



Essentials of Embedded Pragmatic Clinical Trials Seminar

JUNE 1, 2019

Participant Guide



Essentials of ePCTs Seminar

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Preconference Workshop: Essentials of Embedded Pragmatic Clinical Trials
AcademyHealth 2019 Annual Research Meeting
Washington, D.C.
June 1, 2019

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
8:00-8:45 (45 min)	What are Embedded Pragmatic Clinical Trials (ePCTs)?	Catherine Meyers, NIH/NCCIH	<ul style="list-style-type: none"> Welcome and introduction of agenda and objectives Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials Learn about the advantages and disadvantages of ePCTs, and when a pragmatic approach can be used to answer the research question Provide an understanding of the PRECIS-2 tool and its ability to assist teams in the design of an ePCT
8:45-9:15 (30 min)	Engaging Stakeholders and Aligning with Health System Partners	Leah Tuzzio, MPH Kaiser Permanente Washington Health Research Institute	<ul style="list-style-type: none"> Describe the breadth of stakeholders to engage as partners in ePCTs Highlight strategies for understanding the priorities and perspectives of health system stakeholders through all phases of the study
9:15-9:45 (30 min)	Measuring Outcomes	Emily O'Brien, DCRI	<ul style="list-style-type: none"> Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
9:45-10:15 (30 min)	ePCT Design	David Murray, NIH/Office of Disease Prevention	<ul style="list-style-type: none"> Learn about group- or cluster-randomized trials, individually randomized group-treatment trials, and stepped wedge group- or cluster-randomized trials
10:15-10:30 (15 min)	Break		
10:30-11:00 (30 min)	ePCT Analysis	David Murray, NIH/Office of Disease Prevention	<ul style="list-style-type: none"> Learn about the special analytic requirements for these designs and about the current recommendations for their analysis
11:00-Noon (60 min)	ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs	Moderator: Kevin Weinfurt, DCRI Panel: Susan Huang, ABATE; Vince Mor, PROVEN	<ul style="list-style-type: none"> Introduce PIs of 2 ongoing ePCTs to reflect on the morning topics, discussing challenges, solutions, and lessons learned Q & A with attendees
Noon-1:00 (60 min)	Lunch		

DURATION	AGENDA TOPIC	SPEAKERS	GOALS
1:00-1:30 (30 min)	Pilot & Feasibility Testing	Wendy Weber, NIH/NICCH	<ul style="list-style-type: none"> Identify approaches to evaluate the capabilities and challenges of the partner healthcare system and test key elements of the intervention during pilot or feasibility studies
1:30-2:00 (30 min)	Ethical and Regulatory Oversight Considerations	Kevin Weinfurt, co-PI, NIH Collaboratory Coordinating Center Julie Kaneshiro, OHRP	<ul style="list-style-type: none"> Learn about the regulatory and ethical considerations specific to conducting ePCTs
2:00-2:30 (30 min)	Dissemination and Implementation	Wynne Norton, NIH/NCI	<ul style="list-style-type: none"> Learn methods for designing ePCTs so findings can be easily implemented Build in sustainability from the beginning Identify considerations for dissemination of study results
2:30-3:30 (60 min)	ePCTs in Context: Panel Discussion with Collaboratory Demonstration Project PIs	Moderator: Kevin Weinfurt, DCRI Panel: Susan Mitchell, PROVEN; Laura Dember, TiME	<ul style="list-style-type: none"> Introduce PIs of 2 ongoing ePCTs to reflect on the afternoon topics, discussing challenges, solutions, and lessons learned Q & A with attendees
3:30-3:45 (15 min)	Break		
3:45-4:45 (60 min)	Assembling an ePCT Team & Writing a Grant Application	Robin Boineau, NIH/NCCIH Marcel Salive, NIH/NIA	<ul style="list-style-type: none"> Identify skills needed for a strong study team Learn how to develop a compelling ePCT application
4:45-5:00 (15 min)	Next Steps	Kevin Weinfurt, DCRI	<ul style="list-style-type: none"> Final Q & A Wrap up including identifying sources for further learning

AcademyHealth Seminar
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Speaker Biographies



Robin Elizabeth Boineau, MD, MA

National Center for Complementary and Integrative Health (NCCIH), NIH

Dr. Boineau joined the NCCIH Office of Clinical and Regulatory Affairs (OCRA) as a medical officer in 2015. A cardiologist with a background in exercise physiology, she is also an experienced National Institutes of Health (NIH) trialist with extensive experience in managing large NIH-funded clinical research operations. In OCRA, Dr. Boineau provides guidance on clinical study designs in the NCCIH portfolio and plays a leading role in large ongoing trial operations, including the Trial to Assess Chelation Therapy 2 (TACT2), as well as the NIH Health Care Systems Research Collaboratory. She is also a member of the Division of Extramural Research and manages a clinical research portfolio focused on NCCIH-supported clinical trials. Her focus at NCCIH is on the conduct of large-scale clinical studies.

Before coming to NCCIH, Dr. Boineau was a medical officer at the National Heart, Lung, and Blood Institute's (NHLBI) Division of Cardiovascular Diseases for more than 15 years, where she had a primary oversight role in many large-scale NIH-funded clinical studies. She was the NIH lead scientist and then project officer for the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial and project officer on the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), the Late Sodium Current Blockade in High-Risk ICD Patients—Ranolazine ICD Trial (RAID), Cardiovascular Health Study (CHS). She was deputy project officer on Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, and the Multi-Ethnic Study of Atherosclerosis (MESA). She is also the primary developer of a self-administered questionnaire to determine functional capacity in cardiovascular disease patients, the Duke Activity Status Index (DASI).



Laura M. Dember, MD

University of Pennsylvania Perelman School of Medicine

Dr. Dember is Professor of Medicine and Epidemiology at the University Of Pennsylvania Perelman School of Medicine where she is a faculty member in the Renal-Electrolyte and Hypertension Division and a Senior Scholar in the Center for Clinical Epidemiology and Biostatistics. Dr. Dember conducts patient-oriented research in chronic kidney disease and end-stage renal disease and has particular interests in interventions to improve clinical outcomes for patients treated with maintenance hemodialysis. She has leadership roles in several multicenter observational studies and clinical trials including the Dialysis Access Consortium, the Hemodialysis Fistula Maturation Study, the Hemodialysis Novel Therapies Consortium, and the Chronic Renal Insufficiency Cohort study, all funded by the National Institutes of Diabetes and Digestive and Kidney Diseases, as well as two large pragmatic trial demonstration projects of the NIH Health Care

Systems Research Collaboratory: Time to Reduce Mortality in End-Stage Renal Disease (TiME) and HiLo. Dr. Dember has been a member of several committees of the American Society of Nephrology and is a Deputy Editor for the American Journal of Kidney Diseases.



Susan Huang, MD, MPH
University of California Irvine School of Medicine

Dr. Huang is Professor of Medicine in the Division of Infectious Diseases and Health Policy Research Institute at the University Of California Irvine School Of Medicine, and Medical Director of Epidemiology and Infection Prevention at UC Irvine Health. She received her medical degree from Johns Hopkins School of Medicine and her master's in quantitative methods from the Harvard School of Public Health.

For nearly 20 years, Dr. Huang has been studying healthcare-associated infections with a focus on multidrug-resistant organisms (MDROs). Her clinical epidemiologic research seeks to identify the burden and risk factors for acquisition and disease, and preventative strategies for containment. Dr. Huang has led several randomized clinical trials to prevent MRSA disease and other healthcare-associated infections. She also studies the regional prevention of MDROs in hospitals and nursing homes through epidemiologic studies as well as simulation models. Additional significant areas of research include surgical site infections, outbreak detection, and electronic efficiencies for infection prevention. Dr. Huang has 150 publications in peer-reviewed journals and received a Top 10 U.S. Clinical Research Achievement Award from the Clinical Research Forum in 2014.

Dr. Huang has served as a member of HICPAC (federal guidelines committee for infection prevention), the Antibiotic Resistance Working Group for the Centers for Disease Control and Prevention, and the Antibiotic Resistance Committee for the Infectious Diseases Society of America. She has also served on the technical expert panel for infection prevention and care transitions between acute and long-term care facilities for the Centers for Medicare and Medicaid Services.



Julie Kaneshiro, MA
Office for Human Research Protections (OHRP)

Ms. Kaneshiro is Deputy Director of OHRP and shares the Director's responsibility and authority to develop, coordinate, and execute the full range of OHRP programs and activities. Previously she was Policy Team Leader at OHRP and played a central role in the development of regulations and policies related to the HHS regulations for the protection of human subjects. Prior to joining OHRP, she worked in several different institutes at the National Institutes of Health, and in the Office of the Director, where she assisted in developing the research provisions of the proposed and final versions of the HIPAA Privacy Rules. Ms. Kaneshiro received her undergraduate degree in English Literature from the University of Maryland in 1991, and her graduate degree in Public Policy with Concentrations in Philosophy and Social Policy (MA) from George Washington University in 1996.



Catherine M. Meyers, MD
National Center for Complementary and Integrative Health (NCCIH), NIH

Dr. Meyers is Director of NCCIH's Office of Clinical and Regulatory Affairs (OCRA), which plays a major role in the planning, coordinating, and monitoring of the clinical research program. She and her staff serve as a resource for NCCIH's program staff and clinical investigators to facilitate safe implementation of NCCIH-funded clinical studies. As NCCIH plays a major role in leadership of the National Institutes of Health (NIH) Common Fund Health Care Systems Research Collaboratory, Dr. Meyers is also a lead scientist for the Collaboratory. This Common Fund program is a 10-year effort to conduct pragmatic clinical trials in partnership with clinical investigators, patients, and health care

systems in the United States. Prior to her 2009 arrival at NCCIH, Dr. Meyers devoted nearly a decade to work focused on clinical research of end-stage kidney disease. After a 3-year tenure at the FDA, where she provided oversight for trials of products for extracorporeal therapies, Dr. Meyers joined NIH in 2002 as a Senior Scientific Advisor within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), where she was Director of Renal Inflammatory Programs within the Kidney, Urology, and Hematology Division. She also worked on several NIH projects, including the NIH Transplantation Research Coordinating Committee, and was a co-chair of the NIDDK Clinical Studies Working Group.

Dr. Meyers earned her undergraduate degree in chemistry at the University of Chicago and received her MD from the University of Illinois College of Medicine at Chicago. She completed postgraduate residency training in internal medicine at the University of Chicago (Michael Reese Hospital) and a clinical nephrology fellowship at the University of Pennsylvania, Philadelphia. She then completed a research fellowship in renal immunology at the School of Medicine at the University of Pennsylvania. In 1992, she joined the faculty of the School of Medicine at the University of Pennsylvania with an appointment in the Department of Internal Medicine, Renal-Electrolyte and Hypertension Division. Dr. Meyers's research program focused on characterizing mechanisms of immune-mediated kidney injury. Her research interests include autoimmune mechanisms of disease and vascular inflammation, as well as the ethics of clinical research oversight. She has authored more than 100 research articles and other scientific publications. She is a Fellow of the American Heart Association, and a long-standing member of its Council on the Kidney in Cardiovascular Disease. She is the recipient of several awards, including the Donald B. Martin Teaching Award from the University of Pennsylvania, an FDA Honor Award for her work in dialysis products oversight, and the NIH Director's Awards for her role in the development of the NIH Health Care Systems Research Collaboratory and for her leadership of the NCCIH/OCRA process for oversight of clinical research.



Susan L. Mitchell, MD, MPH
Harvard Medical School
Hebrew SeniorLife

Dr. Mitchell is Professor of Medicine at Harvard Medical School and Senior Scientist at the Hinda and Arthur Marcus Institute for Aging Research at Hebrew SeniorLife in Boston. She is a geriatrician and health services researcher. Dr. Mitchell's research interests focus on decision-making, health outcomes, and resource utilization for older people near the end of life, particularly those with dementia. She is widely published and the Principal Investigator on several large NIH-funded projects, including pragmatic clinical trials, in this field. Dr. Mitchell is a recipient of an NIH-NIA K24 Mid-Career Investigator Award and an NIH-NIA R37 MERIT Award. She is also an attending geriatrician at the Beth Israel Deaconess Medical Center in Boston.



Vincent Mor, PhD
Brown University School of Public Health

Dr. Mor is the Florence Pirce Grant Professor of Community Health in the Brown University School of Public Health and a senior health scientist at the Providence VA Medical Center. He has been Principal Investigator for more than 40 NIH-funded grants and has published over 400 peer-reviewed articles focusing on the use of health services and the outcomes frail and chronically ill persons experience. He received the Robert Wood Johnson Foundation health policy investigator award, a MERIT award from the National Institute on Aging, the Distinguished Investigator Award from AcademyHealth, the John Eisenberg Mentoring Excellence Award from the Agency for Healthcare Research and Quality (AHRQ), and is a member of the National Academy of Medicine. He has evaluated the impact of programs and policies in aging and long-term care including Medicare funding of hospice, changes in Medicare nursing home payment, and the introduction of quality measures. He was one of the authors of the congressionally mandated

Minimum Data Set (MDS) for Nursing Home Resident Assessment and the architect of an integrated Medicare claims and clinical assessment data base used for policy analysis, pharmaco-epidemiology, population outcome measurement, and cluster-randomized clinical trials. He has had extensive experience working with CMS mandatory assessment data such as the OASIS and MDS, merging these data with Medicare fee-for-service (FFS) claims as well as Medicare Advantage (MA) HEDIS data for the purpose of comparing the use of post-acute care service use by MA and FFS beneficiaries and how that has changed over time and across different markets in the US. He has been particularly focused on the disenrollment from MA of complex, chronically ill patients using post-acute care.



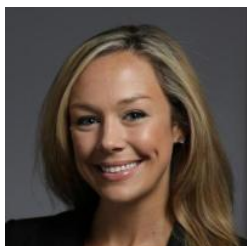
David M. Murray, PhD
Office of Disease Prevention, NIH

Dr. Murray completed his Bachelor of Arts in Psychology from Denison University in 1973. He completed his PhD in Experimental Psychology at the University of Tennessee, Knoxville, in 1978. In 1981, he completed a National Heart, Lung, and Blood Institute (NHLBI)-funded postdoctoral fellowship in cardiovascular health behavior in the Laboratory of Physiological Hygiene, a division of the School of Public Health at the University of Minnesota. He joined the faculty of the Laboratory immediately after his fellowship. The Laboratory was founded by Ancel Keys and was the home of Henry Taylor, Henry Blackburn, and other pioneers in cardiovascular epidemiology. Over the past 40 years, Dr. Murray has worked on more than 50 health promotion and disease prevention research projects funded by the NIH and other agencies. He served on more than 40 grant review panels for the NIH and as the first Chair of the Community Level Health Promotion study section. He has published more than 250 articles in the peer-reviewed literature.



Wynne E. Norton, PhD
National Cancer Institute, NIH

Dr. Norton is a program director for the Implementation Science Team in the Office of the Director in the Division of Cancer Control and Population Sciences at the National Cancer Institute (NCI). Within the Division, she assists with the expansion of research activities in implementation science, focusing on health care delivery and de-implementation across the cancer control continuum. Before joining the NCI in July 2015, Dr. Norton was an assistant professor in the School of Public Health at the University of Alabama at Birmingham. She was a fellow in the Implementation Research Institute (2009–2010) and a scholar in the Mixed Methods Research Training Program (2015). She has received funding from NIH, AHRQ, the Commonwealth Fund, CDC, the Bill and Melinda Gates Foundation, and the Donaghue Foundation. Dr. Norton is on the editorial board of the journal *Implementation Science*. She received her PhD in social psychology from the University of Connecticut (2009).



Emily O'Brien, PhD
Duke University School of Medicine

Dr. O'Brien is Assistant Professor in the Department of Population Health Sciences at the Duke University School of Medicine and an outcomes researcher at the Duke Clinical Research Institute. After completing undergraduate training at Duke University, she received a PhD in Epidemiology at the University of North Carolina in Chapel Hill in 2012. Dr. O'Brien's research focuses on comparative effectiveness, patient-centered outcomes, pharmacoepidemiology, and pragmatic health services research in cardiovascular and pulmonary disease. She has expertise in the use of administrative claims data for longitudinal outcomes assessment in Medicare populations and national registries.

Dr. O'Brien's projects include a PCORI-funded study examining commonly-used stroke therapies, an NHLBI-funded study assessing cardiovascular risk factors in the Jackson Heart Study, in addition to multiple projects evaluating patient-reported outcomes in idiopathic pulmonary fibrosis, atrial fibrillation, and familial hypercholesterolemia. She

is the Director of the DCRI Research Conference and serves on the editorial boards of the *American Heart Journal* and *Stroke*.



Marcel Salive MD, MPH
National Institute on Aging, NIH

Dr. Salive joined the Division of Geriatrics and Gerontology and administers the research portfolio on comorbidity (multiple chronic conditions) treatment and prevention, polypharmacy, and some aspects of comparative effectiveness. He earned chemistry and medical degrees from the University of Michigan and completed his preventive medicine residency and a master's in public health at Johns Hopkins University. From 1990-1995, he was a senior investigator in the Laboratory of Epidemiology, Demography, and Biometry in the NIA intramural program.

Subsequently he has held leadership positions in the Centers for Medicare and Medicaid Services (CMS), National Heart, Lung, and Blood Institute, and the Food and Drug Administration. From 2003-2010, he served as Director of the Division of Medical and Surgical Services within the Coverage and Analysis Group of CMS and was responsible for developing and maintaining national coverage decisions for Medicare beneficiaries using a rigorous and open evidence-based process. His work in developing Medicare coverage of new and innovative services was recognized with the PHS Meritorious Service Medal in 2010. Dr. Salive has developed and led research initiatives in several areas including outcomes research, Alzheimer disease etiology, vaccine safety, and translation of clinical research into primary care practice. He is a Captain in the U.S. Public Health Service Commissioned Corps and serves on the PHS-2 rapid deployment force.



