



NIH Collaboratory ePCT Training Workshop

FEBRUARY 20–21, 2018

Participant Guide



Collaboratory ePCT Training Workshop

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Collaboratory ePCT Training Workshop

February 20-21, 2018

JB Duke Hotel

230 Science Dr.

Durham, North Carolina 27708

Agenda

Workshop Purpose

The purpose of this workshop is to (1) train investigators in the design and conduct of embedded pragmatic clinical trials (ePCTs) and (2) pilot the educational materials and collect feedback on their quality and appropriateness from both the attendees and the subject matter experts.

DAY 1			
DURATION	AGENDA TOPIC	WHO	GOAL
7:00 – 8:00 a.m.	Breakfast <i>The Marketplace</i>		
8:00 – 8:15 a.m.	Welcome and opening remarks	Kevin Weinfurt and Wendy Weber	<i>Learning objectives and goals for workshop</i>
8:15 – 9:00 a.m.	Introduction exercise (30 mins) Introduction to the 2 case studies (15 mins)	Facilitator: Kevin Weinfurt Gloria Coronado and Doug Zatzick	<i>Introductions</i>
9:00 – 9:45 a.m.	Topic 1: What are Embedded Pragmatic Clinical Trials? (Part 1)	Instructor: Lesley Curtis	<i>Identify key considerations in the design and conduct of ePCTs and how they differ from explanatory trials</i>
9:45 – 10:00 a.m.	Break		
10:00 – 10:45 a.m.	Topic 1: What are Embedded Pragmatic Clinical Trials? (Part 2)	Facilitators: Gloria Coronado and Doug Zatzick	<i>Demonstrate understanding of ePCTs and how they differ from explanatory trials as illustrated by the 2 case studies</i>

DAY 1			
DURATION	AGENDA TOPIC	WHO	GOAL
10:45 – 12:15 p.m.	Topic 2: Engaging All Stakeholders & Aligning with Healthcare System Partners	Instructor: Leah Tuzzio	<p><i>Describe the breadth of stakeholders to engage as partners in an ePCT and approaches for engaging them through all phases of a research study</i></p> <p><i>Understand the real-world priorities and perspectives of health system leaders and how to obtain their support</i></p>
12:15 – 1:15 p.m.	Lunch - <i>The Marketplace</i>		
1:15 – 1:45 p.m.	Topic 3: Designing with Implementation in Mind	Instructor: Doug Zatzick	<i>Consider how to design ePCTs so that findings can be successfully implemented and sustained in real-world healthcare settings</i>
1:45 – 2:45 p.m.	Topic 4: Design and Analytic Considerations (Part 1)	Instructor: Liz Turner Consultant: Liz DeLong	<i>Recognize analytical challenges of cluster-randomized and stepped-wedge study designs</i>
2:45 – 3:00 p.m.	Break		
3:00 – 4:00 p.m.	Topic 4: Design and Analytic Considerations (Part 2)	Instructor: Liz Turner Consultant: Liz DeLong	<i>Recognize analytical challenges of cluster-randomized and stepped-wedge study designs</i>
4:00 – 5:00 p.m.	Topic 5: Regulatory and Ethical Challenges of ePCTs	Instructor: Kevin Weinfurt	<i>Learn about the regulatory and ethics considerations specific to ePCTs</i>
5:00 – 5:15 p.m.	Closing remarks	Kevin Weinfurt and Wendy Weber	<i>Summary of Day 1</i>
	Dinner - <i>The Marketplace</i>		

DAY 2			
DURATION	AGENDA TOPIC	WHO	GOAL
7:00 – 8:00 a.m.	Breakfast <i>The Marketplace</i>		
8:00 – 8:15 a.m.	Announcements	Kevin Weinfurt and Wendy Weber	<i>Summary of Day 1</i> <i>Meeting goals for Day 2</i>
8:15 – 9:15 a.m.	Topic 6: Measuring Outcomes	Instructors: Lesley Curtis and Rachel Richesson	<i>Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)</i>
9:15 – 10:15 a.m.	Topic 7: Pilot and Feasibility Testing	Instructor: Wendy Weber	<i>Identify approaches to evaluate the capabilities and challenges of partner healthcare system and test key elements of various types of interventions</i>
10:15 – 10:30 a.m.	Break		
10:30 – 11:00 a.m.	Topic 8: Dissemination	Instructor: Doug Zatzick	<i>Identify considerations for dissemination of study results</i>
11:00 – 11:15 a.m.	Topic 9: ePCT Team Composition	Instructor: Lesley Curtis	<i>Identify ideal composition and skills needed in an ePCT study team</i>
11:15 – 11:45 a.m.	Topic 10: Developing a Compelling Application (Part 1)	Instructor: Marcel Salive	<i>Provide participants information on how to develop a compelling ePCT application</i>
11:45 – 1:00 p.m.	Lunch - <i>The Marketplace</i>		
1:00 – 2:30 p.m.	Topic 10: Developing a Compelling Application (Part 2)	Facilitator: Kevin Weinfurt	<i>Demonstrate learning around how to develop specific aims and study plans for an ePCT</i>
2:30 – 3:00 p.m.	Q&A	Facilitator: Kevin Weinfurt	<i>Opportunity for additional questions that may not have been previously addressed</i>
3:00 – 3:15 p.m.	Closing remarks and evaluation	Kevin Weinfurt, Wendy Weber, Gloria Coronado, and Doug Zatzick	<i>Summarize the workshop and offer parting advice from SMEs</i> <i>Complete the evaluation</i>

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Instructor Biographies



Gloria Coronado, PhD

Senior Investigator, Mitch Greenlick Endowed Scientist for Health Disparities

Kaiser Permanente Center for Health Research

Gloria.D.Coronado@kpchr.org

Gloria Coronado, PhD, is an epidemiologist who conducts research on health disparities related to cancer prevention among underserved populations. She designs and evaluates clinic-based interventions to improve participation in cancer prevention screening and diagnostic follow-up among patients at Latino-serving community health clinics. Currently, she is leading a large pragmatic study to test a direct-mail approach to raising rates of colon cancer screening in community health centers in Oregon, Washington, and California.

In addition to her research on cancer prevention, Dr. Coronado has examined Latino parents' acceptance of the human papillomavirus (HPV) vaccine for girls, evaluated strategies for reducing pesticide exposure for children of farm workers, and developed innovative, culturally tailored programs for reducing diabetes and cancer risks among Latinos in a rural setting. She has collaborated broadly with Latino-serving community-based organizations both locally and nationally.

Dr. Coronado came to the Center for Health Research from the Cancer Prevention Program at the Fred Hutchinson Cancer Research Center, where she led a training program that prepared diverse undergraduate and postbaccalaureate students to conduct cancer research. The program provides mentored research and professional development workshops to accelerate students' readiness to attend graduate programs in biomedical sciences.

Dr. Coronado received her PhD in epidemiology from the University of Washington and became a research associate professor in the university's Department of Epidemiology. She also received training at Stanford University. In 2009, she participated in the National Hispana Leadership Institute, an executive leadership training program.



Lesley Curtis, PhD

Chair, Department of Population Health Sciences

Director, Center for Pragmatic Health Systems Research, Duke Clinical Research Institute

Professor in Medicine, Duke University School of Medicine

Lesley.curtis@duke.edu

Lesley H. Curtis, PhD, is Professor in Medicine, directs the Center for Population Health Sciences in the Duke University School of Medicine, and directs the Center for Pragmatic Health Systems Research in the Duke Clinical Research Institute.

A health services researcher by training, Dr. Curtis oversees a portfolio of projects that use observational data to address questions related to clinical and comparative effectiveness, pharmacoepidemiology, health care delivery, and epidemiological trends across a broad array of clinical conditions and clinical care settings. An expert in the use of Medicare claims data for health services and clinical outcomes research, she has led the linkage of Medicare claims with several large clinical registries and epidemiological cohort studies including the Framingham Heart Study and the Cardiovascular Health Study.

Dr. Curtis serves on the American Heart Association/American College of Cardiology Task Force on Practice Guidelines and on the American Heart Association's Task Force on Performance Measures, working to continuously improve the incorporation of evidence into health care delivery. Additionally, she serves as Co-Lead of the Data Core for the FDA's Sentinel Initiative, Co-PI of the NIH Health Care Systems Collaboratory, and Lead of the Distributed Research Network Operations Center for PCORI's National Clinical Research Network (PCORnet), working with health systems and patient networks to develop a harmonized data infrastructure for robust observational and interventional research.



Elizabeth DeLong, PhD
Professor and Chair, Department of Biostatistics and Bioinformatics
Duke University Medical Center
elizabeth.delong@duke.edu

Elizabeth DeLong, PhD is Professor and Chair, Department of Biostatistics and Bioinformatics, Duke University Medical Center and Co-Director of the Cardiovascular Outcomes Research group in the Duke Clinical Research Institute (DCRI). Her interests are in the field of comparative effectiveness with regard to cardiovascular outcomes and quality-of-care, with emphasis on risk adjustment methodology, assessment of risk prediction models, and provider profiling. With more than 20 years of biostatistics, clinical research, and bioinformatics experience, her responsibilities have included administrative and data analytic functions, as well as statistical methods development.

Prior to joining the DCRI, she spent over three years as Director of Biostatistics for a leading contract research organization. Dr. DeLong has held government grants studying statistical issues in Validating Risk Prediction Models in Cardiology and also Features of Managed Care Affecting Quality for Cardiovascular Disease. She has also been statistical director of the risk modeling and analysis initiatives for the CRUSADE/ACTION and the ACC/NCDR Data Coordination and Analysis Centers. She is currently the Principal Investigator for the analysis center for the ASCERT GO grant, a unique collaboration between the American College of Cardiology Foundation (ACCF) and The Society for Thoracic Surgeons (STS).

In her years of experience, Dr. DeLong also has developed a strong record of teaching and mentoring. She has taught several Biostatistics courses in the Medical School, including statistics for medical students and survival analysis for students in the Clinical Research Training Program (CRTP) and has mentored a large number of statistical staff, fellows, and junior faculty. She is currently a Principal Investigator on a Mentored CER KM1 grant that trains young investigators in the methods of comparative effectiveness.



Rachel Richesson, MS, PhD, MPH, FACMI

Associate Professor

Duke University, School of Nursing

Rachel.richesson@duke.edu

Rachel Richesson, MS, PhD, MPH, FACMI, a noted informaticist, joined the DUSON faculty in December 2011. Dr. Richesson earned her BS (Biology) at the University of Massachusetts in 1991, and holds graduate degrees in Community Health (MPH, 1995) and Health Informatics (MS, 2000 and PhD, 2003) from the University of Texas Health Sciences Center in Houston. Her dissertation involved the integration of heterogeneous data from multiple emergency departments. Dr. Richesson spent 7 years as at the University of South Florida College of Medicine directing strategy for the identification and implementation of data standards for a variety of multi-national multi-site clinical research and epidemiological studies housed within the USF Department of Pediatrics, including the NIH Rare Diseases Clinical Research Network (RDCRN) and The Environmental Determinants of Diabetes in the Young (TEDDY) study.

Dr. Richesson has conducted original research on the quality and usability of various terminological data standards, particularly in the context of clinical research, and has presented dozens of posters and invited talks on the topic of data standards in clinical research. She has fostered numerous interdisciplinary research collaborations and is nationally and internationally recognized for her extensive clinical informatics experiences. In 2012, she edited Clinical Research Informatics, the first textbook dedicated to this topic, and co-authored several chapters.

Dr. Richesson is particularly interested in new applications and technologies and standards specifications that will increase the efficiency of clinical research data collection and analysis, and that will enable interoperability between clinical research and health care systems. She co-leads the Phenotyping, Data Standards, and Data Quality Core for the NIH Health Care Systems Research Collaboratory, a demonstration program for the transformation of clinical trials based upon use of electronic health records (EHRs) and healthcare systems partnerships. In this role, she is developing standard approaches and guidance for the extraction of clinical data to support research and learning healthcare systems. She is also the co-lead of the Rare Diseases Task Force for the national distributed Patient Centered Outcomes Research Network (PCORnet), specifically promoting standardized EHR-based condition definitions (“computable phenotypes”) for rare diseases, and helping to develop a national research infrastructure that can support observational and interventional research for various types of conditions.

At DUSON, Dr. Richesson teaches Health Information Exchange Standards, Methods and Models (N410) and Health Information Systems (N409), supports informatics practica (N498), and co-teaches Data-Driven Health Care Improvements (N653). She also engages in informatics-focused initiatives across the Duke campus, particularly within the Duke Center for Health Informatics and Duke Clinical Research Institute programs. Dr. Richesson was elected as a fellow of the College of Medical Informatics 2014.



Marcel Salive MD, MPH

Health Scientist Administrator, Division of Geriatrics and Gerontology

National Institute on Aging, National Institutes of Health

marcel.salive@nih.gov

Marcel Salive, MD, MPH, 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 & 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. He 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 US Public Health Service Commissioned Corps and serves on the PHS-2 rapid deployment force.



Elizabeth Turner, PhD
Assistant Professor, Biostatistics and Bioinformatics and Global Health
Duke Global Health Institute
liz.turner@duke.edu

Elizabeth Turner, PhD joined the Duke Global Health Institute and the Department of Biostatistics and Bioinformatics in March 2012 to collaborate with, and provide biostatistical support to DGHI faculty and affiliates. With a PhD in statistics from McGill University, Canada, followed by four years working as a collaborative biostatistician in the Department of Medical Statistics, Faculty of Epidemiology and Population Health of the London School of Hygiene and Tropical Medicine (LSHTM), Liz has extensive experience working in both epidemiological studies and randomized trials across a range of substantive areas in developed world and resource poor settings.

Thanks to her participation in multi-disciplinary projects, she has a great appreciation for the importance of good study design and data collection and is well aware that no fancy statistical analyses can save researchers from the scourge of bad data. Through those experiences and her teaching in different settings, including the UK, Canada, France and Tanzania, she is aware that statisticians and their collaborators sometimes "speak a different language". As a result, her approach is very much one of translation, pragmatism and collaboration. Her current substantive interests include malaria, disability and disease burden with an emphasis on eye diseases, cardiovascular disease and mental health, together with child health and education.



Leah Tuzzio, MPH
Research Associate
Kaiser Permanente Washington Health Research Institute
tuzzio.l@ghc.org

Leah Tuzzio, MPH'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.

Leah'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.

Leah 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
Acting Deputy Director
National Center for Complementary and Integrative Health (NCCIH)
National Institutes of Health (NIH)
weberwj@mail.nih.gov

Wendy J. Weber, N.D., Ph.D., M.P.H., 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. Dr. Weber's interests include the use of complementary medicine interventions for common pediatric conditions, mental health conditions, promoting healthy behaviors, and health services research.

Dr. Weber earned a doctorate of philosophy in epidemiology and a master of public health from the University of Washington. She earned a doctorate of naturopathic medicine (N.D.) from Bastyr University. Prior to joining NCCIH, she was a research associate professor at Bastyr University, where her research included the study of herbal treatments for pediatric conditions. Her clinical practice focused on the treatment of children and adolescents with mental health conditions, abdominal pain, headaches, and allergies.

She has published on treatment of pain with complementary health approaches, echinacea's effect on colds in children, naturopathic treatment of children, and complementary medicine treatments for attention-deficit

hyperactivity disorder. Her articles have appeared in *Mayo Clinic Proceedings*, *JAMA: The Journal of the American Medical Association*, *The Journal of Alternative and Complementary Medicine*, and *Pediatrics*.



Kevin Weinfurt, PhD

Professor and Vice Chair for Research, Department of Population Health Sciences

Duke University School of Medicine

Professor of Psychiatry and Behavioral Science

Duke University Medical Center

Duke Clinical Research Institute

kevin.weinfurt@duke.edu

Kevin Weinfurt, PhD, 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 a 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 US 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.



Douglas Zatzick, MD

Professor of Psychiatry and Behavioral Sciences

University of Washington

dzatzick@uw.edu

Douglas Zatzick, MD, is a board-certified psychiatrist. Dr. Zatzick's clinical interests include post-traumatic behavioral and emotional disturbances, traumatic injury, health services and cross-cultural psychiatry. His intervention studies target post-traumatic stress disorder and depression reduction and the modification of high-risk behaviors that risk recurrent injury, such as alcohol and drug abuse/dependence.

Dr. Zatzick is a professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington, Seattle. He is also a member of the Core Research Faculty at the Harborview Medical Center Injury Prevention and Research Center.

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ATTENDEE LIST

Participants

Cathleen Colon-Emeric, MD
Duke University
colon001@mc.duke.edu

Elizabeth Cox, MD, PhD
University of Wisconsin
ecox@wisc.edu

Cynthia Dougherty, PhD
University of Washington
cindyd@uw.edu

Kealy Ham, MD
Regions Hospital
kealy.r.ham@healthpartners.com

Theodore Levin, MD
Kaiser Permanente
theodore.levin@kp.org

James Lock, MD
Stanford University
jimlock@stanford.edu

Ellen McCreedy, PhD
Brown University
ellen_mccreedy@brown.edu

Maria O'Connell, PhD
Yale University
maria.oconnell@yale.edu

Quincy Samus, PhD
Johns Hopkins University
qmiles@jhmi.edu

Kirsten Corazzini, PhD, FGSA
Duke University
kirsten.corazzini@duke.edu

Beth Devine, PhD
University of Washington
bdevine@uw.edu

Brent Griffith, MD
Henry Ford Health System
brentg@rad.hfh.edu

Paul Hebert, PhD
VA Puget Sound Medical System
paul.hebert2@va.gov

Peter Lindenauer, MD, MSc
Baystate Health
Peter.Lindenauer@baystatehealth.org

Michelle Lofwall, MD
University of Kentucky
michelle.lofwall@uky.edu

Catherine Monk, PhD
Columbia University
cem31@columbia.edu

Lila Rutten, PhD
Mayo Clinic
rutten.lila@mayo.edu

Yael Schenker, MD
University of Pittsburgh
schenkery@upmc.edu

Robert Schonberger, MD
Yale University
robert.schonberger@yale.edu

Jessica Snowden, MD
University of Nebraska
jsnowden@unmc.edu

Anthony Spirito, PhD
Brown University
anthony_spirito@brown.edu

Paula Tanabe, PhD
Duke University
paula.tanabe@duke.edu

Kimberly Vesco, MD
Kaiser Permanente Center for Health Research
Kimberly.K.Vesco@kpchr.org

Naomi Simon, MD, MSc
New York University
naomi.simon@nyumc.org

John Spertus, MD
University of Missouri - Kansas City
spertusj@umkc.edu

Cheryl Stein, PhD
New York University
cheryl.stein@nyumc.org

Delphine Tuot, MD
University of California, San Francisco
delphine.tuot@ucsf.edu

Instructors

Gloria Coronado, PhD
Kaiser Permanente Center for
Health Research
Gloria.D.Coronado@kpchr.org

Elizabeth DeLong, PhD
Duke University Medical Center
elizabeth.delong@duke.edu

Marcel Salive MD, MPH
National Institute on Aging (NIA)
National Institutes of Health (NIH)
marcel.salive@nih.gov

Leah Tuzzio, MPH
Kaiser Permanente Washington
Health Research Institute
tuzzio.l@ghc.org

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

Lesley Curtis, PhD
Duke University School of Medicine
Duke Clinical Research Institute
Lesley.curtis@duke.edu

Rachel Richesson, PhD, MPH, FACMI
Duke University, School of Nursing
Rachel.richesson@duke.edu

Elizabeth Turner, PhD
Duke Global Health Institute
Duke University
liz.turner@duke.edu

Wendy J. Weber, ND, PhD, MPH
National Center for Complementary and
Integrative Health (NCCIH)
National Institutes of Health (NIH)
weberwj@mail.nih.gov

Douglas Zatzick, MD
University of Washington
dzatzick@uw.edu

National Institutes of Health (NIH)

Leslie Derr, PhD

Office of Strategic Coordination (OSC)
Office of the Director (OD)
National Institutes of Health (NIH)
Leslie.derr@nih.gov

Charles Washabaugh, PhD

National Institute of Arthritis and
Musculoskeletal and Skin Diseases (NIAMS)
National Institutes of Health (NIH)
washabac@mail.nih.gov

Coordinating Center

Darcy Louzao, PhD

Duke Clinical Research Institute
Duke University
darcy.louzao@duke.edu

MariJo Mencini

Duke Clinical Research Institute
Duke University
marijo.mencini@duke.edu

Alyssa Platt, MA

Duke Global Health Institute
Duke University
alyssa.platt@duke.edu

Tammy Reece, MS, PMP, CCRA

Duke Clinical Research Institute
Duke University
tammy.reece@duke.edu

Damon Seils, MA

Duke Clinical Research Institute
Duke University
damon.seils@duke.edu

Karen Staman, MS

Duke Clinical Research Institute
Duke University
karen.staman@duke.edu

Gina Uhlenbrauck

Duke Clinical Research Institute
Duke University
gina.uhlenbrauck@duke.edu

Liz Wing, MA

Duke Clinical Research Institute
Duke University
liz.wing@duke.edu



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Case Studies

Featured NIH Collaboratory UH3 Demonstration Project Case Studies	Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC) , Gloria Coronado, PI A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity (Trauma Survivors Outcomes and Support [TSOS]) , Doug Zatzick, PI
Additional NIH Collaboratory UH3 Demonstration Projects	Active Bathing to Eliminate (ABATE) Infection , Susan Huang, PI Collaborative Care for Chronic Pain in Primary Care (PPACT) , Lynn DeBar, PI Improving Chronic Disease Management with Pieces (ICD-Pieces) , Miguel Vazquez, PI Lumbar Imaging with Reporting of Epidemiology (LIRE) , Jerry Jarvik, PI Pragmatic Trial of Video Education in Nursing Homes (PROVEN) , Vincent Mor, Susan Mitchell, Angelo Volandes, Co-PIs Suicide Prevention Outreach Trial (SPOT) , Greg Simon, PI Time to Reduce Mortality in End-Stage Renal Disease (TiME) , Laura Dember, PI

Introducing the ePCT Case Studies

Gloria Coronado, PhD, Kaiser Permanente Center for Health Research
Doug Zatzick, MD, University of Washington School of Medicine

Collaboratory ePCT Training Workshop

Featuring 2 of the 9 NIH Collaboratory Demonstration Projects

- STOP CRC:
 - Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations
 - Gloria Coronado, Co-Principal Investigator
- TSOS:
 - A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity (Trauma Survivors Outcomes and Support)
 - Doug Zatzick, Principal Investigator

STOP CRC overview

Question: Does an evidence-based, culturally tailored approach increase colorectal cancer (CRC) screening in clinics that serve minority and low-income populations?

Setting: 26 federally qualified health center clinics

Population: 40,000 adults aged 50-74 with no evidence of recent CRC screening

Intervention: Cluster-randomized, EHR-linked, data-driven program tracks eligibility, mails fecal immunochemical test kits, tracks patient test results & follow-up

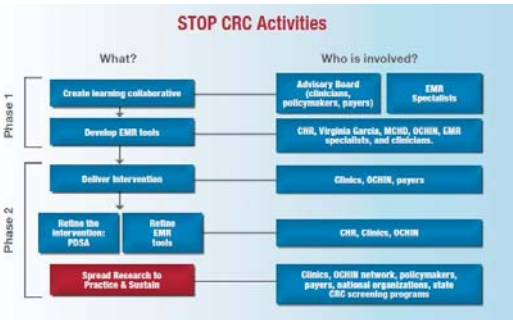
Outcome measures: CRC screening rates by age, sex, insurance status, ethnicity, race

Relevance: Results will provide valuable information on how to use EHR resources to optimize guideline-based screening

STOP CRC ePCT characteristics

- Goal: Increase rate of CRC screening in underserved patients
- Pragmatic design:
 - Broad patient eligibility
 - Comparative effectiveness intervention
 - Cluster randomization
- Embedded across 26 federally qualified health centers
- Data driven:
 - Uses EHR to identify eligible patients & generate test kit mailings
 - Uses EHR to track CRC-related outcomes using routine processes of care
- Leverages existing clinic staff

Study snapshot



TSOS overview

Question: Is a collaborative care intervention more effective than usual care in reducing PTSD and related symptoms and improving physical function?

Setting: 25 level I trauma centers across United States

Population: 960 adult patients with PTSD and related conditions

Intervention: Intervention training & support targets trauma center-based screening and treatment for PTSD and related conditions as well as care coordination from trauma center to primary care & community settings

Outcome measures: Change in scores on civilian PTSD checklist, patient health questionnaire depression scale, alcohol use disorders scale & short form physical function scale

Relevance: Results will be incorporated in the American College of Surgeons' regulatory policy for trauma care

TSOS: multiple potentially chronic conditions & the need for trauma center-to-community linkage

Traumatic injury:

- PTSD, depression, suicidal ideation
- High-risk behaviors (eg, alcohol)
- traumatic brain injury, all common



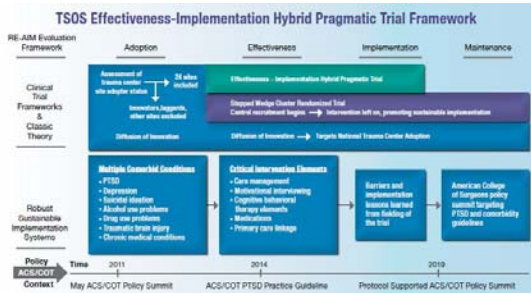
Patients "sail off of a flat earth" after trauma center care

From Darnell & Zatzick TSOS Training Slide Set

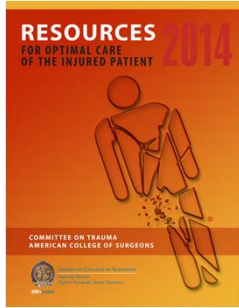
TSOS ePCT characteristics

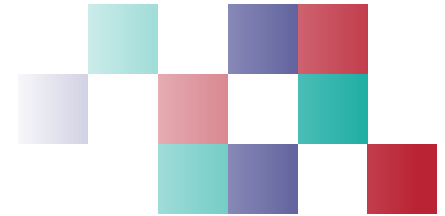
- Goal: Directly inform national trauma care system policy
- Pragmatic design:
 - Comparative effectiveness intervention
 - Stepped-wedge cluster randomization
 - Hybrid effectiveness-implementation framework, emphasizing sustainability
- Embedded in 25 U.S. level I trauma center sites
- Data driven: Uses EHR to conduct high-quality screening of patients

TSOS study snapshot



American College of Surgeons Regulatory Policy
Targeting PTSD & Comorbidity





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

Study Snapshot

Principal Investigator: Gloria D. Coronado, PhD

Co-Principal Investigator: Beverly B. Green, MD, MPH

Sponsoring Institution: Kaiser Permanente Center for Health Research

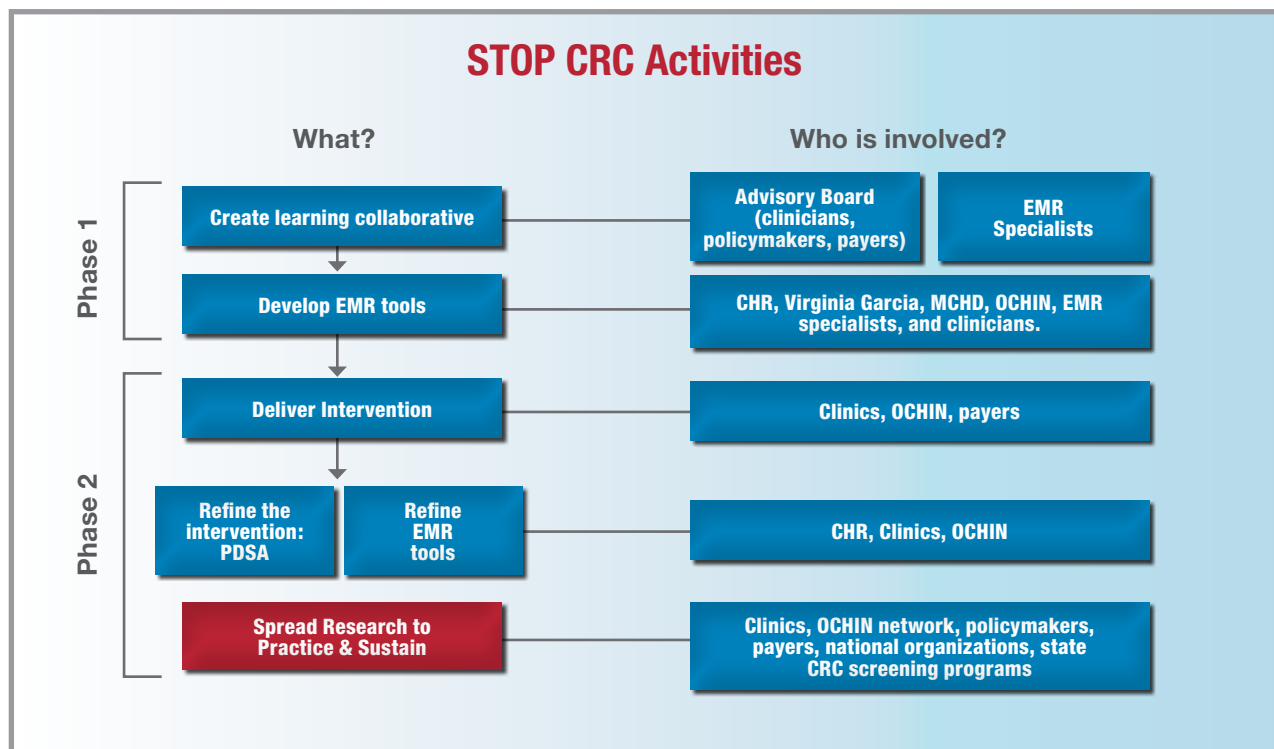
ClinicalTrials.gov: [NCT01742065](https://clinicaltrials.gov/ct2/show/study/NCT01742065)

Collaborating Healthcare Systems: Federally qualified health centers in the Oregon Community Health Information Network (OCHIN); Kaiser Permanente Washington; National Center for Complementary and Integrative Health (NCCIH)

NIH Institute Oversight: National Cancer Institute (NCI)

Abstract: Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Yet CRC is 90% curable with timely detection and appropriate treatment of precancerous polyps; increased screening could reduce incidence by up to 50%. Rates of CRC screening are extremely low in patients at federally qualified health centers (FQHCs), which serve nearly 19 million patients annually. To address this disparity, the STOP CRC trial tests a culturally

tailored, health care system-based program to improve CRC screening rates in OCHIN, a community-based collaborative network of more than 200 FQHCs. Results will provide information on how to use electronic health record resources to optimize guideline-based screening in FQHC clinics whose patient populations have disproportionately low CRC screening rates.



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	

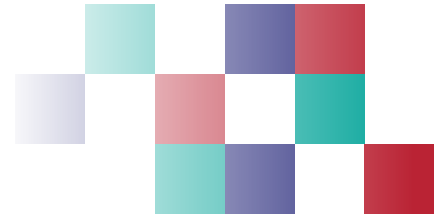
1 = little difficulty
5 = extreme difficulty

Challenge	Solution
High amounts of health system leadership turnover due to preexisting pressures and challenges inherent in community clinics	Met regularly with leadership teams and established an advisory board and other infrastructure to help engage leaders and gatekeepers.
Some patients lacked health insurance coverage to pay for follow-up colonoscopy after a positive fecal test	Medicaid expansion resulted in higher insurance coverage rates, some local community organizations provide a free colonoscopy through a network of donated care, and the advisory board includes legislators who changed state law to require commercial insurance plans cover follow-up diagnostic colonoscopy with no patient out-of-pocket costs.
Updates in real-time with the use of the electronic health record (EMR) meant that the lists of eligible and active patients at the clinics were continuously changing, causing discordance between lists that were gathered for research purposes	The team worked with the Collaboratory's Biostatistics and Study Design Core and added a secondary analysis.

Selected Publications & Presentations

June 2017	Applying the Plan-Do-Study-Act (PDSA) approach to a large pragmatic study involving safety net clinics. <i>BMC Health Serv Res</i> , Coury et al.
February 2017	Implementation successes and challenges in participating in a pragmatic study to improve colon cancer screening: perspectives of health center leaders. <i>Transl Behav Med</i> , Coronado et al.
February 2016	The validation of electronic health records in accurately identifying patients eligible for colorectal cancer screening in safety net clinics. <i>Fam Pract</i> , Petrik et al.





