and Disclosures

- Pilot study funded by the NIA IMPACT Collaboratory
  - Registered at ClinicalTrials.gov: NCT05080777

- No financial disclosures

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Rationale/Objectives of Pilot Study

- **Rationale:** Interventions offering meaningful benefits to care partners of older adults with ADRD would be attractive to office-based practitioners if a pragmatic linkage could be made between these interventions and outpatient health care settings.
- **Objectives:**
  - Embed a pragmatic care partner identification and invitation strategy into the daily workflow of outpatient centers, enabling care partners to join online efficacious dementia care education programs, specifically Tele-Savvy and Caregiving During Crisis.
  - Evaluate Tele-Savvy effectiveness, compared to Caregiving During Crisis, when offered pragmatically.
  - Determine viability of routinely collecting and storing care partner outcomes data into electronic health record systems.
  - Evaluate implementation of all of the above.

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Setting/Population/Design

- **Setting:** Geriatric medicine and dementia care outpatient centers in two health care systems:
  - UConn Health: Geriatrics Associates
  - Emory Healthcare: Integrated Memory Care Clinic[1]
- **Population:** 100 care partners of older adults living with ADRD who are patients in one of the two outpatient care settings.
- **Design:** Care partners at each site will be randomized in 3 waves to receive either Tele-Savvy or Caregiving During Crisis

[1]Clevenger C, et al. *J Am Geriatr Soc* 2018 Dec;66(12):2401-2407.

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Interventions

Tele-Savvy[1]

- 7-week synchronous and asynchronous program for care partners
- Care partners join an on-line class for weekly educational sessions and access Tele-Savvy website resources to help them learn more.
- Topics include dementia symptom management, environmental changes to enhance quality of life for care partner and person living with ADRD, and self-care for the care partner.

Caregiving During Crisis

- Online, asynchronous, self-guided education course designed to help care partners ensure safety of persons with dementia and themselves during COVID-19 pandemic.
- Topics include strategies for creating safe home space, safely leaving and re-entering the home, safely allowing service personnel into the home, and risk management beyond COVID-19 restrictions.

[1]Hepburn K, et al. *Gerontologist*, 2021, doi:10.1093/geront/gnab029

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Outcomes

- **Primary outcome** is self-reported caregiving mastery[1]
- **Secondary outcomes** are self-reported care partner reactions to memory and behavior problems[2], and self-reported perceived stress[3]
- All outcomes used in Tele-Savvy efficacy clinical trial.

[1]Pearlin L.I. et al. *Gerontologist*, 30(5), 583–594. [2]Teri L et al. *Psychology & Aging*, 7, 622–631.
[3]Cohen S et al. *Journal of Health and Social Behavior*, 24(4), 385–396.

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Implementation Evaluation

- Guiding framework: Normalization Process Theory[1]
- Account for individual participant and organizational factors that influence implementation
- Determine potential to sustain Tele-Savvy as a care partner support offering and the routine use of care partner assessment tools in the participating health care systems.

Murray E et al. BMC Medicine 2010, 8:63

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Implementation Evaluation

- Stakeholder interviews will help determine feasibility, acceptability, sustainability of implementation.
- Stakeholders include:
  - care partners
  - clinicians and clinician assistants
  - Tele Savvy group facilitators
  - IT staff responsible for producing technical enhancements in EHR systems to routinize care partner invitations, care partner data capture, and care partner data storage in EHR records.

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Current Status of Implementation

- Emory site has enrolled first wave of care partners; Tele-Savvy program ongoing.
- UConn site preparing to invite care partners using EHR system and clinician verification of care partners identified in patient EHRs.
  - First wave of care partners will be randomized and Tele-Savvy program started in January 2022.

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Impact

- If this pilot study successfully achieves its objectives, we will be poised to design a multi-site embedded pragmatic trial engaging sites from the large pool of geriatric and dementia care clinics nationwide.
- Our long-term goals are to:
  - routinely offer Tele-Savvy and other evidence-based education and support programs to care partners of persons living at home with ADRD
  - routinely store care partner outcome data, in health care systems that provide outpatient care to persons living with ADRD and their families.