Leah Tuzzio, MPH
Kaiser Permanente Washington Health Research Institute

Ms. Tuzzio's research focuses on improving patient experience, reducing health care costs, and improving the health of populations. She is currently working with teams at KPWHRI's MacColl Center for Health Care Innovation and the Center for Community Health and Evaluation on projects related to quality improvement in primary care, patient-centered care, community-based research, and translating evidence into practice. One of her main projects is Healthy Hearts Northwest, an Agency for Healthcare Research and Quality-funded project to implement and evaluate quality improvement approaches in primary care. In addition, she is working with the National Institutes of Health (NIH) Collaboratory's Health Care Systems Interactions core to report on lessons learned from implementing pragmatic trials. Ms. Tuzzio's other projects include writing manuscripts from the Robert Wood Johnson Foundation-funded Learning from Effective Ambulatory Practices (LEAP) project, studying the primary care workforce and the role of lay health workers, providing technical assistance to the Patient-Centered Outcomes Research Institute's first Evidence-to-Action Network focused on asthma research, and studying the use and adaptation of the Decision-to-Implement toolkit funded by the University of Washington's Institute of Translational Health Sciences.

She has co-led Kaiser Permanente Washington's patient-centered care interest group since 2012, and she is a member of the Health Care Research Systems Network (HCSRN) Patient Engagement in Research Workgroup. She earned a Master of Public Health (MPH) at the Emory University Rollins School of Public Health in the Behavioral Sciences and Health Education program. Her master's thesis was about the quality of life of people with dementia and their caregiver's burden. While at Emory she helped disseminate the Center for Disease Control and Prevention's Healthy Days quality of life measure across the United States and edited consumer books at the American Cancer Society's national office.



Wendy J. Weber, ND, PhD, MPH

National Center for Complementary and Integrative Health (NCCIH), NIH

Dr. Weber is Acting Deputy Director at the National Center for Complementary and Integrative Health (NCCIH) at NIH. She also serves as Branch Chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at NCCIH. 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 all 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

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 Professor of Psychiatry and Behavioral Science at Duke University Medical Center and a faculty member of the Duke Clinical Research Institute; Professor of Psychology and Neuroscience; and Faculty Associate of the Trent Center for the Study of Medical Humanities 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 serves as the President of the PROMIS Health Organization, is co-chair of the coordinating center for the NIH Health Systems Research Collaboratory, and co-chair of NIDDK's Symptoms of Lower Urinary Tract Dysfunction Research Network. 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's research has been featured on NPR Marketplace, Business Week, ABC News, and U.S. News & World Report. 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. Dr. Weinfurt conducts research on measuring patient-reported outcomes, medical decision making, and bioethics.

Health Care Systems Research Collaboratory

GOAL

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

WHAT ARE EMBEDDED PRAGMATIC CLINICAL TRIALS (ePCTs)?

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

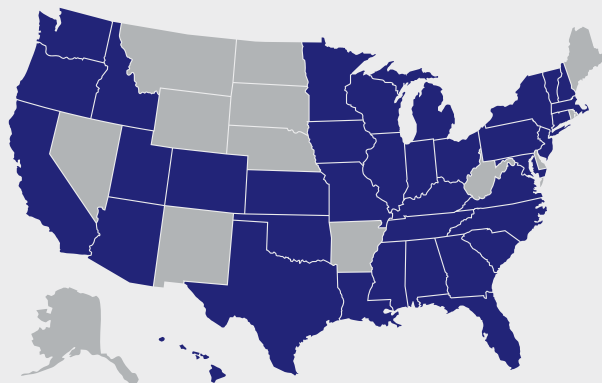
PROGRAM

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

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

15 DEMONSTRATION PROJECTS

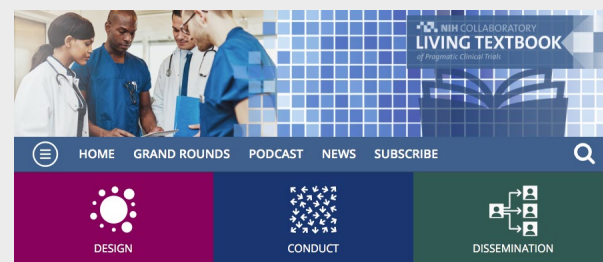
- Conducted in partnership with healthcare systems
- Studying diverse clinical areas spanning 12 NIH Institutes and Centers
- >850 clinical sites across 80% of United States; >800,000 active subjects



RESOURCES

Living Textbook of Pragmatic Clinical Trials

Comprehensive resource expanding on lessons from the Demonstration Projects and Cores



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

CONDUCT describes considerations for study startup and participant recruitment

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

Plus:

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

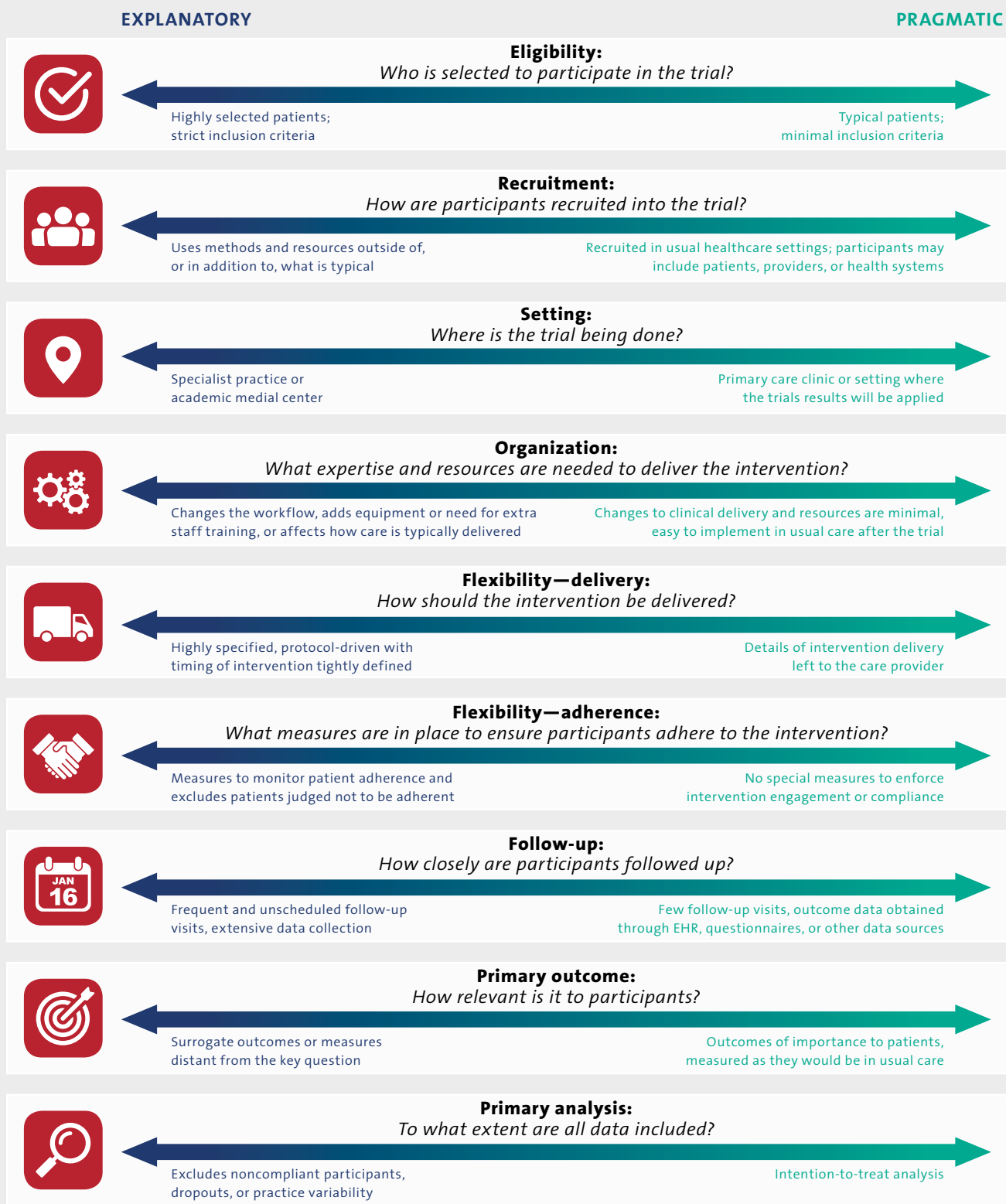
Visit the Living Textbook:
www.rethinkingclinicaltrials.org

HOW IS A CLINICAL TRIAL CONSIDERED PRAGMATIC?

An **EXPLANATORY** approach answers the question, “Can this intervention work under ideal conditions?”

A **PRAGMATIC** approach answers the question, “Does this intervention work under usual conditions?”

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



NIH Collaboratory Case Studies

<p>Featured UH3 Demonstration Project Case Studies</p>	<p>Active Bathing to Eliminate (ABATE) Infection Susan Huang, PI</p> <p>Pragmatic Trial of Video Education in Nursing Homes (PROVEN) Vincent Mor, Susan Mitchell, Angelo Volandes, Co-PIs</p> <p>Time to Reduce Mortality in End-Stage Renal Disease (TiME) Laura Dember, PI</p>
<p>Additional UH3 Demonstration Projects</p>	<p>A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity (Trauma Survivors Outcomes and Support [TSOS]) Doug Zatzick, PI</p> <p>Collaborative Care for Chronic Pain in Primary Care (PPACT) Lynn DeBar, PI</p> <p>Improving Chronic Disease Management with Pieces (ICD-Pieces) Miguel Vazquez, PI</p> <p>Lumbar Imaging with Reporting of Epidemiology (LIRE) Jerry Jarvik, PI</p> <p>Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC) Gloria Coronado, PI</p> <p>Suicide Prevention Outreach Trial (SPOT) Greg Simon, PI</p>
<p>UG3 Demonstration Projects</p>	<p>Guiding Good Choices for Health (GGC4H): Testing Feasibility and Effectiveness of Universal Parent-Focused Prevention in Three Healthcare System Richard Catalano, Margaret Kuklinski, Stacy Sterling, Co-PIs</p> <p>Improving Advance Care Planning in Oncology: A Pragmatic, Cluster-Randomized Trial Integrating Patient Videos and Clinician Communication Training (ACP PEACE) James Tulsky, Angelo Volandes, Co-PIs</p> <p>Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications (Nudge) Michael Ho, Sheana Bull, Co-PIs</p> <p>Pragmatic Trial of User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder (EMBED) Ted Melnick, Gail D’Onofrio, Co-PIs</p> <p>Pragmatic Trial of Higher vs. Lower Serum Phosphate Targets in Patients Undergoing Hemodialysis (HiLo) Myles Wolf, PI</p> <p>Primary Palliative Care for Emergency Medicine (PRIM-ER) Corita Grudzen, PI</p>



Active Bathing to Eliminate (ABATE) Infection

Study Snapshot

Principal Investigator: Susan Huang, MD, MPH

Sponsoring Institution: University of California, Irvine School of Medicine

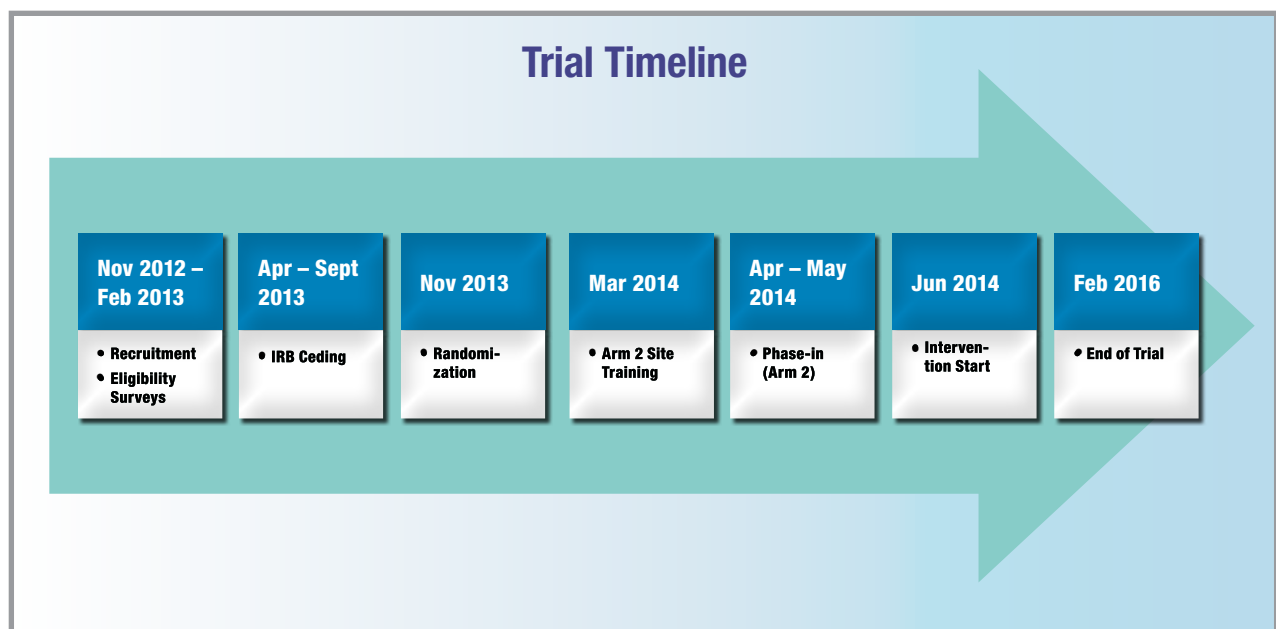
ClinicalTrials.gov: [NCT02063867](https://clinicaltrials.gov/ct2/show/study/NCT02063867)

Collaborating Healthcare Systems: Hospital Corporation of America; Harvard Pilgrim Health Care; Harvard Medical School; University of California, Irvine, School of Medicine; Rush University; John H. Stroger Hospital; Centers for Disease Control and Prevention

NIH Institute Oversight: National Institute of Allergy and Infectious Diseases (NIAID)

Abstract: Healthcare-associated infections (HAIs) are one of the most frequent causes of death in the United States and incur more than \$6.5 billion in annual healthcare costs. Prevention of HAIs is a national priority for patient safety and best practice to reduce morbidity, mortality, and cost. Most infections are caused by common bacteria that normally live on the skin or in the nose and which overcome the body's normal defenses because of invasive medical devices, surgical incisions, or the physiologic effects of hospitalization.

Studies in intensive care units (ICUs) indicate that decolonization of patients' skin with chlorhexidine, and nares with mupirocin, can prevent many HAIs. However, evidence is lacking about the effectiveness of decolonization in non-ICU settings, where the majority of HAIs occur. Decolonization is thus rarely used in these settings, despite its potential to meaningfully decrease the HAI rate. ABATE Infection is a cluster-randomized controlled trial of hospitals that compares 2 quality improvement strategies to reduce multidrug-resistant organisms and HAIs in non-ICUs.



What We've Learned So Far

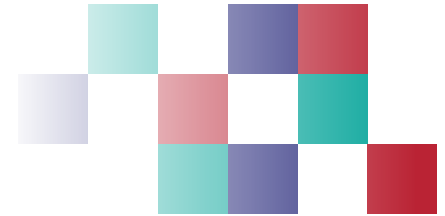
Current Barriers	Level of Difficulty				
	1	2	3	4	5
Enrollment and engagement of patients/ subjects	X				
Engagement of clinicians and health systems	X				
Data collection and merging datasets			X		
Regulatory issues (IRBs and consent)	X				
Stability of control intervention	X				
Implementing/delivering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

1 = little difficulty
5 = extreme difficulty

Challenge	Solution
Participating hospitals reported considering new competing hospital practices, products, or technologies that could potentially conflict with the trial (study outcomes)	Study team monitored all participating hospitals for potentially conflicting interventions. If an intervention was deemed in conflict by the trial steering committee, the hospital was given the option to either not pursue the intervention or to drop from the trial.
Quality improvement initiatives adopted by hospitals require some maintenance over time	Study team found that consistent coaching calls, compliance reports, and comparative feedback were useful.