Trauma Survivors Outcomes and Support (TSOS): A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity

Study Snapshot

Principal Investigator: Douglas Zatzick, MD

Co-Investigators: Gregory Jurkovich, MD; Patrick Heagerty, PhD; Joan Russo, PhD; Erik Van Eaton, MD; Doyanne Darnell, PhD

Sponsoring Institution: University of Washington School of Medicine

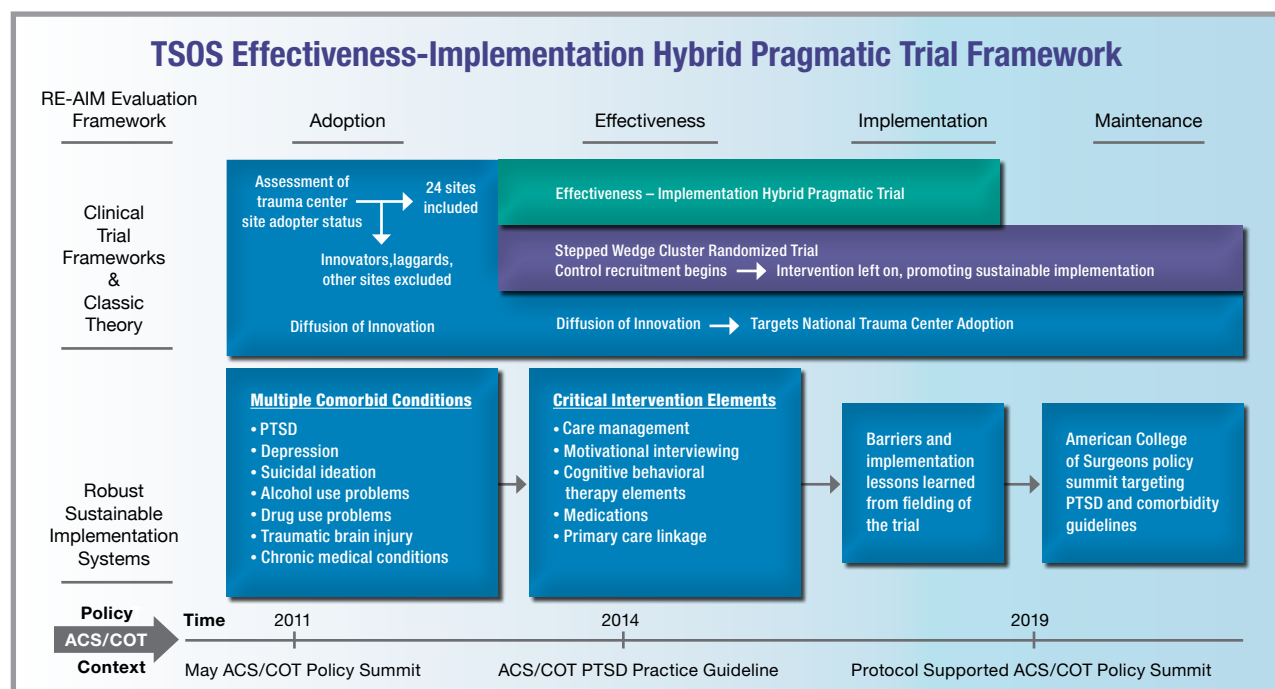
ClinicalTrials.gov: [NCT02655354](https://clinicaltrials.gov/ct2/show/study/NCT02655354)

NIH Institute Oversight: National Institute of Mental Health (NIMH)

Abstract: Each year, more than 30 million Americans present to trauma centers, emergency departments, and other acute-care settings for treatment of physical injuries. Multiple long-term conditions, including posttraumatic stress disorder (PTSD), alcohol and drug use problems, depression and associated suicidal ideation, pain and somatic symptoms, and preexisting long-term medical conditions are endemic among survivors of physical trauma, including those with and without traumatic brain injuries (TBIs). PTSD and related comorbid conditions are associated with marked functional impairments and societal costs. Evidence-based treatments for PTSD and comorbidity exist but have yet

to be broadly implemented throughout U.S. trauma care systems. The challenges presented by this constellation of PTSD and comorbid conditions in survivors of both TBI and non-TBI injuries require novel research approaches that cut across the traditional domains of multiple NIH Institutes.

The TSOS project will enable a series of innovations in the efficient development and implementation of a large-scale, policy-relevant, pragmatic randomized clinical trial targeting PTSD and comorbidity for injured patients cared for at U.S. trauma centers. The trial will be conducted at 24 level 1 trauma care centers across the United States.



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
Capabilities of the EHR systems were varied with no single administrative database	Asked all level 1 and 2 trauma centers to complete a survey regarding EHR capabilities and found that while some sites were able to automate PTSD screening, other sites needed to screen manually. Developed methods to work with all sites regardless of capability and created a 10-domain EHR screen for risk factors for PTSD and other comorbid conditions.
DSMB suggested that the study team ensure every site distributes a suicide hotline number to patients at baseline; however, only 1 of the 24 sites routinely gives a suicide hotline number	The study team did not implement this suggestion because in PCTs, the usual care condition is not malleable, and the goal is to compare the intervention with usual care.

Selected Publications & Presentations	
June 2017	The Cumulative Burden of Mental, Substance Use, and General Medical Disorders and Rehospitalization and Mortality After an Injury , <i>Psychiatr Serv</i> , Zatzick et al.
April 2017	PCT Grand Rounds Presentation: Toward National Trauma Care Practice Change for PTSD & Comorbidity: Lessons Learned from the TSOS Pragmatic Trial
April 2016	An effectiveness-implementation hybrid trial study protocol targeting posttraumatic stress disorder and comorbidity , <i>Implement Sci</i> , Zatzick et al.



Collaboratory ePCT Training Workshop

Topic 1

What are Embedded Pragmatic Clinical Trials?

Learning objectives	Part 1: Identify key considerations in the design and conduct of embedded pragmatic clinical trials (ePCTs) and how they differ from explanatory trials Part 2: Demonstrate understanding of ePCTs as illustrated by the 2 Demonstration Project case studies, STOP CRC and TSOS
Instructors	Lesley Curtis, Gloria Coronado, Doug Zatzick
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations (STOP CRC)• Trauma Survivors Outcomes and Support (TSOS)• What is a Pragmatic Clinical Trial?• Differentiating Between RCTs, PCTs, and Quality Improvement Activities• Pragmatic Elements: An Introduction to PRECIS-2 <p>PCT 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

Topic 1: What Are Embedded Pragmatic Clinical Trials?

Part 1: Lesley Curtis, PhD
Director, Center for Pragmatic Health Systems Research
Duke Clinical Research Institute

Collaboratory ePCT Training Workshop

Overview

- How ePCTs are different from traditional explanatory trials
 - Rationale
 - Setting
 - Design
 - Outcomes
- ePCTs bridge real-world clinical care & research
- Emphasizing the pragmatic in ePCTs
 - Introducing PRECIS-2 as a tool for study teams in the design phase

Key ePCT characteristics

- ePCT intervention is embedded in healthcare system culture & workflow
- Needs broad stakeholder engagement & support (Topic 2)
- Uses data collected from EHR in routine clinic visits (Topic 6)
- Will involve tradeoffs in flexibility, adherence & generalizability
- Promotes a learning healthcare system where research informs practice & practice informs research

Differences

	EXPLANATORY	PRAGMATIC
Research question	Efficacy: Can the intervention work under the best conditions	Effectiveness: Does the intervention work when used in normal practice?
Setting	Well-resourced "ideal" setting	Normal care settings including primary care, community clinics, hospitals
Population	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
Outcomes	Often short-term surrogate or process measures; data collected outside routine care	Clinically important endpoints; data collected in routine care
Clinical relevance	Indirect: Not usually designed for making decisions in real-world settings	Direct: Purposely designed for making decisions in real-world settings

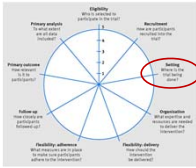
Where does QI fit?

- QI is designed to change local processes to achieve accepted standards of care
- ePCTs are designed to determine standards of care

PRECIS-2: Trials fit for purpose

- Pragmatic–Explanatory Continuum Indicator Summary (2nd version) evaluates 9 domains of the trial
 - Eligibility
 - Recruitment
 - Setting
 - Organization
 - Flexibility: delivery
 - Flexibility: adherence
 - Follow-up
 - Primary outcomes
 - Primary analysis

PRECIS-2: Setting



The more similar the setting of the trial to the setting in which the results will be applied, the higher the PRECIS-2 score

Community-based practices vs academic medical centers

PRECIS-2: Organization



The easier to implement in usual care, the higher the PRECIS-2 score

Oral tablet with simple instructions vs an infused medication

PRECIS-2: Flexibility: delivery



The more the trial intervention looks like the way the intervention will be used in practice, the higher the PRECIS-2 score

Strict protocol, monitoring to improve compliance vs flexibility that's consistent with usual care

PRECIS-2: Flexibility: adherence



The less enforcement of compliance with intervention, the higher the PRECIS-2 score

Usual encouragement to adhere to the intervention vs exclusion based on adherence

PRECIS-2: Follow-up



The less intense the study follow-up, the higher the PRECIS-2 score

Obtaining endpoints from EHR and routine visits vs scheduled study visits

PRECIS-2: Primary outcome



The more patient-centric the endpoint, the higher the PRECIS-2 score

Symptoms, quality of life vs biomarkers

PRECIS-2: Primary analysis



Intention-to-treat analyses yield highest PRECIS-2 score

Excluding dropouts or noncompliant patients from the primary analysis “per protocol” analyses scores low



Important things to know

- ePCTs bridge real-world clinical care & research
- Broad stakeholder engagement & support are essential
- Tradeoffs between flexibility, adherence & generalizability are inevitable
- Trials range across the spectrum from explanatory to pragmatic



Important things to do

- Consider carefully the pragmatism of ALL domains of the trial

Topic 1: What Are Embedded Pragmatic Clinical Trials?

Part 2: ePCT Case Studies: STOP CRC and TSOS
Gloria Coronado, PhD, Kaiser Permanente Center for Health Research
Doug Zatzick, MD, University of Washington School of Medicine

Collaboratory ePCT Training Workshop

Case studies

1. STOP CRC: Gloria Coronado, PI
2. TSOS: Doug Zatzick, PI



STOP CRC PRECIS-2 wheel



TSOS PRECIS-2 wheel





Important things to know

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

What would a PRECIS wheel diagram look like for the trial you are developing?

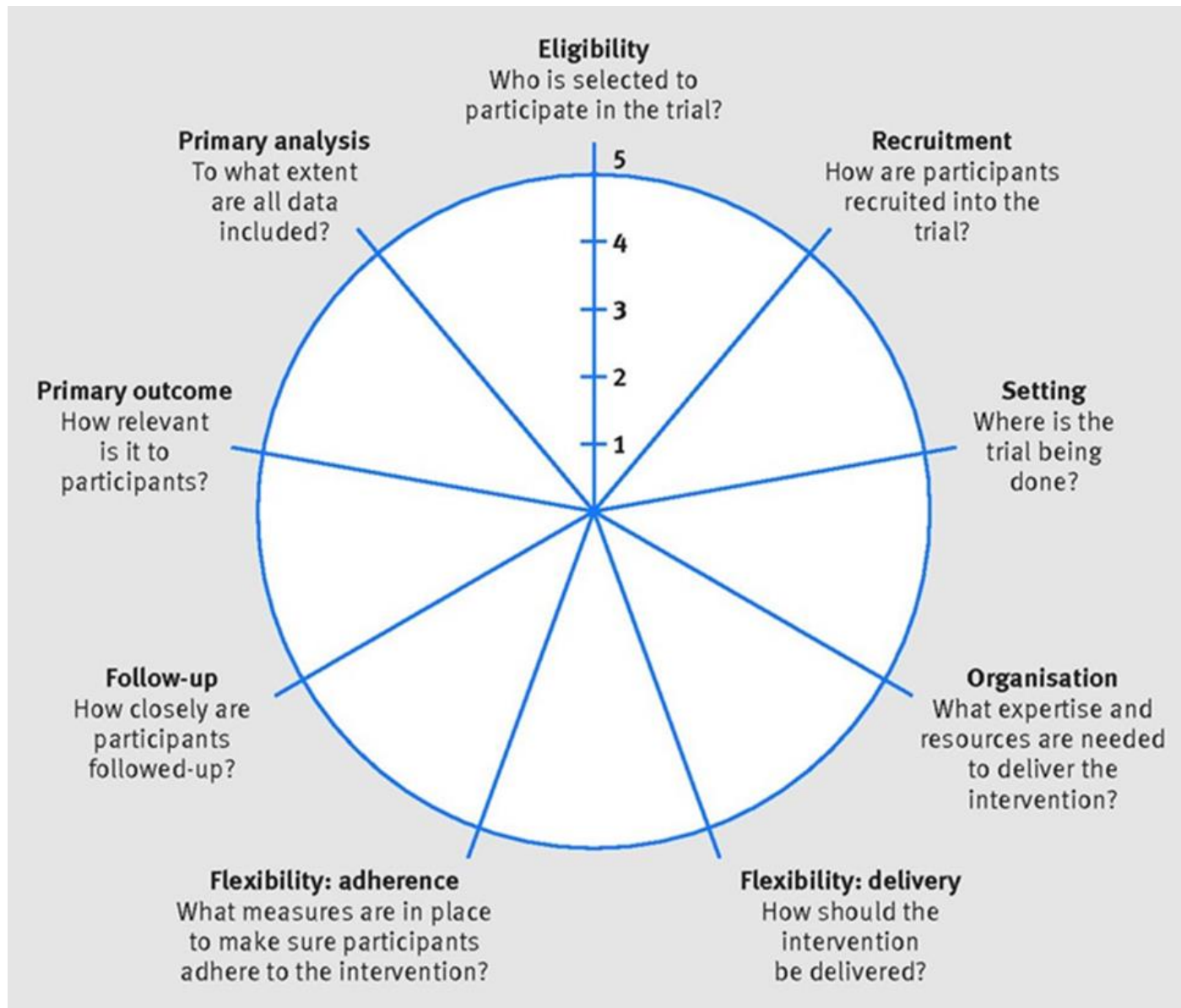
5 min



10 min



PRECIS-2 Wheel



Collaboratory ePCT Training Workshop

Topic 2

Engaging All Stakeholders & Aligning with Healthcare System Partners

Learning objectives	<ul style="list-style-type: none">• Describe the breadth of stakeholders to engage as partners in an ePCT and approaches for engaging them through all phases of a research study• Understand the real-world priorities and perspectives of health system leaders and how to obtain their support
Instructor	Leah Tuzzio
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN: Delineating the Roles of All Stakeholders to Determine Training Needs• DESIGN: Establishing Close Partnerships With Participating Healthcare System Leaders and Staff• Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial• Health Care Systems Interaction Core <p>PCT 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">• 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

Topic 2: Engaging Stakeholders & Aligning with Healthcare System Partners

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

Collaboratory ePCT Training Workshop

Agenda

- The breadth of stakeholders
- Challenges with stakeholder engagement in research
- Tactics and strategies to engage & align stakeholder priorities & perspectives with research
- Discussion

Lessons from NIH Collaboratory

LISTEN TO THE FRONTLINE

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

– Greg Simon, MD, MPH (SPOT)

PILOT & ASSESS CAPACITY

"A pilot study helps set the groundwork for conversations."

– Jerry Jarvik, MD, MPH (LIRE)

What's the value of engagement?

- Identifies priorities, values & perspectives early & throughout the research continuum
- Defines relevant questions & selects high-priority outcomes
- Improves efficiency of recruitment approaches, diversity of participants & enrollment rates
- Continuously helps improve methods & overcome challenges
- Reduces missing data & loss to follow-up
- Increases the uptake & impact of research

Who are ePCT stakeholders?

Stakeholders have different priorities, values, work cultures & expectations

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

Which stakeholders are important for your trial?

1. Who can help minimize potential barriers to study completion?
2. Who will use the evidence from the study to make decisions or be affected by those decisions?

Source: Living Textbook & [Moloney et al. 2016](#)





Strategies for Engagement Throughout the Life Cycle of the Trial

Learning healthcare systems & ePCTs

"In a learning healthcare system, research influences practice and practice influences research."

Implementing the Learning Health System: From Concept to Action (See Figure 1)
Sarah M. Greene, MPH; Robert J. Reid, MD, PhD; Eric B. Larson, MD, MPH
Ann Intern Med. 2012;157(3):207-210. DOI: 10.7326/0003-4819-157-3-201208070-00012

Engagement during the life cycle

-  Identifying stakeholders
-  Designing the trial
-  Conducting the trial and analyzing results
-  Disseminating the results



Identify & assess potential HCS partners

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



Design phase: get to know each other

- Set expectations to work collaboratively & build trust from the beginning
- Learn about each other's goals, needs, priorities & motivations for implementing a trial
- Learn about ideal "wins" & potential conflicts & competing priorities




Design phase: 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
- Solve problems & remove barriers
- Consider privacy & data sharing issues
- Advise on analyses
- Interpret study results

 **Lessons from NIH Collaboratory**


**DON'T START FROM SCRATCH,
ADAPT**

"Each system is going to implement the trial in a slightly different way that works best for them and their workflows."
– Miguel Vazquez, MD (ICD Pieces)


 **Lessons from NIH Collaboratory**

USE EXISTING WORKFLOWS


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

 **Nurturing relationships: challenges and solutions**

Challenge	Solution
Intervention is in the primary care setting where schedules are busy and space is tight	Teamed with clinicians to understand workflow and schedule study-related patient visits during slower clinic periods and held patient visits in less conventional ways (after hours, groups met in lobby spaces)

 **Nurturing relationships: challenges and solutions**

Challenge	Solution
High amounts of leadership turnover at medical director and provider levels due to preexisting pressures and challenges inherent in community clinics.	Met regularly with leadership teams and established an advisory board and other infrastructure to help engage leaders and gatekeepers.

 **Nurturing relationships: challenges and solutions**

Challenge	Solution
Leadership approval of the study was delayed because different departments within a single healthcare system were unable to initiate approval without the other departments going first. For example, Stakeholder A could not approve the study before Stakeholder B approved	Facilitated in-depth discussions of the project with all the relevant stakeholders on the phone or web at the same time, when face-to-face meetings were not possible. A prior history of collaboration among investigators and support from senior officers in the healthcare systems was instrumental in obtaining approval



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



Tips for disseminating to HCS leaders

Prepare a brief, clear abstract that includes

- Reasons to invest in the intervention
- Ways the intervention is aligned with organizational priorities & benefits the system
- Level of acceptability by the clinical teams & impact on workflows
- Potential harms like liability issues
- Downstream implications
- Plans to sustain the intervention & what resources are needed
- How the intervention aligns with payers & policymakers

Reflections from Doug Zatzick & Gloria Coronado





Important things to know

- Be patient, relationships take time to build & nurture
- Expect change & disruptions
- “A successful PCT starts with a strong partnership between researcher and healthcare system, goes through a rigorous objective evaluation of the ability of the partner healthcare system(s) to participate, and ends with evidence about sustainable ways to improve care, as well as long-term scientific relationships.” *

*Source: Johnson, KE et al. A guide to research partnerships for pragmatic clinical trials. BMJ. 2014; 349.



Important things to do

- Set expectations to work collaboratively & build trust from the beginning & throughout the life cycle of your trial
- Get to know your stakeholders & their values, priorities & expectations
- Assess capacity & capabilities of your partners
- Keep in touch regularly, ask & track challenges, delays, potential solutions & adaptations to the intervention

Think, pair, share

Fill in the engagement worksheet for your study, then pair up and discuss

5 min



10 min



Topic 2: Engaging Stakeholders & Aligning with Healthcare System Partners

Think, Pair, Share Activity

Stakeholders – People who can help minimize potential barriers to study completion and who will use the evidence from the study to make decisions or be affected by those decisions

Type of stakeholder	Phase of study (proposal writing, design, recruitment, intervention, analysis, dissemination)	Engagement strategies
Operational personnel, specify:		
Healthcare delivery organization leaders, specify:		
Patients, caregivers, patient advocacy groups, specify:		
Clinicians, specify:		
Other (payers, policy makers, funders, researchers, etc.), specify:		

Collaboratory ePCT Training Workshop

Topic 3

Designing with Implementation in Mind

Learning objective	Consider how to design ePCTs so that findings can be successfully implemented and sustained in real-world healthcare settings
Instructor	Doug Zatzick
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN: Designing with Implementation and Dissemination in Mind• DISSEMINATION: Dissemination and Implementation• Pragmatic Elements: An Introduction to PRECIS-2 <p>PCT Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none">• Toward National Trauma Care Practice Change for PTSD and Comorbidity• 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 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

Topic 3: Designing with Implementation in Mind

Doug Zatzick, MD, University of Washington School of Medicine

Collaboratory ePCT Training Workshop

Implementation research defined

The scientific study of the use of strategies to adopt & integrate evidence-based health interventions into clinical & community settings in order to improve patient outcomes & benefit population health

Source: NIH Dissemination and Implementation Research in Health PAR-16-238

Assumption: “If you build it ...”



Source: David Chambers' May 24, 2017, NIH Collaboratory Workshop

Translated to ePCTs: “If you build it pragmatically ... they will implement”



**NIH Collaboratory ePCT case example:
Lumbar Imaging with Reporting of Epidemiology**

- LIRE is a large pragmatic, cluster-randomized controlled trial testing the effectiveness of a simple & inexpensive intervention: Inserting epidemiologic benchmarks into lumbar spine imaging reports
- Total patient N ~250,000
- Exemplary PRECIS-2 pragmatic trial
- Stepped-wedge design leaves Intervention “turned on” after study completion

LIRE PRECIS-2 wheel (J. Jarvik, PI)



Source: Johnson et al., 2016. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory

Why give up-front consideration to sustainable implementation?

Challenges in the roll-out of the LIRE ePCT:

- Providers/radiologists adopting the intervention prior to the start of the trial (*substituting*)
- Providers/radiologists accepting the intervention leading to adoption of the intervention prior to the final aggregate study findings (*adoption*)
- Providers/radiologists selectively removing the intervention from reports (*discontinuation*)
- Providers/radiologists temporarily at select clinics discontinuing the intervention during the trial (*discontinuation*, or "mini-revolt")
- HCS discontinuing use of LIRE EHR platform (interrupts naturalistic stepped-wedge continuation of intervention after the trial)

Where to look for cutting-edge information on ePCT sustainable implementation?

NIH COLLABORATORY
LIVING TEXTBOOK
of Pragmatic Clinical Trials

HOME WELCOME GRAND ROUNDS NEWS

DESIGN CONDUCT DISSEMINATION

DESIGNING WITH IMPLEMENTATION AND DISSEMINATION IN MIND

Introduction

Contributors
David Chakrabarti, MD
Maura Conrath, PhD
Meredith Davis, MD, MPH
Jeffrey Griggs, MD, MPH
Edward J. Steiner, MD, PhD

SECTIONS

- Introduction
- Key Considerations
- Pragmatic Designs
- Stepped-Wedge Designs

The NIH Collaboratory's *Living Textbook of Pragmatic Clinical Trials*:
www.rethinkingclinicaltrials.org

Designing with implementation & dissemination in mind

Up-front considerations

- What are the needs of the audiences who will use the research findings to make decisions?
- What is the fit with the target patient population & setting?
- Who is able to deliver the intervention?
- Building in tests of training, support & adherence/fidelity
- Methods for observing during the trial roll-out, barriers to high-quality, sustainable intervention delivery

To what extent are the implementation procedures being proposed in an ePCT linked to evidence-based implementation strategies?

Effectiveness-implementation hybrid pragmatic trials

ANNALS OF IHR

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

Geoffrey M. Curran, PhD,* Mark Bauer, MD, Brian Mittman, PhD,†
Jeffrey M. Pyno, MD,* and Cheryl Sforzo, PhD‡

Objective: This study presents methods for designing hybrid effectiveness and implementation research trials that bridge the gap between research and practice. The study identifies the key elements of such trials and provides a framework for their design and implementation. The study also identifies the key elements of such trials and provides a framework for their design and implementation.

Methods: An effectiveness-implementation hybrid design is one that integrates the key elements of clinical effectiveness and implementation research. The study identifies the key elements of such trials and provides a framework for their design and implementation.

Conclusions: The hybrid approach provides a framework for designing trials that bridge the gap between research and practice. The study identifies the key elements of such trials and provides a framework for their design and implementation.

Key Words: Effectiveness, implementation, pragmatic, hybrid, trial, design, research, practice, public health, impact.

Source: Curran et al., 2012 Medical Care

Curran et al. 2012 (p 18)

The most recent adaptation of these principles, to enhance the relevance of effectiveness designs for translation, are “practical clinical trials,” which have found their newest application in the area of policy-relevant “comparative effectiveness research.” In each of these clinical trial approaches, designs rely on controlling/ensuring delivery of the clinical intervention, albeit in a less restrictive setting, with little attention to implementation processes likely to be of relevance to transitioning the intervention to general practice settings.

Source: Curran et al., 2012 Medical Care

Integrating ePCT & implementation science conceptual frameworks

- Early stages of integration
- Pragmatic trials aim to maximize efficiency in trial design & roll-out thereby minimizing costs per subject randomized
- Implementation science emphasizes understanding implementation processes with less attention to efficiency
- Implementation science with dozens of theories & conceptual frameworks

Integrating implementation science & ePCT methods

Methods development can meld pragmatic trial resource constraints & implementation science process evaluations

Where to look for cutting-edge information on dissemination & implementation frameworks?



DISSEMINATION AND IMPLEMENTATION

SECTION 2

Dissemination and Implementation Frameworks

Contributors
 Douglas Zarkin, MD
 Kelly Tuckey, MPH
 David Chambers, LPTSC
 JESSIE JAFFE, PhD
 Diwanthi Jayaratne, PhD
 Wanda L. Gattuso, PhD
 Lynn Jordan, PhD, MPH

Bonnie Grims, MD, MPH
 Sarah Hooley, MD, MPH
 Jeffrey Jarvis, MD, MPH
 Edward Livingston, MD, PhD
 Gregory Simon, MD, MPH
 Robert Swales, MD

Contributing Editor
 Karen Sisman, MD

There are multiple models and conceptual frameworks for the targeted and widespread dissemination and implementation of health care interventions. A major challenge for research

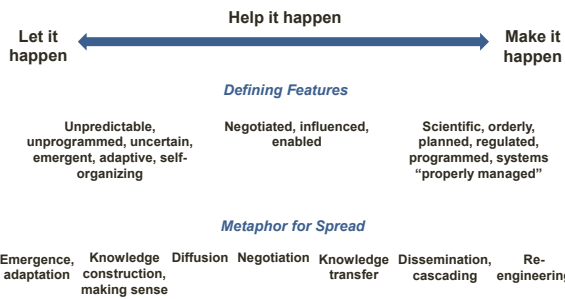


SECTIONS

- 1 Conceptualizing the Challenge
- 2 Dissemination and Implementation Frameworks
- 3 Let It, Help It, Make It Happen
- 4 Changes to Policy and Guidelines
- 5 Legislative Changes
- 6 Creation of Targeted Tools
- 7 Hospital-Wide Design
- 8 Intervention Staffing and Training Feasibility
- 9 Partnering With Quality Improvement and Population

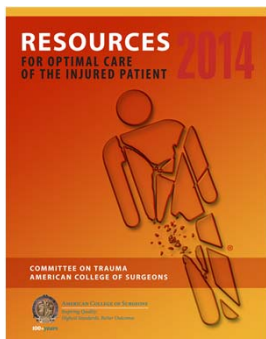
The NIH Collaboratory's *Living Textbook of Pragmatic Clinical Trials*:
www.rethinkingclinicaltrials.org

How does your healthcare system learn?



Adapted from: Greenhalgh et al., 2004, Milbank Quarterly

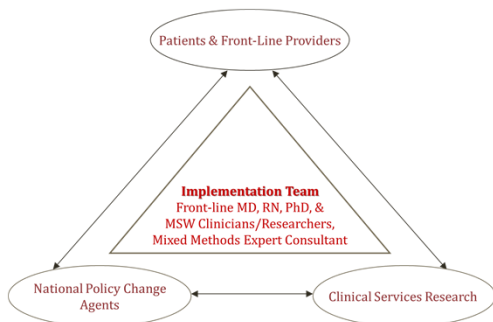
American College of Surgeons Regulatory Policy Targeting PTSD & Comorbidity



TSOS effectiveness-implementation hybrid ePCT design

- Effectiveness aim: reduce PTSD symptoms
- Implementation aim: influence US trauma center requirements for sustainable PTSD screening & intervention procedures

NIH Collaboratory methods innovation: "Embedded Implementation Teams Within Embedded PCTs"



Novel embedded mixed methods: Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE)

- TSOS research team spends hundreds of hours immersed in trauma care system clinical context
- Front-line clinician-researcher conducts participant observation, not driving up costs of trial
- Field notes & jottings taken, key informant interviews recorded
- Field data regularly reviewed with mixed-method expert consultant
- Themes related to trial roll-out and sustainable implementation iteratively reviewed & documented

Source: Palinkas & Zatzick In Preparation; Zatzick et al 2016; Zatzick et al 2011; Palinkas et al 2004



Important things to know

- Pragmatic trials can simultaneously address effectiveness & implementation aims
- HCS may vary with regard to how practice change derived from clinical trial evidence is rolled out
- Methods that integrate pragmatic trial & implementation science conceptual frameworks are in development



Important things to do

- Consider what aspects of the proposed trial address effectiveness
- Consider what aspects address sustainable implementation
- Consider the question, How does the HCS in which I am conducting the trial learn?
- Consider what key policy or practice change levers I might need to engage up-front in order to enhance sustainable implementation

1. How does the healthcare system I am conducting the trial within learn?
2. What aspects of the proposed trial address effectiveness?
3. What aspects address sustainable implementation?
4. What key policy or practice change levers might I need to engage up-front in order to enhance sustainable implementation?

5 min



10 min

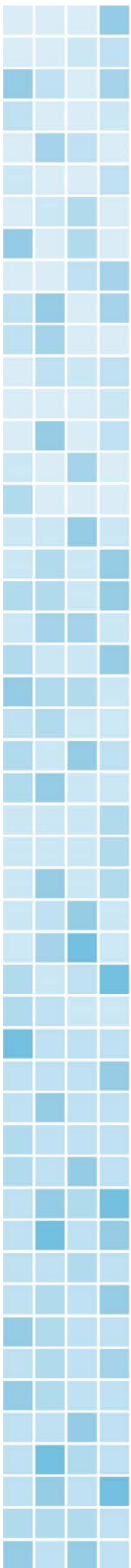


Collaboratory ePCT Training Workshop

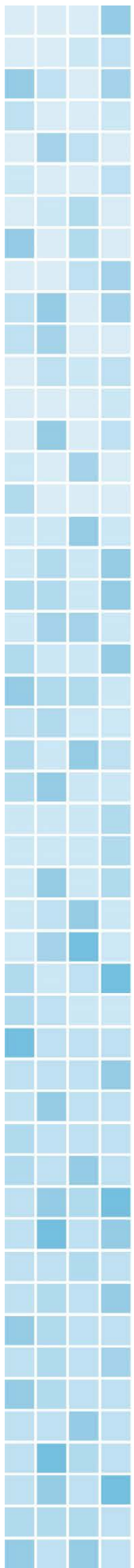
Topic 4

Design and Analytic Considerations

Learning objective	Recognize the analytical challenges of cluster-randomized and stepped-wedge study designs
Instructors	Liz Turner, Liz DeLong
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>PCT Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none">• Lessons Learned from the NIH Collaboratory Biostatistics and Design Core• Thoughts from the Phenotypes, Data Standards & Data Quality Core <p>Key journal articles</p> <ul style="list-style-type: none">• Coronado et al., 2014. Strategies and Opportunities to STOP Colon Cancer in Priority Populations Design of a Cluster-Randomized Pragmatic Trial• Richesson et al., 2017. Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory



Resources	Additional resources <ul style="list-style-type: none">• Pragmatic Trials: A Workshop Handbook• Designing Multi-Center Cluster Randomized Trials: An Introductory Toolkit• Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core• Using Electronic Health Record Data in Pragmatic Clinical Trials
	Five well-known CRT textbooks <ul style="list-style-type: none">• Murray DM. Design and Analysis of Group-Randomized Trials. New York, NY: Oxford University Press; 1998.• Hayes RJ, Moulton LH. Cluster Randomised Trials. Boca Raton: CRC Press; 2009.• Donner A, Klar N. Design and Analysis of Cluster Randomization Trials in Health Research. London: Arnold; 2000.• Eldridge S, Kerry S. A Practical Guide to Cluster Randomised Trials in Health Services Research. Vol 120: John Wiley & Sons; 2012.• Campbell MJ, Walters SJ. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Chichester, West Sussex: John Wiley & Sons; 2014.
	Clustering and ICC <ul style="list-style-type: none">• Campbell et al., 2004. Intracluster correlation coefficients in cluster randomized trials: empirical insights into how they should be reported• Eldridge et al. 2009., The intra-cluster correlation coefficient in cluster randomized trials: a review of definitions• Campbell et al., 2005. Determinants of the intracluster correlation coefficient in cluster randomized trials: the case of implementation research
	Overview of key issues in CRTs <ul style="list-style-type: none">• Turner et al., 2017. Review of recent methodological developments in group-randomized trials: Part 1 – Design• Turner et al., 2017. Review of recent methodological developments in group-randomized trials: Part 2 – Analysis
	Sample size and power <ul style="list-style-type: none">• Rutterford et al., 2015. Methods for sample size determination in cluster randomized trials



Resources	Covariate constrained randomization <ul style="list-style-type: none">• Li F, et al. 2015. An evaluation of constrained randomization for the design and analysis of group-randomized trials• Li F, et al. 2017. An evaluation of constrained randomization for the design and analysis of group-randomized trials with binary outcomes• Gallis JA, et al. In press. Cvcrand and cptest: efficient design and analysis of cluster randomized trials
	Planning (eg, pilot), protocols, and reporting of results <ul style="list-style-type: none">• SPIRIT statement on reporting of trial protocols• Pilot and feasibility studies journal• Information on publishing trial protocol in peer-reviewed journal e.g. <i>Trials</i> journal• CONSORT statement on reporting of trial results• CONSORT extension statement for CRTs• CONSORT reporting checklist• CONSORT Elaboration and Explanation (BMJ)• CONSORT Extension for Pragmatic Trials

Topic 4: Design and Analytic Considerations

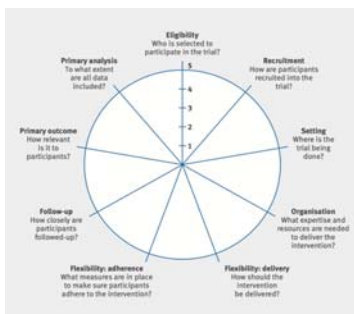
Liz Turner, PhD
 Department of Biostatistics & Bioinformatics and Duke Global Health Institute
 Duke University School of Medicine

Collaboratory ePCT Training Workshop

Overview

- Randomization schemes: cluster vs individual
- Cluster-randomized trials (CRTs)
 - 1: Special considerations for CRTs
 - Clustering of outcomes
 - Small # of clusters
 - 2: Varieties of cluster-randomized trials
 - Parallel
 - Stepped-wedge
- Other considerations
- How do I know I have the right statistician?

ePCTs: to inform decision-making



See: <https://www.precis-2.org/>

Considerations in ePCT design

- Why randomize?
 - Internal validity (ie, comparability of treatment and control arms)
- How to randomize?
 - Individual vs cluster
- Also want good external validity
 - Generalizability
 - Think carefully about eligibility

Overview

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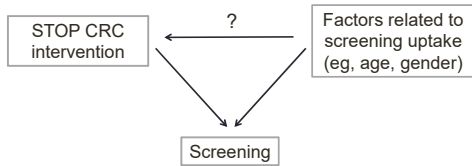
Randomization schemes

- Cluster vs individual
- Explanatory trials
 - Usually randomize individuals patient
- Pragmatic trials
 - Usually randomize clusters
 - Examples: practice, hospital, region

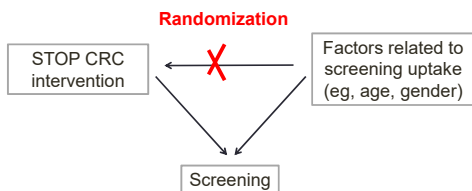
Cluster-randomized trial

- Cluster-randomized trial (CRT) definition
 - Unit of randomization is cluster of individuals
 - Unit of outcome measurement is individual
- 8 of 9 Demonstration Projects are CRTs
- Also known as:
 - Group-randomized trial
 - Community-randomized trial

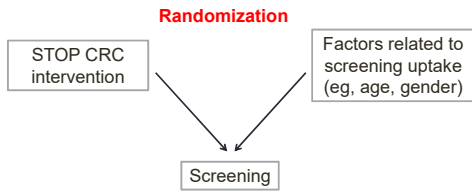
Example CRT: STOP CRC



Example CRT: STOP CRC

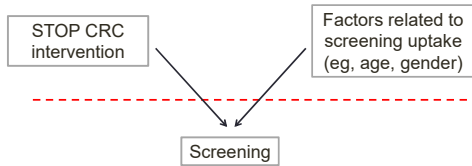


Example CRT: STOP CRC



Example CRT: STOP CRC

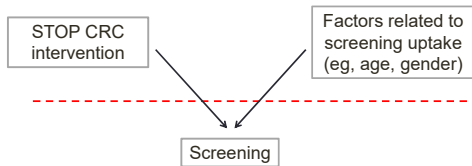
Level 2: Randomization at clinic (ie, cluster) level



Level 1: Individual-level outcomes nested in clinics

Example CRT: STOP CRC

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

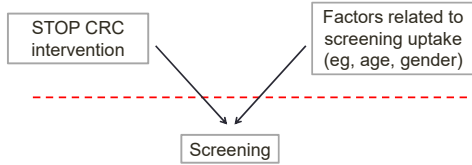


Level 1: Individual-level outcomes nested in clinics

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

Example CRT: STOP CRC

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



Level 1: Individual-level outcomes nested in clinics

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

Reduces power to detect treatment effect if same sample size used as under individual randomization

Implications of using CRT design

- CRT (statistical) price to pay
 - Lower power for same total sample size under individual randomization
 - Harder to detect an intervention effect
- So why use CRT design?
 - Intervention at cluster level (eg, STOP CRC)
 - To avoid treatment contamination under individual randomization
 - Logistically easier to implement trial

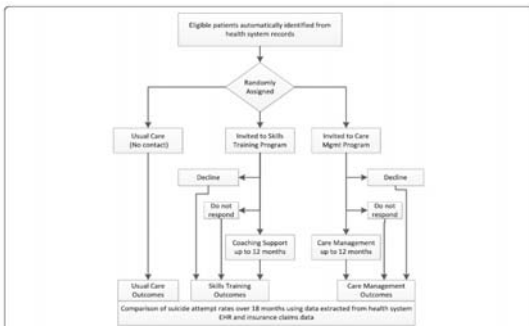
Rationale for CRT design

- STOP CRC
 - Clinic-level intervention
 - Any comments from Gloria?
- TSOS
 - Intervention at cluster level
 - Implementation science framework
 - Any comments from Doug?