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Study Team Members

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Case Study:
ADVANCE-PC: Testing Critical Components for a Trial of Advance Care Planning in Primary Care for Dementia

An NIA IMPACT Pilot Study

Annette M. Totten, PhD
Oregon Health & Science University
Meta-LARC (a consortium of PBRNs)

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Background

Meta-LARC

Prior experience PrimaryCareACP.org

- PCORI-funded Cluster RCT of Advance Care Planning (ACP)
- 40 Primary Care Practices in US and Canada
- Excluded patients without cognitive capacity

Potential need/interest

- Interest among practices
  - how to do ACP well for patients/families with dementia in busy, often under-resourced primary care

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Goal and Aims

- Goal: Foundation for future trial to inform policy and practice
- Aim 1: Assess feasibility of using an ECHO format for training and implementation support
- Aim 2: Test outcome ascertainment

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Details: Aim 1

PBRN Consortium

- Practice recruitment and participation support
- Target: 2 PBRNs, 6 practices

Modified ECHO

- Communications/Serious Illness Care Conversation Training
  - Include multiple practices (Scale)
  - Practice facilitation between sessions

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Advance-PC Program

Communications Training	Implementation Support

• SICP Conversation Guide
  • Didactic, role play, expert coaching
• Dementia and Decision Making
• Family Dynamics
• ACP Tools and Documents
	• Workflow assessment
	• Process development, testing, refinement
	  • Identification of patients
	  • Initiate conversation
	  • Engage in ACP
	  • Document
	  • Follow-up

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Details: Aim 2

Identification	• Assess EHR capacity and level of use • Adapt for dentification of appropriate patients in defined time period (denominator)
Tracking	• Definition of ‘ACP occurring’ • Counts of ACP in defined time period (numerator)

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Challenges (perhaps opportunities)

- Variation in practices
- Ongoing pandemic pressure on primary care
- Limited IT capacity/experience
- Competing priorities

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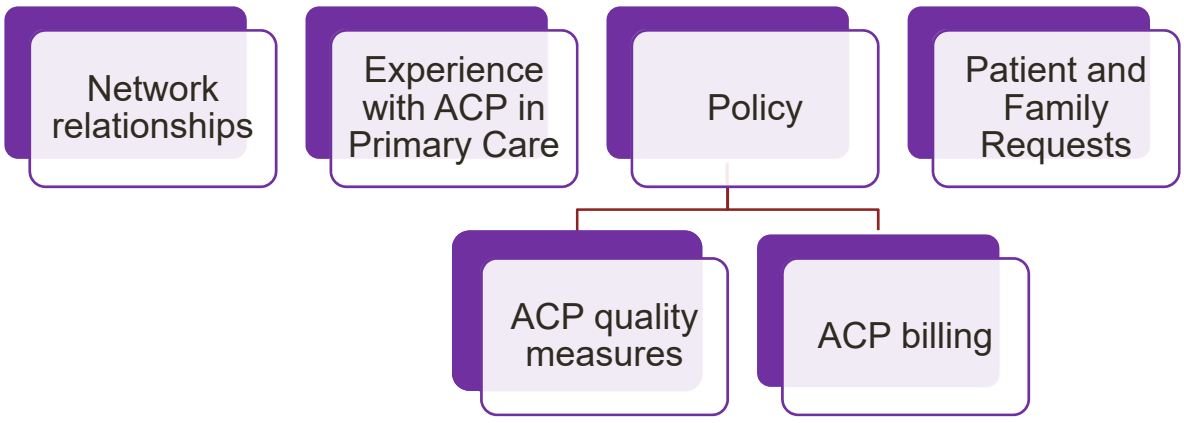
Facilitators (we hope)



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Pragmatic Approach

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Questions?

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Acknowledgements: Pilot Team

- Investigators
- Research Staff
- PBRNs
  - ORPRN
  - SNOCAP
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ORPRN
Oregon Rural Practice-Based Research Network

SNOCAP
State Network of Colorado Ambulatory Practices & Partners

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Resources:
Ethical and Regulatory Considerations

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

Resources:
Pilot and Feasibility Testing

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

Living Textbook readings

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

Collaboratory Grand Rounds webinar recordings & slides

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

Key journal articles

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

Resources:
A Framework for Achieving Health Equity in Pragmatic Trials

NIA IMPACT Collaboratory online resources

- NIA IMPACT Collaboratory Training Modules

Health Equity online resources

- Health Equity Training Resources
- NIA IMPACT Collaboratory Health Equity Team

Collaboratory Grand Rounds webinar recordings & slides

- Grand Rounds/Podcast 16: Inclusion, diversity, and equity in pragmatic clinical trials
- Grand Rounds/Podcast 5: Health equity as foundational to the design of pragmatic trials
- Inclusion of Diverse Participants in Pragmatic Clinical Trials: NIH-Hosted Workshop

Key journal articles

- Gleason CE, et al. Association between enrollment factors and incident cognitive impairment in Blacks and Whites: Data from the Alzheimer's Disease Center. Alzheimers Dementia. 2019;15(12):1533-45.
- Quiñones AR, et al. Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers. JAGS 2020; 68(Suppl 2):S8-S13.


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