Selected Publications & Presentations	
April 2017	PCT Grand Rounds Presentation: Perspective on the Boundary between Quality Improvement Studies and Research: Patients, QI Leaders, IRB Leaders
May 2016	ABATE Infection training video showing how to bathe patients using 2% chlorhexidine gluconate cloths to help protect patients from infection during their hospital stay.
May 2016	PCT Grand Rounds Presentation: The ABATE Infection Trial: Backstage Tour





Pragmatic Trial of Video Education in Nursing Homes (PROVEN)

Study Snapshot

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

Sponsoring Institution: Brown University School of Public Health

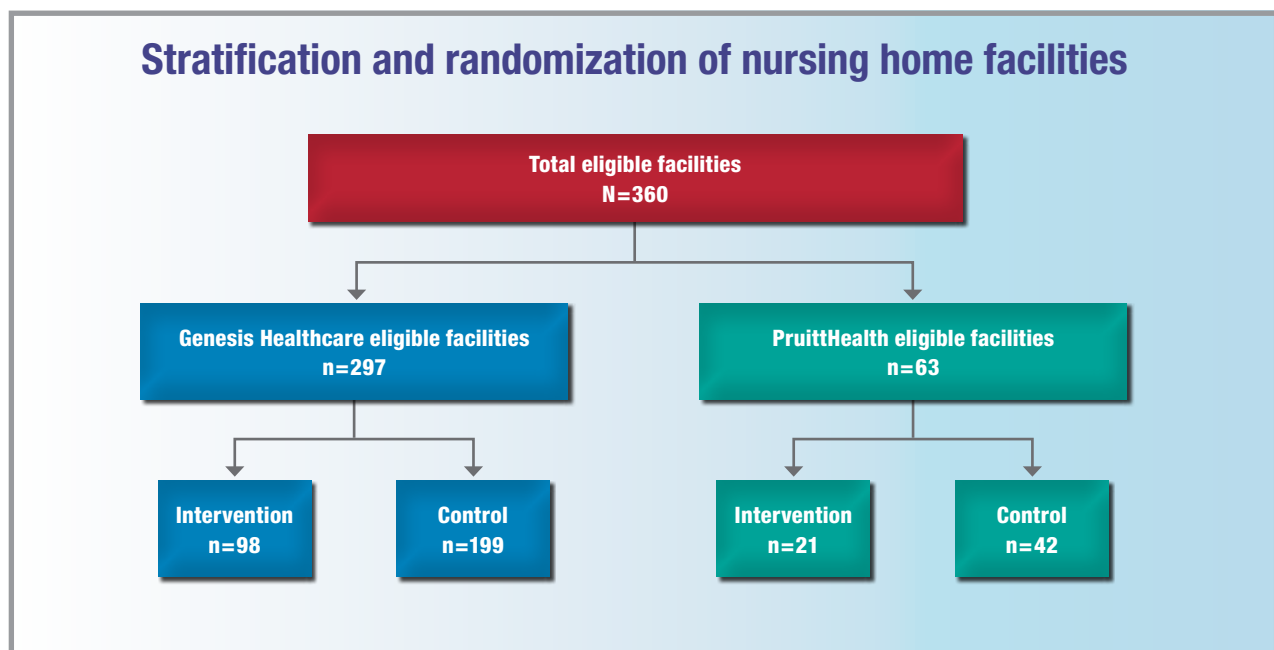
ClinicalTrials.gov: [NCT02612688](https://clinicaltrials.gov/ct2/show/study/NCT02612688)

NIH Institute Oversight: National Institute on Aging (NIA)

Abstract: Nursing homes are often charged with guiding increasingly sick patients through decisions about the direction of their treatment. Patients at nursing homes commonly receive aggressive care that may be inconsistent with their preferences and of little clinical benefit. Identifying effective approaches that nursing homes can use to better promote goal-directed care within existing resources is a research, public health, and clinical priority.

Advance care planning (ACP) is the most consistent factor associated with better palliative care outcomes. However, traditional ACP relies on verbal descriptions of hypothetical health states and treatments, which is limiting because

complex scenarios are difficult to envision and verbal explanations are hindered by literacy and language barriers. The PROVEN project has developed video-assisted ACP decision-support tools that have shown efficacy in small randomized controlled trials. While several large healthcare systems have begun to adopt the videos, outcomes have not been rigorously evaluated. The goal of PROVEN is to conduct a pragmatic cluster-randomized trial to evaluate the effectiveness of the ACP video tools by partnering with 2 large healthcare systems that operate 492 nursing homes nationwide. This work has the potential to improve the care provided to millions of older Americans.



What We've Learned So Far

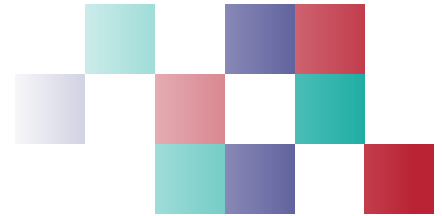
Current Barriers	Level of Difficulty				
	1	2	3	4	5
Enrollment and engagement of patients/ subjects	N/A				
Engagement of clinicians and health systems			X		
Data collection and merging datasets	X				
Regulatory issues (IRBs and consent)	X				
Stability of control intervention	X				
Implementing/delivering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

1 = little difficulty
5 = extreme difficulty

Challenge	Solution
Because the primary outcome is hospitalization rate per person day-alive, the data needed to be matched between nursing homes and hospitals and Medicare vital statistics data since nursing home data alone could have biased results.	Added additional IT resources to help link the systems.
The study team and healthcare system partners did not want to recruit facility leadership to participate in the study and then say they were assigned to control since the partners felt that all facilities would want to have the videos.	The team chose to “prerandomize” by first applying eligibility criteria to existing data on all partner facilities and then giving them the opportunity to exclude other facilities based on recent leadership changes. They next divided facilities into <i>a priori</i> strata and randomly selected the 120 treatment facilities from the pool, leaving the rest as controls. In this way, no facilities that wanted to participate were disappointed; the partners were confident that they would have a high participation rate.

Selected Publications & Presentations	
April 2017	Pragmatic Trial of Video Education in Nursing Homes: The design and rationale for a pragmatic cluster randomized trial in the nursing home setting. <i>Clinical Trials</i> , Mor et al.
March 2017	PCT Grand Rounds Presentation: Implementing PROVEN





Time to Reduce Mortality in End-Stage Renal Disease (TiME)

Study Snapshot

Principal Investigator: Laura Dember, MD

Sponsoring Institution: University of Pennsylvania

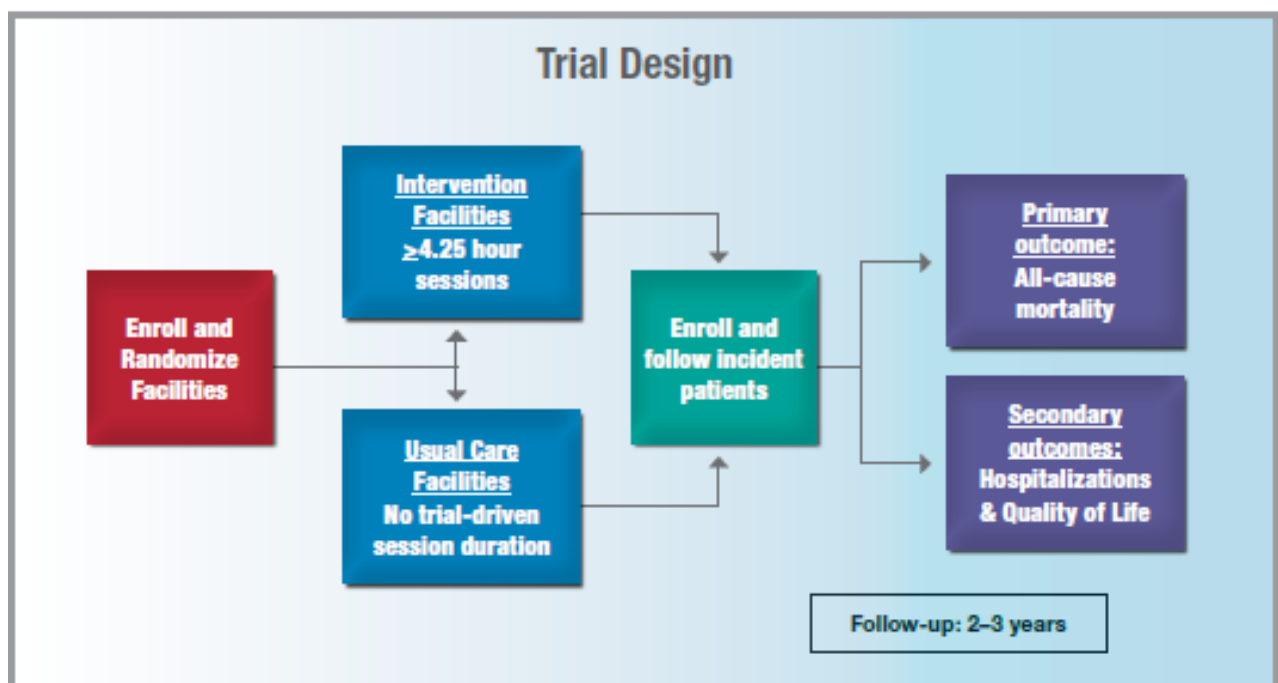
ClinicalTrials.gov: [NCT02019225](https://clinicaltrials.gov/ct2/show/study/NCT02019225)

Collaborating Healthcare Systems: Fresenius Medical Care North America, DaVita Clinical Research

NIH Institute Oversight: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Abstract: TiME is a large pragmatic, cluster-randomized clinical trial testing a simple intervention to improve survival and quality of life for patients with kidney failure who require chronic treatment with dialysis. The trial evaluates a minimum hemodialysis session duration of 4.25 hours compared with usual care for patients with end-stage renal disease initiating treatment with thrice weekly maintenance hemodialysis.

The TiME trial is conducted through a partnership between academic investigators and 2 large dialysis provider organizations in approximately 320 dialysis facilities. The pragmatic design of the trial, the use of multiple electronic health record systems for trial implementation, and the partnership between academia and industry will establish a framework for conducting research within health care delivery systems that will be relevant to a broad range of diseases and research questions.



What We've Learned So Far


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

1 = little difficulty
5 = extreme difficulty

Challenge	Solution
Because observational data suggest better outcomes with longer dialysis sessions, dialysis units, including some of those randomized to usual care, have increased session durations for their patients	In many PCTs, the control group is usual care and is “not controlled.” This may require larger sample sizes and a design that allows for rapid completion of the trial.
A small change to workflow or the IT system was often viewed as a large change by health system personnel	More activity than expected was required at the local level and with individual practitioners and administrators to engage the personnel at the facilities.
There were fundamental questions about minimal risk that arose for this trial, which enrolls a high-risk population (patients with end-stage renal disease) and has an outcome of mortality	The incremental risk of the research was considered minimal both from a medical standpoint and because treating physicians and patients maintain autonomy with respect to intervention implementation.

Selected Publications & Presentations	
September 2017	PCT Grand Rounds Presentation: Who To Include in a Pragmatic Trial? It Depends
October 2016	Pragmatic Trials in Maintenance Dialysis: Perspectives from the Kidney Health Initiative , <i>J Am Soc Nephrol</i> , Dember et al.
February 2015	PCT Grand Rounds Presentation: The TIME Trial: From Planning to Implementation





Essentials of Embedded Pragmatic Clinical Trials


AcademyHealth 2019 Annual Research Meeting
Pre-Conference Seminar
Washington, D.C.
June 1, 2019

Embedded Pragmatic Clinical Trials (ePCTs) Seminar


- Lessons learned from the NIH Health Care Systems Research Collaboratory – the “NIH Collaboratory”
- Seminar overview
 - Topics
 - Speakers

The NIH Health Care Systems Research Collaboratory Coordinating Center is supported by the **NIH Common Fund**, through a cooperative agreement from the Office of Strategic Coordination within the Office of the NIH Director (Grant #U24AT009676-01)


The NIH Collaboratory story



Initiated by the NIH Common Fund in 2012



Goal: To strengthen the national capacity to implement cost effective large-scale research studies that engage health care delivery organizations as research partners



Aim: To provide a framework of implementation methods and best practices that will enable the participation of many health care systems in clinical research

Contemporary challenges for clinical research

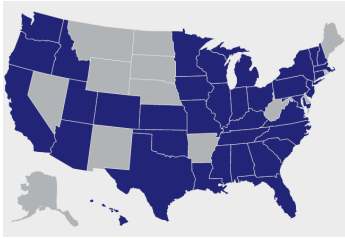
COMMENTS

Using Science to Improve
the Nation's Health System
NIH's Commitment to Comparative Effectiveness Research
Michael S. Lauer, MD
Francis S. Collins, MD, PhD
general@hhs.gov | www.ehr.gov | www.nih.gov
mailto:ce@hhs.gov | www.ehr.gov | www.nih.gov
This could serve as a resource for practice and public policy.

- New approaches and strategies for the clinical trials enterprise
 - Stakeholder interactions and leveraging multidisciplinary expertise
 - Methods for preserving randomized trial design and optimizing use of available data
 - Dissemination and implementation

Lauer MS, Collins FS. JAMA 2010;303:2182-3

NIH Collaboratory ePCTs



- 15 embedded Demonstration Projects
- Diverse clinical settings, across 12 NIH Institutes
- >850 clinical sites, >80% of the US, >800,000 participants

Morning sessions

What are ePCTs?	Catherine Meyers
Engaging Stakeholders	Leah Tuzzio
Measuring Outcomes	Emily O'Brien
ePCT Design	David Murray
ePCT Analysis	David Murray
ePCTs in Context	PI Panel



Afternoon sessions

Pilot & Feasibility Testing	Wendy Weber
Ethics & Regulatory Oversight	Kevin Weinfurt Julie Kaneshiro
Dissemination & Implementation	Wynne Norton
ePCTs in Context	PI Panel
Assembling an ePCT Team & Writing a Grant Application	Robin Boineau Marcel Salive

What Are Embedded Pragmatic Clinical Trials?

Learning objectives	<ul style="list-style-type: none"> • Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials • Learn about the advantages and disadvantages of ePCTs, and when a pragmatic approach can be used to answer the research question • Provide an understanding of the PRECIS-2 tool and its ability to assist teams in the design of an ePCT
Instructor	Catherine Meyers
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • Why are We Talking About Pragmatic Clinical Trials? • Pragmatic Elements: An Introduction to PRECIS-2 <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Introduction to Pragmatic Clinical Trials • Embedded Pragmatic Clinical Trials • Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory <p>Key journal articles</p> <ul style="list-style-type: none"> • 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

What are ePCTs?

Catherine M. Meyers, MD
Director, Office of Clinical & Regulatory Affairs
National Center for Complementary and Integrative Health (NCCIH)

Essentials of Embedded Pragmatic Clinical Trials Seminar



Learning goals

- Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials
- Learn about the advantages and disadvantages of ePCTs, and when a pragmatic approach can be used to answer the research question
- Provide an understanding of the PRECIS-2 tool and its ability to assist teams in the design of an ePCT



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
- Tradeoffs in flexibility, adherence, and generalizability are inevitable

ePCT characteristics

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

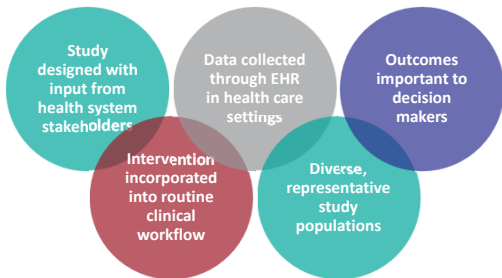


Why conduct ePCTs?



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

ePCTs bridge clinical care and research



Key differences between explanatory and pragmatic trials

	EXPLANATORY	PRAGMATIC
Research question	Efficacy: Can the intervention work under the best conditions?	Effectiveness: Does the intervention work in routine practice?
Setting	Well-resourced "ideal" setting	Routine care settings including primary care, community clinics, hospitals
Participants	Highly selected	More representative with less strict eligibility criteria
Intervention design	Tests against placebo, enforcing strict protocols & adherence	Tests 2 or more real-world treatments using flexible protocols, as would be used in routine practice
Outcomes	Often short-term surrogates or process measures; data collected outside of routine care	Clinically important endpoints; at least some data collected in routine care
Relevance to practice	Indirect: Not usually designed for making decisions in real-world settings	Direct: Purposefully designed for making decisions in real-world settings

Adapted from Zwarenstein M, Treweek S, Gagnier JJ, et al. *BMJ*. 2008;337:a2390. doi: 10.1136/bmj.a2390. PMID: 19001484

Common-sense definition

Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.

Califf RM, Sugarman J. *Clin Trials*. 2015 Oct;12(5):436-41. doi: 10.1177/1740774515598334

Balancing relevance and efficiency

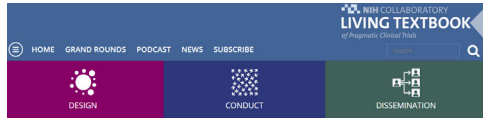


- Achieving both relevance and efficiency is a goal of pragmatic trials, yet high relevance to real-world decision-making may come at the expense of trial efficiency
- For example, a trial measuring outcomes that matter most to patients and health systems may not be able to rely exclusively on information from the EHR, and instead need to assess patient-reported outcomes, which is more expensive and less efficient

Resource: What are ePCTs?

Why Are We Talking About Pragmatic Clinical Trials?

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



Introducing PRECIS-2

Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool

PRECIS-2 can be a useful tool for understanding variability in pragmatic trial characteristics



PRECIS-2: Kirsty Loudon et al. BMJ 2015;350:bmj.h2147. Copyright 2015 by British Medical Journal Publishing Group. Used by permission.



PRECIS-2: Designing trials fit for purpose

Tool assesses trial across 9 domains



1. Eligibility
2. Recruitment
3. Setting
4. Organization
5. Flexibility: delivery
6. Flexibility: adherence
7. Follow-up
8. Primary outcomes
9. Primary analysis



PRECIS-2: Eligibility

Who is selected to participate in the trial?



Explanatory

Pragmatic

Highly selected patients,
strict
inclusion criteria

Typical patients,
minimal
inclusion criteria



PRECIS-2: Recruitment

How are participants recruited into the trial?



Explanatory

Pragmatic

Uses methods and
resources outside
of, or in addition to,
what is typical

Recruited in usual
healthcare settings;
participants may
include patients,
providers, or health
systems



PRECIS-2: Setting

Where is the trial being done?



Explanatory

Pragmatic

Specialist practice
or academic
medical center

Settings where
the trial's results
will be applied



PRECIS-2: Organization

What expertise and resources are needed to deliver the intervention?



Changes the workflow, adds equipment or staff training, or affects how care is typically delivered

Changes to clinical delivery and resources are minimal, easy to implement in usual care after the trial



PRECIS-2: Flexibility-delivery

How should the intervention be delivered?