Example RCT: SPOT RCT

- Only Demonstration Project with individual randomization
- Goal: suicide prevention
- Two active arms
 - Both interventions are individual-level
 - Intervention contact mostly through EHR, so expect low risk of contamination

Example RCT: SPOT study flow



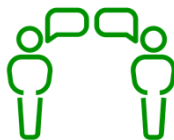
Source: Simon G et al. *Trials* 2016;17:452

What unit of randomization makes the most sense for your study and why?

2 min



4 min



Overview: stats & design for ePCTs

- Randomization schemes: cluster vs individual
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 - Stepped-wedge
- Other considerations
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Special considerations for CRTs

1. Clustering of outcomes
 - Clustering (of a particular outcome)
 - Accounting for clustering in analysis
 - Accounting for clustering in design
2. Small # of clusters
 - Potential for baseline covariate imbalance
 - How small is too small?

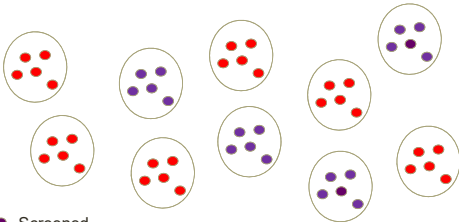
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Clustering example: motivated by STOP CRC

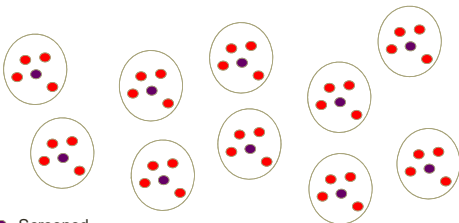
- Suppose 10 clinics
- Each with 5 age-eligible patients
 - ie, not up-to-date with CRC screening
- Outcome:
 - Binary outcome: refused screening
 - "No screening within year of enrollment"

Complete clustering (ICC = 1)



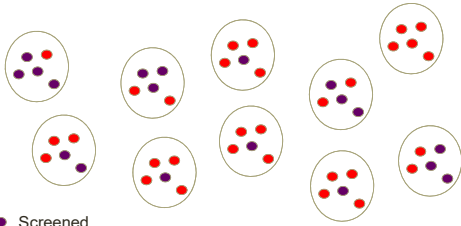
>1 participant/clinic gives no more information than 1 participant/clinic since every participant in a given clinic has same outcome

No clustering (ICC = 0)



20% uptake of CRC screening in each clinic
No structure by clinic - more like a random sample of eligible participants

Some clustering ($0 < ICC < 1$)



A more typical situation: proportion screened ranges from 0% - 80%

Clustering in CRTs

- Outcomes in same clusters more similar to each other than to outcomes in other clusters
- STOP CRC:
 - Planned: >450 participant/clinic in 26 clinics
 - Effective sample size: 26 – approx. 450
- Implications for statistical inference
- Major challenge in design & analysis

Measure of clustering: ICC

- Intra-cluster correlation coefficient (ICC, ρ)
- Most commonly used measure of clustering
 - Ranges: 0-1; 0= no clustering; 1= total clustering
 - Typically < 0.2, commonly around 0.01 - 0.05
 - "Between-cluster variance of outcome / total variance"

ICC for continuous outcomes:

$$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2} = \frac{\sigma_B^2}{\sigma_{Total}^2}$$

- Involves both between-cluster & within-cluster variance

Measure of clustering: ICC & CV

- Need measure of clustering for sample size
- Coefficient of variation (CV) alternative to ICC

$$k = \frac{\sigma_B}{\mu}$$

where μ is overall mean of outcome

- Multiple definitions of ICC for binary outcomes
 - Some authors prefer CV for binary

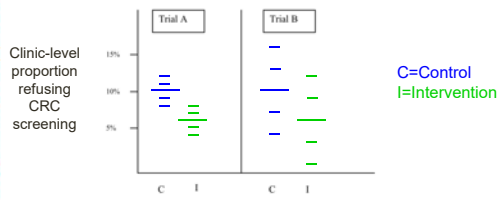
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Two example CRTs

- Inspired by STOP CRC
- 10 clinics/trial
 - 5 intervention (I) & 5 control (C)
 - 100 patients/clinic
- 1000 patients per trial
 - 500 intervention vs 500 control
- Binary outcome
 - Refused screening (yes/no)
 - "No screening within year enrollment"

Clustering in CRTs: implications for analysis

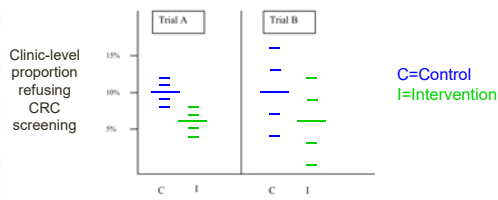


- 5 clinics each randomized to **control** and **intervention**
- 100 eligible participants per clinic measured

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

Example from Hayes & Moulton (2009)

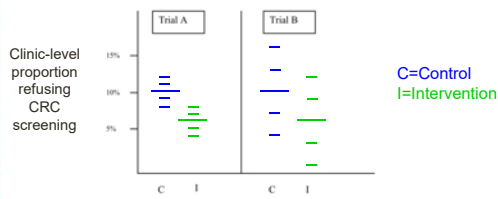
Clustering in CRTs: implications for analysis



Which trial shows more evidence of benefit?

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

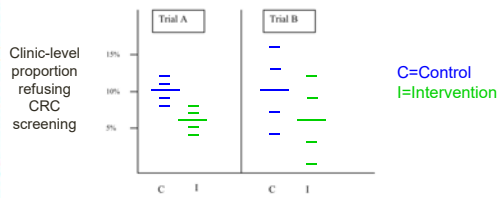


Study features

?

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

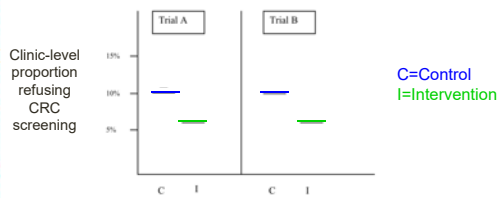


Study features

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

Example from Hayes & Moulton (2009)

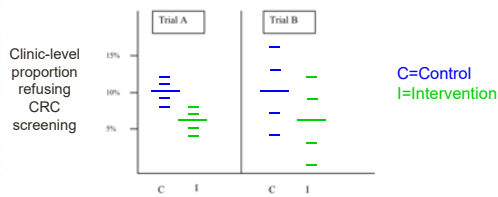
Clustering in CRTs: implications for analysis



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

Example from Hayes & Moulton (2009)

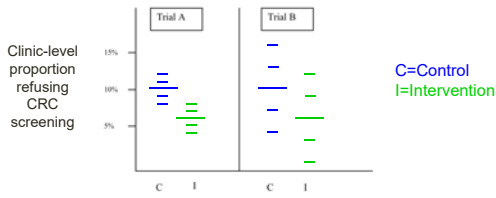
Clustering in CRTs: implications for analysis



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

Example from Hayes & Moulton (2009)

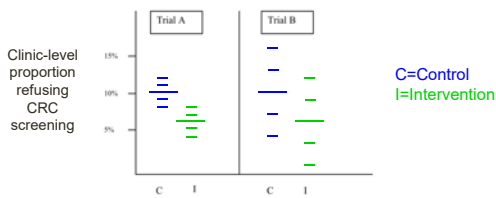
Clustering in CRTs: implications for analysis



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

Example from Hayes & Moulton (2009)

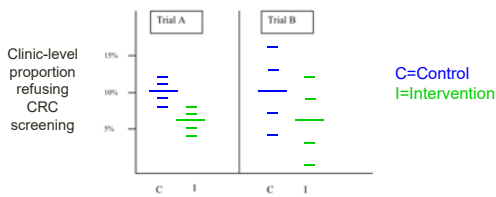
Clustering in CRTs: implications for analysis



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

Example from Hayes & Moulton (2009)

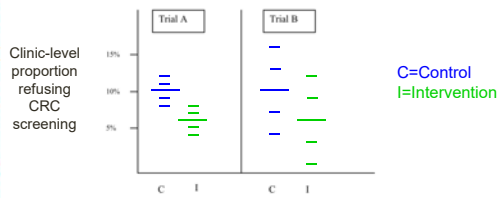
Clustering in CRTs: implications for analysis



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

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

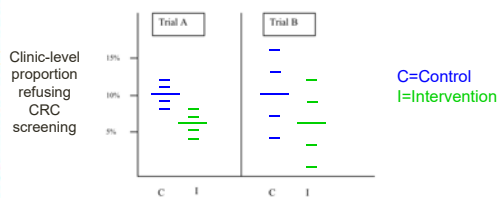


- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

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

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis



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

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

Example from Hayes & Moulton (2009)

Summary: clustering & analysis

- Two example trials
 - Analyzed with cluster-level analysis
 - Overall sample size (# clinics/trial) = 10
- Both trials had same signal (10% vs 6%)
 - Totally different conclusions from each trial
 - Between-cluster variability Trial A < Trial B
 - P-value Trial A < P-value Trial B
- Important
 - If ignore clustered design, could claim 'significant' when not (eg, Trial B)

Summary: clustering & analysis

- Cluster-level analysis rarely used
- Typically use regression methods
 - Analyze individual-level data, eg, data from 1000 participants/trial not only 10 clinics
 - Methods to account for clustering
 - Random effects / mixed effects models
 - Generalized estimating equations (GEE)
- Work with statistician to ensure properly account for clustering

Special considerations for CRTs

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Clustering: design considerations

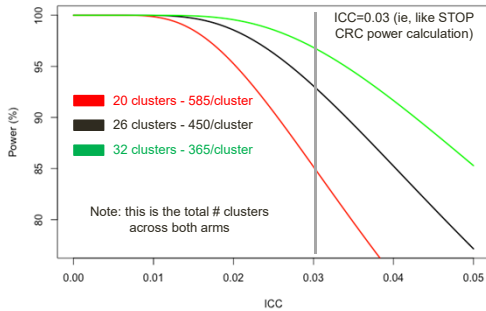
- Power & sample size
 - Account for anticipated clustering
 - Inflate RCT sample size
 - Work with statistician to do this correctly
- Use ICC (or CV) for outcome
 - ICC often 0.01-0.05
 - STOP CRC: ICC = 0.03 for primary outcome
 - Depends on outcome & study characteristics
 - Different outcome = different ICC, **even in same CRT**

Clustering in STOP CRC: design considerations

"Assumed equal numbers of subjects per clinic and equal numbers of clinics ($n = 13$) per group. In practice, the clinic sizes will not be equal, but since almost all clinics have at least 450 active age-eligible patients, we conservatively use this figure for all sites. We based our calculations on the simple paradigm of comparing two binomial proportions with a type I error rate of 5%, and adjusted both for intraclass correlation (ICC) and the reduced degrees-of-freedom ($n = 24$) for the critical values. Based on analyses by Dr. Green using the data from her Systems Of Support study [12,28], we expect the ICC to be about .03. Using this figure, we will have very good power (>91%) to detect absolute differences as small as 10 percentage points even if the FIT completion rate in the UC arm is as high as 15% (fecal testing rates for 2013 for usual care clinics was 10%). For an ICC of .05 we would still have >91% power for detecting effect sizes of at least 13 percentage points."

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

Clustering: impact on power



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

Clustering: design considerations

- Many references on CRT power and sample size
- Important to account for clustering
 - Some adjust RCT sample size by design effect: $1 + (m-1)\rho$, where $m = \#$ participants/cluster
 - Better to be more explicit
 - eg, want to determine # clusters needed for fixed # participants/cluster or vice-versa?
- **Work with a statistician!**

Resources

- NIH: <https://researchmethodsresources.nih.gov/>
- 5 textbooks (see reference list)
- See reference list: Turner et al. (2017) and Rutterford et al. (2015)

Clustering: design considerations

- How to get good initial estimate of ICC for a particular outcome?¹
 - It depends on outcome & study characteristics
 - CONSORT² statement on reporting of CRTs recommends ICC reported
 - Look at other articles with similar settings
- Be cautious when using pilot data from small study
 - ICC might have wide confidence interval

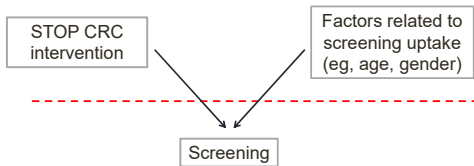
1. See FAQ 13 at: <https://researchmethodsresources.nih.gov/>
2. <http://www.bmj.com/content/345/bmj.e5661>

Special considerations for CRTs

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Example CRT: STOP CRC

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



- **Goal:** randomization → baseline balance of covariates
- **Challenge:** baseline imbalance may occur if not many clusters enrolled (eg, there are 26 clinics in STOP CRC)

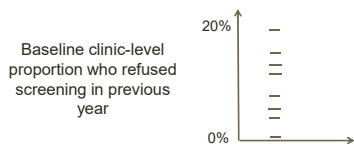
Small # of clusters & baseline covariate imbalance

- Pragmatic CRTs often enroll small # (<40) clusters
- Randomization may not balance baseline covariates
- Baseline covariate imbalance threatens internal validity ie, comparability of treatment arms
 - Challenge: claim intervention effect is causal but there may be confounding due to non-comparability of treatment arms

Baseline covariate imbalance

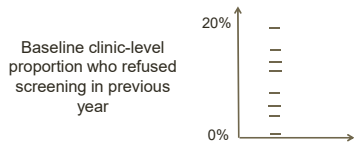
- Threat to internal validity of trial
- Could address with adjusted analysis
- Better to use design strategy
 - 'Restricted randomization'
- Three types of restricted randomization
 - Pair-matching
 - Stratification
 - Covariate-constrained randomization

Baseline covariate imbalance Example: 8 clinics (clusters)



Baseline covariate imbalance

Example: 8 clinics (clusters)



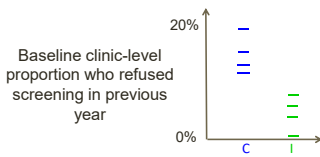
Question: Why do we care about getting balance between treatment arms on clinic-level proportion who refused screening in previous year?

It might be related to proportion in the next year!

Baseline covariate imbalance

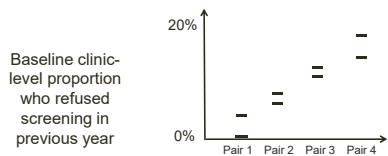
Example: 8 clinics (clusters)

Example of extreme baseline imbalance using simple (ie, regular) randomization



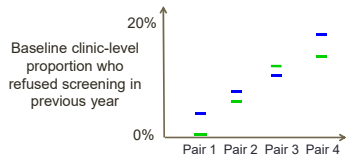
Baseline covariate imbalance

Possible design solution 1: Pair-matching



Baseline covariate imbalance Possible design solution 1: Pair-matching

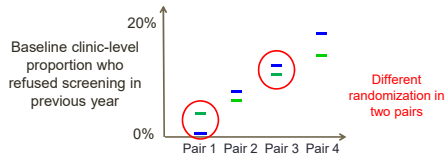
One example of pair-matched randomization to control & intervention arms



Intervention and control perfectly balanced on "pair" ie, exactly 1 cluster from each pair in intervention and 1 in control

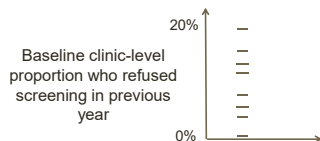
Baseline covariate imbalance Possible design solution 1: Pair-matching

Another example of pair-matched randomization to control & intervention arms

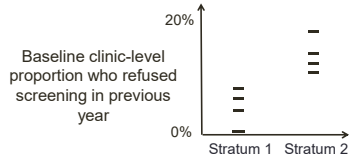


Important: account for paired design in the analysis (eg, paired t-test or Wilcoxon signed rank test for cluster-level analysis or matched regression model)

Baseline covariate imbalance Example: 8 clinics (clusters)

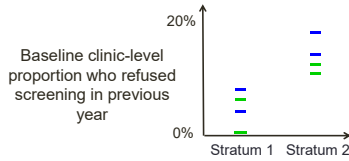


Baseline covariate imbalance
Possible design solution 2: Stratification



Baseline covariate imbalance
Possible design solution 2: Stratification

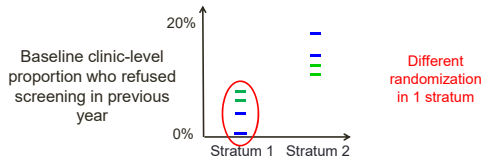
One example of stratified randomization to control & intervention arms



Intervention and control perfectly balanced on "stratum" ie, exactly 2 clusters in intervention and 2 in control in each stratum

Baseline covariate imbalance
Possible design solution 2: Stratification

Another example of stratified randomization to control & intervention arms



Important: account for stratified design in the analysis (eg, stratified permutation test or fixed effect for strata in model-based analysis)

Baseline covariate imbalance

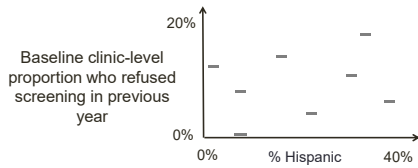
Possible design solution 3: Constrained randomization

- Previous examples
 - Baseline balance of 1 clinic-level covariate ie, % refused screening in previous year
- Often have multiple clinic-level covariates
 - Categorical & continuous
 - Pair-matching & stratification cannot easily handle this
- Need more general form of restricted randomization
 - Covariate-constrained randomization

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

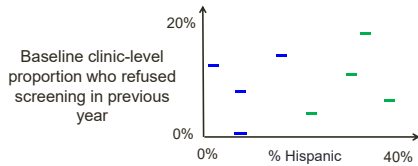
Example: balance two continuous cluster covariates



Baseline covariate imbalance

Possible design solution 3: Constrained randomization

One example of simple randomization to **control** & **intervention** arms

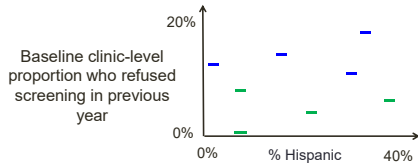


On average, % Hispanic in **control** < % Hispanic in **intervention** (ie, not well-balanced) but reasonable balance on proportion who refused screening

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

Another example of simple randomization to control & intervention conditions

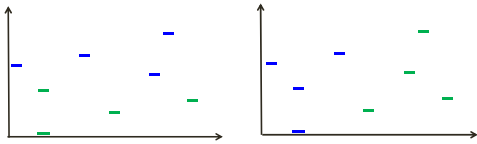


Not well-balanced on % refused screening but reasonable balance on % Hispanic

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

Neither randomization has good balance of both covariates across trial arms.

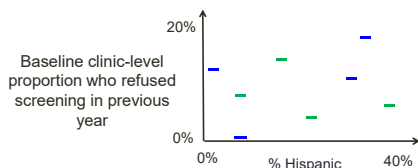


Solution: only allow randomizations that are "balanced enough" as measured by a "balance score" ie, use constrained randomization

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

This randomization could be "balanced enough"



Work with a statistician!
Must account for the design in the analysis

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

- More general than stratification
- Can include more cluster-level covariates
- Both continuous and categorical covariates
- Example:
 - % Hispanic
 - % refused screening in previous year
 - Rural/urban
- Measure “balanced enough” with a balance metric (no details here – use statistical rationale)

Baseline covariate imbalance

Possible design solution: Restricted randomization

- Three types of restricted randomization
 - Pair-matching
 - Stratification (sort-of a special case of CCR)
 - Covariate-constrained randomization (CCR)
- Recommendation
 - Use restricted randomization if total # clusters < 40 and know of predictive baseline covariates
 - Avoid pair-matching (for statistical reasons)
- In practice, analysis must account for whatever type of restricted randomization is used in design

Baseline covariate imbalance

Example: Restricted randomization

- For STOP CRC:
 - Used stratification by “clinic organization”
 - So “each organization will have both intervention and control clinics”
 - Considered using constrained randomization, but:
 - “unpublished simulation models suggested that, for our relatively limited number of clusters, this approach might underperform relative to simple randomization”

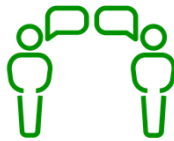
(If you are planning a cluster-randomized design)

What cluster-level covariates might be important to balance on?

2 min



4 min



Special considerations for CRTs

1. Clustering of outcomes
 - Clustering (of a particular outcome)
 - Accounting for clustering in analysis
 - Accounting for clustering in design
2. Small # of clusters
 - Potential for baseline covariate imbalance
 - How small is too small?

Few clusters: How low can you go?

- CONSORT extension for cluster RCTs
 - Recommends at least 4 clusters/arm
 - This is just a guide
- Statistical reasons may require much more than 8 clusters in total in a 2-arm trial!
- Remember: # clusters drives the power of trial more so than # participants
- CRTs require a lot of time and effort
 - Consider a pilot trial to get procedures in place*

* <https://pilotfeasibilitystudies.biomedcentral.com/>

Overview

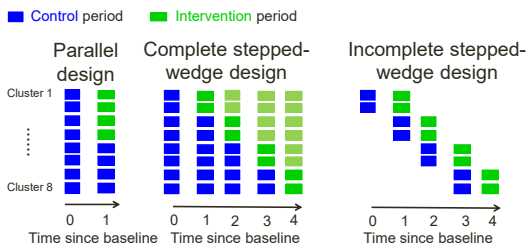
- Randomization schemes: cluster vs individual
- Cluster-randomized trials (CRT)
 - 1: Special considerations for CRTs
 - Clustering
 - Small # of clusters
 - 2: Varieties of cluster-randomized trials
 - Parallel
 - Stepped-wedge
- Other considerations
- How do I know I have the right statistician?

Varieties of CRT

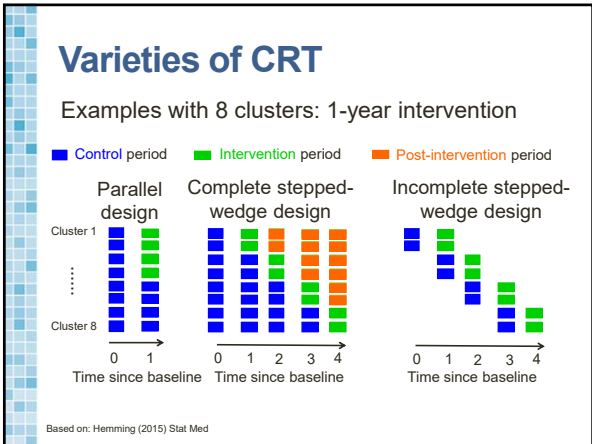
1. Parallel
2. Stepped-wedge

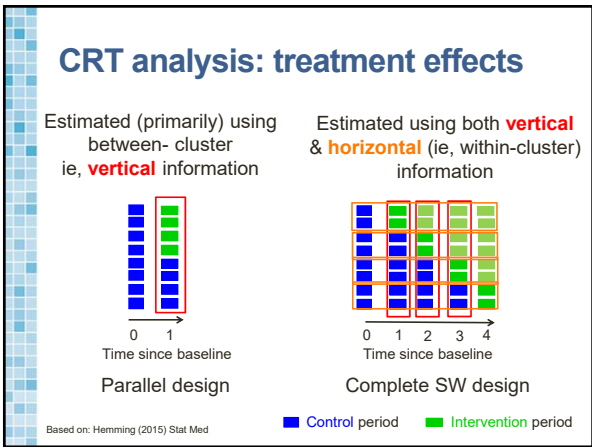
Varieties of CRT

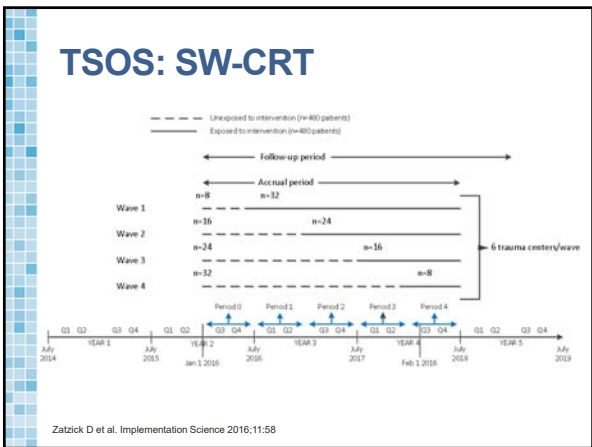
Examples with 8 clusters: 1-year intervention



Based on: Hemming (2015) Stat Med







Choosing CRT type: parallel vs SW

- Arguments **for** SW-CRT:
 - Can't immediately implement intervention in ½ clusters (eg, TSOS)
 - Pragmatic research: plan to implement in all clusters
 - Have few clusters + might gain power in SW-CRT
- Arguments **against** SW-CRT:
 - Risk confounding treatment effect with time effect
 - Could do staggered-start parallel-CRT if can't start implementation in ½ clusters immediately
 - Roll out to all clusters at end of evaluation, if effective

See: Hargreaves et al. Trials (2015). Five questions to consider before conducting a stepped wedge trial

Choosing CRT type: parallel vs SW

Statistical recommendations:

- Use a parallel CRT design if you can
- If not, plan for time effects in designing & analyzing SW-CRT
- Work with statistician to account for clustering in design & analysis of both designs

See: Hargreaves et al. Trials (2015). Five questions to consider before conducting a stepped wedge trial

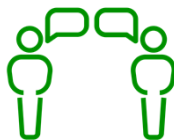
(If you are planning a cluster-randomized design)

What are the pros and cons of using a parallel vs stepped-wedge design for your trial?

2 min



4 min



Overview

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Other considerations for ePCTs

1. ITT vs PP analysis
2. Blinding and concealment
3. Monitoring and managing unexpected changes

Other considerations for ePCTs

1. ITT vs PP analysis
2. Blinding and concealment
3. Monitoring and managing unexpected changes

Intent-to-treat vs per protocol analysis

- Pragmatic nature → ITT commonly used
- PP often difficult to define
 - Screening yes/no is easy
 - Other interventions might have degrees of adherence to protocol
- Might be interested in other types of treatment effect
 - Average treatment effect on the treated

Other considerations for ePCTs

1. ITT vs PP analysis
2. Blinding and concealment
3. Monitoring and managing unexpected changes

ePCTs: blinding & concealment

- Concealment of randomization assignment to avoid selection bias
 - Less a problem in CRTs than RCTs if clusters all randomized together
- Blinding (masking)
 - May not be possible or practicable for CRTs
 - Objective assessment criteria should be consistently applied

Other considerations for ePCTs

1. ITT vs PP analysis
2. Blinding and concealment
3. Monitoring and managing unexpected changes

ePCTs: managing unexpected changes

- Study designs can be affected by:
 - Changes in study populations
 - Changes in coverage patterns
 - Changes in patient perceptions/decisions
 - Decisions by hospital/health system leadership
 - Changes in regulations or practice standards
 - Site turnover
- See examples of implications of ACA on STOP CRC (Vollmer et al, 2015)
- Careful planning and monitoring are needed

See: [dx.doi.org/10.13063/2327-9214.1200](https://doi.org/10.13063/2327-9214.1200)

Overview

- Randomization schemes: cluster vs individual
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How do I know I have the right statistician?

- Someone who...
 - Wants to be involved from beginning of development of research proposal
 - Has experience with pragmatic trials & is familiar with the PRECIS tool
 - Has experience of EHR data?
 - Has experience of CRT design & analysis (if using a clustered design)

Important things to know

- Question drives design; design drives analysis
- Randomization
 - Individual preferred (for stat. reasons)
 - But cluster often needed (ie, a CRT)
- Considerations in both design and analysis
 - **Must** account for clustering (if CRT)
 - Best to account for baseline imbalance
- Good design is difficult, but critical
 - Need input from diverse team
 - Analysis may not be able to overcome design flaws

Important things to do

- Focus on the research question
- Collaborate with a faculty statistician – even when developing research question
- Choose individual randomization (but **only** if possible and defensible)
- Select design features with analysis in mind
- Weigh statistical choices vs implementation challenges
- Write a protocol paper and publish it!

STUDY PROTOCOL

Open Access



An effectiveness-implementation hybrid trial study protocol targeting posttraumatic stress disorder and comorbidity

Douglas F. Zatzick^{1,5*}, Joan Russo¹, Doyanne Darnell¹, David A. Chambers², Lawrence Palinkas³, Erik Van Eaton⁴, Jin Wang⁵, Leah M. Ingraham¹, Roxanne Guiney¹, Patrick Heagerty⁶, Bryan Comstock⁶, Lauren K. Whiteside⁷ and Gregory Jurkovich⁸

Abstract

Background: Each year in the USA, 1.5–2.5 million Americans are so severely injured that they require inpatient hospitalization. Multiple conditions including posttraumatic stress disorder (PTSD), alcohol and drug use problems, depression, and chronic medical conditions are endemic among physical trauma survivors with and without traumatic brain injuries.

Methods/design: The trauma survivors outcomes and support (TSOS) effectiveness-implementation hybrid trial is designed to test the delivery of high-quality screening and intervention for PTSD and comorbidities across 24 US level I trauma center sites. The pragmatic trial aims to recruit 960 patients. The TSOS investigation employs a stepped wedge cluster randomized design in which sites are randomized sequentially to initiate the intervention. Patients identified by a 10-domain electronic health record screen as high risk for PTSD are formally assessed with the PTSD Checklist for study entry. Patients randomized to the intervention condition will receive stepped collaborative care, while patients randomized to the control condition will receive enhanced usual care. The intervention training begins with a 1-day on-site workshop in the collaborative care intervention core elements that include care management, medication, cognitive behavioral therapy, and motivational-interviewing elements targeting PTSD and comorbidity. The training is followed by site supervision from the study team. The investigation aims to determine if intervention patients demonstrate significant reductions in PTSD and depressive symptoms, suicidal ideation, alcohol consumption, and improvements in physical function when compared to control patients. The study uses implementation science conceptual frameworks to evaluate the uptake of the intervention model. At the completion of the pragmatic trial, results will be presented at an American College of Surgeons' policy summit. Twenty-four representative US level I trauma centers have been selected for the study, and the protocol is being rolled out nationally.

(Continued on next page)

* Correspondence: dzatzick@uw.edu

¹Department of Psychiatry & Behavioral Sciences, University of Washington, 325 Ninth Ave, Box 359911, Seattle, WA 98104, USA

⁵Harborview Injury Prevention Research Center, University of Washington, 325 Ninth Ave, Box 359960, Seattle, WA 98104, USA

Full list of author information is available at the end of the article



(Continued from previous page)

Discussion: The TSOS pragmatic trial simultaneously aims to establish the effectiveness of the collaborative care intervention targeting PTSD and comorbidity while also addressing sustainable implementation through American College of Surgeons' regulatory policy. The TSOS effectiveness-implementation hybrid design highlights the importance of partnerships with professional societies that can provide regulatory mandates targeting enhanced health care system sustainability of pragmatic trial results.

Trial registration: ClinicalTrials.gov NCT02655354. Registered 27 July 2015.

Keywords: Traumatic injury, Multiple chronic conditions, Posttraumatic stress disorder, Depression, Suicidal ideation, Substance abuse, Effectiveness-implementation hybrid, Pragmatic clinical trial, American College of Surgeons, Policy

Background

The overarching goal of the trauma survivors outcomes and support (TSOS) effectiveness-implementation hybrid clinical trial is to develop and implement a large scale, cluster randomized pragmatic demonstration project that directly informs national trauma care system policy targeting injured patients with presentations of posttraumatic stress disorder (PTSD) and related comorbidity. Physical injury occurs frequently in the USA and constitutes both a substantial source of individual suffering and a significant public health burden. Each year in the USA, over 30 million individuals present to acute care medical trauma center and emergency department settings for the treatment of traumatic physical injury [1–5]. Injured trauma survivors present to acute care medical settings after both intentional (e.g., gunshots, stabbings, physical assaults) and unintentional (natural disasters, motor vehicle crashes) injury events [6]. Annually, 1.5–2.5 million Americans are so severely injured that they require inpatient hospitalization [1–5]. Estimates suggest that approximately 1.5 million American youth and adults experience traumatic brain injury (TBI) annually [7, 8]. Physical injury with and without TBI constitutes a major public health problem for both civilian and veteran patient populations [9, 10]. Globally, traumatic injury accounts for approximately 16 % of the world's burden of disease [11–13].

Multiple chronic conditions appear to be endemic among physical trauma survivors treated in US trauma care systems [14–16]. Recent commentary has explicated chronic conditions as conditions that last 1 year or more and require ongoing medical attention and/or limit activities of daily living [17–19]. Highly prevalent comorbidities include enduring PTSD, depression, and associated suicidal ideation, alcohol, and drug use problems, TBI, and chronic medical conditions such as hypertension, coronary artery disease, diabetes, and pulmonary disease [14, 20, 21].

Evidence-based, collaborative care intervention models for PTSD and related comorbidities exist [16, 22–25]. Collaborative care treatment models however, have yet to be broadly implemented throughout US trauma care systems; prior investigation by members of the interdisciplinary

study team suggest that less than 10 % of US trauma centers routinely provide post-injury screening or integrated care management treatment targeting the cluster of PTSD and related comorbidities [26]. The enduring challenges presented by the chronic disease cluster of PTSD and comorbidities after injury require innovative research approaches that cut across the traditional domains of multiple NIH institutes (<https://www.nihcollaboratory.org>).

The investigation is designed as an effectiveness-implementation hybrid pragmatic trial that simultaneously aims to assess the treatment outcomes of the collaborative care intervention targeting PTSD and comorbidity, while also assessing the potential utility of the implementation strategy [27]. The study aims to determine if injured patients receiving the collaborative care intervention demonstrate significant reductions in PTSD symptoms when compared to control patients receiving care as usual. The study also aims to determine if intervention patients, when compared to control patients, will demonstrate significant reductions in depressive symptoms and associated suicidal ideation, alcohol use problems, and improvements in physical function.

Over the past decade, the study team has established a stakeholder partnership with the American College of Surgeons' Committee on Trauma, whereby the results of pragmatic comparative effectiveness trials can be directly translated into policy mandates and best practice guidelines for the regulation of US trauma care systems [26, 28–31]. The investigative team will employ implementation science conceptual frameworks to better understand the potential uptake of the intervention model by trauma care systems nationwide.

Implementation science and randomized clinical trial conceptual frameworks informing the TSOS trial

Recent commentary has noted a proliferation of models and conceptual frameworks that can potentially inform the design of investigations that target the widespread dissemination and implementation of health care interventions; in reviewing this literature, commentary suggests

a systematic selection of optimal approaches for a particular investigation or health care delivery system [32–34].

By necessity, multiple theoretical and applied perspectives inform the conceptual framework underlying the TSOS pragmatic trial design and implementation [32] (Fig. 1). The TSOS pragmatic trial design and implementation incorporates implementation science evaluation frameworks [35], and classic theories [36], as well as frameworks that address sustainable health care system change [37, 38]. The TSOS study is also informed by effectiveness-implementation hybrid design [27], pragmatic trials [39], and stepped wedge [40–43] clinical trial design considerations.

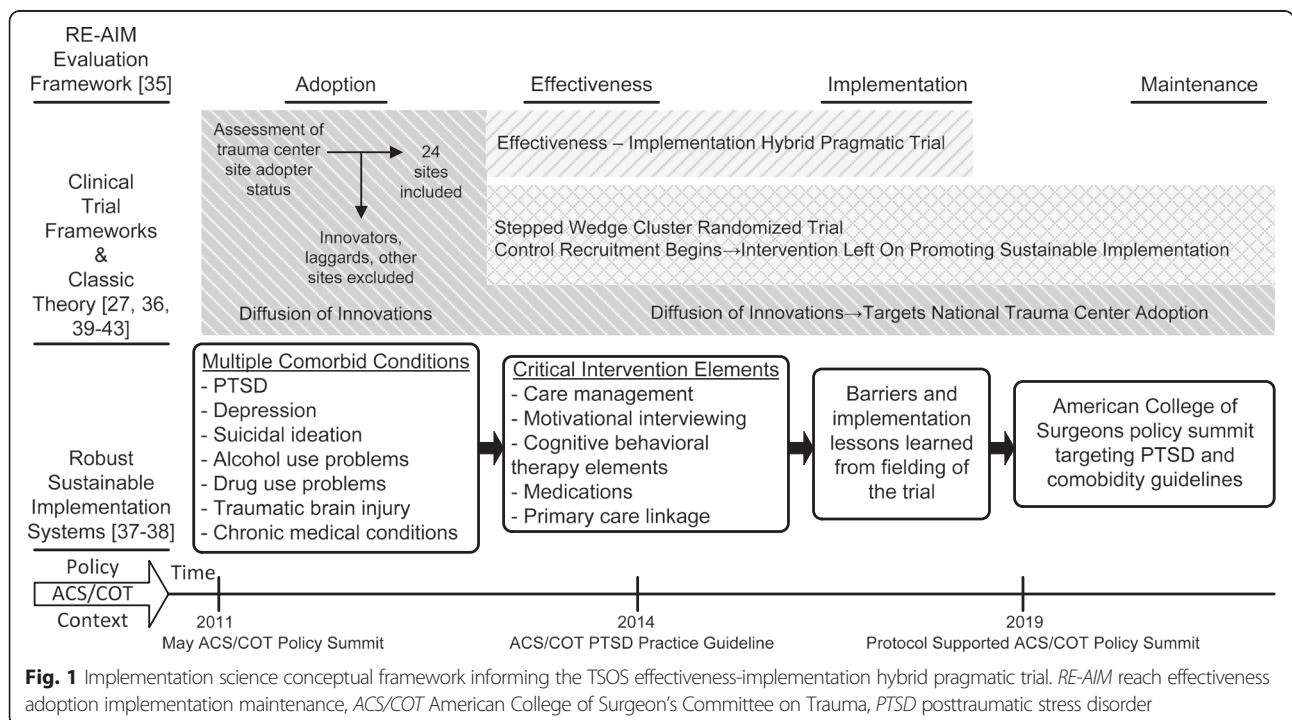
The implementation science conceptual frameworks influencing study design begin with the reach effectiveness adoption implementation maintenance (RE-AIM) evaluation framework that outlines clear stages of assessment for both effectiveness and implementation outcomes (Fig. 1). The RE-AIM framework provides a model for the integration of pragmatic trial results into routine trauma center practice [37]. Diffusion of innovation theory, which emphasizes the factors related to the intervention and setting characteristics, aids in the framing of the population-based sampling and adoption of trauma centers as well as descriptions of maintenance, based on the trial's ability to target American College of Surgeons' policy in order to shift "S-shaped" adopter curves nationally [36].

Clinical trial specific constructs and design features also contribute to the conceptual framework informing the TSOS study (Fig. 1). These include the emerging

effectiveness-implementation hybrid design construct [27]. The TSOS trial simultaneously aims to determine the effectiveness of the stepped collaborative care intervention model in reducing PTSD symptoms and comorbid conditions, while also assessing the potential utility of the implementation strategy that uses American College of Surgeons' policy to target regulatory mandates for trauma care systems nationally [37, 44].

The pragmatic-explanatory continuum indicator summary (PRECIS) pragmatic trial framework also informs the TSOS study [39]. Gold standards for pragmatic trial design and implementation include broad participant eligibility criteria, flexible intervention delivery, application by the full range of practitioners, and incorporation of rigorous prospective controls, preferably by randomization. Usual practice comparison conditions are frequently used in pragmatic trials [39, 44–48]. The optimal pragmatic trial is characterized by an intent-to-treat data analytic approach that includes all patients regardless of adherence [39]. The TSOS trial encompasses these pragmatic trial attributes by fielding a readily implementable collaborative care intervention that targets injured patients with the full spectrum of PTSD and related comorbidity with minimal exclusionary criteria.

Pragmatic trial process and outcome assessments have been conceptualized to be centrally measured, clinically meaningful, and require minimal adjudication [39, 44–48]. With regard to pragmatic trials in US trauma care systems, no one or even multiple administrative databases can be used to track outcomes among injured trauma



survivors; thus for trauma care system pragmatic trials, scheduled telephone outcome assessments may by necessity occur as an addition to naturalistic follow-up. The PRECIS framework suggests that for some trials, outcome assessments must by necessity be obtained through contact with participants [39]. Similarly, the PRECIS framework takes into consideration the observation that in some trials that rely heavily on patient reported outcomes, some training in the assessment and adjudication may be desirable [39].

As an integrative model (Fig. 1), the Robust, Sustainable, Implementation Systems Framework [37] aids in combining the implementation science, pragmatic trial, and health care systems change conceptual frameworks that inform the TSOS study; conceptually the Robust, Sustainable, Implementation Systems Framework integrates elements of process and implementation models, determinant frameworks, and clinical trial frameworks (e.g., multiple comorbid condition targets and critical intervention elements) as well as the RE-AIM evaluation framework [32, 37] (Fig. 1). A further advantage of the framework is the flexible integration of recent work on barriers and facilitators of acute care medical screening and intervention guideline implementation ([49–51]). Policy relevance that ultimately enhances clinical trial population impact is also relevant to the Robust, Sustainable, Implementation Systems Framework [37, 52, 53]).

Methods/design

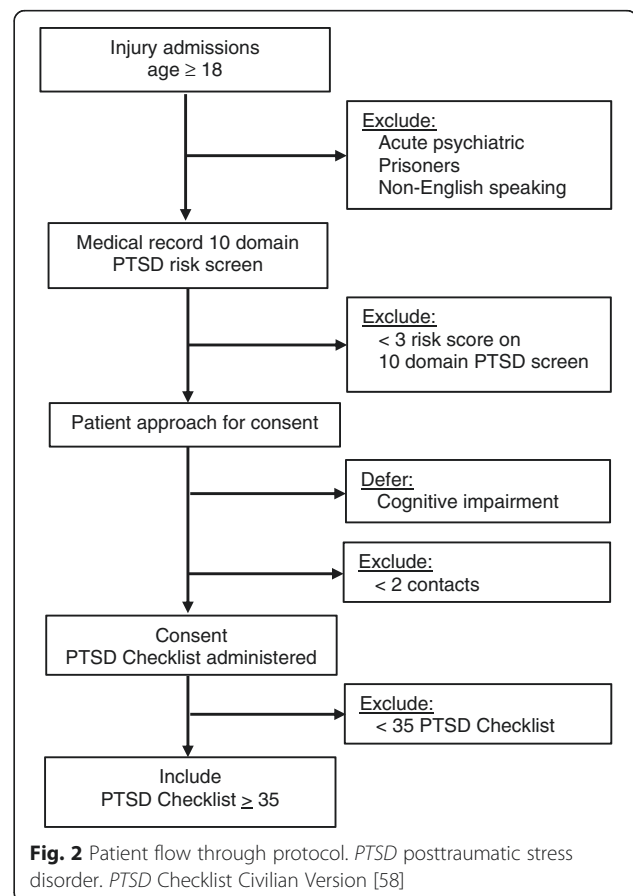
Design overview

The TSOS trial aims to recruit 960 patients, 40 at each trauma center site. The TSOS investigation employs a stepped wedge cluster randomized design in which sites are randomized sequentially to initiate the intervention. Patients are assessed at baseline in the emergency department or as trauma inpatients and again 3, 6, and 12 months after the injury. All sites have worked with the study team to implement an electronic health record (EHR) initial PTSD risk evaluation. Patients identified by the EHR evaluation as high risk for PTSD are formally assessed with the PTSD Checklist for study entry. Patients in the control condition will receive enhanced trauma center care as usual. Patients in the intervention condition will receive a stepped collaborative care intervention targeting PTSD and related comorbidities. The intervention begins with a 1-day workshop training in the collaborative care intervention core elements that include care management, medication, cognitive behavioral therapy (CBT), and motivational interviewing targeting PTSD and comorbidity. After the 1-day workshop, the site will receive supervision from the study team. Outcome analyses will incorporate both effectiveness and implementation spectrum assessments.

Injury cohort definition, exclusions, and PTSD risk screening

Prior to the initiation of recruitment for the TSOS study, the investigative team worked with each trauma center site to define injury cohorts, characterize inclusion and exclusion phenotypes within the EHR [54], and implement the 10 domain EHR PTSD risk screen [16, 55]. The procedures used to define injury cohorts and characterize potential emergency department and trauma inpatient subjects for the recruitment process varied across sites depending on the capacity of individual sites to automate the screening procedure within or external to the EHR [56]. The automated form of the evaluation can be performed using EHR data queries or scheduled reports, while the manual form of the abstraction procedure involves reviewing individual health records; many sites have combined automated and manual procedures into a partially automated (i.e., hybrid) 10-domain risk screen.

Injured patients of both genders over the age of 18 are included in the trial (Fig. 2). Prisoners and non-English speaking patients, will be excluded. Patients whose index injury was self-inflicted or are psychotic will receive immediate psychiatric treatment and will also be excluded from the trial. In order to assure adequate follow-up rates, patients must be able to provide two pieces of follow-up contact information.



Patients identified by EHR evaluation as at-risk for high early PTSD symptom levels with a score of >3 risk domains positive will then be formally screened for study entry with the PTSD Checklist Civilian Version [57, 58]. Patients scoring >35 on the PTSD Checklist will be followed longitudinally in the clinical trial portion of the investigation.

Randomization

Prior to initiation of patient recruitment, each of the 24 sites was randomized to one of four waves in the stepped wedge design. Each wave was assigned a specific proportion of control and intervention patient recruitment (Fig. 3). The study biostatistician randomized sites to waves using a computer generated algorithm. All interviewers conducting follow-up assessments will be blinded to patient intervention and control group status.

Enhanced usual care control condition

The control patient subjects will receive enhanced usual trauma center care. Prior investigation suggests that usual posttraumatic care includes routine surgical, primary care, and emergency department visits, as well as the occasional use of specialty mental health services. The enhanced aspect of the usual care will consist of the recruiting provider informing the ward nurse currently covering the patient subject’s care of any distress they are experiencing as identified by a PTSD Checklist score of >35 or Patient Health Questionnaire (PHQ-9) item 9 > 1 indicating suicidal ideation, administered during the baseline interview.

Stepped collaborative care intervention [16, 22–25]

Collaborative care treatment models that combine effective intervention elements and incorporate IT innovations have the potential to be flexibly implemented in order to prevent the development of the chronic condition cluster that includes PTSD and related comorbidity; collaborative care treatment models may also be effective in mitigating the impact of the acute injury event on symptom exacerbations in the large subpopulation of injury survivors who already carry a substantial pre-injury burden of chronic medical and other conditions [22, 25, 59–63] (Table 1).

A large body of research has established the effectiveness of integrated care delivery models such as collaborative care in reducing depressive, anxiety, pain, and other somatic symptom presentations in conjunction with comorbid medical conditions in primary care settings [22, 23, 25, 61, 64–78]. Collaborative care treatments bring together effective medication and psychotherapeutic intervention elements with care management strategies that target reductions in care fragmentation and enhanced care coordination for patients with multiple chronic conditions (Table 1). A series of single site acute care medical studies now support the effectiveness of collaborative care models in targeting the PTSD and comorbidity chronic condition cluster [16, 22–25].

Study staff will visit the trauma center sites in order to perform a 1-day intervention workshop training. The workshop will provide an overview of the core elements of the PTSD and comorbidity intervention (Table 1). The trainers will review the intervention elements including care management, medications, motivational interviewing (MI) and CBT elements, and community

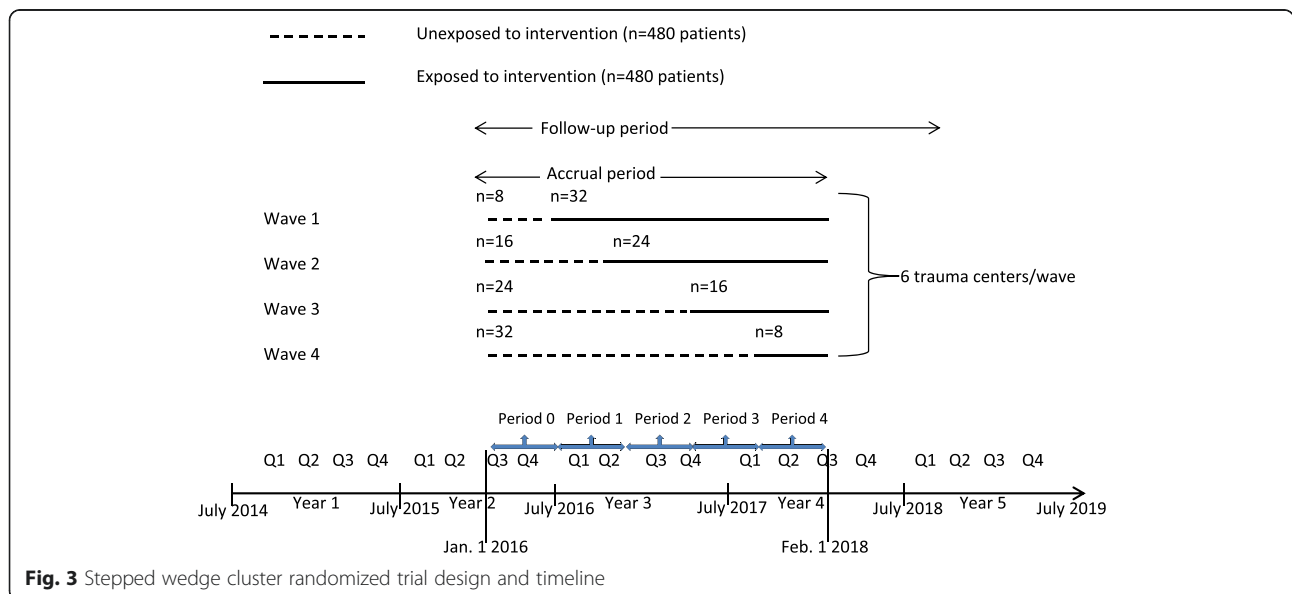


Fig. 3 Stepped wedge cluster randomized trial design and timeline

Table 1 Core elements of collaborative care intervention targeting PTSD and comorbidity after injury

Essential element	Which disorders targeted	MCC strategic framework goals addressed ^a
Population-based EHR PTSD and comorbidity risk prediction	PTSD, depression, suicidal ideation, alcohol and drug use problems, TBI and chronic medical conditions after acute injury	Goal 1 objective D implement and efficiently use health information technology; EHR screening efficiently identifies constellation of PTSD and comorbidity in injured populations
Care management with trauma center to primary care linkage	Coordination of acute injury mental health and pre-existing chronic medical condition care	Goal 2 facilitate use of community based services and self-care management
Early post-injury medication history, reconciliation, and care coordination	PTSD, depression, pain, and TBI symptoms prevention. Chronic medical condition reconciliation and coordination	Goal 1 objective E prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions Goal 2 objective C provide tools for medication management
Evidence-based MI embedded within care management	Targets alcohol and drug use problems and enhanced patient engagement	Goal 1 objective E prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions
Evidence-based CBT embedded within care management	Targets PTSD, depression, pain, and TBI symptoms. Also targets enhanced patient self-efficacy	Goal 1 objective E prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions Goal 2 objective A facilitate self-care management
Patient and caregiver-centered posttraumatic concern elicitation and improvement	Patient-centered concerns elicitation and improvement targets patient and family engagement in care of full MCC constellation	Goal 2 optimize self-care management and coordinated use of services by patient and caregivers
Caseload supervision and stepped measurement-based care implementation	PTSD, depression and associated suicidal ideation, alcohol and drug use problems, chronic medical conditions and acute physical injury	Goal 3 provide better information and education on treatment of MCCs to health care workers

MCC multiple chronic condition, EHR electronic health record, PTSD posttraumatic stress disorder, TBI traumatic brain injury, MI motivational interviewing, CBT cognitive behavioral therapy

^aAll study elements address MCC Goal 4 of Enhancing Research Knowledge on MCCs [17–19]

linkage. Specific intervention procedures have been detailed previously [16, 22–25].

After the 1-day workshop training, the study team will initiate regular site care management supervisory calls in which the site interventionists will present cases to the supervisory team [16, 79]. These sessions will include coaching in concern elicitation, CBT, and MI elements embedded within care management, as well as problem-solving barriers to screening and intervention implementation for PTSD and related comorbidity. These calls will also include coaching on evidence-based medication prescription and supervisory team written feedback. The care managers will be able to contact MD and PhD study team members on a 24-h study cell phone or study assistance email should more urgent questions arise. While final patient subject follow-up interviews take place approximately 12 months post-consent, intervention activities are anticipated to conclude approximately 6 months after patient subjects consent into the trial. During the final months of treatment, the interventionist will discuss with the patient strategies for maintaining treatment gains. This means proper handoff of medication prescription management to a patient subject's preferred primary care or other medical provider, linkage to community resources, engaging family and community support, and when indicated psychotherapy referrals.

Assessments

The TSOS assessment approach incorporates both effectiveness and implementation outcome evaluations [80]. The timing and content of the TSOS outcome assessments are delineated in Tables 2 and 3. The primary effectiveness evaluations are patient-reported outcome measures that include assessments of the study primary and secondary outcomes (Table 2). The RE-AIM evaluation framework informs the implementation outcome assessments [35] (Table 3). Selected outcome assessments are described in further detail below.

- A. Primary study patient-reported outcome: PTSD symptom assessment [58, 81]
The PTSD Checklist is a 17-item self-report questionnaire that will be used to assess PTSD symptoms. A series of investigations have demonstrated the reliability and validity of the PTSD Checklist across trauma-exposed populations. PTSD Checklist scores of >35 in the days and weeks after injury admission have been shown to be associated with the development of higher PTSD symptom levels over the course of the year after injury [55].
- B. Secondary study patient-reported outcomes: depressive symptoms, suicidal ideation, alcohol use problems, and physical function

Table 2 Effectiveness assessments and timing of administration

Study measure	Baseline	3 months	6 months	12 months
EHR 10 item PTSD evaluation [55]	X			
ICD injury severity	X			
ICD TBI severity	X			
ICD/self-report chronic medical conditions	X	X		
EHR and self-reported demographics	X			
Consciousness/Glasgow Coma Scale [144, 145]	X			
PTSD (PTSD Checklist DSM-IV & DSM-5) [58, 81]	X	X	X	X
Depression (PHQ-9) [82]	X	X	X	X
Suicidal ideation (PHQ-9 item 9) [82, 84]				
Alcohol (AUDIT) [85]	X	X	X	X
Illegal and prescription drug use (DAST) [146]	X	X	X	X
Pain (Brief Pain Inventory) [147, 148]	X	X	X	X
Postconcussive symptoms [90, 149, 150]	X	X	X	X
Functioning (MOS SF12/36) [88]	X	X	X	X
Violence risk behaviors [24]	X	X	X	X
Pre-injury trauma [6, 106, 107]		X		
Recurrent traumatic events [6, 106, 107]			X	X
Reactions to research participation [25]	X	X	X	X
Satisfaction with care [16, 25]	X	X	X	X
Health services, work and cost [14, 151–154]	X	X	X	X
Medication use [14, 16, 25, 151]	X	X	X	X
EHR/trauma registry data [14, 151]	Ongoing automated data			

EHR electronic health record, *PTSD* posttraumatic stress disorder, *ICD* international classification of diseases, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *PHQ-9* Patient Health Questionnaire, *AUDIT* Alcohol Use Disorders Identification Test, *DAST* Drug Abuse Screen Test, *MOS SF* Medical Outcomes Study Short Form

Table 3 TSOS implementation assessments and corresponding RE-AIM framework domains

Assessment	Patient, provider or site assessment	How assessed	N	RE-AIM domain, level
Characteristics of 24 study sites versus all other US sites [35]	Site recruitment	CONSORT	24/224	Adoption, site
Organizational change, climate and culture surveys [95–102]	Trauma center providers	Web-based survey	10*24	Implementation, provider
Weekly recruitment log activity [16, 25, 70]	PTSD interventionist	Recruiting logs	24	Implementation, provider and site
Clinical notes in decision support tool [16]	PTSD interventionist	Decision support tool	24	Implementation, provider
Patient flow through protocol utilizing trauma registry, recruitment data [16, 25, 70]	Patient flow	CONSORT	960	Reach, patient
PTSD and comorbidity, gender and ethnicity groups [16, 25, 70]	Patient outcomes	Telephone interview	960	Effectiveness, patient
EHR, trauma registry, self-report logs [16, 25, 70]	Patient outcomes	Multiple sources	960	Implementation, patient
>6 months follow-up after intervention [16, 25, 70]	Patient 12-month follow-up	Phone	960	Maintenance, patient
Semi-structured key informant interviews [121–125]	PTSD interventionist	Phone	24	Implementation and maintenance, provider and site
National trauma center questionnaire [26, 30]	All US level I centers	Web	224	Maintenance, site

RE-AIM reach effectiveness adoption implementation maintenance, *EHR* electronic health record

Depressive symptoms. The 9-item Patient Health Questionnaire (PHQ-9) brief depression severity measure will be used to assess depressive symptoms [82]. The PHQ-9 has established reliability and validity in acute and primary care medical patients [16, 25, 83].

Suicidal ideation. The PHQ-9, item 9, will be used to assess for suicidal ideation [84].

Alcohol use problems. The Alcohol Use Disorder Identification Test (AUDIT), a ten-item screening instrument for the early identification of problem drinkers will be used to assess alcohol use problems before and after the injury hospitalization [85]. The AUDIT's reliability and validity are well established, and the scale has been widely used in acute and primary care medical settings [16, 25, 85–87].

Limitations in physical function. The investigation will use the Medical Outcomes Study Short Form (MOS SF) SF-12 at baseline and SF-36 at 3-, 6-, and 12-month follow-up to assess physical, role, and social functional outcomes. The SF-12/36 has established reliability and validity [88], and the measure has been used extensively with traumatically injured populations [89–91].

C. Baseline patient trauma center/emergency department electronic health record (EHR) assessment

EHR data will be collected from each of the 24 sites during the recruitment of study patients. Similarly, trauma registry data will be obtained from each of the 24 sites that will contain EHR derived international classification of diseases (ICD) codes and other clinical data.

EHR 10 item PTSD risk factor screen. A previously developed EHR screen will be used to assess admitted injured trauma survivors at risk for the development of PTSD [55]. The screen utilized ten data elements that are both associated with increased risk for PTSD and that are readily available in any robust EHR system. When the ten data elements were used to predict scores on the PTSD Checklist of >35, the EHR screen demonstrated adequate sensitivity (0.71), specificity (0.66), and area under the ROC curve (0.72) [55].

Injury severity. Injury severity will be abstracted from the medical record using a conversion software program that transforms recognized ICD codes into the Abbreviated Injury Scale (AIS) and subsequent injury severity scores (ISS) [92].

Traumatic brain injury (TBI). Mild, moderate, and severe TBI will be identified and categorized from electronic record abstracted ICD codes indicative of traumatic injury.

Medical conditions. Comorbid chronic medical conditions will also be taken from medical record

and trauma registry data and will be derived from ICD diagnostic codes [93, 94]. Chronic medical comorbidity will also be assessed through patient self-report during the follow-up interviews.

D. Provider assessments

Trauma center organizational assessments [95–100]. The study will modify previously developed organizational culture and climate assessment scales to evaluate trauma center organizational characteristics related to PTSD and comorbidity service implementation [95, 101, 102].

Organizational implementation scales will assess the extent to which trauma centers were able to adapt to the changes required by PTSD and comorbidity screening and intervention service development [96, 101]. Trauma center provider attrition from the study and turnover will also be examined. Following the procedure established in the study team's previous Disseminating Organizational Screening and Brief Intervention Services (DO-SBIS) pragmatic trial, ten providers from each of the 24 sites will be identified through an organizational mapping procedure to be part of the organizational work unit impacted by screening and intervention service delivery [101, 103]. These ten providers will complete the organizational assessment prior to beginning intervention activities and again in study year 4 after all patient intervention is complete.

Trauma center provider exposure to critical incidents and job stress [104, 105]. Previously developed items will be used to assess trauma center provider job-related stress (e.g., call frequency, work volume) [104]. Provider secondary traumatic stress, lifetime trauma, and PTSD symptoms will also be assessed [6, 58, 81, 106, 107].

Intervention provider standardized patient assessments [108]. In the study team's prior DO-SBIS pragmatic trial focusing on alcohol screening and intervention, standardized patient fidelity assessments were used to assess fidelity to MI interventions delivered by front-line trauma center providers. Each standardized patient interview was scored using the Motivational Interviewing Treatment Integrity (MITI) coding system. The MITI will again be used to code patient standardized interviews in the current TSOS study.

E. Exploratory health economic evaluation

The cost assessments are intended to contribute to an understanding of the resource implications of the intervention and to American College of Surgeons' and other national policy dialogues of post-injury health service utilization and costs to support subsequent intervention scale-up and spread [109–118]. The investigation will collect detailed information on

the following: (1) the costs of intervention implementation and delivery, (2) post-injury health service utilization costs (e.g., inpatient, skilled nursing facility, emergency room, and outpatient utilization), and (3) the costs of patient medications post-injury. Costs of intervention are likely to be dwarfed by the total costs of post-injury care, which would make it difficult to estimate the incremental costs of intervention precisely, given our sample size. The health care resource utilization and cost analyses constitute an important exploratory aim of the investigation.

F. Study team logging procedures

The approach to trial logging simultaneously aimed to satisfy the pragmatic trial requisite for the minimization of time intensive research methods that require extensive adjudication [39] and the implementation science goal of understanding and documentation of trial processes that could yield sustainable maintenance of screening and intervention procedures [27].

Because pragmatic trials tacitly aim to provide health care delivery settings with readily implementable intervention models, logging procedures that differentiate study team activities related to (1) the fielding of the trial, (2) the implementation of evidence-based interventions, (3) costing and economic analyses, and (4) regulatory procedures may be critical for pragmatic trial design and implementation. Previously articulated procedures for the logging of clinical trial and implementation activities were adapted for the current pragmatic trial approach [119, 120]. A pragmatic trial framework that emphasized time efficiency and minimal adjudication of logged activities argued for optimizing parsimony in the logging approach [39]. All study research team site contacts, including email, phone, and in-person site contacts, and all study team consultant (e.g., trauma surgery champion) contact with sites are logged. Both 24 site specific logs and domain specific logs (i.e., trial specific activities, evidence-based intervention implementation, sustainability, and economic considerations) will be maintained. As part of the study's mixed method assessment procedures, the logs and field notes will be reviewed on an approximately monthly basis with the investigation's mixed methods consultant [70, 121–123].

G. Semi-structured provider interviews [124, 125]

After the completion of recruitment and intervention activities, semi-structured interviews will be conducted with interventionists from each of the 24 trauma center sites. The interviews will explore barriers and facilitators of implementation of screening, intervention, and quality documentation

procedures for PTSD and comorbidity at trauma center sites. The interviews will also explore the potential sustainability of study procedures.

Statistical analysis plan

Study aims and hypotheses

The primary hypothesis is that the intervention group when compared to the control group will demonstrate significant reductions in PTSD symptoms over the course of the year after injury. Secondary hypotheses are that intervention patients when compared to control patients will demonstrate significant reductions in depressive symptoms and associated suicidal ideation, significant reductions in alcohol use problems, and improved post-injury physical function.

All primary statistical analyses will be conducted using intent-to-treat methods. The primary goal of the statistical analyses is to examine and compare trends over time in the symptoms of PTSD. This analytic approach will be replicated for all secondary outcomes; secondary analyses will examine trends over time for depression, alcohol use, and physical function. The major outcome variables are the continuous and dichotomous assessments of PTSD (PTSD Checklist [81]), depression (PHQ-9 [82]), alcohol use problems (AUDIT [85]), and physical function (MOS SF-36 PCS [88, 126]).