Highly specified, protocol-driven with timing of intervention tightly defined

Details of intervention delivery left to the care provider



PRECIS-2: Flexibility-adherence

What measures are in place to ensure participants adhere to the intervention?



Measures to monitor patient adherence and excludes patients judged not to be adherent

No special measures to enforce intervention engagement or compliance



PRECIS-2: Follow-up

How closely are participants followed up?



Explanatory

Pragmatic

Frequent follow-up visits scheduled outside of clinical encounters, extensive data collection

Few follow-up visits, outcome data obtained through EHR, questionnaires, or other data sources



PRECIS-2: Primary outcome

How relevant is it to participants?



Explanatory

Pragmatic

Surrogate outcomes or measures distinct from the research question

Outcomes of importance to patients, measured as they would be in usual care



PRECIS-2: Primary analysis

To what extent are all data included?



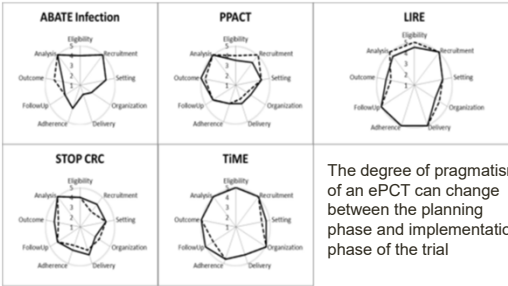
Explanatory

Pragmatic

Excludes noncompliant participants, dropouts, or practice variability

Intent-to-treat analysis

Sample PRECIS-2 wheels



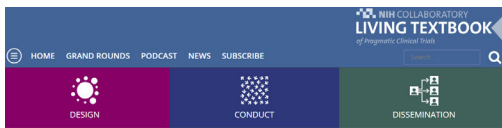
The degree of pragmatism of an ePCT can change between the planning phase and implementation phase of the trial

--- Planning phase
— Implementation phase

Resource: Using PRECIS-2

Pragmatic Elements: An Introduction to PRECIS-2

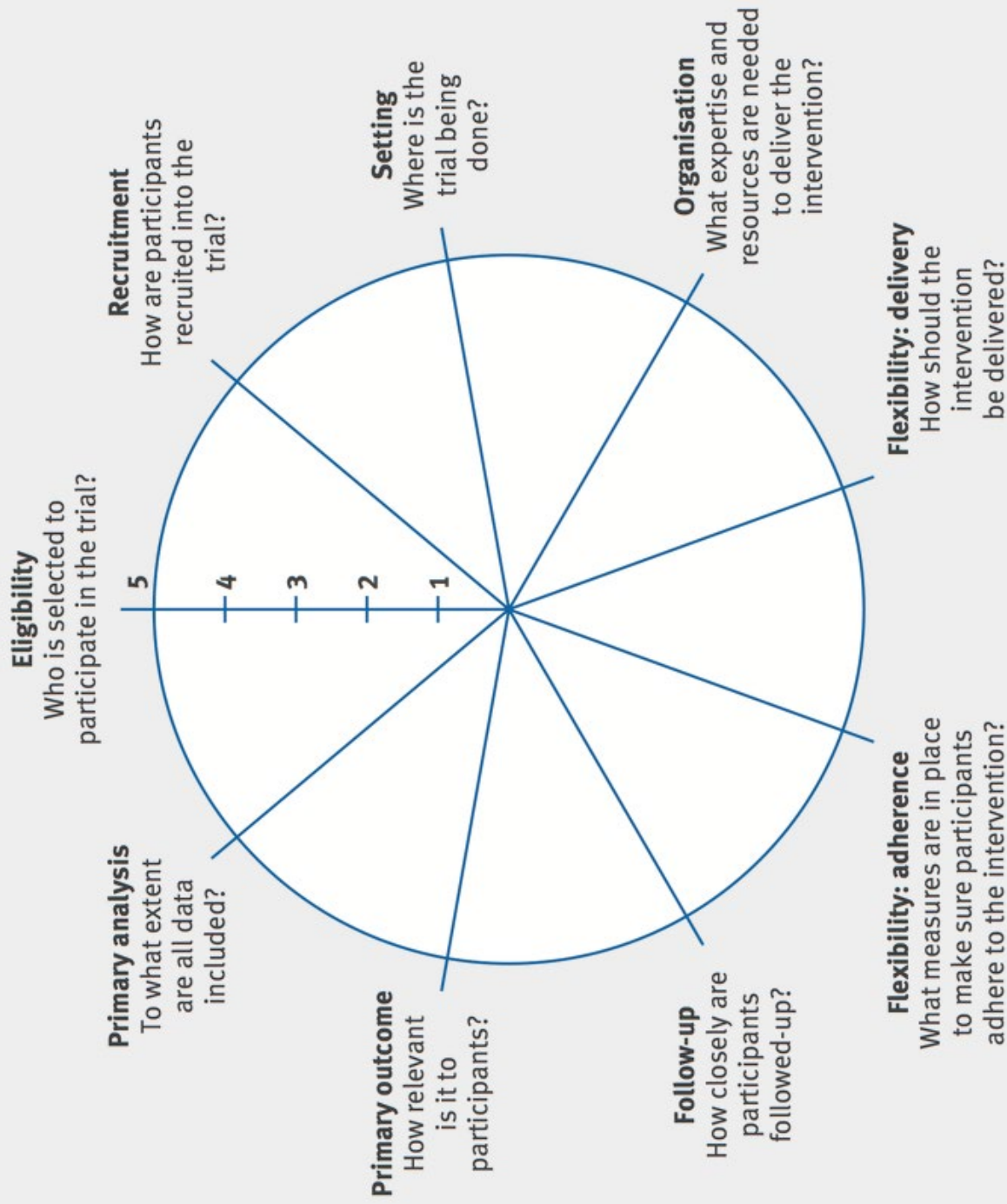
From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org



Important things to do

- For each domain of PRECIS-2, determine the approach along the pragmatic-explanatory continuum that is most appropriate for answering your research question
- Remember that trials may have some elements that are more pragmatic and some that are more explanatory

PRECIS -2 Wheel
Source: Loudon K, et al. 2015. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 350:h2147. doi:10.1136/bmj.h2147. PMID: 25956159.



Engaging Stakeholders & Aligning with Healthcare System Partners

Learning objectives	<ul style="list-style-type: none"> • Describe the breadth of stakeholders to engage as partners in ePCTs • Highlight strategies for understanding the priorities and perspectives of health system stakeholders through all phases of the study
Instructor	Leah Tuzzio
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial • Delineating the Roles of All Stakeholders to Determine Training Needs • Establishing Close Partnerships With Participating Healthcare System Leaders and Staff • Health Care Systems Interaction Core <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Integrating Research Into Health Care Systems: Executives' Views • PCTs and Learning Health Care Systems: Strategies to Facilitate Implementation of Results into Clinical Care <p>Key journal articles</p> <ul style="list-style-type: none"> • 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 <p>Other</p> <ul style="list-style-type: none"> • Health Care Services Research Network website

Engaging Stakeholders and Aligning with Health System Partners

Leah Tuzzio, MPH
Kaiser Permanente Washington Health Research Institute
NIH Collaboratory Health Care Systems Interactions Core

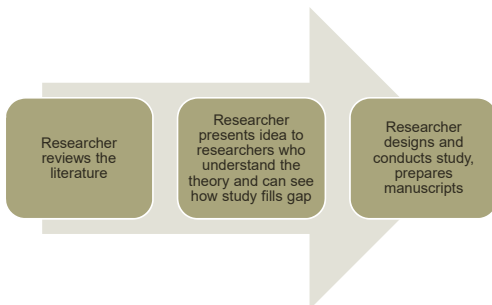
Essentials of Embedded Pragmatic Clinical Trials Seminar



Learning goals

- Describe the breadth of stakeholders to engage as partners in ePCTs
- Highlight strategies for understanding the priorities and perspectives of health system stakeholders through all phases of the study

How researchers approach stakeholders in traditional RCTs



Researchers partner with stakeholders in ePCTs differently

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

Important things to know

- Start engagement much earlier than you think, even before you have a research question or study design
- Be patient: relationships take time to build and nurture
- Consider whether your intervention will add value
- Expect change and disruptions

Early and continuous engagement

Early and continuous engagement with health system stakeholders is time-consuming and the most important thing you'll do.

NIH Collaboratory ePCT
Demonstration Project Principal Investigators

Who will ePCTs impact? Who will make decisions about what to do with the results?

Stakeholders have varied priorities, values, expectations. For example,

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



What are some stakeholder questions?

- **Healthcare organization leaders:** *What's the cost to our system? What will the return on investment be?*
- **Clinicians:** *How can we minimize the impact on our workload?*
- **Operational personnel:** *How can we prevent hiring new staff?*
- **Patients, caregivers, patient advocacy groups:** *How can you make the intervention be meaningful and low cost to us?*
- **Payers, purchasers:** *How will the study help us make coverage decisions?*
- **Policymakers, regulators:** *How localized or broad will the benefits from the research reach?*
- **Research funders:** *What generalized knowledge will be gained?*
- **Researchers:** *How can we minimize regulatory issues?*
- **Product manufacturers:** *Will our market increase?*

Roles of stakeholders

- The wider community of stakeholders is needed to define the question and design the intervention. Researchers could ask:

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

- Each site has its own set of stakeholders who are essential to implementing the PCT at the health system level. To facilitate practicality, researchers could ask:

***What's a feasible way to do this research?
We really need your help to get this done.***

Source: Greg Simon, MD, MPH

Designing the trial:
How stakeholders can partner

- Choose a research question
- Design the intervention & inform potential sustainability
- Select outcome measures
- Determine inclusion & exclusion criteria
- Design the study protocol to minimize burden for patients & clinicians
- Determine study requirements (eg, regulatory)
- Promote & support the study
- Draft/review study materials
- Provide resources

Conducting the trial:
Stakeholder roles

- Develop recruitment strategies
- Promote & assess compliance with study requirements (eg, regulatory)
- Serve as study champions
- Track challenges and adaptations
- Solve problems & remove barriers
- Consider privacy & data sharing issues
- Advise on analyses
- Interpret study results

Disseminating the results:
Stakeholder roles

- Determine key messages for different stakeholder groups
- Identify avenues for dissemination
- Assist with the development of manuscripts & other dissemination materials
- Share findings via professional networks & social media
- Support implementation or de-implementation of intervention
- Consider changes to policies & guidelines

How to engage stakeholders

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

Identify and form collaborations

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

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

Get to know each other

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

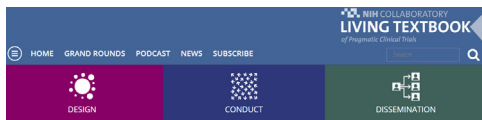
Pilot and assess stakeholders' capacity and capabilities

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

Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

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



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



Important things to do

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

Measuring Outcomes


Learning objective	Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
Instructor	Emily O'Brien
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • Electronic Health Records Core • Patient-Reported Outcomes Core • Choosing and Specifying Endpoints • Using Electronic Health Record Data in Pragmatic Clinical Trials • Assessing Data Quality for Healthcare Systems Data Used in Clinical Research • PCT Reporting Template <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Approaches to Patient Follow-Up for Clinical Trials: What's the Right Choice for Your Study? • Thoughts from the Phenotypes, Data Standards & Data Quality Core • Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-OUTCOMES EHR Ancillary Study • Update from the Phenotypes, Data Standards, and Data Quality Core • Enhancing EHR Data for Research and Learning Healthcare <p>Key journal articles</p> <ul style="list-style-type: none"> • Richesson et al., 2017. Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory • Bradley et al., 2010. Health Services Research and Data Linkages: Issues, Methods, and Directions for the Future • Weber et al., 2014. Finding the Missing Link for Big Biomedical Data • Hersh et al., Caveats for the use of operational electronic health record data in comparative effectiveness research • Richesson et al., A comparison of phenotype definitions for diabetes mellitus

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

Measuring Outcomes

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

Essentials of Embedded Pragmatic Clinical Trials Seminar

 **Learning goal**

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

Outline

- Definitions
- Choosing endpoints
- Possible sources of error
- Data quality assessment
- Clinical phenotypes
- Patient-reported outcomes
- Conclusions & recommendations



Important things to know

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

Endpoints and outcomes

An **endpoint** usually refers to an analyzed parameter (eg, change from baseline at 6 weeks in mean PROMIS Fatigue score)

An **outcome** usually refers to a measured variable (eg, peak volume of oxygen or PROMIS Fatigue score)



Data sources for endpoints in ePCTs

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

Finding the Missing Link for Big Biomedical Data
Griffin M. Weber, MD; Kenneth D. Mandl, MD, MPH; Isaac S. Kohane, MD, PhD.
JAMA. 2014;311(24):2479-2480. doi:10.1001/jama.2014.4228 (Figure 1)

Data sources for endpoints in ePCTs

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

Endpoints in ePCTs

- All research endpoints should be meaningful to providers and patients
- More pragmatic endpoints ...
 - Matter to providers and patients
 - Are captured reliably as part of routine clinical care
 - Do not require central adjudication
 - Are shorter-term in nature

Choosing an endpoint that is not captured reliably as part of routine clinical care or impedes the clinical workflow is not pragmatic!

Choosing and specifying endpoints in ePCTs

Endpoints and outcomes need to be available as part of routine care



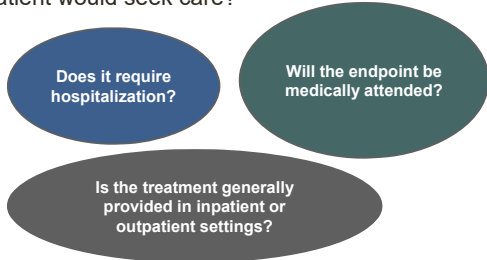
- Acute MI
- Broken bone
- Hospitalization



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

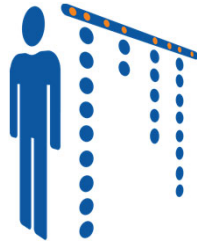
Key questions for choosing endpoints

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



Caveats when using EHR data for research (selected)

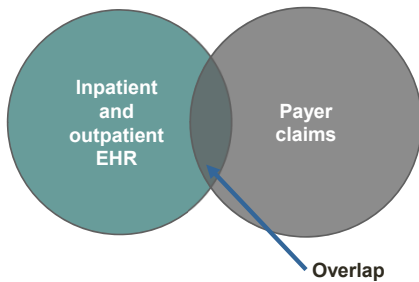
EHRs often do not tell a complete story

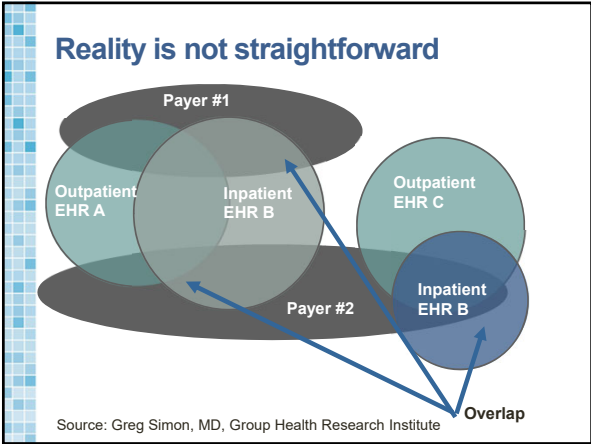


Source: Hersh WR et al. Med Care 2013;51:S30-S37

Where is the signal?

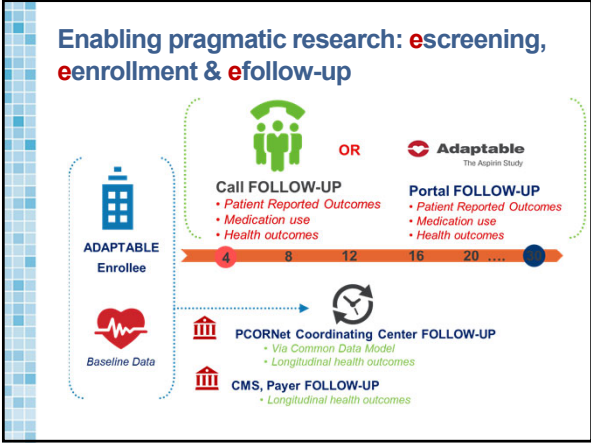
- EHR (laboratory values, treatments, etc)
- Claims data (does the event generate a bill?)





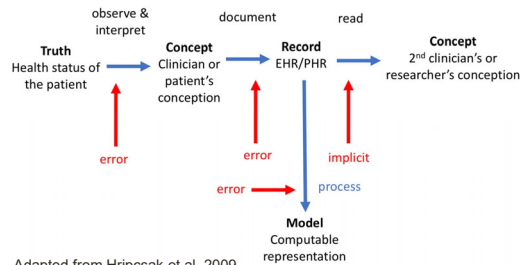
Longitudinal data linkage

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



Data is a surrogate for clinical phenomena

Error Impact on Trials



Data quality assessment

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

Resources

[Electronic Health Records Core](#) [Assessing Outcomes](#)

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

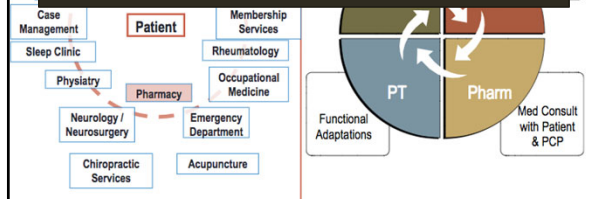


Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)

Pain Management: Usual Care

Interdisciplinary Management
Embedded in Primary Care

PROs were needed, but were not standardly collected across diverse regions



Case example: PPACT

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

Defining outcomes with clinical phenotypes

Differences across phenotype definitions can potentially affect their application in healthcare organizations and the subsequent interpretation of data.