The study team will use mixed effects regression models to test the hypotheses. The investigative group has extensive experience with these analytic approaches in the analyses of longitudinal data after injury. These analytic approaches allow for the modeling of longitudinal data on patients, nested within trauma center sites (see also sample size and power discussion below for a more in-depth explanation of clustering). An important potential advantage of using longitudinal mixed models is the ability to use partial data on those subjects with missing data, and therefore potentially ameliorate selection bias due to drop out. In addition, mixed models naturally structure patient and trauma center heterogeneity specifically allowing for random effects such as individual intercepts and slopes over time. Longitudinal regression models also allow the use of baseline covariates that may be prognostic or reflective of the study design.

Exploratory analyses will assess the impact of the intervention on primary and secondary outcomes for patients with and without pre-injury chronic medical conditions and those with and without TBI. Exploratory analyses will also assess for significant reductions in suicidal ideation, pain, and drug use problems in intervention patients when compared to control patients.

The study team will use a stepped wedge cluster randomized design for the TSOS protocol [40–43] (Fig. 3). Variability in multiple trauma center characteristics can

impact rates of recruitment (e.g., admission volumes, EHR capacity), rates of PTSD (e.g., percentages of patients with violent injury admissions, intensive care unit admission rates), and the ability to follow patients longitudinally (e.g., patient demographic characteristics such as being homeless, clinical characteristics such as substance use problems). The stepped wedge design randomizes level I trauma center sites to sequentially initiate the intervention, thus allowing within site pre- and post-intervention comparisons, as well as between site comparisons. An additional advantage of the stepped wedge design for the protocol is that it would be impractical to roll out the entire intervention at 24 sites simultaneously. Finally, from an implementation science perspective, there is an advantage to having the intervention ongoing at the end of the study at every site, should the intervention demonstrate a significant impact on PTSD and comorbidity (Fig. 1). Given that there is little threat of contamination at each site across intervention and control patients and that the UH3 can accommodate the increased potential length of active recruitment and follow-up, the stepped wedge design appears to be an optimal choice for the TSOS protocol.

Sample size and power

A number of issues specific to the design and analyses of cluster randomized trials are addressed by the current power analyses [127–131]. A key consideration for the trial is the nesting of patients within trauma center sites and the ascertainment of associated intraclass correlations (ICC). The study team has extensive experience with prior multisite trauma center observational and pragmatic clinical trial investigations. Sample size estimates were therefore adjusted for the clustering of patients within trauma center sites, using appropriate ICCs derived from the study team's prior multisite investigations (Table 4).

Some attrition is expected in the study sample due to the research context and the population under study (i.e., low income, ethnoculturally diverse, injured trauma survivors). Prior studies by the investigative group have consistently achieved follow-up completion rates >75–80 % at 6–12 months post-injury with this population [16, 24, 25, 132]. Estimates derived from these rates are incorporated into the descriptions of subject flow and power analyses. Table 4 delineates the parameters used to estimate power for the PTSD Checklist, PHQ-9, AUDIT, and MOS SF-PCS. Sample size estimates were derived using the STATA statistical package [133]. With each of the 24 trauma center sites recruiting 40 patients into the study, the study has 80 % power to detect effect sizes of 0.23. These effect sizes are smaller than our previously observed treatment effect for PTSD symptoms of 0.34. In prior investigations, PTSD treatment effects of

Table 4 Stepped wedge power for TSOS outcomes

Continuous outcomes	PTSD Checklist	PHQ-9	AUDIT	MOS SF-PCS
Cluster size at baseline	40	40	40	40
Cluster size estimation at 12-month (25 % attrition)	30	30	30	30
Total number of clusters	24	24	24	24
Alpha	0.05	0.05	0.05	0.05
Power	0.8	0.8	0.8	0.8
ICC	0.02	0.0259	0.02	0.02
Baseline mean (SD)	50 (15)	14 (6)	10 (5)	50 (10)
Autocorrelation	0.7	0.7	0.7	0.7
Follow-up time points (including baseline)	4	4	4	4
Minimal detectable effect size	0.23	0.23	0.23	0.23

PTSD posttraumatic stress disorder, PTSD Checklist Civilian Version [58], PHQ-9 Patient Health Questionnaire [82], AUDIT Alcohol Use Disorders Identification Test [85], MOS SF PCS Medical Outcomes Study Short Form Physical Components Summary Score [126], ICC intraclass correlation, SD standard deviation

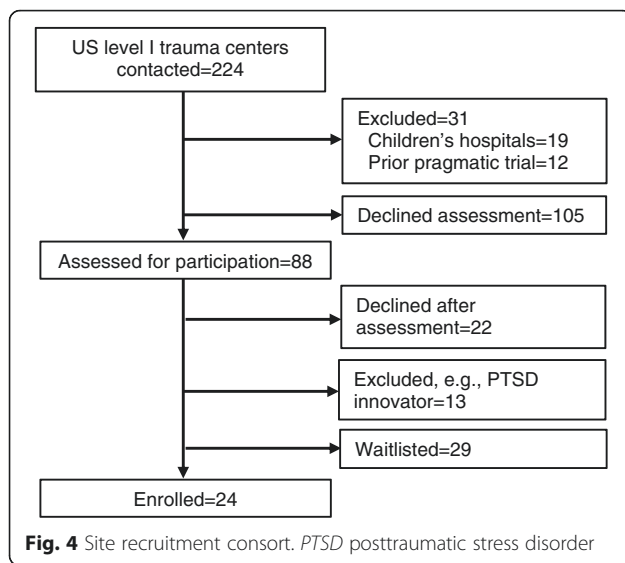
0.34 have been associated with clinically significant and policy relevant functional outcome improvements [25].

Mixed method analysis

Mixed methods will be used to integrate the findings from the key informant interviews with pragmatic trial results. The design taxonomy follows a sequential (QUAN → qual) structure in which qualitative data collected from key informants will be used to explain quantitative data results from the pragmatic trial [134, 135]. Qualitative data will therefore be used to expand upon the results of the pragmatic trial in order to understand the implementation and policy processes as experienced by key stakeholders. Second, the sequential QUAN → qual mixed methods design will be used to provide an understanding of pragmatic trial results that require further explanation (e.g., control patients that demonstrate substantial improvement in outcomes, despite not receiving intervention). Results of the mixed method analyses will be presented through a number of modalities that may include key informant narratives, tabular representation of themes with illustrative quotes, and thematic counts [136–139].

Trial status

Over the course of the pre-recruitment phase, the TSOS study team has enrolled the 24 trauma center sites that will participate in the trial. The goal of the selection process was to recruit 24 level I trauma centers nationally that would be capable of efficiently implementing the study procedures. The study team sent notification emails and/or contacted by telephone individuals at all US level I trauma centers (Fig. 4). Responding centers were asked questions about current PTSD screening and



intervention practices; the study excluded the less than 10 % of “innovator” sites nationally that were already routinely screening and intervening for PTSD and related comorbidity [26]. Pediatric specialty trauma centers were also excluded from the investigation, as elements of the intervention (e.g., the administration of psychopharmacological agents targeting PTSD) are less well established for patients under the age of 18.

With the exception of pediatric trauma center specialty status, the organizational characteristics of the 24 participating sites does not substantially differ from the characteristics of all US level I trauma centers potentially eligible for the study (Table 5). Broad adoption and site level generalizability is an important aim of the investigation as it targets American College of Surgeons’ policy for PTSD and comorbidity screening and intervention for all trauma centers nationwide.

Discussion

The current effectiveness-implementation hybrid is innovative in its combination of pragmatic trial and implementation science conceptual frameworks. The effectiveness-implementation trial is a “hybrid type II” design that uses a novel, yet time-tested, American College of Surgeons’ policy mechanism as a targeted implementation strategy [27]. Curran and colleagues note that to enhance the relevance of pragmatic studies, comparative effectiveness trials may require modification in order to have increased policy relevance [27]. Curran and colleagues also critique pragmatic comparative effectiveness studies for exclusively targeting effectiveness outcomes with little attention to the implementation processes relevant to general practice settings; these authors note that in contrast, implementation trials focus on the

Table 5 Organizational characteristics of TSOS study versus other US level I trauma centers ($N = 222$)^a

Characteristic	TSOS TC $n = 24$ n (%)	Other TCs $n = 198$ n (%)	P
American College of Surgeons accredited	17 (70.8)	74 (37.4)	0.01
Region of country			0.40
Midwest	7 (29.2)	64 (32.3)	
South/Southeast	4 (16.7)	30 (15.2)	
Northeast/East	5 (20.8)	63 (31.8)	
West	4 (16.7)	28 (14.1)	
Central	4 (16.7)	13 (6.6)	
Rural status	3 (12.5)	24 (12.1)	1.0
Population served			0.03
Adult	7 (29.2)	92 (46.5)	
Adult and pediatrics	17 (70.8)	82 (41.4)	
Pediatrics	0 (0.0)	23 (11.6)	
Missing	0 (0.0)	1 (0.5)	
Teaching hospital	23 (95.8)	162 (81.8)	0.14
Council of teaching hospitals	22 (91.7)	143 (72.2)	0.04
University affiliation	24 (100.0)	189 (95.5)	0.60
Median (IQR)			
Number of interns/residents	327 (282)	224 (297)	0.11
Number of hospital beds	575 (296)	534 (318)	0.40
Number of inpatient admits	26,971 (16,311)	25,699 (14,978)	0.28

TC trauma center, IQR interquartile range

^aTwo of 224 sites were missing organizational data

uptake and adoption of clinical interventions by providers and systems of care [27].

As part of the study’s emphasis on implementation, an American College of Surgeons’ policy summit is scheduled in the final years of the trial. The aim of the policy summit is to facilitate rapid translation of trial results into national policy. The College oversees the development of national policy mandates and clinical best practice guidelines that inform the integrated operation of US trauma centers and affiliated trauma care systems [28, 29, 140]. The College has successfully linked trauma center funding to verification site visits and other quality indicators [28, 141, 142].

In January of 2005, the College made a landmark policy decision to mandate health services targeting screening and intervention for alcohol-related disorders as a requisite for trauma center accreditation [28]. Prior pragmatic randomized clinical trial investigations from the study team provided evidence supporting the College’s alcohol mandate [22, 30, 143]. In May of 2011, the investigators presented results from effective, NIH funded, PTSD screening and intervention trials at a College policy summit [22–24, 70]. For the first time, the College has included PTSD screening and intervention

as a best practice level recommendation in national guidelines for trauma center care. These new College clinical guidelines set the stage for the current effectiveness-implementation hybrid trial that tests high quality, feasibly implemented, screening and intervention procedures for PTSD and related comorbidity. Simultaneously, as the investigation is being conducted, the study team will be actively developing a policy agenda targeting the use of pragmatic trial results to directly inform the policy discussion in the final years of the grant.

The potential for a policy target sets up a novel staged implementation context whereby the fielding of the trial and the implementation of the evidence-based intervention can yield insight into the sustainable delivery of PTSD screening and intervention procedures for trauma centers nationwide. In this context, previously described Rapid Assessment Procedures that harness clinical ethnographic methods to embed participant observation within front-line implementation teams have great potential utility [70, 121–123]. These methods rely on the study team collection of implementation logs and field notes; these logs and field notes can be productively reviewed on a regular basis with the study mixed method consultant in order to maximally harness field observations. This Rapid Assessment Procedures approach simultaneously satisfies the pragmatic trial requisite for minimization of time intensive research methods that require extensive adjudication and the implementation science goal of understanding and documentation of trial processes that could yield sustainable maintenance of screening and intervention procedures.

In summary, a hybrid effectiveness-implementation spectrum pragmatic trial targeting screening and intervention for PTSD and comorbidity can be readily designed and feasibly implemented across US level I trauma centers. These findings highlight the importance of partnerships with professional societies such as the American College of Surgeons' that can provide regulatory mandates in order to enhance widespread implementation of pragmatic trials results.

Abbreviations

CBT: cognitive behavioral therapy; DO-SBIS: disseminating organizational screening and brief intervention services; DSM: diagnostic and statistical manual; EHR: electronic health record; ICC: intraclass correlation; ICD: international classification of diseases; MI: motivational interviewing; PRECIS: pragmatic-explanatory continuum indicator summary; PTSD: posttraumatic stress disorder; RE-AIM: reach effectiveness adoption implementation maintenance; SD: standard deviations; TBI: traumatic brain injury; TSOS: trauma survivors outcomes and support.

Competing interests

The authors declare that they have no competing interests

Authors' contributions

DFZ, JR, DD, DC, EVE, PH, BC, and GJ conceptualized and designed the study. DFZ, JR, DD, JW, LI, RG, and LW acquired the data. JR and JW analyzed the data. DFZ, JR, DD, DC, LP, EVE, JW, LI, RG, PH, BC, LW, and GJ interpreted the

data. DFZ, JR, DD, DC, LP, EVE, JW, LI, RG, PH, BC, LW, and GJ drafted and critically revised the manuscript. DFZ, JR, DD, DC, LP, EVE, JW, LI, RG, PH, BC, LW, and GJ approved the final manuscript.

Authors' information

DFZ is a medical doctor and Professor at the University of Washington. JR is a PhD degree holder and an Associate Professor at the University of Washington. DD is a PhD degree holder and an Acting Professor at the University of Washington. DC is a DPhil degree holder and Deputy Director for Implementation Science at the National Cancer Institute. LP is a PhD degree holder and Professor at the University of Southern California. EVE is a medical doctor and Associate Professor at the University of Washington. JW is a PhD degree holder and Research Consultant at the University of Washington. LI is a BS degree holder and a Research Coordinator at the University of Washington. RG is a BA degree holder and a Research Coordinator at the University of Washington. PH is a PhD degree holder, Professor and Chair of the Department of Biostatistics at the University of Washington. BC is a MS degree holder and Senior Biostatistician at the University of Washington. LW is a medical doctor and Acting Assistant Professor at the University of Washington. GJ is a medical doctor, Professor, and Vice Chairman of the Department of Surgery at the University of California in Davis.

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Author details

¹Department of Psychiatry & Behavioral Sciences, University of Washington, 325 Ninth Ave, Box 359911, Seattle, WA 98104, USA. ²Division of Cancer Control and Population Sciences, National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760, USA. ³School of Social Work, University of Southern California, Montgomery Ross Fisher Building, Room 339, Los Angeles, CA 90089, USA. ⁴Department of Surgery, University of Washington, 325 Ninth Ave, Box 359796, Seattle, WA 98104, USA. ⁵Harborview Injury Prevention Research Center, University of Washington, 325 Ninth Ave, Box 359960, Seattle, WA 98104, USA. ⁶Department of Biostatistics, University of Washington, 1705 NE Pacific St, Box 357232, Seattle, WA 98195, USA. ⁷Division of Emergency Medicine,

University of Washington, 25 Ninth Ave, Box 359702, Seattle, WA 98104, USA.
⁸Department of Surgery, University of California in Davis, 2221 Stockton Blvd, Cypress #3111, Sacramento, CA 95817, USA.

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STUDY PROTOCOL

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Population-based outreach versus care as usual to prevent suicide attempt: study protocol for a randomized controlled trial

Gregory E. Simon^{1*}, Arne Beck², Rebecca Rossom³, Julie Richards¹, Beth Kirlin¹, Deborah King¹, Lisa Shulman¹, Evette J. Ludman¹, Robert Penfold¹, Susan M. Shortreed¹ and Ursula Whiteside¹

Abstract

Background: Suicide remains the 10th-ranked most frequent cause of death in the United States, accounting for over 40,000 deaths per year. Nonfatal suicide attempts lead to over 200,000 hospitalizations and 600,000 emergency department visits annually. Recent evidence indicates that responses to the commonly used Patient Health Questionnaire (PHQ9) can identify outpatients who are at risk of suicide attempt and suicide death and that specific psychotherapy or Care Management programs can prevent suicide attempts in high-risk patients. Motivated by these developments, the NIMH-funded Mental Health Research Network has undertaken a multisite trial of two outreach programs to prevent suicide attempts among outpatients identified by routinely administered PHQ9 questionnaires.

Methods/design: Outpatients who are at risk of suicide attempt are automatically identified using data from electronic health records (EHRs). Following a modified Zelen design, all those identified are assigned to continued usual care (i.e., no contact) or to be offered one of two population-based outreach programs. A Care Management intervention includes systematic outreach to assess suicide risk, EHR-based tools to implement risk-based care pathways, and care management to facilitate recommended follow-up. A Skills Training intervention includes interactive online training in Dialectical Behavior Therapy skills, supported by reminder and reinforcement messages from a skills coach. Each intervention supplements, rather than replaces, usual care; participants may receive any other services normally available. Interventions are delivered primarily by secure messaging through EHR patient portals. Suicide attempts and deaths following randomization are identified using state vital statistics data and health system EHR and insurance claim data. Primary evaluation will compare risk of suicide attempt or death over 18 months according to the initial assignment, regardless of intervention participation. Recruitment is underway in three health systems (Group Health Cooperative, HealthPartners, and Kaiser Permanente Colorado). Over 2500 participants have been randomized as of 1 March 2016, with enrollment averaging approximately 100 per week.

Discussion: Assessing the effectiveness of population-based suicide prevention requires adherence to the principles of pragmatic trials: population-based enrollment, accepting variable treatment participation, assessing outcomes using health record data, and analyses based on intent-to-treat.

Trial registration: ClinicalTrials.gov registration #NCT02326883, registered on 23 December 2014.

Keywords: Suicide, Prevention, Pragmatic trial, Care management, Consent waiver

* Correspondence: simon.g@ghr.org

¹Group Health Research Institute, 1730 Minor Ave. #1600, Seattle, WA 98101, USA

Full list of author information is available at the end of the article



Background

Suicide remains the 10th-ranked most frequent cause of death in the United States, accounting for over 40,000 deaths per year [1]. Nonfatal suicide attempts lead to over 200,000 hospitalizations and 600,000 emergency department visits each year [2, 3]. In contrast with other common causes of death, suicide mortality has not decreased over the last 25 years.

While prevention of suicide attempts and suicide death is a public health priority, existing evidence does not clearly support selective or secondary prevention programs. In 2013, the US Preventive Services Task Force found insufficient evidence to support the benefits of screening for suicide risk in general medical outpatients [4]. That review found insufficient evidence both for the accuracy of screening tests and for the effectiveness of interventions in those identified by screening.

More recent evidence indicates that responses to the commonly used Patient Health Questionnaire (PHQ9) can identify outpatients who are at increased risk of suicide attempt and suicide death [5, 6]. Patients reporting frequent thoughts of death or self-injury (the ninth item of the PHQ9) show a sustained increase in risk, with cumulative hazard approaching 4 % over 12 months. Reflecting this new evidence, the Joint Commission recently issued a Sentinel Event Alert [7] regarding detection of suicidal ideation in health care settings.

In addition, growing evidence supports the effectiveness of tertiary or indicated prevention interventions for high-risk patients. Structured psychotherapy emphasizing specific behavioral and cognitive skills has been proven to reduce risk among people who have made recent suicide attempts [8–10]. Outreach and Care Management programs appear to reduce risk among people who have made recent suicide attempts or high-risk patients treated in mental health specialty clinics [11]. This evidence for tertiary prevention suggests that similar interventions could reduce risk in the broader (secondary prevention) population of patients who are experiencing frequent suicidal ideation.

Motivated by these developments, the National Institute of Mental Health-funded Mental Health Research Network has undertaken a multisite trial of two population-based programs to prevent suicide attempts among outpatients identified by routinely administered depression questionnaires. Both programs include systematic outreach and regular supportive contact. One focuses on risk assessment and care management [11], while the other includes online training in specific skills from Dialectical Behavior Therapy (DBT) [12]. This pragmatic trial will examine whether either program can reduce long-term risk compared to care as usual.

Methods

Overview

At participating health systems, outpatients who are at increased risk of suicide attempt are identified using data from electronic health records (EHRs). Following a modified Zelen [13–15] design, all those identified are automatically assigned to continue in usual care (i.e., no contact) or to be offered one of two population-based prevention programs:

- A Care Management intervention including: systematic outreach to assess risk of suicidal behavior, EHR-based tools to implement risk-based care pathways, and care management to facilitate and monitor recommended follow-up care
- A Skills Training intervention including: interactive online training in DBT skills [12], supported by reminder and reinforcement messages from a skills coach

Each intervention is intended to supplement, rather than replace, usual care provided by specialty mental health or primary care providers. Participants in all three treatment groups are free to receive any other services that are normally available, including pharmacotherapy, individual or group psychotherapy, or inpatient care. Intervention services are delivered primarily by online secure messaging through EHR patient portals [16, 17]. Nonfatal and fatal suicide attempts following randomization are identified using state vital statistics data and diagnoses of self-inflicted injury from health system clinical and insurance claim records [18, 19]. Primary evaluation will compare risk of first suicide attempt (nonfatal or fatal) over the 18 months following randomization. Groups will be compared according to initial treatment assignment, regardless of level of participation in either intervention program.

Study settings

The study sites include three members of the Mental Health Research Network: Group Health Cooperative, HealthPartners, and Kaiser Permanente of Colorado. These health systems provide general medical and mental health specialty care as well as insurance coverage to defined member/patient populations. Patients served are representative of each health system's geographic service area in terms of race, ethnicity, educational attainment, and household income.

All three participating health care systems recommend the routine use of the PHQ9 depression questionnaire [20] at all mental health specialty visits and all primary care visits for treatment of depression [21]. All three sites participated in previous research [5] demonstrating that the response to item 9 of the PHQ9 (regarding thoughts

of death or self-harm) predicts markedly elevated risk of suicide attempt over the following 18 months (Fig. 1).

Eligibility

Eligibility criteria for automatic inclusion in the trial include:

- Completion of a PHQ9 questionnaire [20] at an outpatient mental health or general medical visit
- Age 18 years or older on the visit date
- Response of “more than half the days” or “nearly every day” to item 9 of the PHQ9
- Use of EHR patient portal secure messaging during the prior year
- Currently enrolled in participating health system insurance plan (to ensure adequate ascertainment of subsequent suicide attempts)

Exclusion criteria include:

- Recorded diagnosis of dementia or developmental delay in the previous 2 years
- Limited English proficiency (as indicated by “need for interpreter” recorded in the EHRs)
- Previous request to be excluded from research invitations

- Already enrolled and randomized via a previous visit

Enrollment and randomization

Each week, EHR and insurance claim databases at each study site are used to identify all patients who meet eligibility criteria during the previous week. Immediately after sampling, all eligible patients are randomly assigned in equal proportions (1/3:1/3:1/3) to continue in usual care or to be offered one of the two intervention programs. At each site, randomization occurs automatically within the sampling computer program, stratified by eligible PHQ9 response (“more than half the days” or “nearly every day”) and site. A computer-generated concealed allocation table at each site provides randomly generated assignments in block sizes of either six or nine.

Invitation and consent

Participants assigned to the Care Management intervention receive an initial invitation message from the study care manager via the EHR-based online secure messaging system [16, 17]. This invitation includes a brief description of the Care Management program and abbreviated information regarding required elements of informed consent (study purpose, study procedures, potential risks or harms, and right to refuse or withdraw at any time). Each participant can decline participation by replying to the invitation

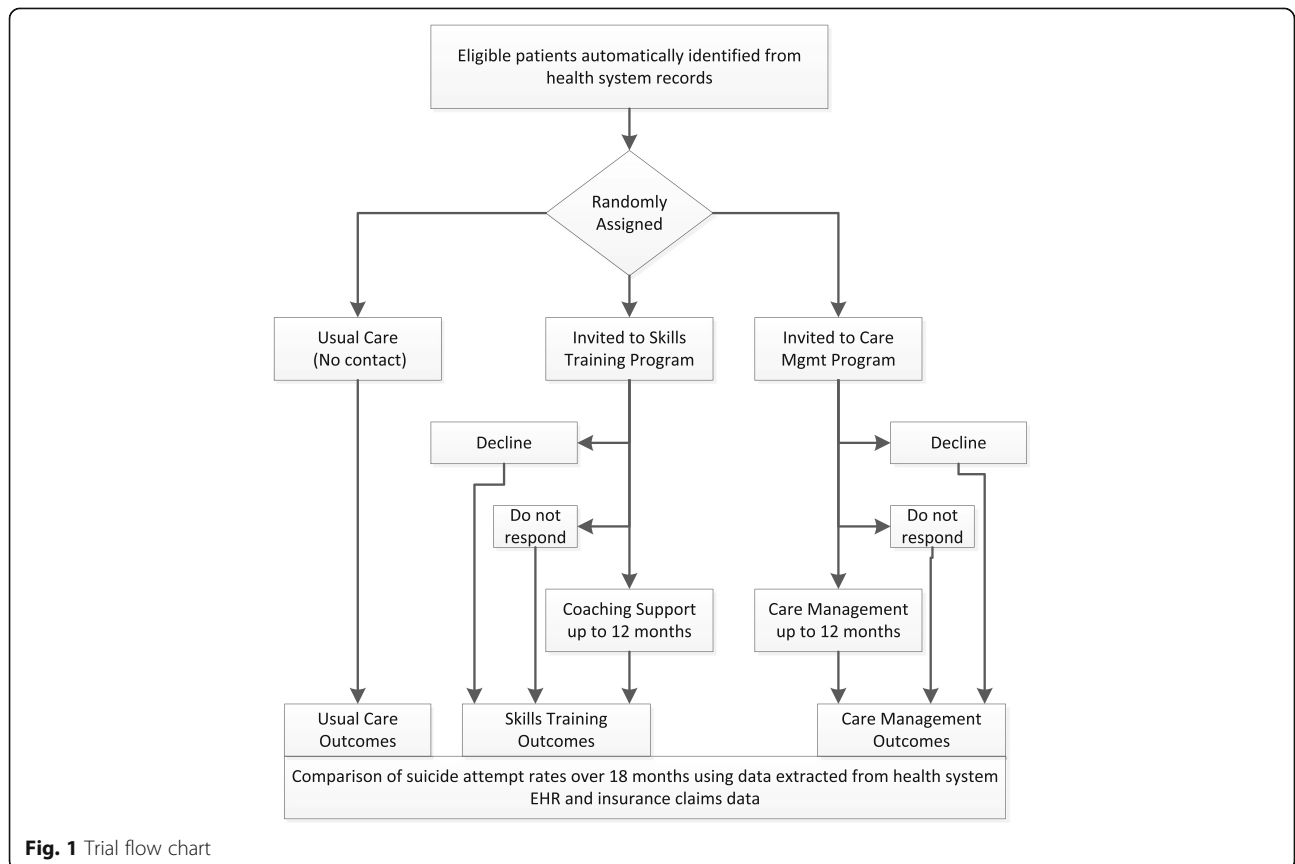


Fig. 1 Trial flow chart

message or can consent to receive intervention services by either replying to the message or returning the attached risk assessment questionnaire. Participants who neither decline nor consent receive a reminder (either by online message or telephone message) after 1 week. Participants who neither decline nor consent after that reminder message receive a second invitation message (with possible reminder) 4 weeks later and may receive a third invitation message after an additional 4 weeks. Those who decline at any point are not contacted again. Those who do not respond after three cycles of invitation are not contacted again.

The invitation and consent process for participants assigned to the Skills Training program parallels that for the Care Management program: an invitation message including abbreviated informed consent information and up to three cycles of invitation and reminder for those not responding. A participant can consent to receive intervention services by replying to an invitation message or by making an initial visit to the online intervention program. Those who decline at any point are not contacted again. Those who do not respond after three cycles of invitation are not contacted again.

Participants assigned to continue in usual care are never contacted by study staff. Providers are not notified regarding participants' assignment to continued usual care.

Care Management intervention

Rationale

Following the design of previous Care Management interventions [17], including the Perfect Depression Care program at Henry Ford Health System [11], this program aims to reduce risk of suicide attempt by monitoring and maintaining engagement in effective mental health treatment.

Assessment tools

In collaboration with developers of the Columbia Suicide Severity Rating Scale [22] (CSSRS), study investigators developed a simplified CSSRS for self-report administration via online secure messaging. This abbreviated CSSRS provides a 6-point ordinal rating of current suicide risk based on frequency and intensity of suicidal thoughts, presence and specificity of suicidal plans, and clarity of suicidal intent during the last week. For example, a score of 0 would indicate no recent thoughts of self-injury or suicide, a score of 3 would indicate suicidal ideation with some recent thoughts about specific means, and a score of 5 would indicate a current and specific suicidal plan.

Follow-up algorithms

In collaboration with health system stakeholders (see below), investigators developed rules for risk-based care pathways specifying appropriate level of care, minimum

standards for follow-up visit intervals and timing of outreach messages. For example: a CSSRS score of 1 would lead to a recommendation for follow-up within 1 month (sooner if clinically appropriate) in either primary care or specialty mental health care, a score of 3 would lead to a recommendation for follow-up in specialty mental health care within 2 weeks, and a score of 5 would lead to a recommendation for specialty mental health follow-up within two business days (or sooner as clinically indicated).

Care manager role

At each site, one or more care managers are responsible for:

- Initial and follow-up invitations to all participants assigned to be offered Care Management
- Periodic outreach to assess current risk (using an online version of the CSSRS)
- Application of follow-up algorithms, supported by informatics tools (see below)
- Regular feedback to treating providers regarding risk assessments and follow-up plans
- As-needed communication with participants and providers to facilitate follow-up care

Care managers communicate with participants primarily by online secure messaging through EHR patient portals, but may communicate by telephone as needed. Care managers are expected to consider individual patients' clinical circumstances and providers' treatment plans when applying algorithms regarding outreach and visit frequency. At all sites, care managers are Master's-prepared mental health clinicians.

Informatics tools

Intervention delivery is supported by existing functions of health system EHRs:

- Online patient-provider secure messaging via the EHR patient portal [16, 17] for invitation and outreach to participants
- Online administration of structured questionnaires such as the CSSRS
- Secure provider-to-provider messaging for care managers' communications with primary care and mental health specialty providers
- Population management and reporting tools to apply follow-up algorithms and deliver algorithm-based recommendations to care managers regarding outreach and follow-up

Engagement with health system stakeholders

During the pilot phase, regular meetings with clinical leaders from all sites (representing both primary care

and mental health specialty care) developed consensus regarding content and workflow of the Care Management program, including:

- Language for outreach messages
- Recommended follow-up intervals
- Criteria for referral from primary care to mental health specialty care
- Processes for communicating with primary care and mental health specialty providers
- Procedures for urgent assessment and referral

Training and supervision

Training of care managers across sites was conducted by videoconference and teleconference, led by clinical investigators from the Group Health site. Initial training included:

- 6 h of clinical training regarding suicide risk assessment
- 2 h of general orientation to project aims and procedures
- 6 h of specific training regarding care management aims, tools, and procedures

Ongoing teleconference supervision for all care managers is led by clinical investigators from the Group Health site. Supervision meetings were scheduled weekly for 6 months and twice monthly thereafter. Consistent with the principles of pragmatic trials [23], no detailed monitoring of intervention fidelity (e.g., review of content of online messaging or phone contacts) is conducted.

Skills Training intervention

Rationale

Following the content and structure of proven Dialectical Behavior Therapy (DBT) treatments [8, 12], this program aimed to reduce risk of suicide attempt through training in specific DBT skills shown to mediate the beneficial effects of traditional in-person DBT [12].

Specific skills content

The online program and coaching support focuses on four specific skills:

- Mindfulness – Introduction to mindfulness skills, emphasizing nonjudgmental observation
- Mindfulness of Current Emotion – Nonjudgmental observation of sensations associated with difficult or painful emotions
- Opposite Action – Acting in opposition to urges associated with painful or difficult emotions
- Paced Breathing – Use of breathing techniques to manage overwhelming emotions or crises

Adaptation for online delivery

The web-based interactive program includes an introductory section, personal profiles of team members (including coaches and contributing peer experts described below), and four skill modules (one for each DBT skill listed above). Each module includes:

- A brief video introduction to the skill concept
- A longer teaching video describing the skill, including in vivo practice
- Example videos of peers (see below) describing use of the skill in daily life
- Interactive exercises for use during the online session
- Customizable worksheets to support between-session practice

Each participant is free to visit skills modules in any order and use the program at any pace, returning as frequently as desired. Coaches send reinforcement and outreach messages (see below) to encourage regular use.

Skills coach role

At each site, one or more skills coaches is responsible for:

- Initial and follow-up invitations to all participants assigned to be offered Skills Training
- For participants visiting the online program, messages to reinforce use of the program and practice of specific skills
- For participants not visiting the program, periodic outreach messages to encourage return visits
- As-needed communication with treating providers regarding participants' progress

Skills coaches communicate with participants primarily by online secure messaging through EHR patient portals, but may communicate by telephone as needed. At all sites, skills coaches are Master's-prepared mental health clinicians.

Informatics tools

The online program is delivered through the DatStat survey platform (DatStat Inc., Seattle, WA, USA). This platform supports secure access, detailed tracking of participant activity, and participant-level reports to guide the timing and content of coaches' reinforcement and reminder messages. Participants access the online program via secure personalized links embedded in messages from skills coaches.

Engagement with patient stakeholders

Peer experts (people with lived experience of suicidal ideation and suicide attempts) were essential collaborators in

the development of the Skills Training intervention and continue to support intervention delivery [24]. Design of outreach messages and content of the online program were informed by anonymous online surveys and focus group interviews with peer experts [24]. People with lived experience contributed video descriptions of the use of DBT skills, and continue to contribute to development of training and support materials for skills coaches.

Training and supervision

Training of skills coaches was conducted by videoconference and teleconference, led by clinical investigators from the Group Health site. Initial training included:

- 6 h of clinical training regarding suicide risk assessment
- 2 h of general orientation to project aims and procedures
- 6 h of specific training regarding skills coaching aims, tools, and procedures

Ongoing teleconference supervision for all skills coaches is led by clinical investigators from the Group Health site. Supervision meetings were scheduled weekly for 6 months and twice monthly thereafter. Consistent with the principles of pragmatic trials [23], no detailed monitoring of intervention fidelity (e.g., review of content of online messaging or phone contacts) is conducted.

Outcome definitions

The primary study outcome is the time to first suicide attempt following randomization. Fatal suicide attempts will be identified by death certificate diagnoses of self-inflicted injury or poisoning. All three study sites routinely link membership files to state vital record data to ascertain cause of death for all enrolled members. Nonfatal suicide attempts will be identified from EHRs (for care delivered by participating health systems) and insurance claim data (for care received outside of participating health systems) using three criteria:

- Any outpatient or inpatient diagnosis of definite self-inflicted injury or poisoning
- Any outpatient or inpatient diagnosis of possible self-inflicted injury or poisoning
- Any outpatient or inpatient diagnosis of other injury or poisoning associated with a diagnosis of suicidal ideation during the same encounter

For these three criteria, review of full-text medical records documented high positive predictive value for self-inflicted injury with suicidal intent [18, 25]. Because this validation work was completed prior to health care systems' transition from the *International Classification*

of Diseases, version 9 (ICD-9) to ICD-10 diagnoses, additional work will be necessary in 2016 to revalidate outcome definitions based on ICD-10 diagnostic codes. Given that participants may seek care for self-injury at external facilities, ascertainment will include both insurance claim and EHR data, and the sample is limited to patients who are enrolled in a health system insurance plan.

Analysis plan

Primary analyses will use the log-rank test to compare risk of diagnosed suicide attempt (defined above) over 18 months following randomization. For each intervention condition, risk among those assigned to the intervention will be compared to risk among those assigned to usual care – regardless of level of participation in either intervention. Individuals will be censored at time of health system disenrollment, death from cause other than suicide, or administratively, at 18 months following randomization. We evaluate the effect of each of the interventions compared to usual care using a log-rank test stratified by site and initial response to PHQ9 item 9 (2 versus 3). Sensitivity analyses will use weighted log-rank tests to account for a possible association between pre-randomization characteristics (ascertained from EHRs) and censoring. In censoring weights, we will include sex, age group (18–29, 30–64, and 65 or more), race/ethnicity (Black American, Asian American, Hispanic, other), and visit type at which the initial PHQ9 questionnaire was completed (primary care versus mental health specialty).

Sample size

Original sample size estimates were based on previous research [5] suggesting an approximately 4 % risk of suicide attempt over 18 months among those meeting study eligibility criteria. Consultation with health system stakeholders indicated that implementation of a systematic outreach program was unlikely unless a program could be expected to reduce that risk to 3 % (relative risk reduction of 25 %). We used PASS software [26] to estimate the sample size required for a log-rank test [27] with 90 % power to compare the survival curves assuming a 3.8 % risk over 18 months in the comparison group and a 25 % risk reduction in the intervention group. We assumed 2 % disenrollment rate each month, resulting in approximately 25 % censorship over the 18 months of follow-up. The primary comparison for this trial is each of the interventions compared to usual care; we use a Bonferroni correction to account for the two tests in our primary analysis. Assuming a two-sided log-rank test, with a type-1 error rate of 0.025 and 90 %, we plan on enrolling 6500 patients per arm (total $n = 19,500$).

Enrollment progress

The trial was funded through the NIH Health Care Systems Collaboratory as one of the initial Pragmatic Clinical Trials Demonstration Projects [28]. Following a pilot phase to validate outcome definitions and to demonstrate the feasibility and acceptability of the intervention programs, participant enrollment and randomization began at the Group Health site in March 2015, expanding to three sites in July 2015. Approximately 4000 participants have been enrolled and randomized as of 1 July 2016. Approximately 100 participants are enrolled and randomized each week, and that rate is expected to increase to approximately 150 in the fall of 2016.

Ethical and regulatory approval

Study design and procedures were reviewed and approved by Institutional Review Boards at all three health systems. That review process addressed several issues common to pragmatic trials of prevention interventions.

Waiver of informed consent

Limiting a randomized trial of outreach to those who actively consent to receive outreach would yield a result of questionable validity and generalizability. Consequently, a modified Zelen design [13–15], randomizing all eligible patients without first obtaining consent, is necessary for valid test of the study question. This design, however, requires a waiver of the usual requirement for informed consent prior to enrollment or randomization. While it is not practicable to obtain informed consent prior to randomization, it is practicable to provide appropriate information to participants at the time intervention services are offered. As described above, invitation messages to participants assigned to either intervention include a brief description of the study purpose, study procedures, potential risks, and the right to decline participation. This design, therefore, includes a waiver of consent for enrollment/randomization and a modified consent procedure for receipt of intervention services.

Defining minimal risk

Current regulations regarding protection of human research participants allow waiver of consent for research involving no more than minimal risk. Our proposal to waive the requirement for informed consent in patients who are at risk of suicide attempt led to extensive discussions with health system Institutional Review Boards, leadership of the NIH Healthcare Systems Research Collaboratory, and the federal Office for Human Research Protections [29]. Those discussions helped to clarify four issues:

- Research risk versus preexisting risk – Given that the trial enrolls patients who are at risk of suicide attempt, we encountered concern that study procedures could not be classified as having minimal

risk. To address this concern, we relied on regulatory guidance distinguishing between preexisting risk due to a research participant's health state (i.e., increased risk of suicide attempt) and incremental risk created by study procedures. This distinction led to the appreciation of this trial as evaluating minimal-risk interventions in a high-risk population

- Risk of assignment to continued usual care – We also encountered concern regarding the ethical acceptability of randomly assigning patients who are at risk of suicide attempt to a usual care control condition. We clarified that a participant assigned to usual care will, by definition, receive the same treatment that she or he would have received if the study were not occurring
- Risk of assignment to offer of intervention programs – We also encountered concern that assignment to either intervention group might increase risk. Both intervention programs are based on effective interventions and are intended to reduce risk of suicide attempt. Participants are free to receive any other services that are normally available. Nevertheless, it is possible that some participants will experience negative effects from either program. We addressed this concern by clarifying that participants are assigned to the offer of an intervention, with no obligation to participate. Invitation messages clearly identify intervention programs as research activities, make no promise of benefit, and advise that participation is completely voluntary
- Intrusiveness or invasion of privacy – Different stakeholders expressed concern regarding both inappropriate intrusiveness of repeated outreach and inadequate vigor of outreach given the known increased risk of suicide attempt. In consultation with peer experts, we designed the outreach strategy described above, including up to three cycles of invitation, as a reasonable compromise between these two concerns.

At all participating health systems, notices regarding privacy practices specifically advise members regarding the use of health records for research. Members who have previously requested exclusion from research contact are excluded from the study sample.

Monitoring for adverse events

In most clinical trials of mental health treatments, a suicide attempt would be considered a serious adverse event, subject to immediate reporting and review to determine the “relatedness” of an individual suicide attempt to study participation. This traditional approach was clearly not appropriate for a large-scale trial of population-based prevention programs [30]. First, record data regarding suicide attempts may not be available for 3 months or more following an

event. Second, several hundred suicide attempts are expected to occur among study participants, and review of individual events could not determine causal relationship to study participation. While it is possible that either intervention could paradoxically increase risk of suicide attempt, that could only be determined by comparison to suicide attempt rates in usual care (see below).

Interim analyses of benefit or harm

We do not plan any interim analyses to evaluate benefit of the intervention programs. First, early detection of a benefit of either intervention is extremely unlikely. We project that randomization will be complete before complete outcome data are available for half of the participants. Second, early termination of randomization or intervention delivery would not offer any additional protection to current or future study participants. Premature termination would instead return all current and potential participants to care as usual.

We do, however, plan interim analyses testing for evidence of significant harm (increased risk of suicide attempt) in either intervention group compared to usual care. Clear evidence that either intervention resulted in

significantly increased risk of suicide attempt would certainly warrant suspending assignment of patients to that program or suspending delivery of that program to participants already assigned. Interim analyses comparing risk of suicide attempt in each intervention group to that in usual care will be conducted three times per year, beginning 12 months after start of enrollment. Interim analyses will be reported to the National Institute of Mental Health Data and Safety Monitoring Board by the study statistician, but all other study staff will be blinded to these results.

Data and resource sharing

A deidentified version of the analytic dataset will be made available at the time of the initial publication of primary study findings. Consistent with policies of the NIH Collaboratory, all resources (intervention materials, specifications, computer code, etc.) will be shared at or before the publication of study results.

Discussion

This suicide prevention outreach trial addresses a practical question that is relevant to practicing clinicians or

Table 1 PRECIS domains defining pragmatic trials

	PRECIS criteria for pragmatic trials	Design of suicide prevention outreach trial
Participants	All eligible participants enrolled, regardless of risk, responsiveness, comorbidities or past compliance	Adult health plan members reporting frequent suicidal ideation on routine depression questionnaires are automatically enrolled
Intervention condition	Interventions are highly flexible, offering providers leeway in formulation and application	Both interventions allow personalization to patients' needs and preferences. Varying levels of participation are expected
Intervention practitioners	Interventions are applied by the full range of practitioners in the full range of settings with only ordinary attention to dose and side effects	Intervention clinicians will be recruited from existing local workforces. Each site will be responsible for selection and supervision of clinicians (using standard quality control tools)
Comparison condition	"Usual practice" (or the best alternative), offering practitioners considerable leeway in application	Each prevention program will be compared to usual care
Comparison practitioners	The control intervention is applied by the full range of clinicians in the full range of settings, with only ordinary attention to training, experience, and performance	Usual care will be provided by real-world providers (mental health and general medical clinicians) under usual practice conditions – with no additional training or supervision
Follow-up assessments	There are no research assessments; administrative databases are searched for outcomes	All outcome data are collected from EHR, insurance claim data, and death certificate data
Outcome definition	The primary outcome is objectively measured, meaningful to study participants, and does not depend on central adjudication	Primary and secondary outcomes are defined by specific ICD-9/ICD-10 diagnosis codes – no clinical assessment is required
Intervention compliance	There are no special strategies to improve compliance, and compliance is unobtrusively measured	Patients assigned to interventions are free to participate (or not participate) at any level. Participation or compliance is assessed passively using EHRs and online intervention databases
Practitioner adherence	There are no special strategies to maintain practitioner adherence, and adherence is unobtrusively measured	Care managers and skills coaches work independently at each site, but receive initial training and regular supervision from study investigators
Primary comparison	The analysis includes all patients regardless of compliance, eligibility, or others	All outcomes will be analyzed according to initial assignment – regardless of intervention participation or compliance

EHR electronic health record, ICD International Classification of Diseases

health system leaders: Will population-based outreach programs reduce risk of suicide attempt among patients identified as being at risk by routinely administered depression questionnaires? This focus on a practical or pragmatic question has several implications for trial design. Table 1 describes how specific aspects of this trial conform to the characteristics of pragmatic trials described by Thorpe [31]. Central pragmatic trial features include:

- Population-based enrollment – If we hope to inform policy or implementation decisions by health system leaders, then it is necessary to evaluate program effectiveness in the full population of those to whom the program would eventually be offered
- Allowing variable participation or compliance – Restricting enrollment to those willing to participate in outreach or prevention programs would not allow a valid assessment of program effectiveness. Low participation or high rates of dropout should be considered essential indicators of effectiveness rather than threats to internal validity
- Analysis by intent-to-treat – A valid evaluation of prevention program effectiveness must examine risk among all those offered the prevention service, rather than those who accept or participate. Any “as treated” or “completers” analysis (limited to those who participate in prevention services) would certainly be biased

Our trial differs from a purely pragmatic design in one aspect: the training and supervision of clinical staff delivering the prevention interventions. All care managers and skills coaches complete approximately 14 h of initial training followed by weekly or bi-weekly supervision teleconferences. This training and supervision was necessary because both of these clinical roles required implementation of new clinical work processes and the use of new informatics tools. If either program is proven effective, we would recommend that any subsequent implementation include a similar level of training as well as a period of regular supervision.

Assessing the effectiveness of any population-based prevention program requires a clinical trial following the core principles of pragmatic trials: population-based enrollment, accepting variable treatment participation, assessing outcomes using health record data, and analyses based on intent-to-treat. We describe the design and implementation of such a trial, now underway in three large integrated health systems.

Trial status

Enrollment is ongoing and is expected to be complete in early 2018.

Abbreviations

CSSRS: Columbia Suicide Severity Rating Scale; DBT: Dialectical Behavior Therapy; EHR: Electronic health record; PHQ9: Patient Health Questionnaire depression scale

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Availability of supporting data

Outcome data will not be available until 12 months following completion of recruitment. A deidentified analytic dataset will be made available for public use following publication of the main results.

Authors' contributions

GS led the design of the trial and pilot testing of interventions and had primary responsibility for drafting of this manuscript. AB participated in trial design and led testing and implementation of trial procedures at the Colorado site. RR participated in trial design and led testing and implementation of trial procedures at the Minnesota site. JR organized the implementation of the Care Management intervention. BK organized the implementation of the Skills Training intervention. DK led pilot-testing and co-led training and supervision for the Care Management intervention. LS co-led training and supervision for the Skills Training intervention. EL co-led training and supervision for the Skills Training and Care Management interventions. RP participated in trial design and the development of informatics specification and tools. SS participate in trial design and led the development of sample size estimation and analysis plans. UW led the development and pilot testing of the Skills Training intervention. All authors participated in critical revision of this manuscript for intellectual content. All authors read and approved the final manuscript.

Additional authors' information

None.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All study procedures were reviewed and approved by the Institutional Review Boards at Group Health Cooperative, HealthPartners, and Kaiser Permanente of Colorado. All three boards approved a waiver of consent for research use of health records, a waiver of consent for randomization of all eligible participants to usual care or intervention conditions, and an abbreviated consent procedure for receipt of intervention programs.

Author details

¹Group Health Research Institute, 1730 Minor Ave. #1600, Seattle, WA 98101, USA. ²Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA. ³HealthPartners Institute, Minneapolis, MN, USA.

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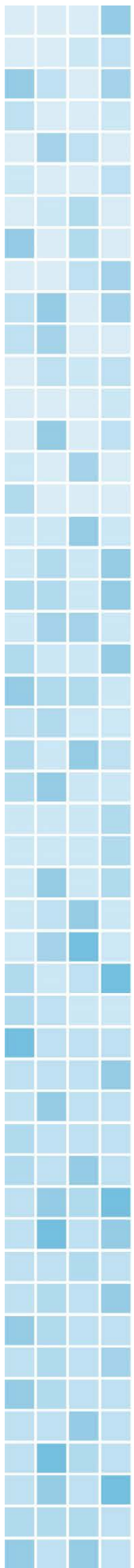


Collaboratory ePCT Training Workshop

Topic 5

Ethical and Regulatory Challenges of ePCTs

Learning objective	Learn about the regulatory and ethical considerations specific to ePCTs
Instructor	Kevin Weinfurt
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN: Consent, Disclosure, and Non-disclosure• DESIGN: Data & Safety Monitoring• Regulatory/Ethics Core• Collaboratory Demonstration Projects: Ethics and Regulatory Documentation <p>PCT 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">• <u><i>Clinical Trials</i> special issue on ethical and regulatory issues in pragmatic clinical trials (October 2015)</u>• <u>Sugarman et al., 2014. Ethics and regulatory complexities for pragmatic clinical trials</u>• <u>Weinfurt et al., 2017. Comparison of approaches for notification and authorization in pragmatic clinical research evaluating commonly used medical practices</u>• <u>Topazian et al., 2016. Physicians' perspectives regarding pragmatic clinical trials</u>• <u>Sugarman, 2016. Ethics of research in usual care settings: data on point</u>• <u>Weinfurt et al., 2015. Patients' views regarding research on medical practices: implications for consent</u>• <u>Mentz et al., 2016. Good clinical practice guidelines and pragmatic clinical trials: balancing the best of both worlds</u>
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Topic 5: Regulatory and Ethical Challenges of ePCTs

Kevin Weinfurt, PhD
Duke Clinical Research Institute

Collaboratory ePCT Training Workshop

Overview

- 1** Introduction
- 2** Whose rights/welfare need to be protected?
- 3** What are different approaches for notification and authorization?
- 4** Working with human subjects oversight bodies
- 5** A plea

1

Introduction

ePCTs are motivated by ethical imperatives



ePCTs also raise interesting ethical and regulatory questions

VOLUME 12, NUMBER 5, OCTOBER 2015 ISSN 1740-7745

CLINICAL TRIALS

Journal of the Society for Clinical Trials

EXPLORING THE ETHICAL AND REGULATORY ISSUES IN PRAGMATIC CLINICAL TRIALS
LEADING A SERIES OF 12 ARTICLES ON DIFFERENT ASPECTS OF THIS TOPIC

COLUMNS

Clinical Trialist Roundtable: When RCT Participants are Lost to Follow-Up, Part I: Why Even a Few Can Matter
Harris, P. Haines and D. Lurie

TRIBUTE

An Interview with David Sakzewski
By Haines and P. Haines

Evolving understanding of unique ethical/regulatory issues for ePCTs

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

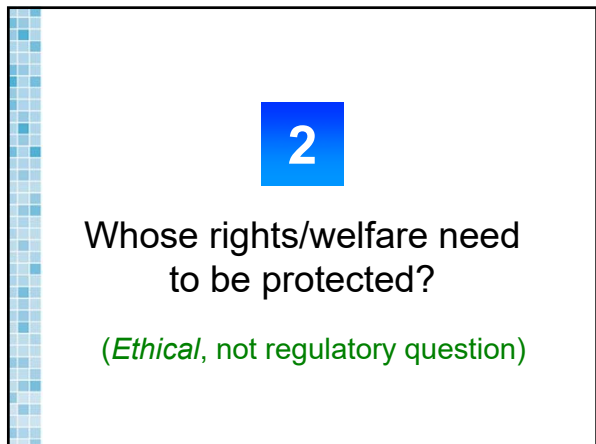


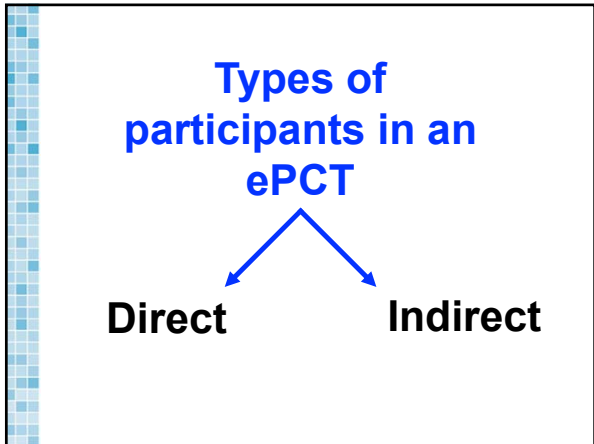


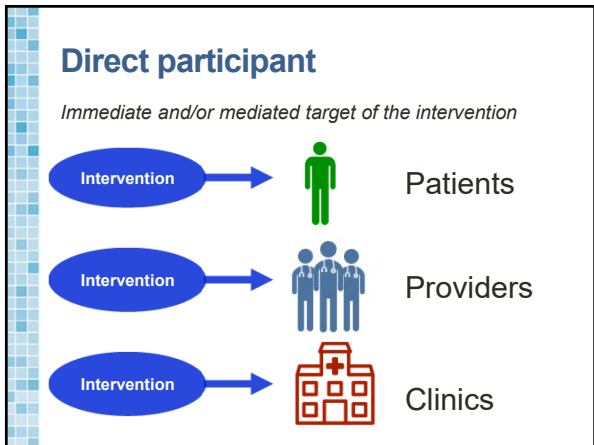


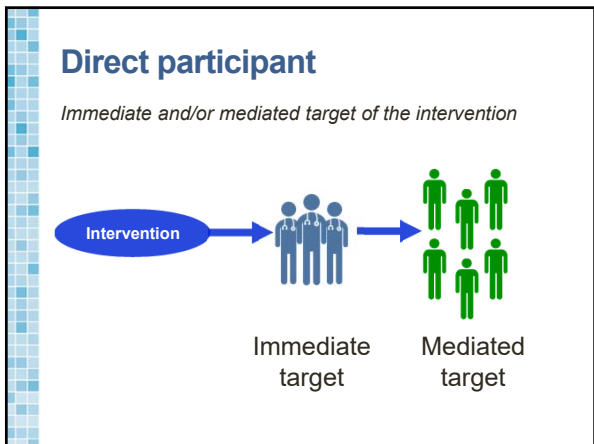






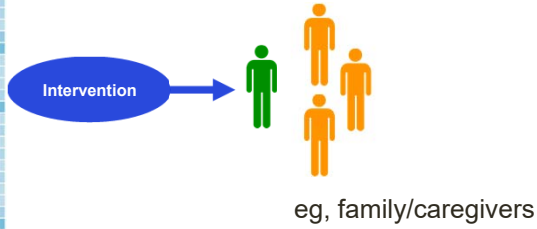




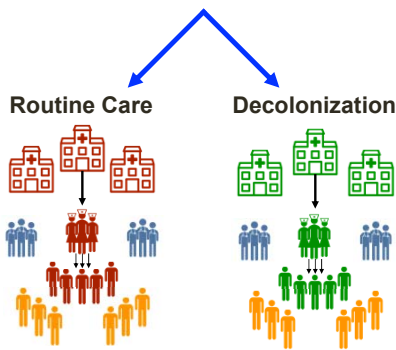


Indirect participant

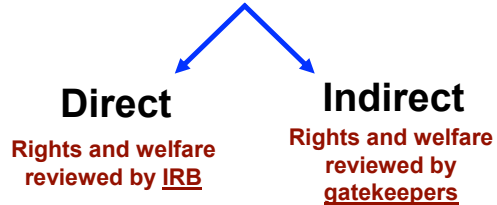
PCTs may affect people by way of routine exposure to the environment



Example: Active Bathing to Eliminate Infection (ABATE) trial





Types of participants in an ePCT



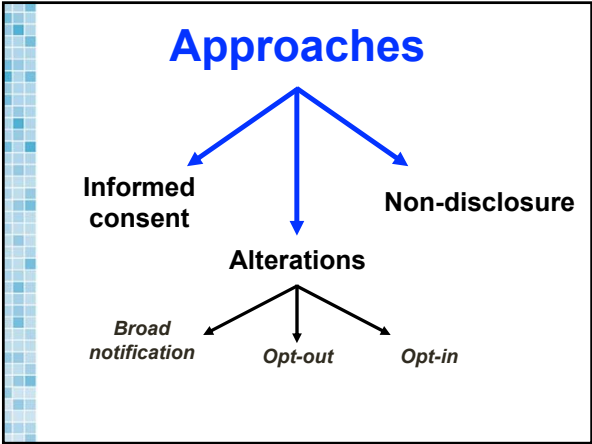
Who are the direct and indirect participants for your study?
What are the potential risks and benefits for each?

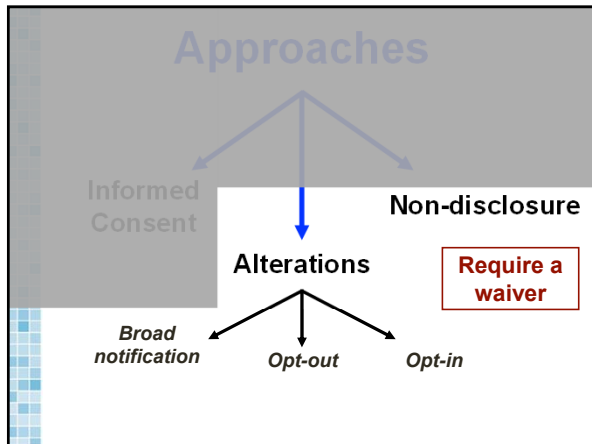
1 min **4 min**



3

What are different approaches for notification and authorization?





Conditions for waiver of consent

An IRB may waive or alter the requirements of informed consent if all of the below are deemed true:

- “The research involves no more than **minimal risk** to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not **practicably** be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.” [§46.116](#)

Minimal risk

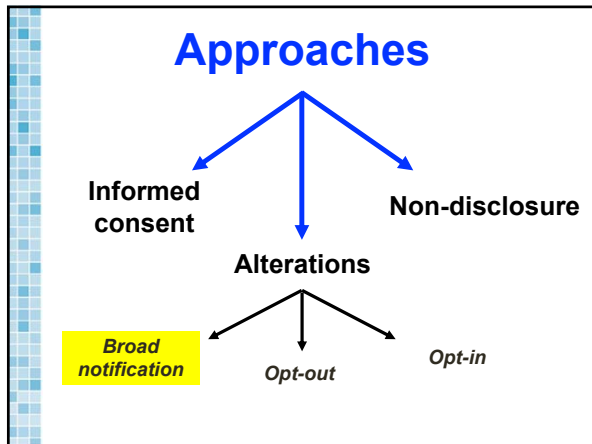
“In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).”

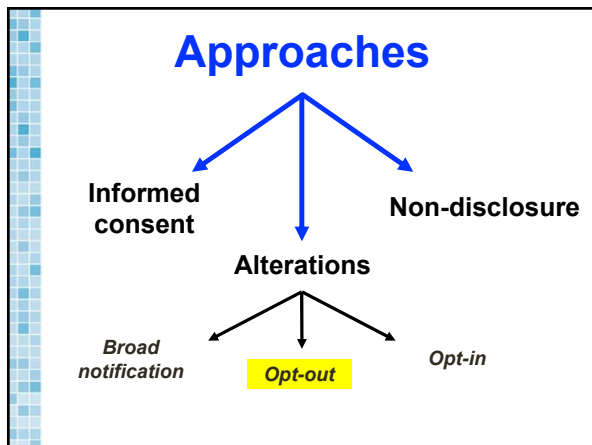
Common Rule: CFR 46.111 (a)(2)

“The reasonably foreseeable risks of research include already identified risks of the standards of care being evaluated as a purpose of the research.”

From the OHRP Draft Guidance

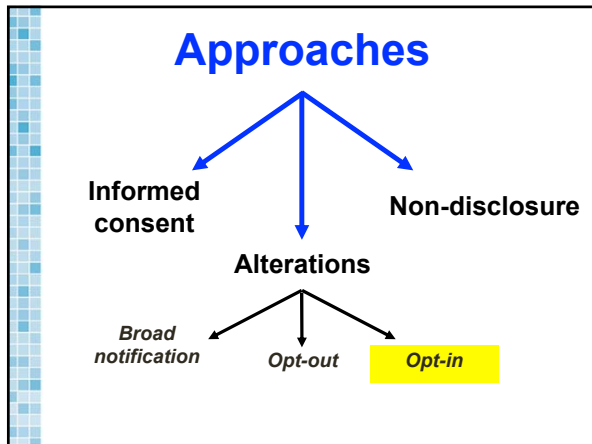
Some debate here!!!

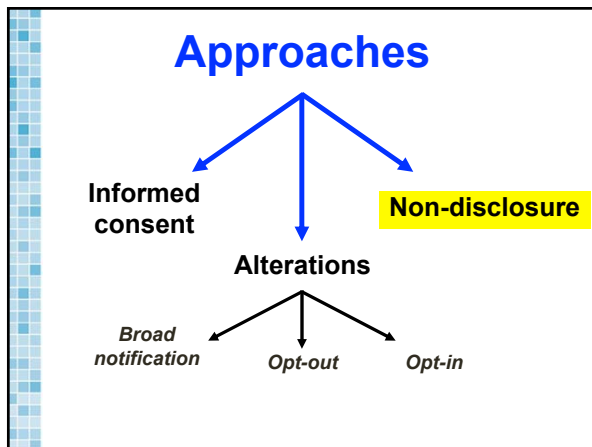




TiME consent process

- Time to Reduce Mortality in End-stage renal (TiME) disease hypotheses: Facility implementation of ≥4.25-hour dialysis session duration improves outcomes compared with usual care
- Patients starting dialysis at participating facilities are given a brief information document with:
 - Purpose of the trial
 - How session duration will be affected by the trial
 - Toll-free telephone number to obtain additional information from the research team and to **opt-out of participation**
- Informational posters in participating dialysis facilities throughout the duration of the trial

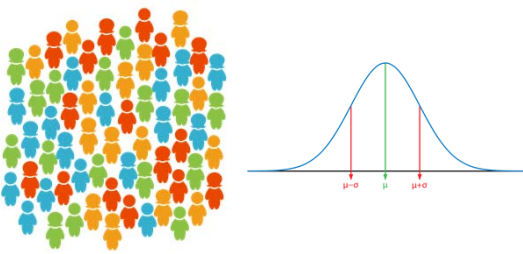




LIRE trial

- Tests whether inserting epidemiological evidence in lumbar spine imaging reports will reduce subsequent diagnostic and therapeutic interventions
- Waiver of consent was granted
 - Risk of contacting subjects deemed greater than the risk of study procedures
 - By informing primary care providers and patients, they risk invalidating the results

What do data suggest about different approaches?



ORIGINAL ARTICLE

Comparison of Approaches for Notification and Authorization in Pragmatic Clinical Research Evaluating Commonly Used Medical Practices

Kevin P. Weinfurt, PhD*† Juli M. Bollinger, MS‡ Kathleen M. Brelsford, MA, MPH, PhD*
Martina Bresciani, BA* Zachary Lampron, MPH* Li Lin, MS* Rachel J. Topazian, BA,‡
and Jeremy Sugarman, MA, MPH, MD§¶

Background: For pragmatic clinical research comparing commonly used treatments, questions exist about if and how to notify participants about it and secure their authorization for participation.

Objective: To determine how patients react when they seek clinical care and encounter one of several different pragmatic clinical research studies.

Research Design: In an online survey using a between-subjects experimental design, respondents read and responded to 1 of 24 hypothetical research scenarios reflecting different types of studies and approaches to notification and authorization (eg, general notification, oral consent, written consent).

Subjects: English-speaking US adults 18 years and older.

Most respondents (77%-94%) felt that participation in the hypothetical study posed no risks of harm to their health or privacy.

Conclusions: Current attitudes about notification and authorization approaches and difficulties understanding pragmatic clinical research pose significant challenges for pragmatic research. Data from this study provide a starting point to developing solutions to these surprisingly complex issues.

Key Words: comparative effectiveness research, ethics, informed consent
(Med Care 2017;00: 000-000)

▮ Substantial efforts are now being directed at improving the

Approaches to Notification & Authorization

- Written consent (with clinical risks included)
- Written consent
- Oral consent + info sheet
- Oral consent
- General notification (with opt-out)
- Post-notification after study done

1 Difficulty understanding aspects of pragmatic trials of accepted medical practices

2

3

4

5

P3-514-529

SCENARIO 29

You go to the local clinic for a routine checkup. There is a sign on the waiting room wall describing a research study in which the clinic is participating.

- Our clinic, along with other clinics around the country, is taking part in a research study. Researchers want to find out the best method for taking blood for routine tests. Clinics typically collect blood using one of two different types of needles. Researchers want to know if one type of needle is better than the other in terms of the number of attempts (times patients need to be stuck with a needle) needed to get enough blood.
- As part of the study, different clinics have been randomly selected to use one type of needle or the other. This means that some clinics were selected to use the first type of needle, and all the doctors and nurses there are using that type, while other clinics were selected to use the second type of needle, so all the doctors and nurses there are using that type.
- Later on, to see if one type works better than the other, researchers will look at specific parts of patients' medical records to see how many attempts were needed to get enough blood. *To draw enough blood*
- Researchers have to follow the same rules that are already in place to protect health information and keep it secure. *and*
- There will be ~~no extra~~ follow-up calls or visits that patients need to do related to the study.
- If you have any questions, please contact Dr. Smith at 123-4567.

which type works better

will they be same

“There will be no extra follow-up calls or visits that patients need to do related to the study.”

Our clinic, along with other clinics around the country, is taking part in a research study. Researchers want to find out the best method for taking blood for routine tests. Clinics typically collect blood using one of two different types of needles. Researchers want to know if one type of needle is better than the other in terms of the number of attempts (times patients need to be stuck with a needle) needed to get enough blood.

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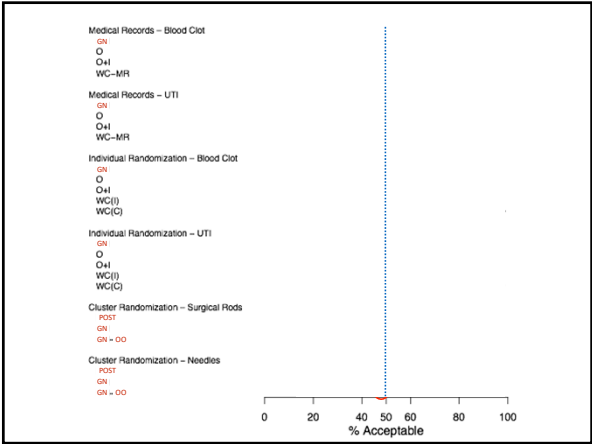
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There will be ~~no extra~~ follow-up calls or visits that patients need to do related to the study. If you have any questions, please contact Dr. Smith at 123-4567.

Experimental
~~Therapeutic~~ Misconception ?

- 1 Difficulty understanding aspects of pragmatic trials of accepted medical practices
- 2 Nontrivial consent bias, but it's the same for all approaches for N&A
- 3 Less active approaches to N&A viewed as unacceptable for some types of pragmatic research
- 4
- 5



- 1** Difficulty understanding aspects of pragmatic trials of accepted medical practices
- 2** Nontrivial consent bias, but it's the same for all approaches for N&A
- 3** Less active approaches to N&A viewed as unacceptable for some types of pragmatic research
- 4** Including descriptions of background clinical risks increased length of form, but did not change any outcome
- 5**

WHAT ARE THE RISKS OF THE STUDY?