A comparison of phenotype definitions for diabetes mellitus
Richesson R et al. J Am Med Inform Assoc. Volume 20, Issue e2, 1 December 2013, Pages e319–e326; doi.org/10.1136/amiainj-2013-001952 (Figure 1 and Table 1)



Important things to do

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



Concluding Points

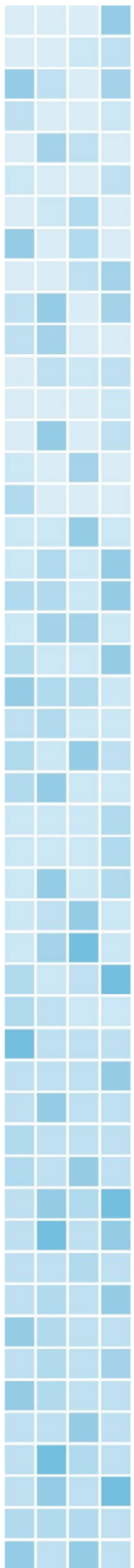
- The data available from the EHR may be convenient and pragmatic, but might not actually drive clinical practice or policy if used as endpoints
- Need to make sure that the endpoint that IS conveniently available will also be accepted as one that will be influential for stakeholders when the PCT results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

ePCT Design and Analysis


Learning objective	<ul style="list-style-type: none"> • ePCT Design: Learn about group- or cluster-randomized trials, individually randomized group-treatment trials, and stepped wedge group- or cluster-randomized trials • ePCT Analysis: Learn about the special analytic requirements for these designs and about the current recommendations for their analysis.
Instructor	David Murray
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • 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 <p>NIH Research Methods</p> <ul style="list-style-type: none"> • 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 <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Lessons Learned from the NIH Collaboratory Biostatistics and Design Core

<p>Resources</p>	<p>Key journal articles</p> <ul style="list-style-type: none"> • 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 <p>Additional resources</p> <ul style="list-style-type: none"> • Murray DM. Design and Analysis of Group-Randomized Trials. New York, NY: Oxford University Press; 1998. • Pragmatic Trials: A Workshop Handbook • Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Healthcare Systems Collaboratory Biostatistic and Design Core <hr/> <p>Bibliography from Seminar Session</p> <ul style="list-style-type: none"> • Donner A, Taljaard M, et al. The merits of breaking the matches: a cautionary tale. Statistics in Medicine. 2007;26(9):2036-51. • Raab GM, Butcher I. Balance in cluster randomized trials. Statistics in medicine. 2001;20(3):351-365. PMID11180306. • Li F, Lokhnygina Y, et al. An evaluation of constrained randomization for the design and analysis of group-randomized trials. Stat Med. 2016;35(10):1565-79. PMID26598212. • Li F, Turner EL, et al. An evaluation of constrained randomization for the design and analysis of group-randomized trials with binary outcomes. Stat Med. 2017;36(24):3791-806. PMID28786223. • Hemming, K, Taljaard M, et al. Reporting of The CONSORT extension for Stepped-Wedge Cluster Randomised Trials: Extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614. PMID30413417. • Chen et al. Secular trends and evaluation of complex interventions: the rising tide phenomenon. BMJ Qual Saf. 2016 May;25(5):303-10. • Copas AJ, et al. (2015) Designing a stepped wedge trial: three main designs, carry-over effects and randomisation approaches. Trials; 16:352(1):352. PMID26279154. • Hughes JP, Granston TS, et al. (2015) On the design and analysis of stepped wedge trials. Contemporary Clinical Trials. 45(Pt A):55-60 • Zucker DM. An analysis of variance pitfall: The fixed effects analysis in a nested design. Educ and Psych Measuremnt. 1990;50(4):731-8.
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	<ul style="list-style-type: none">• Moerbeek M, Teerenstra S. Power analysis of trials with multilevel data. Boca Raton: CRC Press; 2016.• Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. <i>J Clin Epi.</i> 2016;69:137-46. PMID26344808.• Hooper R, Teerenstra S, et al. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. <i>Stat in Med.</i> 2016;35(26):4718-28. PMID27350420.• Kasza J, Hemming K et al. Impact of non-uniform correlation structure on sample size and power in multiple-period cluster randomised trials. <i>Stat Meth in Med Res.</i> 2017;0(0)1-14. PMID29027505.• Li F, Turner EL, et al. Sample size determination for GEE analyses of stepped wedge cluster randomized trials. <i>Biometrics.</i> 2018;74(4):1450-8. PMID29921006.• Candel MJ, Van Breukelen GJ. Varying cluster sizes in trials with clusters in one treatment arm: sample size adjustments when testing treatment effects with linear mixed models. <i>Statistics in Medicine.</i> 2009;28(18):2307-24.• Candel MJ, Van Breukelen GJ. Sample size adjustments for varying cluster sizes in cluster randomized trials with binary outcomes analyzed with second-order PQL mixed logistic regression. <i>Statistics in Medicine.</i> 2010;29(14):1488-501.• You Z, Williams OD, Aban I, Kabagambe EK, Tiwari HK, Cutter G. Relative efficiency and sample size for cluster randomized trials with variable cluster sizes. <i>Clinical Trials.</i> 2011;8(1):27-36.• Candel MJ, Van Breukelen GJ. Repairing the efficiency loss due to varying cluster sizes in two-level two-armed randomized trials with heterogeneous clustering. <i>Statistics in Medicine.</i> 2016;35(12):2000-15.• Moerbeek M, Teerenstra S. Power analysis of trials with multilevel data. Boca Raton: CRC Press; 2016.
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NIH Collaboratory
 Health Care Systems Research Collaboratory
*Rethinking Clinical Trials**


Design and Analysis of Embedded Pragmatic Trials

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

Essentials of Embedded Pragmatic Clinical Trials Seminar


Learning goals

- ePCT Design: Learn about group- or cluster-randomized trials, individually randomized group-treatment trials, and stepped wedge group- or cluster-randomized trials
- ePCT Analysis: Learn about the special analytic requirements for these designs and about the current recommendations for their analysis


Important things to know

- Studies that randomize groups or deliver interventions to groups face special analytic challenges not found in traditional randomized controlled 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

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.

4

Three kinds of randomized trials

- Randomized Controlled Trials (RCTs)
 - Individuals randomized to study conditions, no interaction among participants after randomization
 - Most drug trials
- Individually Randomized Group Treatment Trials (IRGTs)
 - Individuals randomized to study conditions, interaction among participants post randomization in at least one condition
 - Many surgical trials
 - Many behavioral trials
- Group-Randomized Trials (GRTs)
 - Groups randomized to study conditions, interaction among members of the same group before and after randomization
 - Many trials conducted in communities, worksites, schools, etc.

5

Two kinds of group-randomized trials

- Parallel GRT
 - Separate but parallel intervention and control conditions throughout the trial, with no crossover
- Stepped Wedge GRT
 - All groups start in the control condition.
 - All groups crossover to the intervention condition, but in a random order and on a staggered schedule.
 - All groups receive the intervention before the end of the trial.

6

Alternative labels

- Individually randomized controlled trials are also called....
 - Randomized controlled trials,
 - Randomized clinical trials,
 - Controlled clinical trials.
 - These labels are interchangeable.
- Individually randomized group treatment trials are also called...
 - Partially nested designs or partially clustered designs.
 - IRGT is the more general label.
- Group-randomized trials are also called...
 - Cluster-randomized trials,
 - Community trials.
 - These labels are interchangeable.

7

Impact on the design

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

8

Impact on the design

- Parallel group-randomized trials
 - GRTs often involve a limited number of groups, often < 50 .
 - In any single realization, there is limited opportunity for randomization to distribute all potential confounders evenly.
 - Confounding is a concern in GRTs if $G < 50$.
- Stepped wedge GRTs
 - Crossing of groups with study conditions avoids most confounding.
 - However, intervention effects are confounded with calendar time, as more groups are in the intervention condition as the trial progresses.
 - SW-GRTs are inherently less rigorous than parallel GRTs and should be considered only when a parallel GRT is not appropriate.

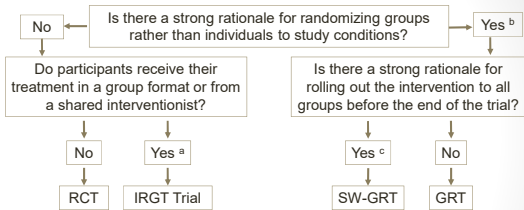
9

The need for these designs

- An RCT is the best comparative design whenever...
 - Individual randomization is possible without post-randomization interaction.
- An IRGT is the best comparative design whenever...
 - Individual randomization is possible but there are reasons to allow post-randomization interaction.
- A GRT is the best comparative design whenever the investigator wants to evaluate an intervention that...
 - Cannot be delivered to individuals without risk of contamination.
- An SW-GRT is an alternative to a parallel GRT if...
 - It is unethical to withhold the intervention from any groups.
 - It is impossible to implement the intervention in many groups simultaneously.
 - External events are unlikely to affect the outcomes.

10

Choosing among these designs



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

^b There may be logistical reasons to randomize groups or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

^c There may be legitimate political or logistical reasons to roll out the intervention to all groups before the end of the trial.

11

Planning the trial

- The driving force must be the research question.
 - The question will identify the target population, the setting, the endpoints, and the intervention.
 - Those factors will shape the design and analytic plan.
- The primary criteria for choosing that question should be:
 - Is it important enough to do?
 - Will the trial address an important public health question?
 - Will the results advance the field?
 - Is this the right time to do it?
 - Is there preliminary evidence of feasibility and efficacy for the intervention?
 - Are there good estimates for the parameters needed to size the study?
- The investigators should proceed only if the answer to both questions is yes, and keep the question in mind.

12

Fundamentals of research design

- The goal in any comparative trial is to allow valid inference that the intervention as implemented caused the result as observed.
- Three elements are required:
 - Control observations
 - A minimum of bias in the estimate of the intervention effect
 - Sufficient precision for that estimate
- The three most important tools to limit bias and improve precision in any comparative trial are:
 - Randomization
 - Replication
 - Variance reduction

13

Threats to internal validity

- Four primary threats in a trial are:
 - Selection refers to pre-existing differences between the study conditions associated with the groups or members that are nested within conditions.
 - Differential history is any external influence other than the intervention that can affect the outcome and that affects one condition more than the other.
 - Differential maturation reflects growth or development at the group or member level that can affect the outcome and that affects one condition more than the other.
 - Contamination exists when important components of the intervention find their way into the control condition, either directly, or indirectly.

14

Strategies to protect internal validity

- Randomization
- A priori matching, stratification, or constrained randomization
 - Of groups in GRTs and SW-GRTs, of members in IRGTs
- Objective measures
- Independent evaluation personnel who are blind to conditions
- Analytic strategies
 - Regression adjustment for covariates
 - In SW-GRTs, regression adjustment for calendar time
- Avoid the pitfalls that invite threats to internal validity
 - Testing and differential testing
 - Instrumentation and differential instrumentation
 - Regression to the mean and differential regression to the mean
 - Attrition and differential attrition

15

Parallel group-randomized trial designs

- Single factor and factorial designs
- Time as a factor
- Cross-sectional and cohort designs
- *A priori* matching and stratification
- Constrained randomization

16

Single factor and factorial designs

- Most involve only one treatment factor.
 - Condition
- Most have only two levels of that treatment factor.
 - Intervention vs. control.
- Most cross Condition with Time.
 - Nested cohort designs
 - Nested cross-sectional designs
- Some GRTs include stratification factors.
 - Multi-center GRTs cross Condition with Field Center.
 - Single-center GRTs often stratify on factors related to the outcome or to the ease of implementation of the intervention.
- Some IRGTs have post-randomization interaction in one condition only, others have it in both.

17

Time as a factor

- Posttest-only design
- Pretest-posttest design
- Extended designs
 - Additional discrete time intervals before and/or after intervention
 - Continuous surveillance

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Cross-sectional and cohort designs

- Nested cohort design
 - The research question involves change in specific members.
 - Measure the same sample at each time data are collected.
- Nested cross-sectional design
 - The research question involves change in an entire population.
 - Select a new sample each time data are collected.

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Cross-sectional and cohort designs

- Strengths and weaknesses

Cross-section
in and out migration
group change
recruitment costs
less powerful?
full dose?

Cohort
mortality
individual change
tracking and follow-up costs
more powerful?
full dose?

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A priori matching and stratification

- Rationale
 - Either can be used if the investigators want to ensure balance on a potential source of bias.
 - A priori stratification is preferred if the investigators expect the intervention effect to be different across strata.
 - A priori matching is useful if the matching factors are well correlated with the primary endpoint.
 - The choice of matching vs. stratification will often depend on the number of groups available and on the expected correlation.
 - Work by Donner et al. (2007) favors stratification when $m < 100$.

• Donner A, Tajaard M, et al. The merits of breaking the matches: a cautionary tale. *Statistics in Medicine*. 2007;26(9):2036-51.

21

Constrained randomization

- Stratification or matching are difficult if there are multiple factors and a limited number of groups to be randomized.
- Constrained randomization has been suggested as a solution (Raab and Butcher, 2001).
 - Generate all possible allocations.
 - Identify those that are sufficiently well balanced across conditions on key covariates.
 - Choose one allocation at random to use for the trial.
- Li et al. (2016, 2017) evaluated constrained randomization for power and type 1 error.
 - Raab GM, Butcher I. Balance in cluster randomized trials. *Statistics in medicine*. 2001;20(3):351-365. PMID11180306.
 - Li F, Lohnygina Y, et al. An evaluation of constrained randomization for the design and analysis of group-randomized trials. *Stat Med*. 2016;35(10):1565-79. PMID26598212.
 - Li F, Turner EL, et al. An evaluation of constrained randomization for the design and analysis of group-randomized trials with binary outcomes. *Stat Med*. 2017;36(24):3791-806. PMID28786223.

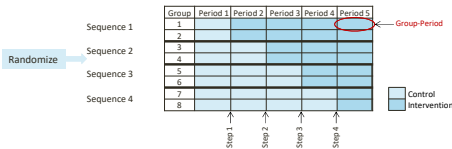
22

Stepped wedge group randomized trial designs

- The basic stepped wedge design
- Main type of stepped wedge designs
- Key methodological considerations
 - Confounding by time
 - Contamination
 - Time-varying intervention effects
 - Effect heterogeneity
 - Complex correlations

23

Stepped wedge group randomized trial



- Groups are randomized to sequences.
 - This is where matching, stratification, or constrained stratification would be used to improve comparability of the sequences.
- Groups cross to intervention sequentially and in random order, either individually or in sets.
- Outcomes are assessed repeatedly in each group over time.
- All groups provide both intervention and control data.

24

Main types of SW-GRT designs

- Cross-sectional design
 - Different individuals are measured each time.
- Cohort design
 - The same individuals are measured each time.
 - Closed cohort: no individuals may join during the trial
 - Open cohort: some individuals may leave and others may join during the trial

25

Key methodological considerations

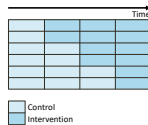
- SW-GRTs have several key characteristics that complicate their design and analysis.
 - May increase the risks of bias
 - Need careful justification for the use of this design
 - Need special care in reporting

- Hemming, K, Taljaard M, et al. Reporting of The CONSORT extension for Stepped-Wedge Cluster Randomised Trials: Extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ*. 2018;363:k1614. PMID30413417.

26

Confounding by time

- Intervention effect is partially confounded with time.
 - Due to staggered implementation, time is correlated with intervention.
 - Time may also be correlated with outcome ("secular trend").
- Analysis must always adjust for time (even if not significant).



- Chen et al. Secular trends and evaluation of complex interventions: the rising tide phenomenon. *BMJ Qual Saf*. 2016 May;25(5):303-10.

27

Contamination

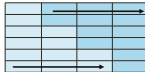
- Increased risk of within-group contamination
 - Groups may implement intervention earlier than planned (they can't wait).
 - Groups may implement intervention later than planned (difficulties in implementation).
- As long as contamination is observed and recorded, an "as treated" analysis is possible (but deviates from "Intention-To-Treat").

• Copas AJ et al. (2015) Designing a stepped wedge trial: three main designs, carry-over effects and randomisation approaches. *Trials*; 16:352(1):352. PMID26279154.

28

Time-varying intervention effects

- Effect of intervention may vary depending on
 - Calendar time
 - Seasonal variation, external events
 - Time since the intervention was introduced
 - Response may increase with more experience.
 - Response may weaken over time (training is forgotten, decrease in adherence).
- An analysis which assumes a constant intervention effect may be biased.



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Effect heterogeneity

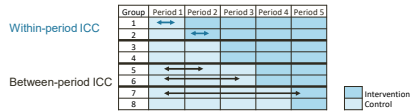
- Treatment effect may vary across groups.
 - Variation in quality of implementation, fidelity, other factors
- An analysis which assumes a homogeneous intervention effect across groups may be biased.
- Heterogeneity can reduce power.

• Hughes JP, Granston TS, et al. (2015) On the design and analysis of stepped wedge trials. *Contemporary Clinical Trials*. 45(Pt A):55-60

30

Complex correlations

- Repeated measures on same groups (and possibly same participants)
- Need to account for within-period ICCs as well as between-period ICCs
- Bias can be introduced by mis-specifying the correlation structure.