In this study, researchers must follow laws to protect health information and keep it secure. However, there is a very small chance that information about you might become known to people outside of the study.

Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of City Medical Center.

- 1** Difficulty understanding aspects of pragmatic trials of accepted medical practices
- 2** Nontrivial consent bias, but it's the same for all approaches for N&A
- 3** Less active approaches to N&A viewed as unacceptable for some types of pragmatic research
- 4** Including descriptions of background clinical risks increased length of form, but did not change any outcome
- 5** Active alternatives to written consent—such as oral consent—may not be expected to compromise consent quality

4

Working with human subjects oversight bodies: *IRBs and Data Safety and Monitoring Committees*

Major Issues

Single IRB review

Lack of experience reviewing/monitoring ePCTs

Single IRB review

- NIH policy on sIRB review, effective January 25, 2018
- Revised Common Rule requires U.S.-based institutions engaged in cooperative research to use a single IRB for regulatory review
- The sites involved in research that uses a single IRB need to
 - Sign a reliance agreement, which outlines who is responsible for what (usually for each protocol)
 - Develop systems for fulfilling institutional responsibilities
 - Develop mechanisms for reporting relevant institutional information to reviewing IRB

TSOS “single” IRB experience

- University of Washington IRB does not have capacity for “centralization”
- Western IRB (WIRB) serves as the centralized IRB
- No single administrative contact
- Only 4 sites “cede” to centralized WIRB review
- 20 individual site IRB submissions (out of 24 sites)

Major Issues

Single IRB review

Lack of experience reviewing/monitoring ePCTs



Budget sufficient time for initial and continuing education/negotiation

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



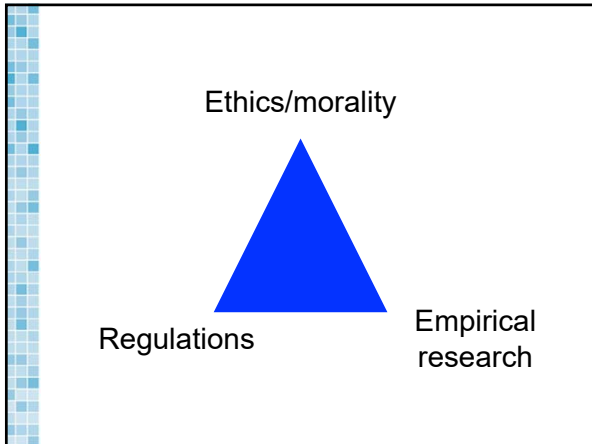
Unique considerations for monitoring ePCTs

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

Adapted from Greg Simon, MD, Collaboratory Grand Rounds, December 8, 2017

5

A plea



Collect data to contribute to the learning!

- Describe current practices and beliefs
- Test assumptions of an ethical argument
- Measure potential impact of different regulatory policies

Important things to know

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



Important things to do

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

Collaboratory ePCT Training Workshop

Topic 6

Measuring Outcomes

Learning objective	Describe methods for measuring outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
Instructors	Rachel Richesson, Lesley Curtis
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN: Choosing and Specifying Endpoints• DESIGN: Using Electronic Health Record Data• Assessing Data Quality for Healthcare Systems Data Used in Clinical Research• Electronic Health Records Core• Patient-Reported Outcomes Core <p>PCT Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none">• 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

Topic 6: Measuring Outcomes

Rachel Richesson, PhD
Duke University School of Nursing
Lesley Curtis, PhD
Duke Clinical Research Institute

Collaboratory ePCT Training Workshop

Outline

- Definitions
- The electronic data puzzle
- Caveats for EHR data in research
- Possible sources of error
- Data quality assessment recommendations
- Clinical phenotypes
- Reporting guidelines for PCTs
- Patient-reported outcomes
- Conclusions & recommendations

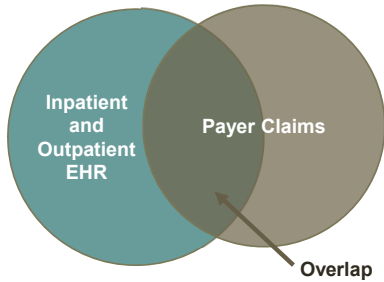
Outcomes vs endpoints



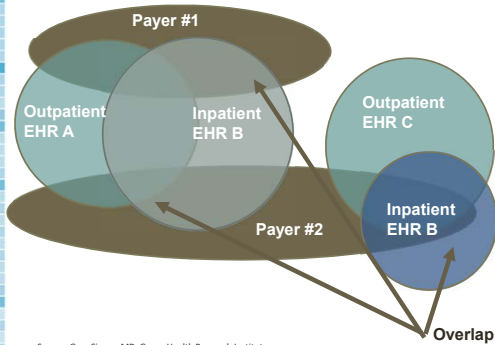
- Direct
- Surrogate
- Composite

Where is the signal?

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



Reality is not straightforward



Source: Greg Simon, MD, Group Health Research Institute

Data sources for endpoints in PCTs

"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
(See Figure 1)

Griffin M. Weber, MD; Kenneth D. Mandl, MD, MPH; Isaac S. Kohane, MD, PhD

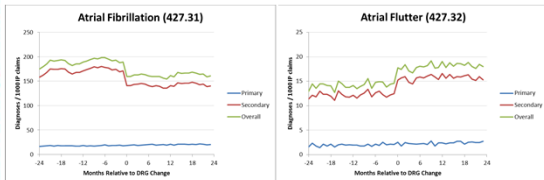
JAMA. 2014;311(24):2479-2480. doi:10.1001/jama.2014.4228

Data sources for endpoints in ePCTs

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

Caveats when using EHR data for endpoints (selected)

- Data may be transformed/coded for purposes other than research & clinical care



Brad Hammill, unpublished

Caveats when using EHR data for research (selected)

- Data captured in clinical notes may not be available
- EHRs are often highly customized
- EHRs may present multiple sources of similar data

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

Caveats when using EHR data for research (selected)

“EHRs may present multiple sources of data that affect data provenance.”

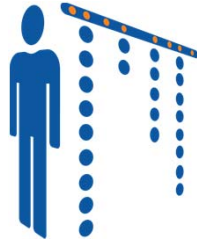
Caveats for the Use of Operational Electronic Health Record Data in Comparative Effectiveness Research (See Figure 1)

William R. Hersh, MD, Mark G. Weiner, MD, Peter J. Embi, MD, MS, Judith R. Logan, MD, MS, Philip R.O. Payne, PhD, Elmer V. Bernstam, MD, MSE, Harold P. Lehmann, MD, PhD, George Hripcsak, MD, MS, Timothy H.artzog, MD, James J. Cimino, MD, and Joel H. Saltz, MD, PhD

Med Care. 2013 Aug; 51(8 0 3): S30–S37
doi: 10.1097/MLR.0b013e31829b1dbd

Caveats when using EHR data for research (selected)

- EHRs often do not tell a complete story

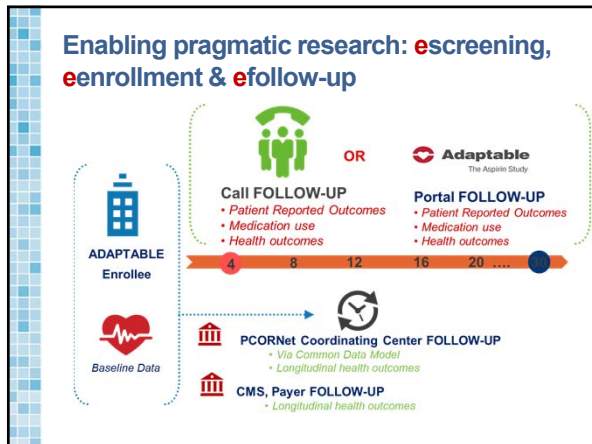


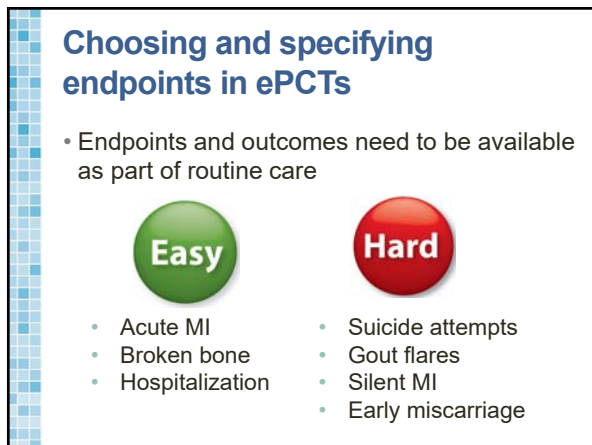
Source: Hersh WR et al. Med Care 2013;51:S30-S37.

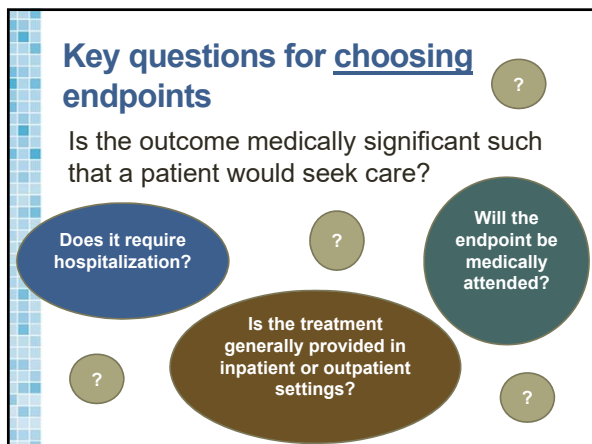
Longitudinal data linkage

- 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









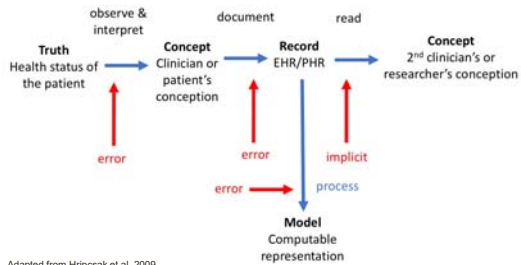
Endpoints in ePCTs

- Endpoints should be meaningful to providers and patients
 - MACE vs myocardial infarction
 - Good example of a blood test vs a clinical event
- 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!

Data is a surrogate for clinical phenomena

Error Impact on Trials



Key questions for using EHR data

What is the phenomenon you are trying to identify or measure?

What are the sources of error?

How can you assess and reduce that error?

In what type of health care activity, event, documentation or data value could a "signal" be detected?

Data quality assessment

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

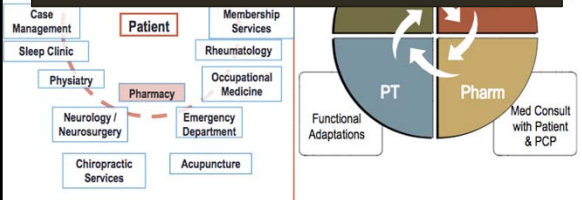


Case example: Collaborative Care for Chronic Pain in Primary Care (PPACT)

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

Outcomes measured via direct patient report

- Patient-reported outcomes (PROs) often best way to measure quality-of-life
- Challenges
 - Not routinely & consistently used in clinical care
 - Not regularly recorded in EHR
- Need mechanism to collect PROs


Mobile devices


- Smartphones, tablet computers, and portable, implantable, or wearable medical devices (mHealth)
 - Some mHealth devices transmit data to a data warehouse every night
 - Largely considered imperfect measures
- Patient-facing mobile phone apps can be used in PCT for passive or active surveillance



Administration
AHRQ Challenge to Focus on PROs in EHRs

According to a [Federal Register notice](#) on December 26, 2017, AHRQ is going to develop user-friendly technical tools to collect and integrate patient-reported outcome data in electronic health records or other health information technology products. AHRQ says that "The limited inclusion of PRO data in electronic health records (EHRs) and other health information technology (IT) solutions reduces the understanding and use of the patient's perspective in research and clinical care... Moreover, standards do not exist for collecting and integrating PRO data into health IT systems, thereby limiting the ability to easily share these data across health systems for research or other purposes including quality improvement." Mark your calendars, as AHRQ has targeted the Fall of 2018 for these challenges.




Perspective 

Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory


Rachel L Richesson,^{1,2} Beverly B Green,³ Reesa Laws,⁴ Jon Puro,⁵ Michael G Kahn,⁶ Alan Bauck,⁴ Michelle Smerok,⁷ Erik G Van Eaton,⁸ Meredith Zozus,⁹ W Ed Hammond,⁷ Kari A Stephens,¹⁰ and Greg E Simon³

- Competition for IT resources
- Need to optimize clinical data for research
- Only small proportion of research in EHRs
- Need to capture intervention or control activities
- Including standard of care
- Need to enable learning & research activities into EHR functions

<https://academic.oup.com/jamia/article/24/5/996/3069877/Pragmatic-trial-informatics-a-perspective-from-the>

 **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
- Good practices for using clinical data in PCTs are based upon scientific principles

 **Very important ...**

- The data available from the EHR may be convenient & 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” (Topic 3)



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

1. *What is your primary endpoint?*
2. *Is that endpoint sufficiently informative for your stakeholders?*
3. *What challenges do you anticipate in trying to ascertain that endpoint?*
4. *How might you address those challenges?*

2 min



5 min



Assessing Data Quality of Clinical Data for PCTs

Background

The credibility and reproducibility of pragmatic clinical research depends on the investigator’s demonstration that the data are of sufficient quality to support the research conclusions. This document highlights recommendations for assessing the quality of data generated from routine patient care for use in PCTs. The [full version](#) of this white paper, along with a full list of references, and other guidelines are available on [Rethinking Clinical Trials®: A Living Textbook of Pragmatic Clinical Trials](#).

Dimensions of Data Quality Assessment

Accuracy, completeness, and consistency closely affect the capacity of data to support research conclusions (Table 1).

Table 1. Data Quality Dimensions Determining Fitness for Use of Research Data

Dimension	Conceptual definition	Operational examples
Completeness	Presence of the necessary data	Presence of necessary data elements, percent of missing values for a data element, percent of records with sufficient data to calculate a required variable (e.g., an outcome)
Accuracy	Closeness of agreement between a data value and the true value*	Percent of data values found to be in error based on a gold standard, percent of physically implausible values, percent of data values that do not conform to range expectations
Consistency	Relevant uniformity in data across clinical investigation sites, facilities, departments, units within a facility, providers, or other assessors	Comparable proportions of relevant diagnoses across sites, comparable proportions of documented order fulfillment (e.g., returned procedure report for ordered diagnostic tests)

*Consistent with the International Organization for Standardization (ISO) 8000 Part 2 definition of accuracy, replaced “property value” in the ISO 8000 definition with “data value” for consistency with the language used in clinical research.

Data Quality Assessment Recommendations for PCTs

1 - Key data quality dimensions

We recommend that accuracy, completeness, and consistency be formally assessed for data elements used in subject identification, outcome measures, and important covariates

2 - Description of formal of assessments for completeness, accuracy, consistency, and impact

See full paper for details and options. See below for different approaches to assess accuracy.

3 – Reporting data quality assessment with research results

Results of data quality assessments should be reported with research results. Data quality assessments are the only way to demonstrate that data quality is sufficient to support the research conclusions, and as such should be accessible to consumers of research.

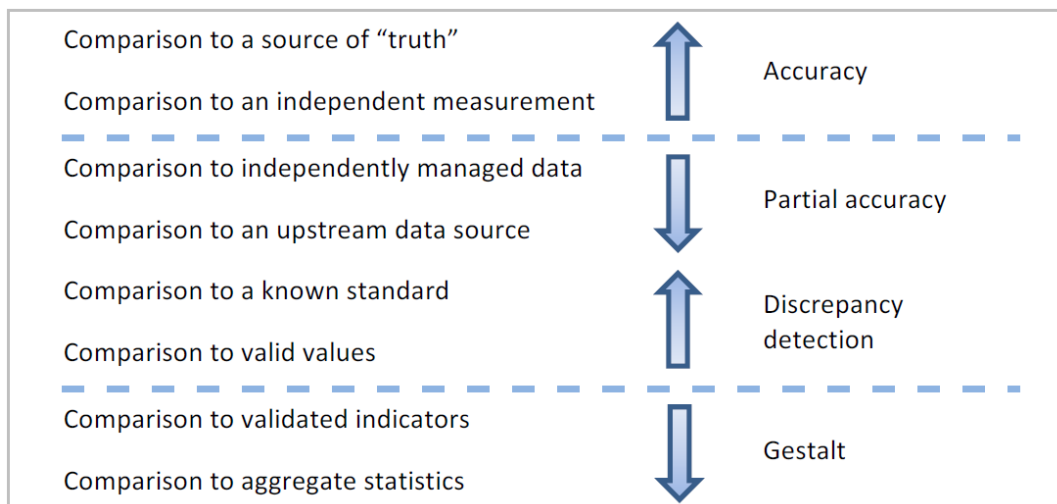
Use of workflow and data flow diagrams to inform data quality assessment

We encourage the creation and use of data flow and workflow diagrams to aid in identifying accuracy and in conducting consistency assessments. If that is not practical, the following questions could be reviewed with personnel at each research site.

1. Talk through each of the data elements used for cohort identification. Explain how and where each is documented in the clinic or unit (i.e., what information system, what screen, at what point in the clinical process, and by whom)?
2. When you send us the data or connect data to a federated system, what data store will you create/use? Describe all data transformations.
3. For each data element used in the cohort identification, are there difference in data capture or documentation practices across clinics or for different subsets of your population?
4. For each data element used in cohort identification, are there any subsets of data that may be documented differently, such as data from specialist or hospital reports external to your group versus data from your practice, or internal vs. external clinical laboratories?

Data Accuracy Assessment Approaches - Comparison Hierarchy

Comparison of data to sources listed above the top line provides full assessment of data accuracy; sources listed below the top line provide only partial assessments of accuracy. Sources above the bottom line can be used to detect actual data discrepancies, whereas sources below the bottom line can only indicate that discrepancies may exist. Items at the top of the list identify actual errors, whereas items in the middle only identify discrepancies that may or may not in fact be an error. Items toward the bottom merely indicate that discrepancies may exist.



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Reporting Pragmatic Clinical Trials

Introduction

Transparent reporting of clinical trials is essential for helping researchers, clinicians, patients, and other stakeholders understand the validity and reliability of the findings. Many have suggested that the quality of trial reporting is suboptimal and have sought consensus on the key elements of transparent reporting. To address this, a group of clinical trial methodologists and journal editors developed the [CONSORT](#) (Consolidated Standards of Reporting Trials) Statement. CONSORT is intended to improve transparency and dissemination of trial findings by providing a checklist and guidance for authors.¹ The original CONSORT statement focused on the reporting of standard, two-group randomized controlled trials (RCTs) that compare an intervention with a control. Over the years, CONSORT has been expanded for clarity and revised, most recently in 2010, and now includes several official extensions to account for variations in trial design, interventions, and data (described in Appendix A).

Pragmatic Clinical Trials

The [NIH Health Care Systems Research Collaboratory](#) supports the design, execution, and dissemination of a set of [Demonstration Projects](#), which are pragmatic clinical trials (PCTs) that address questions of major public health importance and are part of an effort to create a new infrastructure for collaborative research within healthcare systems. In contrast to RCTs, which elucidate a mechanical or biological process, PCTs are “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.”² To be clear, PCTs are on a *continuum* with traditional RCTs, and there are aspects of PCTs that make them either more explanatory or more pragmatic (described in Appendix B). Generally, a PCT is more pragmatic if the data are collected during routine clinical care (usually through the electronic health record [EHR]); if there is some flexibility in the delivery of and adherence to the intervention; if a real-world population is included; and if the outcomes are relevant to patients and other decision makers.

Purpose of this Template

This template is intended to help authors with the transparent reporting of their PCT. While we have looked to the CONSORT guidance and extensions wherever possible, new areas are emerging related to PCTs that the CONSORT checklist and guidance do not address. These include reporting around the secondary use of EHR data, wider stakeholder and health system involvement in the conduct of PCTs, and special ethical and regulatory considerations for PCTs.

Guidance in this template is organized by the recommended reporting elements as presented in the current CONSORT checklist, and also draws on recent experiences and lessons learned from the NIH Collaboratory Demonstration Projects. We hope that the resulting report will assist authors in developing the primary journal publications. We recognize that journals have space limitations and so we encourage authors to use supplements if necessary to report all the recommended elements.

We include the following appendices:

- **Appendix A** contains a table with references to CONSORT and its extensions.
- **Appendix B** provides links to the Pragmatic–Explanatory Continuum Indicator Summary (known as PRECIS-2) tools and resources.
- **Appendix C** lists definitions of PCT-related terminology.
- **Appendix D** has examples of figures.

The Living Textbook

Extensive information and user tools are available on [Rethinking Clinical Trials®: A Living Textbook of Pragmatic Clinical Trials](#), an online resource designed to provide information on how to understand, design, conduct, analyze, and disseminate PCTs. Additional resources for authors are at the end of the reference list.

Title

Identify the study as a randomized, pragmatic clinical trial or, specifically, a cluster-randomized trial, as appropriate. (Optional: Convey the randomization scheme; e.g., parallel, stepped-wedge, adaptive). On the title page, include all author names, degrees, institutional affiliations and give full contact information for the corresponding author. Provide 3-5 keywords.

Abstract

Create a structured summary (background, methods, results, discussion) that includes the following information:

- Trial design (e.g., cluster, noninferiority)
- Randomization scheme (e.g., parallel, stepped-wedge, adaptive)
- Setting (e.g., hospitals, community clinics, regional healthcare system)
- Eligibility criteria for the participants or clusters
- Interventions for each group
- Whether the hypothesis pertains to the cluster level, the individual participant level, or both, and whether the primary outcome pertains to the cluster level, the individual participant level, or both
- For cluster-randomized trials (CRTs), how the clusters were allocated to interventions
- Whether participants, caregivers, and those assessing the outcomes were blinded to group assignment

- The number of participants or clusters randomized to each group and the number analyzed in each group
- Results at the individual participant or cluster level as applicable for each primary outcome
- Important adverse events or side effects
- A general interpretation of the results
- The degree of generalizability of the findings
- The trial registration name and number
- If available, where the protocol can be accessed
- The funding source and role of the funder

Introduction

Background and objectives

Describe:

- The scientific background and rationale
- The health or healthcare problem the intervention addresses
- The rationale for choosing the specific pragmatic design (includes cluster-randomized, stepped-wedge)
- Decisions the trial is intended to inform and in what setting
- Other interventions that are commonly aimed at this problem
- Key features that make the trial feasible in this setting and elsewhere
- Specific objectives, research questions, and hypotheses; for CRTs, describe whether the objectives pertain to the cluster level, individual participant level, or both

Methods

Stakeholder engagement

Because PCTs are generally conducted as part of routine care and are meant to immediately inform the delivery of care, engagement with relevant stakeholders—patients, delivery system leaders, IT personnel, clinicians, and other frontline providers—is important. Briefly describe the extent to which stakeholders were involved (e.g., defining the study question, designing the study, developing workflows, assessing feasibility).

Trial design

Describe the pragmatic aspects of the trial design: decisions related to the real-world healthcare setting, logistical considerations and clinical workflow, and service delivery. Explain the design, such as cluster randomization, stepped-wedge. Indicate if applicable whether this is a population-based study. If possible, include a schematic representation of the study design.

For CRTs, define the clusters and describe how the design features apply to the clusters. For stepped-wedge CRTs, define the timing and randomization of crossover from the control to the intervention.

Describe important changes to the methods after the trial started, and include reasons.

Participants

Frame the eligibility criteria to show the degree to which they include typical participants, providers, institutions, communities, or settings of care. Explain the method of participant recruitment and the attributes of the healthcare system or setting where the data were collected.

Intervention

Readers need a sense of how feasible the intervention would be in their setting. Give a detailed description of the intervention for each group and how it was actually administered; explain the comparator (for example, usual care) in similar detail. If the intervention included multiple components, describe each component in detail. For CRTs, indicate whether the interventions were applied at the cluster level, individual participant level, or both.

Describe any resources added to or removed from usual care to implement the intervention. Indicate whether delivery of the intervention was allowed to vary between participants, providers, or study sites. For pragmatic trials, efforts that may reduce “natural variation in the intervention and its delivery should be described. However, if reducing variation in a care process or shifting practice patterns is itself the main purpose of the intervention, this should be explicit in the title, abstract, and introduction.”³

When relevant, include details on the experience and training (e.g., frequency, intensity) of those who delivered the intervention.

Outcomes

Explain the primary and secondary outcome measures, why they were chosen, and their relevance to participants and key decision makers. Include whether the outcomes relate to health outcomes for patients or to healthcare system improvements/efficiencies. Describe any [patient-reported outcome \(PRO\)](#) measures that were used to assess the intervention; include appropriate references in support of the validity and reliability of the measures used. Describe how and when the outcomes were assessed, as well as any changes to the outcomes after the trial started, with reasons. Include the length of follow-up and how it pertains to the decisions the study is designed to inform.

For CRTs, indicate whether the outcome measures apply to the cluster level, individual participant level, or both.

Sample size

Explain how sample size was determined, interim analyses, and stopping rules. If sample size was “calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference), then report where this difference was obtained.”³ For CRTs, describe the number of clusters and cluster size, including whether equal or unequal cluster sizes are assumed. Indicate the intracluster correlation coefficient, as well as an indication of its uncertainty.

Human subjects protection

Describe approval by an ethics committee (e.g., an institutional review board) as well as any other oversight bodies from which approvals were obtained. If the PCT involved a regulated product, indicate whether it was conducted under IND (or its equivalent). Delineate who is considered to be a human subject in the research (e.g., patients, clinicians, others) as well as indirect subjects of the research. Include details of the type (written, oral) and mode (electronic, mail, in-person) of informed consent used, or explain if a waiver or modification of informed consent was approved and used. If so, describe what if any mechanisms were used to provide information about the research (i.e., disclosure) and if participation was specifically authorized by subjects or if an opt-out mechanism was used. If applicable, describe whether notification and/or consent was obtained before or after randomization. Describe the method of authorization used for the use of protected health information and the standards for data security. Describe the approach used for data monitoring and if applicable, the existence of a data monitoring committee. For CRTs, indicate the nature of engagement with cluster representatives (e.g., discussion, consent) and whether consent was obtained from individual cluster members.

Randomization

Sequence generation

Include the method used to generate the random allocation sequence and describe any restriction used (e.g., blocking, stratification). Describe the type of randomization (e.g., individual, cluster, nonrandomized). For CRTs, explain if stratification or matching was used.

Allocation concealment mechanism

Describe the method used to implement the random allocation sequence, including any steps to conceal the sequence until after intervention assignment. For CRTs, specify that allocation was based on clusters. Indicate whether allocation concealment was at the cluster level, individual participant level, or both.

Implementation

Explain who generated the random allocation sequence, who enrolled participants (or clusters), and who assigned participants (or clusters) to the intervention. For CRTs, describe how individual participants were included in the clusters, such as by random sampling or inclusion of all individuals identified as eligible.

Blinding

Describe whether participants, those administering the intervention, and those assessing the outcomes were blinded to group assignment. If blinding was not done or was not possible, explain why. If relevant, describe the similarity of the interventions.

“In pragmatic trials, as in the real world delivery of care, blinding of participants and clinicians may be impossible. ... Authors should speculate on the effect of any suspected modifying factors, such as belief in the intervention, in the discussion [section] ... Moreover, in pragmatic trials, it is still desirable and often possible to blind the assessor or obtain an objective source of data for evaluation of outcomes.”³

Monitoring for unanticipated changes in care within study arms

As trials evolve, changes may occur in the care provided within the intervention and/or control arms that could affect the conduct or analysis of the study. For example, some components of the intervention may appear in usual care at some control sites/clusters. Contamination can be due to various reasons: unintentional spill-over of intervention effects, other healthcare initiatives that focus on the same problem, or changes in leadership, sites, or healthcare delivery system. Explain how you monitored care provided within all study arms across all sites/clusters and whether you were able to measure treatment fidelity.

Use of data from EHRs or clinical and administrative information systems

If the source of data was from a clinical or billing database instead of one created primarily for research, describe:

- The particular EHR system(s) used in the trial
- The nature of the data source and data
- The steps used in gaining permission to use the data
- How the population of interest was identified (i.e., development of phenotype definitions, use of ICD-10 codes)
 - Reference any specific standards, data elements, or controlled vocabularies used, and provide details of strategies for translating across coding systems where applicable (e.g., methods for ICD-9 to ICD-10 translation or assertion of equivalence.) If the choice of data collection or methods was informed by a data standards initiative (e.g., ACC standards), identify the relevant federal standard, standards development organization, or professional clinical or research organization that named the standard.
- Each clinical phenotype (i.e., EHR-based condition definition) used
 - Reference the location where readers can obtain the detailed definitional logic. Use of a national repository for phenotype definitions, such as [PheKB](#) or [NLM VSAC](#), is preferred. GitHub or another repository for code is valuable as well.
- The process for linking data from different sources, including EHRs, ancillary systems, administrative and billing systems, and external sources such as CMS or regional health information exchange
- The process and results from assessment of the quality of the data. Assessment should be informed by the Collaboratory's Phenotypes, Data Standards, and Data Quality Core [recommendations for data quality](#).
- The data management activities during the study, including a description of different data sources or processes used at different sites
- The plan for archiving or sharing the data after the study, including specific definitions for clinical phenotypes and specifications for coding system (name and version) for any coded data

Use of a clinical research network for data querying

Describe the use of a research network for querying data. This might include, for example, a [distributed research network \(DRN\)](#), a [CTSA network](#), or a [PCORnet partner network](#).

Statistical methods

Describe the statistical methods used to compare groups for primary and secondary outcomes. Include methods for subgroup analyses and adjusted analyses. For CRTs, indicate how clustering was taken into account.

Results

Participant flow

Describe the flow of participants and/or clusters through the trial and include a diagram if possible (see example in Appendix D). Include the number of participants and/or clusters approached to take part, eligible, randomly assigned, receiving the assigned intervention, completing the study protocol, and analyzed for the primary outcome. Include reasons for nonparticipation of those approached to take part. Also report losses and exclusions of participants (and clusters, if applicable) after randomization, with reasons. For CRTs, the CONSORT extension for [cluster trials](#) has helpful examples of participant flow diagrams.

Recruitment

List the dates of recruitment and follow-up. Explain why the trial ended or was stopped.

Baseline data

Include a table showing baseline demographic and clinical characteristics for each group (and cluster, if applicable). If appropriate, give details of [EHR-based phenotyping](#) pertinent to the study.

Unanticipated changes in care within study arms

Report any unanticipated changes in care that occurred in the study arms that could affect the interpretation of the study. Describe any intervention contamination and adjustments made to the analysis to accommodate contamination.

Numbers analyzed

For each group, include the number of participants or clusters (i.e., the denominator) included in each analysis.

Outcomes and estimation

For each primary and secondary outcome, present results for each group and estimated effect size and its precision (e.g., 95% confidence interval). For binary outcomes, give both absolute and relative effect sizes. For CRTs, provide results at the individual or cluster level as applicable, and give a coefficient of intracluster correlation for each primary outcome.

Ancillary analyses

Describe results of any other analyses performed. Distinguish between prespecified and exploratory analyses.

Harms

Explain important harms or unintended effects in each group. Clarify how harms data were collected and analyzed. Describe participant withdrawals due to harms and their experiences with the allocated treatment.

Limitations

Discuss limitations of the study, addressing sources of potential bias and imprecision.

Discussion

Generalizability

Describe key aspects of the setting that determined trial results. Describe possible differences in other settings, where clinical traditions, health service organization, staffing, or resources might vary from those in your study. Keep in mind that “the usefulness of the trial report is critically dependent on how applicable the trial and its results are and how feasible the intervention would be.”³

Interpretation

Discuss the interpretation of results, balancing benefits and harms and considering other relevant evidence. A defining component of a PCT is that it is intended to inform decision makers about benefits, burdens, and risks of an intervention. Describe the relevance to decision makers.

References

Include a full reference list with PMIDs, URLs, or DOIs.

Acknowledgments

Include names of contributors who do not qualify as authors, per [ICMJE guidelines](#).

Figures

Potential figures (examples in Appendix D):

- Participant/cluster flow through the trial
- Stepped-wedge cluster intervention timing

Tables

Potential tables:

- Participant/cluster characteristics
- Baseline data, and if applicable, phenotype descriptions

Supplementary Materials

Authors may consider including the main URL for the trial and making available relevant toolkits, participant materials, videos, or other resources.

References Cited

1. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869. [PMID: 20332511](#). doi: [10.1136/bmj.c869](#).
2. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. *Clin Trials* 2015. [PMID: 26374676](#). doi: [10.1177/1740774515598334](#).
3. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390. [PMID: 19001484](#). doi: [10.1136/bmj.a2390](#).

Additional resources for authors

- EQUATOR (Enhancing the Quality and Transparency of Health Research) Network. Library for Health Research Reporting. This website contains a comprehensive searchable database of reporting guidelines and links to other resources related to research reporting. Available at: <http://www.equator-network.org/>. Accessed May 3, 2016.
- Hemming K, Haines TP, Chilton PJ, et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*. 2015;350:h391. [PMID:25662947](#).
- Johnson KE, Neta G, Dember LM, et al. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. *Trials* 2016;17(1):32. [PMID: 26772801](#). doi:10.1186/s13063-016-1158-y.
- Krist AH, Glenn BA, Glasgow RE, et al. Designing a valid randomized pragmatic primary care implementation trial: the my own health report (MOHR) project. *Implement Sci*. 2013;8:73. [PMID:23799943](#).