31

Individually randomized group treatment designs

- Post-randomization interaction in one condition
 - Creates a heterogeneous correlation structure
- Post-randomization interaction in both conditions
 - Creates a correlation structure similar to a GRT
- The design features available for GRTs are also available for IRGTs.

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Summary of design issues

- All the design features common to RCTs are available to GRTs and IRGTs, with the added complication of an extra level of nesting:
 - Nested cohort and nested 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.

33

Summary of design issues

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

34

Impact on the analysis

- Observations on randomized individuals who do not interact are independent and are analyzed with standard methods.
- The members of the same group in a GRT or SW-GRT will share some physical, geographic, social or other connection.
- The participants who interact in an IRGT will develop similar connections.
- Those connections will create a positive intraclass correlation that reflects extra variation attributable to the group.

$$ICC_{mgc} = \text{corr}(y_{ikl}, y_{i'kl})$$

- The positive ICC reduces the variation among the members of the same group so the within-group variance is:

$$\sigma_c^2 = \sigma_y^2 (1 - ICC_{mgc})$$

35

Impact on the analysis

- The between-group component is the one's complement:

$$\sigma_{gx}^2 = \sigma_y^2 (1 - ICC_{mgc})$$

- The total variance is the sum of the two components:

$$\sigma_y^2 = \sigma_c^2 + \sigma_{gx}^2$$

- The intraclass correlation is the fraction of the total variation in the data that is attributable to the group:

$$ICC_{mgc} = \frac{\sigma_{gx}^2}{\sigma_c^2 + \sigma_{gx}^2}$$

36

Impact on the analysis: GRT, IRGT

- Given m members in each of g groups...

- When group membership is established by random assignment,

$$\sigma_{y_g}^2 = \frac{\sigma_y^2}{m}$$

- When group membership is not established by random assignment,

$$\sigma_{y_g}^2 = \frac{\sigma_e^2}{m} + \sigma_g^2$$

- Or equivalently,

$$\sigma_{y_g}^2 = \frac{\sigma_y^2}{m} (1 + (m-1) ICC)$$

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Impact on the analysis: GRT, IRGT

- Nested factors must be modeled as random effects (Zucker, 1990).
- The variance of any group-level statistic will be larger.
- The df to estimate the group-level component of variance will be based on the number of groups, and so is often limited.
 - This is almost always true in a GRT, can be true in an IRGT.
- Any analysis that ignores the extra variation or the limited df will have a Type I error rate that is inflated, often badly.
 - Type I error rate may be 30-50% in a GRT, even with small ICC
 - Type I error rate may be 15-25% in an IRGT, even with small ICC
- Extra variation and limited df always reduce power.

- Zucker DM. An analysis of variance pitfall: The fixed effects analysis in a nested design. *Educ and Psych Measuremnt.* 1990;50(4):731-8.

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Impact on the analysis: GRT, IRGT

- Scott & Holt (1982) estimate the effect of the ICC as:

$$DEFF = 1 + (m-1) ICC_y ICC_x$$

- DEFF is the ratio of the variance as observed to the variance under simple random sampling.
- ICC_y is the ICC for the dependent variable.
- ICC_x is the ICC for the independent variable.

- Scott AJ, Holt D. The effect of two-stage sampling on ordinary least squares methods. *Journal of the American Statistical Association.* 1982;77(380):848-54.

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Impact on the analysis: GRT, IRGT

- For most health related outcomes, ICC values are ...
 - 0.00-0.05 for large aggregates (e.g., schools, worksites),
 - 0.05-0.25 for small aggregates (e.g., classrooms, departments),
 - 0.25-0.75 for very small aggregates (e.g., families, spouse pairs).
- ICCs tend to be larger for knowledge and attitudes, smaller for behaviors, and smaller still for physiologic measures.
- If the groups are crossed with the levels of the exposure of interest (most observational studies, SW-GRTs), $ICC_x \approx ICC_y$.
- If the groups are nested within the levels of the exposure of interest (IRGTs, GRTs), $ICC_x = 1$, because all members of a group will have the same value for exposure.

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Impact on the analysis: GRT, IRGT

- Given the ICC and m per group, DEFF is...

Surveys			IRGTs			GRTs		
m	$ICC_y = ICC_x$		m	$ICC_x = 1$		m	$ICC_x = 1$	
	0.05	0.01		0.25	0.10		0.05	0.01
50	1.12	1.00	10	3.25	1.90	20	1.95	1.19
100	1.25	1.01	20	5.75	2.90	100	5.95	1.99
200	1.50	1.02	40	10.75	4.90	500	25.95	5.99

- The usual F-test, corrected for the ICC, is:

$$F_{\text{corrected}} = \frac{F_{\text{uncorrected}}}{\text{DEFF}}$$

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Impact on analysis: SW-GRTs

- Groups are crossed rather than nested within conditions.
- Crossing of groups with study conditions reduces the impact of the ICC compared to a parallel GRT or IRGT, either improving power or allowing a smaller study.
- Even so, there are other potential sources of bias:
 - The intervention is confounded with time.
 - SW-GRTs face a greater risk from external events that can affect the outcomes.
 - The intervention effect may vary over time.
- Any analysis that assumes that there is no secular trend, that the intervention effect is constant over time, and that the intervention is the only event that could affect the outcome may be biased.

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The warning

- "Randomization by cluster accompanied by an analysis appropriate to randomization by individual is an exercise in self-deception, however, and should be discouraged."

Cornfield (1978)

- Though Cornfield's remarks were addressed only to GRTs, they also apply to IRGTs, and to SW-GRTs

- Cornfield J. Randomization by group: a formal analysis. Am J Epi. 1978;108(2):100-102.

43

The need for these designs

- The challenge is to create trials that are:
 - Rigorous enough to avoid threats to validity of the design,
 - Analyzed to avoid threats to statistical validity,
 - Powerful enough to provide an answer to the question,
 - And inexpensive enough to be practical.

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Strategies to protect the analysis

- Avoid model misspecification
 - Plan the analysis concurrent with the design.
 - Plan the analysis around the primary endpoints.
 - Anticipate all sources of random variation.
 - Anticipate patterns of over-time correlation.
 - Anticipate the pattern of the intervention effect over time.
 - Particularly important with repeated measures designs, including SW-GRTs
- Assess potential confounding and effect modification.

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Strategies to protect the analysis

- Avoid low power
 - Employ strong interventions with good reach.
 - Maintain reliability of intervention implementation.
 - Employ more and smaller groups instead of a few large groups.
 - Employ more and smaller surveys or continuous surveillance instead of a few large surveys.
 - For SW-GRTs, employ more steps.
 - Employ regression adjustment for covariates to reduce variance and intraclass correlation, and in SW-GRTs, to adjust for calendar time.

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Factors that affect precision in a GRT

- The variance of the condition mean in a GRT is:

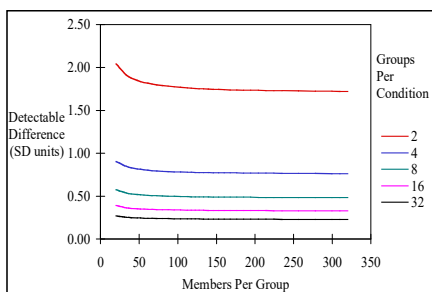
$$\sigma_{y_c}^2 = \frac{\sigma_y^2}{mg} (1 + (m-1)ICC)$$

- This equation must be adapted for more complex analyses, but the precision of the analysis will always be directly related to the components of this formula operative in the proposed analysis:
 - Replication of members and groups
 - Variation in measures
 - Intraclass correlation

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Improving precision in a GRT

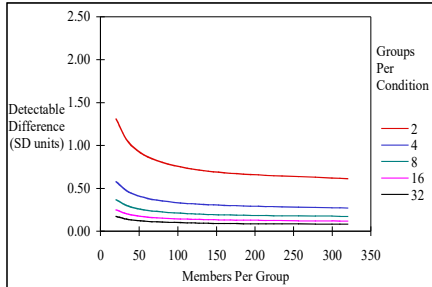
- Increased replication (ICC=0.100)



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Improving precision in a GRT

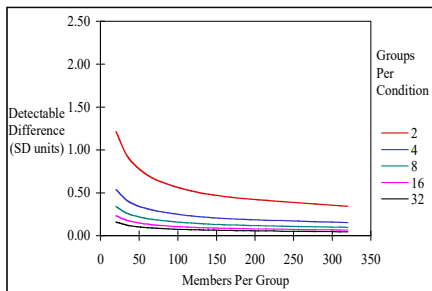
- Reduced ICC (ICC=0.010)



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Improving precision in a GRT

- The law of diminishing returns (ICC=0.001)



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Preferred analytic models for GRTs: 1 or 2 time intervals

- Mixed-model ANOVA/ANCOVA
 - Extension of the familiar ANOVA/ANCOVA based on the General Linear Model
 - Fit using the General Linear Mixed Model or the Generalized Linear Mixed Model
 - Accommodates regression adjustment for covariates
 - Can not misrepresent over-time correlation
 - Can take several forms
 - Posttest-only ANOVA/ANCOVA
 - ANCOVA of posttest with regression adjustment for pretest
 - Repeated measures ANOVA/ANCOVA for pretest-posttest design
 - Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in GRTs.

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Preferred analytic models for GRTs: 3 or more time intervals

- Random coefficients models
 - Also called growth curve models
 - The intervention effect is estimated as the difference in the condition mean trends.
 - Mixed-model ANOVA/ANCOVA assumes homogeneity of group-specific trends.
 - Simulations have shown that mixed-model ANOVA/ANCOVA has an inflated Type I error rate if those trends are heterogeneous (Murray et al., 1998).
 - Random coefficients models allow for heterogeneity of those trends.
 - Simulations have shown these methods have the nominal Type I error rate across a wide range of conditions common in GRTs.
- Murray DM, Hannan PJ, et al. Analysis of data from group-randomized trials with repeat observations on the same groups. *Stat Med.* 1998;17(14):1581-600. PMID9699231.

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Individually randomized group treatment trials

- Analyses that ignore the ICC risk an inflated Type I error rate (cf. Pals et al., 2008; Baldwin et al., 2011).
 - Not as severe as in a GRT, but can exceed 15% under conditions common to these studies.
 - The solution is the same as in a GRT.
 - Analyze to reflect the variation attributable to the groups defined by the patterns of interaction.
 - Base df on the number of groups, not the number of members.
 - Mixed models are the most common approach.
- Pals SL, Murray DM, et al. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. *Am J Public Health.* 2008;98(8):1418-24. PMID18556603.
- Baldwin SA, Bauer DJ, et al. Evaluating models for partially clustered designs. *Psych Methods.* 2011;16(2):149-65. PMID21517179.

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Cross-classification, multiple membership, or dynamic groups

- The GRT and IRGT literature assumes that each member belongs to one group and that group membership does not change over time.
 - These patterns often do not hold in practice and failure to model the correct structure can lead to an inflated type 1 error rate.
 - Roberts and Walwyn (2013), Luo et al. (2015), and Sterba (2017) describe cross-classified, multiple membership multilevel, and dynamic group models that address these complex design features.
- Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. *Stat in Med.* 2013;32(1):81-98. PMID22865729.
- Luo W, Cappaert KJ, et al. Modelling partially cross-classified multilevel data. *Br J Math Stat Psychol.* 2015;68(2):342-62. PMID25773173.
- Sterba SK. Partially nested designs in psychotherapy trials: A review of modeling developments. *Psychother Res.* 2017;27(4):425-36. PMID26686878.

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Stepped wedge group randomized trials

- The original Hussey & Hughes (2007) approach assumed a common secular trend and an immediate and constant intervention effect.
- Hughes et al. (2015) allow the treatment effects to vary across groups.
- Hooper et al. (2016) allow the between-period ICC to be less than the within-period ICC, but allow no further decay.

- Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clinical Trials*. 2007;28(2):182-91. PMID16829207.
- Hughes JP, Granston TS, et al. Current issues in the design and analysis of stepped wedge trials. *Contemp Clinical Trials*. 2015;45(Pt A):55-60. PMID26247569.
- Hooper R, Teerenstra S, et al. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. *Stat Med*. 2016;35(26):4718-28. PMID27350420.

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Stepped wedge group randomized trials

- Kasza et al. (2017) allow the between-period ICC to decay steadily.
- Grantham et al. (2019) allow more flexible decay models.
- Hughes et al. (2015) and Nickless et al. (2018) offer methods that model the intervention effect as a trend over time.

- Kasza J, Hemming K et al. Impact of non-uniform correlation structure on sample size and power in multiple-period cluster randomised trials. *Stat Meth in Med Res*. 2017;0(0)1-14. PMID29027505.
- Grantham KL, Kasza J, et al. Accounting for a decaying correlation structure in cluster randomized trials with continuous recruitment. *Stat Med*. 2019;38(11):1918-34. PMID30663132.
- Nickless A, Voysey M, et al. Mixed effects approach to the analysis of the stepped wedge cluster randomised trial- Investigating the confounding effect of time through simulation. *PLoS One*. 2018;13(12):e0208876. PMID30543671.

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Summary of analytic issues

- GRTs, IRGTs, and SW-GRTs require analyses that reflect their complex designs.
- Used alone and in one stage, the usual methods based on the General or Generalized Linear Model are not valid.
- Methods based on the General Linear Mixed Model and on the Generalized Linear Mixed Model are widely applicable.
- Other methods can be used effectively, with proper care, including randomization tests, GEE, and two-stage methods.

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Power for group-randomized trials

- The usual methods must be adapted to reflect the nested design
 - The variance is greater in a GRT due to the expected ICC.
 - df should be based on the number of groups, not the number of members.
- Power depends heavily on the ICC and the number of groups per condition, less on the number of members per group.
- Many papers now report ICCs and show how to plan a GRT.
- Power in GRTs is tricky, and investigators are advised to get help from someone familiar with these methods.
- A good resource is the NIH Research Methods Resources website
 - <https://researchmethodsresources.nih.gov>

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Power for IRGTs

- Power depends heavily on the ICC and the number of groups per condition.
- Power is better in trials that do not have post-randomization interaction in the control condition.
- Methods for sample size estimation for IRGTs have been published.
 - Pals SP, Murray DM et al. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. *Am J Pub Health.* 2008;98(8):1418-24. PMID18556603.
 - Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. *Stat in Med.* 2013;32(1):81-98. PMID22865729.
 - Moerbeek M, Teerenstra S. Power analysis of trials with multilevel data. Boca Raton: CRC Press; 2016.

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Power for SW-GRTs

- Power depends heavily on the between- and within-period ICCs, on the number of groups, on the number of steps, and on the analytic method.
- Methods for sample size estimation for SW-GRTs have been published.
 - Moerbeek M, Teerenstra S. Power analysis of trials with multilevel data. Boca Raton: CRC Press; 2016.
 - Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. *J Clin Epi.* 2016;69:137-46. PMID26344808.
 - Hooper R, Teerenstra S, et al. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. *Stat in Med.* 2016;35(26):4718-28. PMID27350420.
 - Kasza J, Hemming K et al. Impact of non-uniform correlation structure on sample size and power in multiple-period cluster randomised trials. *Stat Meth in Med Res.* 2017;0(0):1-14. PMID29027505.
 - Li F, Turner EL, et al. Sample size determination for CEE analyses of stepped wedge cluster randomized trials. *Biometrics.* 2018;74(4):1450-8. PMID29921006.

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Unbalanced designs

- Most of the methods for sample size estimation and data analysis assume a balanced design in terms of group size.
- As long as the ratio of the largest to the group is no worse than about 2:1, those methods are fine.
- Given more extreme imbalance reduces power and can lead to an inflated type I error rate if ignored in the analysis.
- Candel MJ, Van Breukelen GJ. Varying cluster sizes in trials with clusters in one treatment arm: sample size adjustments when testing treatment effects with linear mixed models. *Statistics in Medicine*. 2009;28(18):2307-24.
- Candel MJ, Van Breukelen GJ. Sample size adjustments for varying cluster sizes in cluster randomized trials with binary outcomes analyzed with second-order PQL mixed logistic regression. *Statistics in Medicine*. 2010;29(14):1488-501.
- You Z, Williams OD, Aban I, Kabagambe EK, Twari HK, Cutter G. Relative efficiency and sample size for cluster randomized trials with variable cluster sizes. *Clinical Trials*. 2011;8(1):27-36.
- Candel MJ, Van Breukelen GJ. Repairing the efficiency loss due to varying cluster sizes in two-level two-armed randomized trials with heterogeneous clustering. *Statistics in Medicine*. 2016;35(12):2000-15.
- Moerbeek M, Teerenstra S. *Power analysis of trials with multilevel data*. Boca Raton: CRC Press; 2016.

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Analysis and power for SW-GRTs

- Most of the methods and software assumes that the intervention effect develops fully during the step in which it is introduced and persists at a steady state thereafter.
- That pattern may not hold in practice.
- Use of sample size estimation methods that wrongly assume this pattern may greatly overestimate power.
- Use of data analytic methods that wrongly assume this pattern may yield a substantially diluted intervention effect estimate.
- Much work is needed to flesh out methods for sample size estimation and data analysis for studies in which the intervention effect is expected to develop more gradually or to fade over time.

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NIH resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
 - <https://prevention.nih.gov/qrt>
 - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
 - <https://prevention.nih.gov/education-training/methods-mind-gap>
 - SW-GRTs for Disease Prevention Research (Monica Taljaard, July 11, 2018)
 - Design and Analysis of IRGTs in Public Health (Sherri Pals, April 24, 2017)
 - Research Methods Resources for Clinical Trials Involving Groups or Clusters (David Murray, December 13, 2017)
- Research Methods Resources Website
 - <https://researchmethodsresources.nih.gov/>
 - Material on GRTs and IRGTs and a sample size calculator for GRTs

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Important things to do

- Read - Turner EL, Li F, Gallis JA, Prague M, Murray DM. 2017. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1-Design. Am J Public Health 107: 907-15
- Read - 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
- Read - 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
- Read - 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

Pilot and Feasibility Testing

Learning objective	Identify approaches to evaluate the capabilities and challenges of the partner healthcare system and test key elements of the intervention during pilot or feasibility studies
Instructor	Wendy Weber
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • 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 <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Embedded Pragmatic Clinical Trials: Triumphs and Tribulations • ICD-Pieces: From Planning to Performance • Who to Include in a Pragmatic Trial? It Depends <p>Key journal articles</p> <ul style="list-style-type: none"> • Weinfurt et al., 2017. Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory • Hubbard et al., 2016. The feasibility and acceptability of trial procedures for a pragmatic randomised controlled trial of a structured physical activity intervention for people diagnosed with colorectal cancer • Leon et al., 2011. The role and interpretation of pilot studies in clinical research




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

Pilot and Feasibility Testing


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

Essentials of Embedded Pragmatic Clinical Trials Seminar



Learning goal

Identify approaches to evaluate the capabilities and challenges of the partner healthcare system and test key elements of the intervention during pilot or feasibility studies



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

ePCTs are not efficacy trials

- ePCTs bridge research into clinical care
- Intervention is integrated into real-world healthcare settings



During the pilot phase

- Establish close partnerships with healthcare system (HCS) personnel
- Test and validate EHR data collection and extraction
- Assess how well the intervention can be integrated into the clinical workflow
- Identify multiple local champions at each study site

Build partnerships



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

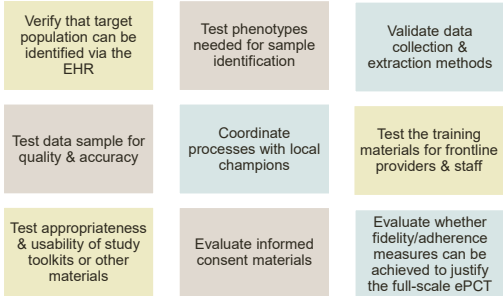


Resource: Health system partnerships

Establishing Close Partnerships with Healthcare System Leaders and Staff

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

Aspects of feasibility that can be piloted



Use what you learn to design the ePCT

Evaluate power calculations



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

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

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

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

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

Resource: 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

Case study from NIH Collaboratory: Suicide Prevention Outreach Trial (SPOT)

SUICIDE
PREVENTION
OUTREACH TRIAL

- Collaborative care model to test treatments intended to reach large groups of adult patients who have serious thoughts of suicide
- 4 clinical sites
- 16,000 expected patients
- Gregory Simon, MD, MPH, Principal Investigator, Kaiser Permanente Washington Health Research Institute

Suicide Prevention Outreach Trial

- Pragmatic trial of outreach programs to prevent suicide attempt
- Automatically enroll outpatients reporting frequent thoughts of death or self-harm on routine depression questionnaires
- Randomly assigned to continued usual care or one of two outreach programs
 - Risk Assessment and Care Management
 - Dialectical Behavior Skills Training
 - Both provided outreach for up to one year
 - Both intended as supplements to existing treatment
- Analysis by intent to treat, regardless of intervention uptake or adherence

A priori limits on interventions

- Total cost no more than \$100 per person
- Centralized delivery by online messaging (via EHR portal)
- Delivered by masters-prepared mental health providers
- Scalable to full health system population

Pilot study process

- Three waves of pilot testing – approx. 40 in each wave
- Full implementation of invitation process
- Care management / coaching limited to 3 months
- No ascertainment of outcomes

Pilot study questions

- Expected rate of initial engagement
- Incremental gain with additional waves of invitation
- Optimal wording of invitation messages
- Proportion requiring telephone follow-up

What they learned / changed:

- Gain from 3rd wave of invitation is worth the effort
- Initial language describing the program was confusing
- Approximately 30% of invites require telephone follow-up
- Uptake rate tops out at 40%-45%

What they didn't do:

- Attempt to assess intervention impact or effectiveness
- Select participants for higher likelihood of participation
- Offer telephone services as alternative to outpatient care
- Extend beyond 3 cycles of invitation
- Personalize program to preferences or concerns of providers or clinics

In the end, it's about

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

Resource: More feasibility examples

Spotlight on Four Demonstration Projects

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

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
 - Ethical/regulatory aspects are addressed
 - Intervention is fully developed and finalized
 - Data collection methods are adequately tested
 - Budget and timeline are realistic and feasible

Readiness checklist

Milestone	Completed
<i>Recruitment plans are finalized</i>	
All sites identified (documentation of site commitment)	
Methods for accurately identifying participants validated	
All agreements for necessary subcontracts in place	
<i>Ethical/regulatory aspects are addressed</i>	
Coordinated IRB oversight in place	
Finalized plans for informed consent or waiver of informed consent	
Finalized data and safety monitoring plan	
<i>Intervention is fully developed and finalized</i>	
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)	
<i>Data collection methods are adequately tested</i>	
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	
<i>Budget is realistic, feasible, and accounts for potential changes</i>	

Resource: Trial readiness criteria

Implementation Readiness Checklist

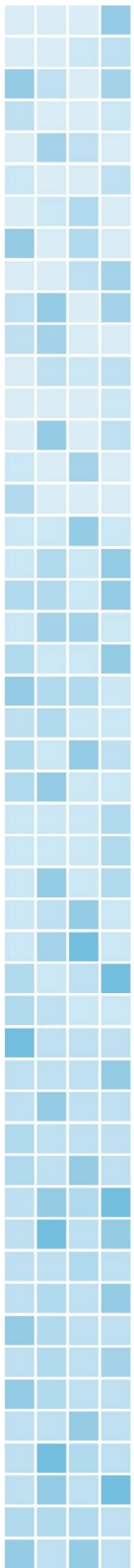
From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Important things to do

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

Ethical and Regulatory Oversight Considerations

Learning objective	Learn about the regulatory and ethical considerations specific to conducting ePCTs
Instructors	Julie Kaneshiro, Kevin Weinfurt
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • Consent, Disclosure, and Non-disclosure • Data & Safety Monitoring • Ethics and Regulatory Core • Collaboratory Demonstration Projects: Ethics and Regulatory Documentation <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • 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)




Resources	<p>Key journal articles</p> <ul style="list-style-type: none">• Sugarman et al., 2014. Ethics and regulatory complexities for pragmatic clinical trials• Weinfurt et al., 2017. Comparison of approaches for notification and authorization in pragmatic clinical research evaluating commonly used medical practices• Topazian et al., 2016. Physicians' perspectives regarding pragmatic clinical trials• Sugarman, 2016. Ethics of research in usual care settings: data on point• Weinfurt et al., 2015. Patients' views regarding research on medical practices: implications for consent• Mentz et al., 2016. Good clinical practice guidelines and pragmatic clinical trials: balancing the best of both worlds
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 **NIH Collaboratory**
Health Care Systems Research Collaboratory
*Rethinking Clinical Trials**


Ethical and Regulatory Oversight Considerations

Julie Kaneshiro, MA
Office for Human Research Protections
Kevin Weinfurt, PhD
Duke University School of Medicine

Essentials of Embedded Pragmatic Clinical Trials Seminar

 **Learning goal**

Learn about the regulatory and ethical considerations specific to conducting ePCTs

 **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

ePCTs are motivated by ethical imperatives



ePCTs also raise interesting ethical and regulatory questions

Evolving understanding of unique ethical/regulatory issues for ePCTs

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

Resources: Regulatory & ethical challenges of ePCTs

[Introduction](#)
and
[Informed Consent](#)

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



Resource: Additional readings on regulatory/ethical considerations

[Special Issue of Clinical Trials](#)

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

Current ethics/regulatory in flux



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**?

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

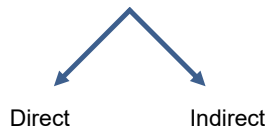
Regulatory & ethical challenges of ePCTs



Ethical, not regulatory, question:

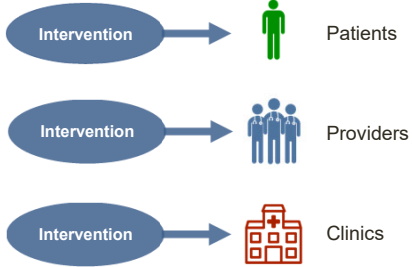
Whose rights and welfare need to be protected?

Types of participants in an ePCT

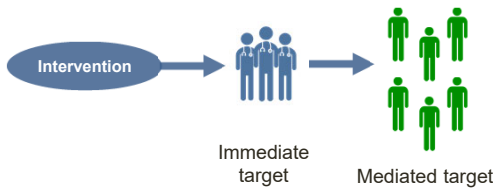


Direct participants

Immediate or mediated targets of the intervention

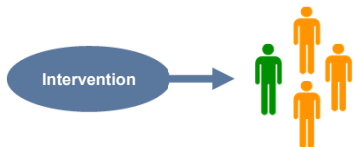


Direct participant



Indirect participants

People affected by routine exposure to the environment (eg, family/caregivers)

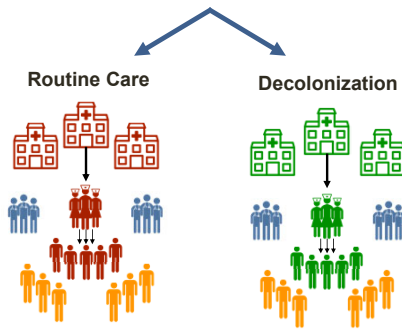


Case study from NIH Collaboratory: Active Bathing to Eliminate (ABATE) Infection



- Cluster trial comparing 2 quality improvement strategies to reduce multidrug-resistant organisms and healthcare-related infections in non-ICU population
- 53 hospitals
- 331,584 patients

Indirect participants: ABATE example



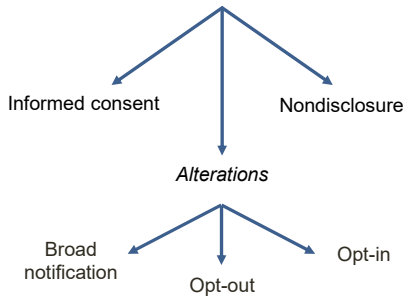
Regulatory Perspective: *Who are the subjects in ePCTs?*

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**

Approaches to notification & authorization



Resource: Regulatory and ethical challenges of ePCTs

Consent, Disclosure, and Nondisclosure

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

Resource: Alternative approaches

Alternative Approaches to Disclosure and Authorization

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

Working with human subjects oversight bodies



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

Requirement for single IRB review

Applicability

- U.S. 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**

Data monitoring committee

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



Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Inference about adverse events
 - Availability of clinical data to assess relatedness
 - Should adverse events still be monitored?
- Limited or delayed access to study outcomes during study conduct
- Are interim analyses actionable?

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

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

OHRP Contacts and Resources

- Please contact us or 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

OHRP PUBLIC OUTREACH WEBSITE
www.hhs.gov/About-Research-Participation
 Resources for the public to learn about participating in research and making informed decisions

Videos Information Tools

OHRP Office for Human Research Protections | *Protecting Human Subjects in Research*

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

OHRP Office for Human Research Protections

Dissemination and Implementation

Learning objective	<ul style="list-style-type: none"> • Learn methods for designing ePCTs so findings can be easily implemented • Build in sustainability from the beginning • Identify considerations for dissemination of study results
Instructor	Wynne Norton
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • Designing with Implementation and Dissemination in Mind • Dissemination and Implementation • Dissemination Approaches for Different Stakeholders • Pragmatic Elements: An Introduction to PRECIS-2 • PCT Reporting Template <p>Collaboratory Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none"> • Who to Include in a Pragmatic Trial? It Depends • Pragmatic Clinical Trials and Learning Health Care Systems: Strategies to Facilitate Implementation of Results into Clinical Care • Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory <p>Key journal article</p> <ul style="list-style-type: none"> • Curran et al., 2012. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact <p>Key websites</p> <ul style="list-style-type: none"> • https://cancercontrol.cancer.gov/IS/tools/research.html • https://cancercontrol.cancer.gov/IS/training-education/Webinars.aspx • http://impsciuw.org/ • NIH Dissemination and Implementation Research in Health (DIRH) Funding Opportunity Announcement (R01, Clinical Trial Optional): https://grants.nih.gov/grants/guide/pa-files/par-19-274.html

Dissemination and Implementation

Wynne E. Norton, PhD
Program Director, Implementation Science
National Cancer Institute

Preconference Workshop:
Essentials of Embedded Pragmatic Clinical Trials

Academy Health Annual Research Meeting
June 1, 2019



Disclosures

- I have no financial relationships to disclose.
- Opinions are mine, not official positions of the National Cancer Institute, the National Institutes of Health, or the U.S. federal government.

Learning Goals

- Learn methods for designing ePCTs so findings can be easily implemented.
- Build in sustainability from the beginning.
- Identify considerations for dissemination of study results.

Important Things to Know

- D&I science provides key insight into how best to disseminate and implement findings from research studies.
- Developing interventions with stakeholder input is critical for future dissemination and implementation of study findings.

What is D&I Science?

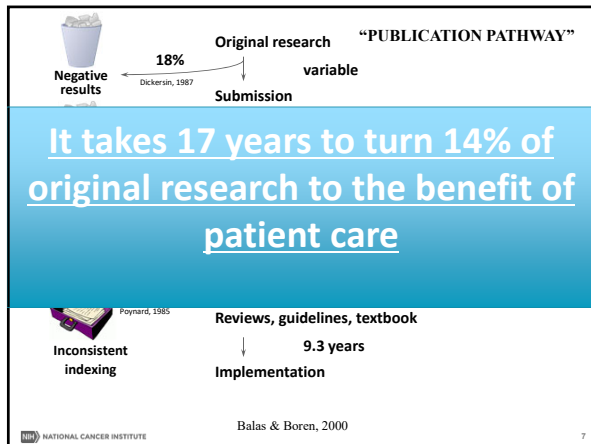
What can we learn from D&I science to inform D&I practice of ePCT research?

Evidence-Based Interventions, Practices, Programs, Guidelines



Research-Tested Intervention Programs (RTIPs) <http://rtips.cancer.gov/rtips/>
▪ RTIPs – Moving Science into Programs for People

Effective Interventions
HIV PREVENTION THAT WORKS



Sometimes, the step from best evidence to best practice is simple; however, most of the time it is not, and we need various strategies targeting obstacles to change at different levels...

Grol & Grimshaw, 2003

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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?

Dissemination and Implementation Research in Health PAR, NIH, 2019

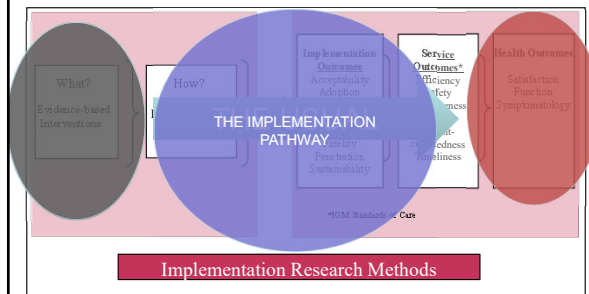
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Implementation Research

- “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?

Dissemination and Implementation Research in Health PAR, NIH, 2019

Implementation Pathway



Proctor et al., 2009

Implementation Strategies

1. Evaluation and iterative strategies <ul style="list-style-type: none"> • Assess readiness • Identify barriers and facilitators 	2. Interactive assistance <ul style="list-style-type: none"> • Facilitation • Technical assistance 	3. Adapting and tailoring to context <ul style="list-style-type: none"> • Tailor strategies • Promote adaptability 	4. Develop stakeholder relationships <ul style="list-style-type: none"> • Identify local opinion leaders • Build coalitions
5. Train/educate stakeholders <ul style="list-style-type: none"> • Conduct training • Develop educational materials 	6. Supporting clinicians <ul style="list-style-type: none"> • Audit and feedback • Revise professional roles 	7. Engage consumers <ul style="list-style-type: none"> • Involve end-users • Use mass media 	8. Use financial strategies <ul style="list-style-type: none"> • Alter incentive structures • Develop disincentives
9. Change infrastructure <ul style="list-style-type: none"> • Mandate change • Change physical structures 			

Powell et al., 2012; Waltz, et al., 2015

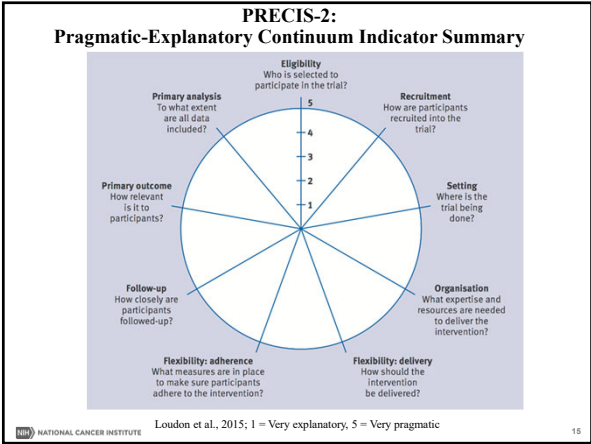
Implications of D&I Research for Practice

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Designing with Dissemination in Mind

- Is this a priority question or issue among end-users?
- To whom would the results apply? Will there be a demand for the study results or intervention?
- Are stakeholders involved in identifying the research question, selecting the appropriate research design, collecting priority outcome data, and sharing results?
- Could this intervention be delivered within the existing structure of the delivery system? What would need to change? Is that type of change feasible, realistic, affordable?

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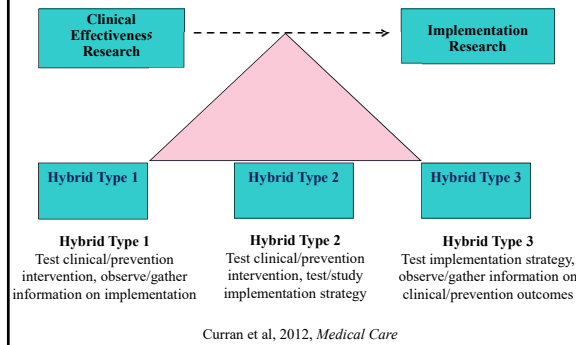
Planning with Implementation in Mind

- Hybrid effectiveness-implementation designs
- Opportunity to collect data on implementation barriers, facilitators, and processes during pragmatic RCTs to anticipate challenges and guide future efforts.
- Qualitative data (e.g., interviews, focus groups)
 - Assess barriers toward using practice during trial
- Quantitative data (e.g., surveys)
 - Measure providers' attitudes toward using practice

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Hybrid Effectiveness-Implementation Designs



A Hybrid Effectiveness-Implementation Trial of an Evidence-Based Exercise Intervention for Breast Cancer Survivors

Rinad S. Beidas, Breah Paciotti, Fran Barg, Andrea R. Branas, Justin C. Brown, Karen Glanz, Angela DeMichele, Laura DiGiovanni, Domenick Salvatore, Kathryn H. Schmitz

The primary aims of this hybrid Type 1 effectiveness-implementation trial were to quantitatively assess whether an evidence-based exercise intervention for breast cancer survivors, Strength After Breast Cancer, was safe and effective in a new setting and to qualitatively assess barriers to implementation.

A cohort of 84 survivors completed measurements related to limb volume, muscle strength, and body image at baseline, 67 survivors completed measurements 12 months later. Qualitative methods were used to understand barriers to implementation experienced by referring oncology clinicians and physical therapists who delivered the program.

Beidas et al. (2014). *JNCI*.

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Using implementation facilitation to implement primary care mental health integration via clinical video telehealth in rural clinics: protocol for a hybrid type 2 cluster randomized stepped-wedge design

Richard R. Owen^{1,2*}, Eva N. Woodward^{1,2,3}, Karen L. Drummond^{1,2}, Tisha L. Deen⁴, Karen Anderson Oliver⁵, Nancy J. Petersen^{6,7}, Scott S. Meitl⁸, John C. Fortney^{8,9} and JoAnn E. Kirchner^{2,10}

Methods: This study is a hybrid type 2 pragmatic effectiveness-implementation trial of tele-PCMH in six sites over 24 months. Tele-PCMH, which will be delivered by clinical staff available in routine care settings, will be compared to usual care. Fidelity to the care model will be monitored but not controlled. We will use the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework to evaluate the patient-level clinical effectiveness of tele-PCMH in rural VA clinics and also to evaluate the fidelity to and outcomes of the implementation strategy, implementation facilitation. The proposed study will employ a stepped-wedge design in

Owen et al. 2017. *Implementation Science*.

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Implementing Alcohol Misuse SBIRT in a National Cohort of Pediatric Trauma Centers—a type III hybrid effectiveness-implementation trial

Michael J. Mello^{1,2,3*}, Sara J. Becker⁴, Julie Bromberg^{1,3}, Janette Baird^{1,3}, Mark R. Zonfrillo^{1,3,5} and Anthony Spirito⁶

Background: The American College of Surgeons mandates universal screening for alcohol misuse and delivery of an intervention for those screening positive as a requirement for certification as a level 1 trauma center. Though this requirement has been mandated for over a decade, its implementation has been challenging. Our research team completed an implementation study supporting seven pediatric trauma centers' compliance with the requirement by developing and implementing an institutional alcohol Screening, Brief Intervention and Referral to Treatment (SBIRT) policy for adolescent trauma patients. A mixed-methods approach indicated that SBIRT adoption rates increased at all sites; however, providers' fidelity to the SBIRT intervention was variable, and providers reported a number of barriers to SBIRT implementation. The goal of this study is to conduct a fully powered type III hybrid effectiveness-implementation trial to test the effectiveness of a comprehensive implementation strategy in increasing the implementation of SBIRT for alcohol and other drug use (AOD) in pediatric trauma centers.

Mello et al. 2018. *Implementation Science*.

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Disseminating Study Findings

- **Go beyond traditional academic publication outlets**
 - Newsletters, listservs, webinars, press releases, policy briefs for relevant patient, consumer, practitioner, professional society groups
 - Tailor format and content to target audience
- **Presentations at non-traditional conferences**
 - Practice (vs. academic/research) meetings, community-based organizations, community health partners, health departments
- **Leverage social networks, social media, and online platforms**
 - Twitter, trusted peer-to-peer networks, online platforms (e.g., Sermo, Doximity, DailyRounds)

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Implementing Study Findings

- **Implementation manuals**
 - Make manuals for interventions readily available and in user-friendly format to end-users
- **Partnerships, collaborations, C-suite executives**
 - Continue partnerships developed during trial
 - Share 'best practices' of implementing study findings
 - Collaborate with C-suite executives throughout trial, measure ROI, cost-effectiveness of intervention, cost-effectiveness of implementation
 - User-friendly version of CONSORT extension for pragmatic trials (Zwarenstein et al., 2008)

Select D&I Research Resources

Training Programs, Webinars



Advanced Topics in Implementation Science Webinars

Listen in as leaders in the field discuss advanced dissemination and implementation research topics and answer questions from the community.



Annual D&I Conference

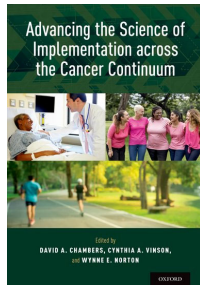
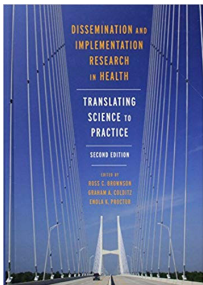
12th Annual Conference on the Science of Dissemination and Implementation in Health


Learn about the latest innovations in the science of D&I;
Explore new research findings and contribute to the next set of research priorities;
Identify and understand challenges facing D&I research; and
Network and collaborate with leading experts in the field.

DATE & TIME December 4-6, 2019 LOCATION Crystal Gateway Marriott, Arlington, VA

Supported by NIH, AcademyHealth, AHRQ, PCORI, RWJF, VA

Textbooks, Journal



 **Implementation Science**

Important Things To Do

- Think about designing your study in ways that can facilitate broader dissemination and implementation.
- Involve patients, providers, organizational leaders, and other key stakeholders in the design and conduct of the trial to increase applicability and relevance to other potential end-users.
- Create materials (e.g., manuals, resources, training documents) that can be distributed after the study to help disseminate findings.
- Use a variety of outlets to share study findings with practitioner communities.

Questions? Comments?

Thank You!

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Wynne E. Norton, PhD
Program Director, Implementation Science
Division of Cancer Control and Population Sciences
National Cancer Institute

wynne.norton@nih.gov

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**NATIONAL
CANCER
INSTITUTE**

www.cancer.gov www.cancer.gov/espanol

Assembling an ePCT Team & Writing a Grant Application

Learning objective	<ul style="list-style-type: none"> • Identify skills needed for a strong study team • Learn how to develop a compelling ePCT application
Instructors	Robin Boineau, Marcel Salive
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none"> • ePCT Team Composition • Developing a Compelling Grant Application • Assessing Feasibility: Developing the Trial Documentation <p>Key journal articles</p> <ul style="list-style-type: none"> • Johnson et al., 2014. A guide to research partnerships for pragmatic clinical trials • Dolor et al., 2014. Guidance for researchers developing and conducting clinical trials in Practice-based Research Networks (PBRNs) <p>Other</p> <ul style="list-style-type: none"> • NIH Reporter (Tool) • National Institute on Aging (NIA) Stage Model for Behavioral Intervention Development • NIA RFA-AG-20-029, Pragmatic Trials of Managing Multimorbidity in Alzheimer's Disease • Health Care Services Research Network website • RFA-RM-16-019: NIH Health Care Systems Research Collaboratory • Clinical Trial-Specific Funding Opportunities • Clinical Trial-Specific Review Criteria • Health Care Systems Research Network • Research Toolkit

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


Assembling an ePCT Team

Robin Boineau, MD, MA
National Centers for Complementary and Integrative Health
National Institutes of Health

Essentials of Embedded Pragmatic Clinical Trials Seminar

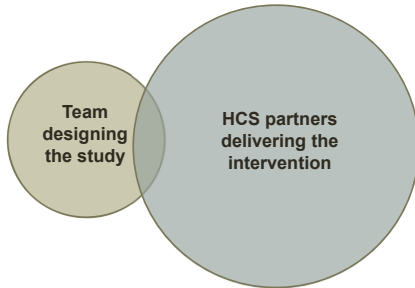
Learning goal

Identify skills needed for a strong study team

 **Important things to know**

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

Who is involved?



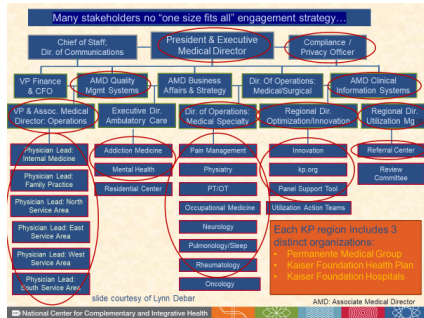
Potential team members

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

What skills will be needed?

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

Collaborative Care for Chronic Pain in Primary Care (PPACT)
 PI: Lynn Debar, Kaiser Permanente Washington Health Research Institute





Important things to do


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

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


Writing a Grant Application

Marcel Salive, MD, MPH
National Institute on Aging

Essentials of Embedded Pragmatic Clinical Trials Seminar

 **Learning goal**

Learn how to develop a compelling ePCT application

 **Important things to know**

- Online resources are available for the development of pragmatic trial grant applications
- NIH has new policies and forms related to clinical trial grant applications
- Some things, such as milestones and safety monitoring, may be negotiable around the time of an award

National Institutes of Health



- NIH is made up of [27 institutes and centers \(IC\)](#)
- ICs award >80% of the NIH budget each year
- Each IC has a budget and a director, and typically their own review for large trials

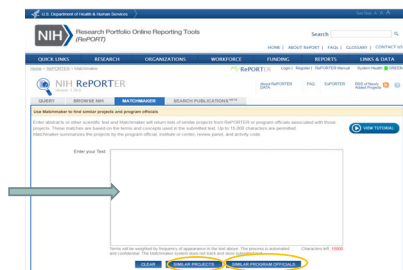


Understand NIH: find the right fit

IC mission and priorities

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

NIH RePORTER



https://projectreporter.nih.gov/reporter_matchmaker.cfm

Matchmaker results



Grant versus cooperative agreement

Under assistance relationships:

- Grants (R) are used when no substantial programmatic involvement is anticipated between the Federal agency and the recipient during performance of the assisted activity
- Cooperative agreements (U) are used when substantial programmatic involvement is anticipated between the Federal agency and the recipient during performance of the assisted activity
- Not necessarily important for developing the application

NIH Research Collaboratory: RFA-RM-16-019

Scientific contacts from participating
NIH Institutes and Centers

NCCIH	Robin Boineau	NIDA	Sarah Duffy
NCI	Erica Breslau	NIDCR	Dena Fischer
NHLBI	Barbara Wells	NIDDK	Andy Narva
NIA	Marcel Salive	NIMH	Jane Pearson
NIAAA	Brett Hagman	NINDS	Robin Conwit
NIAID	Clayton Huntley	NINR	Jeri Miller
NIAIMS	Chuck Washabaugh	ODP	Rachael Ballard
NICHD	Sue Marden		

Use Matchmaker tool in [NIH RePORTER](#) for suggestions

Which study section?

- **Mostly** Institute-specific special emphasis panels
- Center for Scientific Review (CSR) Study sections
 - **Health Services Organization and Delivery Study Section**
 - Health services research studies that include multidisciplinary investigations of the organization, delivery, utilization, and outcomes of health services, including availability, access and acceptability; quality of care; costs and cost-effectiveness; *comparative effectiveness*; and financing of health care. Clinical study settings include inpatient, outpatient, sub-acute, acute, community-based, rehabilitative, and long-term care.
- An important question to discuss with NIH program staff, particularly with respect to pragmatic vs explanatory trial

Source:
<https://public.csr.nih.gov/StudySections/IntegratedReviewGroups/HDMIRG/HSOD/Pages/default.aspx>

Finding a funding announcement: www.grants.nih.gov

The screenshot shows the NIH Grants & Funding website. The header includes the NIH logo and navigation tabs: HOME, ABOUT GRANTS, FUNDING, POLICY & COMPLIANCE, NEWS & EVENTS, and ABOUT OER. The main content area displays 'Advanced Funding Opportunities & Notices Search Results' with a search bar and a 'Search' button. Below the search bar, it indicates 'Matching Records: 109' and 'Sorted by: Release Date (Desc) then Announcement Number'. There are also 'Related Links' for 'Funding Opportunities & Notices', 'Advanced Funding Ops Search', 'Advanced OER Site Search', and 'Search Help'.

Read FOA carefully

- Funding Opportunity Description and Research Opportunities section is crucial, of course
- Application and Submission Information for page limits and specifics for the Aims and Research Strategy sections
- Look at Application Review Information for Review criteria, since they may NOT be STANDARD; they are often specific for the FOA
- READ CAREFULLY and several times

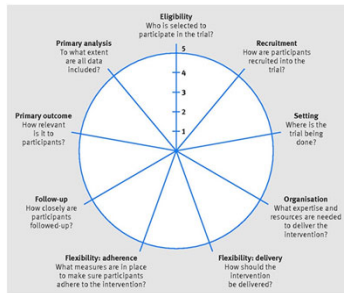
NIH review criteria—clinical trials

- Application may include study design, methods, and intervention that are not by themselves innovative but address important questions or unmet needs
- Has new questions under each of the standard criteria, in particular the Approach section should address Study Design, Data Management and Statistical Analysis.
- One Additional Review Criteria for **Study Timeline**

Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (eg, CTSA, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate? Are potential challenges and corresponding solutions discussed (eg, strategies that can be implemented in the event of enrollment shortfalls)?

Source: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-118.html>

PRECIS-2 domains



PRECIS-2 source: Kirsty Loudon et al. BMJ 2015;350:bmj.h2147. Copyright 2015 by British Medical Journal Publishing Group. Used by permission.

Common application pitfalls

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

Avoid receiving these summary statement comments

Data provided did not establish the feasibility of recruitment

The premise of the study is based on weak evidence

No adequate description of how activities in the planning phase would inform activities in the implementation phase

Concerned whether outcomes of this study would drive a change in clinical practice

Amount budgeted for a biostatistician is much too low

Strategies for success



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

Application dos

- Justify the research
- Include pilot data
- Reduce complexity
- Ensure aims are capable of advancing the field
- Choose appropriate expert personnel
- Link data collection and analysis to aims
- Justify use of multiple sites and sample size

Application don'ts

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

NIH research methods resources

U.S. Department of Health & Human Services

NIH National Institutes of Health
Fostering Discoveries into Health

Research Methods Resources

Home GGT BGT GGT Sample Size Calculator Glossary References FAQs Feedback

The NIH is launching a series of initiatives in 2017-2018 to enhance the accountability and transparency of clinical research. These initiatives target key points along the entire clinical trial lifecycle, from concept to results reporting.

- Expanded ClinicalTrials.gov registration and reporting policy covers all NIH-funded clinical trials, effective January 18, 2017.
- New clinical trial requirements for NIH grants and contracts with due dates on or after January 25, 2018.
- New application forms (SF424(s) and application guide) for all NIH research applications with due dates on or after January 25, 2018.
- New review criteria for clinical trial applications with due dates on or after January 25, 2018.
- New single SBIR policy for research applications for multi-site studies with due dates on or after January 25, 2018.

The Research Methods Resources website provides investigators with important research methods resources to help them satisfy these new requirements. While the website currently only addresses methodological issues inherent in trials that randomize groups or deliver interventions to groups, new methods-related topics and resources will be added in the future. For a guided tour of this website, please refer to a recent Mind the Gap webinar, which presents additional information about its relevance to the new NIH requirements for clinical trial applications, a summary of the methodological issues inherent in random study designs, and a demonstration of how to use the Group Randomized Trials (GRT) Sample Size Calculator.

Trials that Randomize Groups or Deliver Interventions to Groups

<https://researchmethodsresources.nih.gov>

Important things to do

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

NIA resources: Blog

www.nia.nih.gov/research/blog

Pragmatic clinical trials: Testing treatments in the real world

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Clinical Research Funding Opportunities Research

Do you know the difference between an explanatory and a pragmatic clinical trial? Many researchers are familiar with explanatory clinical trials, which look at the effectiveness of a particular intervention to improve health in a controlled setting. But what makes a clinical trial pragmatic?

Blog Topics

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Considerations for Planning Your Embedded Pragmatic Clinical Trial

1. ePCT Aims and Significance

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

2. Engaging All Stakeholders and Aligning with Healthcare System Partners

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

3. Measuring Outcomes

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

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

4. ePCT Design and Analysis

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

6. Pilot and Feasibility Testing

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

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

7. Ethical and Regulatory Oversight Considerations

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

8. Dissemination and Implementation

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

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

9. Assembling Your ePCT Team

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

10. Writing the Grant Application

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