Appendix A: CONSORT Guidance

The Consolidated Standards of Reporting Trials (CONSORT) encompasses various initiatives developed by the CONSORT Group to alleviate problems associated with inadequate reporting of randomized controlled trials. Their website contains user information for the 2010 update and [all the current extensions](#). The table below has links for extensions with particular relevance to pragmatic trials.

CONSORT resources

Description	Link
CONSORT website	http://www.consort-statement.org/
CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials	Moher 2010, PubMed abstract
CONSORT checklist and explanations	http://www.consort-statement.org/checklists/view/32-consort/66-title
CONSORT extensions	
2008	Abstracts
2008	Pragmatic trials
2012	Cluster trials
2013	Patient-reported outcomes

Appendix B: PRECIS-2

The Pragmatic–Explanatory Continuum Indicator Summary tool guides trialists to prospectively consider the design of their trial across 9 domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis (Figure B-1). The rating scale is from 1 (more explanatory) to 5 (more pragmatic).

Figure B-1. PRECIS-2 Wheel

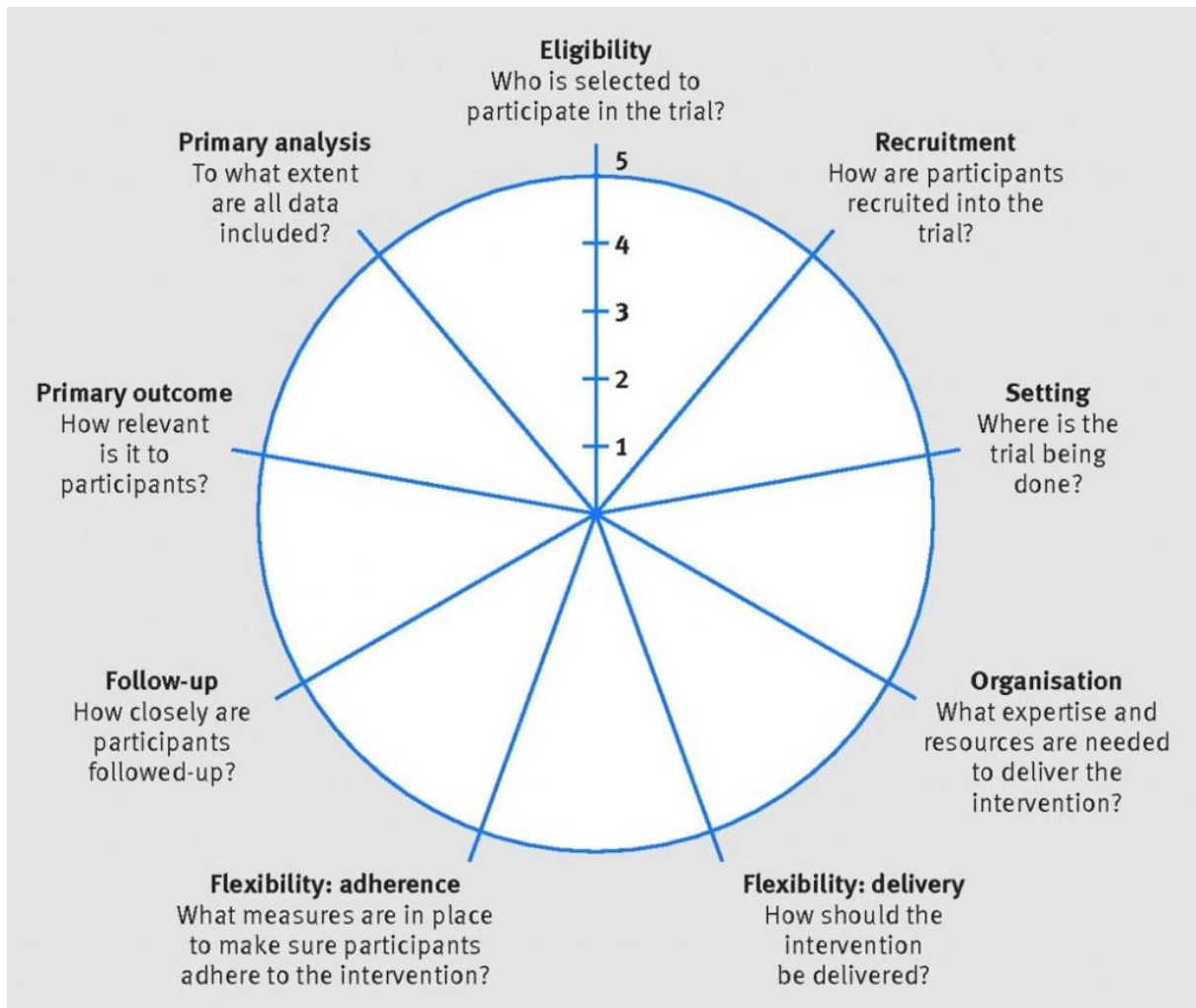


Illustration used by permission. Kirsty Loudon et al. BMJ 2015;350:bmj.h2147. Copyright 2015 by British Medical Journal Publishing Group.

PRECIS-2 resources

Description	Link
The PRECIS-2 tool: designing trials that are fit for purpose. <i>BMJ</i> 2015;350:h2147. PMID:25956159. doi:10.1136/bmj.h2147.	Loudon 2015, PubMed abstract
Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. <i>Trials</i> 2016;17(1):32. PMID:26772801. doi:10.1186/s13063-016-1158-y.	Johnson 2016, PubMed abstract
An introductory YouTube video on PRECIS-2 (2:53) by coauthors Kirsty Loudon and Shaun Treweek.	PRECIS-2 video
Health Informatics Centre at the University of Dundee contains information for trialists on using PRECIS-2. The site has a database of trials spanning the pragmatic spectrum. Users can also register their trials at the website	PRECIS-2 website
An index of registered trials showing wheel ratings and other details.	PRECIS-2 wheel examples

Appendix C: Definitions

Cluster-randomized trial (CRT)

A trial characterized by random assignment of groups or clusters to study conditions and by measurement of outcomes among members of those groups or clusters. In a CRT, the cluster is the unit randomized, whereas in a traditional RCT, the individual study participant is randomized.

Computable phenotype

A clinical condition or characteristic that can be ascertained via a computerized query to an electronic health record (EHR) system or clinical data repository using a defined set of data elements and logical expressions. Queries can identify patients with a particular condition, such as diabetes, obesity, or heart failure, and can be used to support a variety of purposes for observational and interventional research. Standardized computable phenotypes can enable large-scale PCTs across multiple health systems while ensuring reliability and reproducibility.

Distributed research network (DRN)

A network infrastructure that facilitates multicenter studies using electronic clinical, administrative, and research data. A DRN provides multisite distributed querying of data resources while allowing the data to remain in the control of the data owners. It allows searchable discovery of available data resources, health systems, researchers, and reusable analytic tools. A key component of a DRN is the governance that determines how investigators and data partners interact with each another and the permissible activities within the network.

Patient-reported outcome (PRO)

An outcome reported directly by patients without interpretation by clinicians. PRO measures are often used in PCTs to assess endpoints that are meaningful to stakeholders.

Pragmatic clinical trial (PCT)

A clinical trial designed for the primary purpose of informing healthcare decision makers—patients, clinicians, administrators, policymakers, and payers—regarding the comparative balance of benefits, burdens, and risks of a health intervention at the individual or population level. PCTs are distinguished by interventions that are done in the usual care setting in a real-world population, flexibility in the delivery of and adherence to the intervention, and outcomes that are relevant to patients.

PRECIS-2

The Pragmatic–Explanatory Continuum Indicator Summary tool (revised in 2015). Few clinical trials are entirely explanatory (done in an idealized setting) or entirely pragmatic (done in a usual-care setting); rather, trials are situated somewhere along a continuum of applicability. To help trialists assess how closely their trial’s design matches its intended purpose, a group of trialists and methodologists developed PRECIS, a validated design tool that guides trialists to

prospectively consider the design of their trial along 9 domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis.

Secondary use of electronic health record (EHR) data

The use of EHR data for research. In contrast to use of prospectively collected data, secondary use requires control over data definitions and collection in healthcare facilities, procedures for access and permission to use the data, dependence on record linkage, the need for computable definitions for cohorts and outcomes of interest, and the demonstration that data are of adequate quality to support research conclusions.

Stakeholder engagement

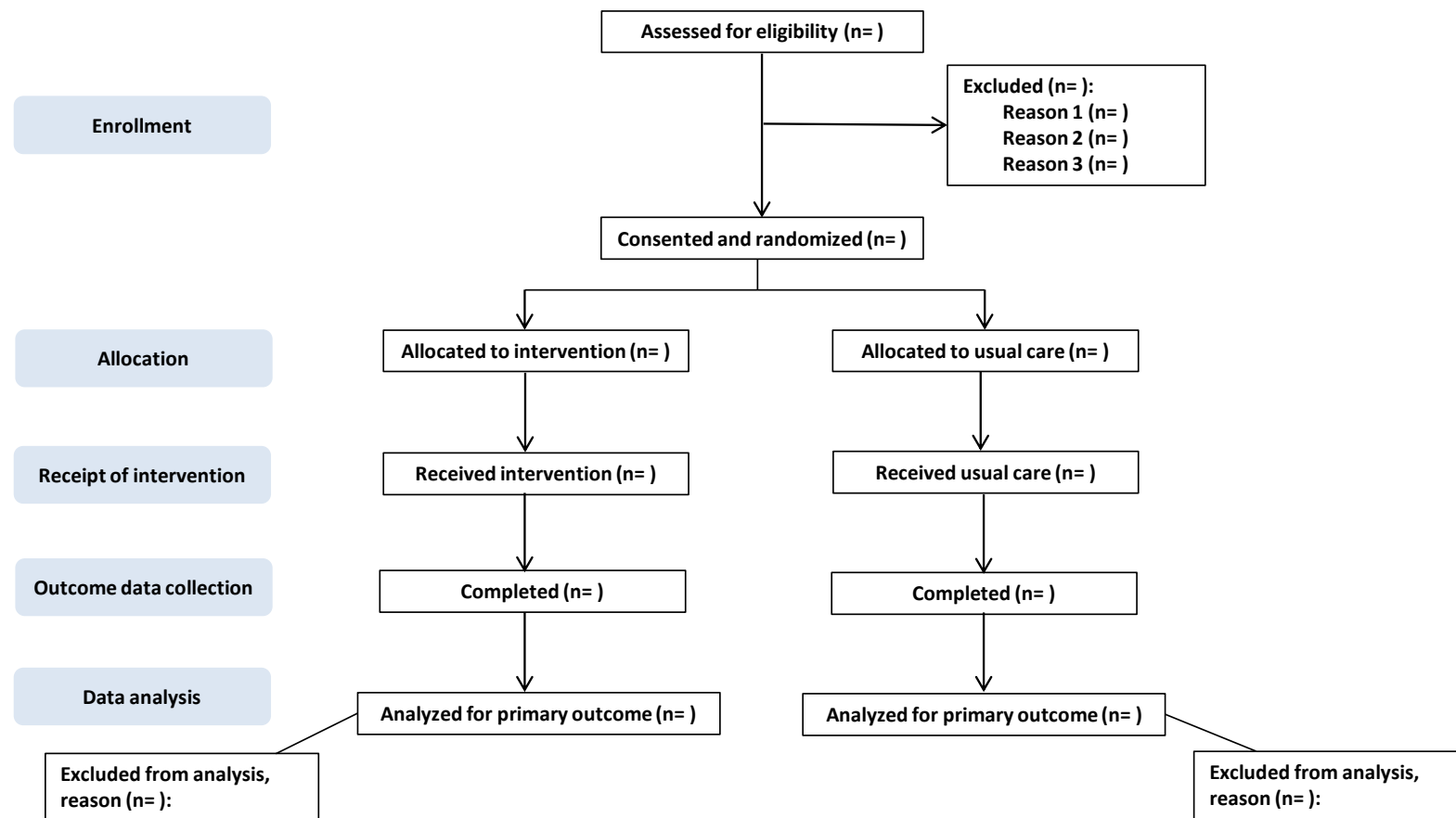
A process by which those who have an interest in the outcomes of trials are engaged in all phases of clinical research activities. Better stakeholder engagement has been proposed to help realign healthcare research with the needs of clinicians, patients, policymakers, and payers.

Stepped-wedge randomization

A form of cluster randomization that involves random and sequential crossover of clusters from control to intervention until all clusters are exposed to the intervention.

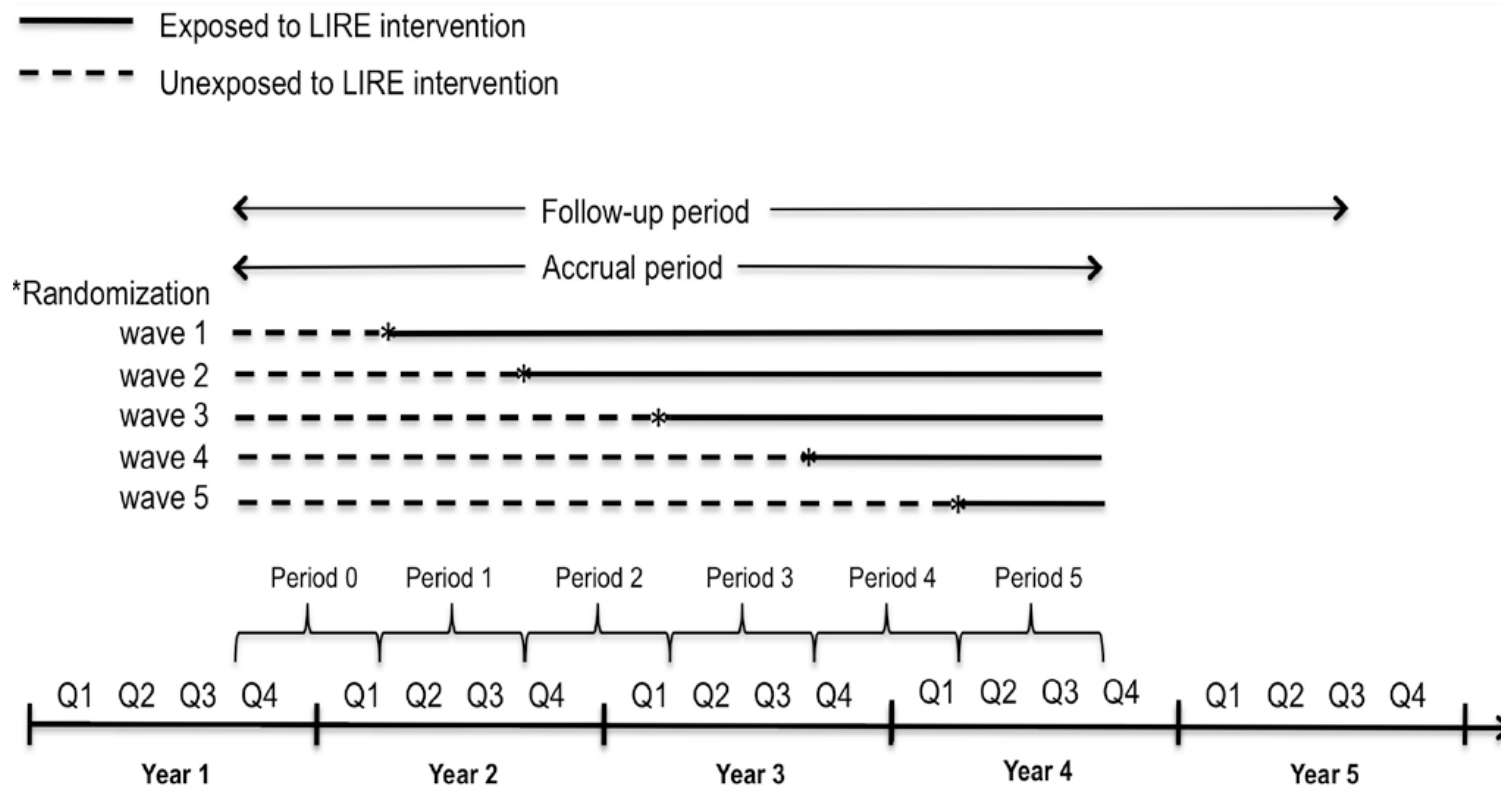
Appendix D: Sample Figures

Figure D-1. Example of participant flow diagram*



* For another example, see the STOP CRC trial's publication (Coronado GD, Vollmer WM, Petrik A, et al. Strategies and opportunities to STOP colon cancer in priority populations: pragmatic pilot study design and outcomes. BMC Cancer 2014;14:55. [PMID: 24571550. doi: 10.1186/1471-2407-14-55](https://doi.org/10.1186/1471-2407-14-55)). More examples are in the [CONSORT](#) guidance documents and extensions.

Figure D-2. Example of stepped-wedge cluster intervention timing



In each wave, 20 new clinics have the LIRE intervention (inserting epidemiologic benchmarks into imaging reports) until all 100 are exposed to the intervention. Figure is from NIH Collaboratory Grand Rounds slide presentation, November 6, 2015: Lumbar Imaging with Reporting of Epidemiology (LIRE): Lessons Learned. Available at: <https://www.nihcollaboratory.org/Pages/GR-Slides-11-06-15.pdf>. Accessed January 20, 2016.

Collaboratory ePCT Training Workshop

Topic 7

Pilot and Feasibility Testing

Learning objective	Identify approaches to evaluate the capabilities and challenges of partner healthcare system(s) and test key elements of various types of interventions
Instructor	Wendy Weber
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN: Assessing Feasibility• Trial Documentation Checklist• Implementation Readiness Checklist <p>PCT 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

Topic 7: Pilot and Feasibility Testing

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

Collaboratory ePCT Training Workshop

Overview

- Importance of piloting the intervention to be embedded (ePCTs can be “messy”)
- Special feasibility considerations for ePCTs
- Context, capabilities & challenges of the partnering HCS
- Piloting key elements of the intervention
- Case study: The SPOT Demonstration Project
- Ensuring trial is ready to launch

ePCTs are not efficacy trials

- ePCTs bridge research into clinical care
- Intervention is integrated into a real-world healthcare setting & is usually compared to usual care
- Primary goal is to gather generalizable information to inform HCS decision-makers
- Special feasibility considerations
 - Establish close partnerships with HCS personnel
 - Test & validate EHR data collection & extraction methods
 - Assess how well the intervention can be integrated into the clinical workflow as seamlessly as possible
 - Identify local champions at each study site

Build the HCS partnership during the pilot study

- Is the intervention aligned with the healthcare priorities of the HCS?
- Has the study team established effective partnerships with HCS leadership, clinicians, providers, and IT staff?
- Readiness of the partner HCS
 - 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 utilize existing HCS infrastructure?
- If the intervention proves successful, what adaptations would be needed to implement it into other healthcare settings?

Aspects of feasibility that can be piloted

- Verify that the eligible target population can be identified via the EHR or other planned methods
- Test any phenotypes needed for sample identification
- Validate data collection and extraction methods & test data sample for quality & accuracy
- Coordinate processes with local champions
- Test the training materials for frontline providers & staff

Aspects of feasibility that can be piloted

- Evaluate informed consent materials and processes
- Test appropriateness & usability of study toolkits or other materials
- Evaluate whether fidelity/adherence measures can be achieved to justify the full-scale ePCT
- If cluster randomization is involved, collect data to confirm estimate of intraclass correlation (ICC) for power calculations

Aspects of feasibility that can be piloted

Use what you learn to design the ePCT

How to quantify feasibility for pilot study aims

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

NEXT: Examples of pilot study aims that quantify feasibility

Example 1

Demonstrate effective recruitment and retention, which is defined 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

Example 2

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

Example 3

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

Case study: SPOT

- Feasibility illustration from the Suicide Prevention Outreach Trial
- Dr. Greg Simon, Principal Investigator
- An NIH Collaboratory Demonstration Project in UH3 phase

Resource: [SPOT Demonstration Project](#) webpage in the Living Textbook



**Pilot-testing Interventions
in Pragmatic Trials:
SPOT Case Study**

Gregory Simon, MD, MPH
Kaiser Permanente Washington Health Research
Institute

Collaboratory ePCT Training Workshop

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 2 outreach programs
- Analysis by intent to treat, regardless of intervention uptake or adherence

SPOT interventions

- Risk assessment and care management
 - Systematic outreach to monitor risk of suicide attempt
 - Risk-based pathways for follow-up care
 - Outreach to maintain engagement in outpatient care
- Dialectical behavior skills training
 - Specific DBT skills shown to reduce risk of suicide attempt
 - Interactive online program for self-guided skills training
 - Supported by outreach from online coach
- Common to both
 - Outreach for up to 1 year
 - Intended as supplements to existing treatment
 - Accommodate different levels of participant engagement
- Each program was "moderate leap" from previous research

Intervention process

- Up to 3 rounds of invitation
 - Invitation by online messaging with option of phone follow-up
 - Participants free to decline at any time
 - Cease invitation if no response after three tries
- Care management
 - Outreach via messaging with option of phone follow-up
 - Frequency depending on risk level and engagement in care
 - As-needed coordination with treating outpatient providers
- Skills coaching
 - Free use of online program
 - Reinforcement messages for those using program
 - Outreach/reminder messages to those overdue

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

- 3 waves of pilot testing ~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 we 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 we 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

Ensuring trial readiness

- Troubleshooting & iterative testing
- Flexibility to accommodate local conditions & changes over time
- Continuous engagement with HCS
- [Readiness criteria checklist](#)
 - Recruitment plans are finalized
 - Ethical/regulatory aspects are addressed
 - Intervention is fully developed & finalized
 - Data collection methods are adequately tested
 - Budget is realistic & 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	
Budget is realistic and feasible	

Source: [Study Startup](#) chapter in the Living Textbook www.rethinkingclinicaltrials.org



Important things to know

- Pilot testing of the ePCT methods increases likelihood of completing the trial, prevents 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 & consider scalability of your intervention



Important things to do

- Conduct a pilot or feasibility study of the ePCT intervention(s)!
- Work with a great biostatistician
- Develop a partnership approach to working with your HCS
- Identify local champions for all of your sites
- Anticipate, identify & make a plan to address changes in the HCS

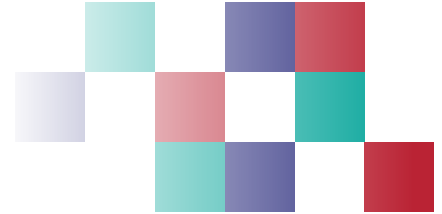
Think of 2 aspects of your trial that are essential to pilot

2 min



4 min





Suicide Prevention Outreach Trial (SPOT)

Study Snapshot

Principal Investigator: Gregory Simon, MD, MPH

Sponsoring Institution: Kaiser Permanente Washington Health Research Institute

ClinicalTrials.gov: [NCT02326883](https://clinicaltrials.gov/ct2/show/study/NCT02326883)

Abstract: Suicide ranks 10th among all causes of mortality in the United States, accounting for more than 40,600 deaths in 2012. Suicide attempts result in 600,000 emergency room visits and nearly 200,000 hospitalizations each year. Reducing this potentially preventable morbidity and mortality is a public health priority.

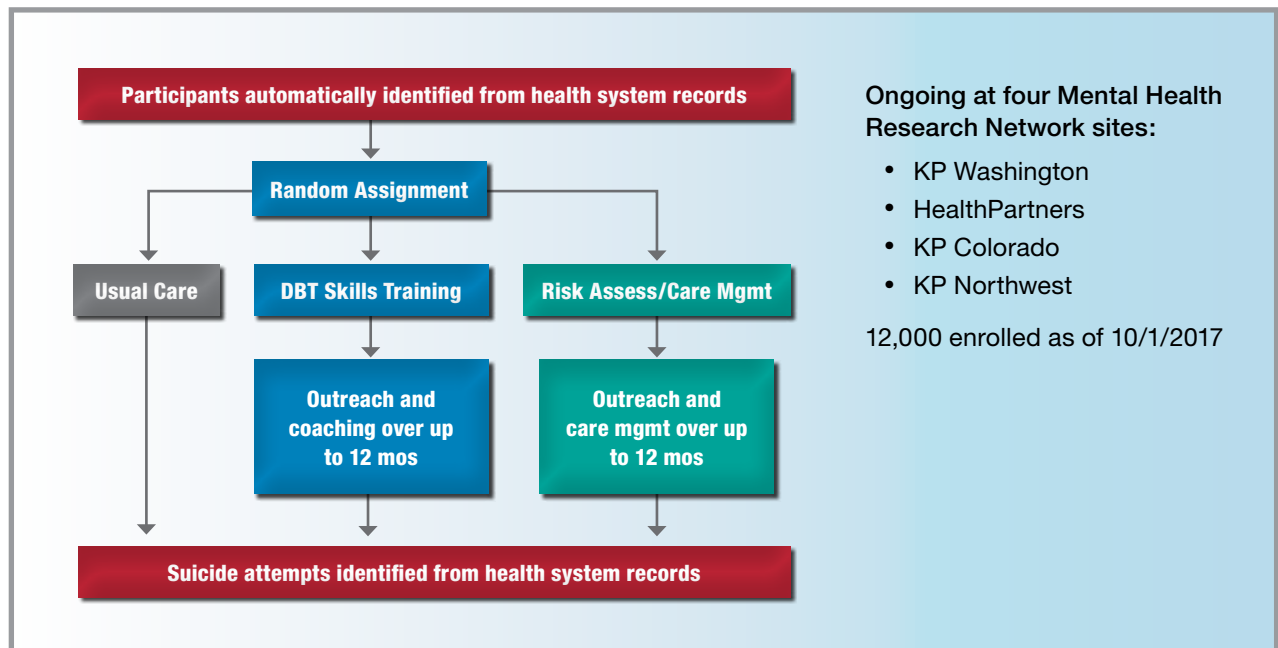
This large pragmatic trial will test treatments intended to reach large groups of adult patients who have serious thoughts of suicide. Patients at risk will be identified and followed through medical records. The research team will test two treatment programs: The first program, a care management approach, draws on two previous efforts,

Collaborating Healthcare Systems: HealthPartners Institute for Education and Research; Kaiser Permanente Northwest; Kaiser Permanente Washington; Kaiser Permanente Colorado

NIH Institute Oversight: National Institute of Mental Health (NIMH)

a collaborative care for depression strategy plus an approach developed at the Henry Ford Health System. The second program is an online skills training method designed to help people manage painful emotions and stressful situations.

To determine the impact of the two prevention strategies, patients will be compared with another group of patients receiving usual care. This 5-year study is designed to enroll 19,500 patients. The study design and intervention programs were developed in collaboration with people with “lived experience,” those who have experienced suicidal thoughts or survived suicide attempts themselves.



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
Finding the right balance between assertive and intrusive for the study intervention outreach	The study team partnered with people with lived experience of suicidal ideation and self-harm to develop and refine their outreach messages. They iterated language carefully, borrowing extensively from motivational interviewing and using first-person content for their skills program.
Process of IRB approval took longer than expected; a fundamental issue was whether one could conduct a minimal-risk study in a high-risk population, such as those at risk for suicide	Stakeholders had strong and often contradictory opinions about suicide, and defining appropriate ways to engage patients and obtain appropriate consent was a challenge.

Selected Publications & Presentations	
September 2017	PCT Grand Rounds Presentation: Who To Include in a Pragmatic Trial? It Depends
September 2016	Population-based outreach versus care as usual to prevent suicide attempt: study protocol for a randomized controlled trial , <i>Trials</i> , Simon et al.



Implementation Readiness Checklist

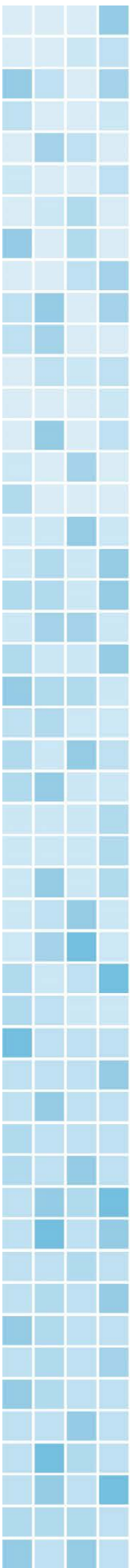
Milestone	Completed
<i>Recruitment plans are finalized</i>	
All sites identified (documentation of site commitment)	
Methods for accurately identifying participants validated	
All agreements for necessary subcontracts in place	
<i>Ethical/regulatory aspects are addressed</i>	
Coordinated IRB oversight 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 and feasible</i>	

Collaboratory ePCT Training Workshop

Topic 8

Dissemination

Learning objective	Identify considerations for wider dissemination of ePCT results
Instructor	Doug Zatzick
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DISSEMINATION: Dissemination Approaches for Different Stakeholders• PCT Reporting Template <p>PCT Grand Rounds webinar recordings & slides</p> <ul style="list-style-type: none">• Pragmatic Clinical Trials and Learning Health Care Systems: Strategies to Facilitate Implementation of Results into Clinical Care• Toward National Trauma Care Practice Change for PTSD and Comorbidity <p>Key journal articles</p> <ul style="list-style-type: none">• Zatzick et al., 2016. An effectiveness-implementation hybrid trial study protocol targeting posttraumatic stress disorder and comorbidity• Ehrlich et al., 2006. Characterization of the drug-positive adolescent trauma population: should we, do we, and does it make a difference if we test?• Findley et al., 2003. The role of psychiatry in the management of acute trauma surgery patients• Madras et al., 2009. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: comparison at intake and 6 months later• Mangram et al., 2011. The creation of a geriatric trauma unit "G-60"• Roberts et al., 2010. Posttraumatic stress disorder: a primer for trauma surgeons• Shih et al., 2010. Prevalence of posttraumatic stress disorder and major depression after trauma center hospitalization



Resources	<ul style="list-style-type: none">• Warren et al., 2013. Rehabilitation psychology's role in the Level I trauma center• Zatzick et al., 2008. Association between posttraumatic stress and depressive symptoms and functional outcomes in adolescents followed up longitudinally after injury hospitalization• Zatzick et al., 2008. A national US study of posttraumatic stress disorder, depression, and work and functional outcomes after hospitalization for traumatic injury• Zatzick et al., 2004. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors
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Topic 8: Dissemination

Doug Zatzick, MD
University of Washington School of Medicine

Collaboratory ePCT Training Workshop

Dissemination research defined

The 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 spread and sustain knowledge and the associated evidence-based interventions.

Source: NIH Dissemination and Implementation Research in Health PAR-16-238

Implementation research reviewed

The 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

Source: NIH Dissemination and Implementation Research in Health PAR-16-238

Putting it together: NIH Collaboratory dissemination case examples

- REDUCE MRSA/ABATE
- STOP CRC
- TSOS

Source: NIH Collaboratory Workshop Demonstration Projects May 24, 2017

REDUCE MRSA dissemination lessons learned

- REDUCE MRSA trial: decolonization in ICUs
 - 37% reduction in MRSA clinical cultures
 - 44% reduction in bloodstream infections
- Post-publication response
 - Protocol inquiries
 - Detailed implementation issues not in paper

Source: Huang, Septimus et al NEJM 2013

REDUCE MRSA toolkit on AHRQ website

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

Health Care Information For Patients & Consumers For Professionals For Policymakers Research Tools & Data Funding & Grants Centers, Portfolios & Initiatives News & Events

Home > For Professionals > Hospitals & Health Systems > Hospital Resources > Universal ICU Decolonization Protocol

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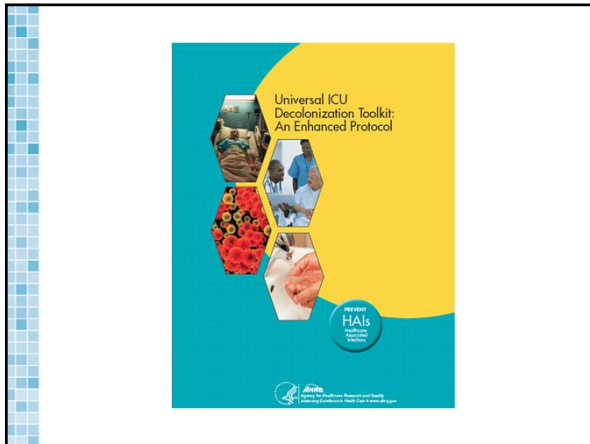
Clinicians & Providers
Education & Training
Hospitals & Health Systems
Emergency Department Tools and Resources
Emergency Severity Index

Universal ICU Decolonization: An Enhanced Protocol
Publication # 13-0052-EF

Introduction and Welcome

This enhanced protocol is based on materials successfully used in the REDUCE MRSA Trial (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Multiclin Resistant *Staphylococcus aureus*), which found that universal decolonization was the most effective intervention. Universal decolonization led to a 37 percent reduction in MRSA clinical cultures and a 44 percent reduction in all-cause bloodstream infections.

Source: http://www.ahrq.gov/professionals/systems/hospital/universal_icu_decolonization.html



REDUCE dissemination manuscript

Clinical Infectious Diseases
MAJOR ARTICLE

AIDSA **hivma**

Closing the Translation Gap: Toolkit-based Implementation of Universal Decolonization in Adult Intensive Care Units Reduces Central Line-associated Bloodstream Infections in 95 Community Hospitals

Edward Sepkowitz,¹ James Stohler,² John Morone,³ Ben Whitmore,⁴ Talina R. Amey,⁵ Susan E. Hoang,⁶ Richard Platt,⁷ and Jonathan Pechl⁸

¹Harvard Center for Antimicrobial Research, Boston, ²Case Western Reserve University School of Medicine, Cleveland, ³University of Michigan School of Public Health, Ann Arbor, Michigan, ⁴University of California, San Diego, ⁵University of Michigan, ⁶University of Michigan School of Public Health, ⁷University of Michigan School of Public Health, ⁸University of Michigan School of Public Health

Background. Challenges exist in implementing evidence-based strategies, reaching high compliance, and achieving desired outcomes. The rapid adoption of a publicly available toolkit featuring routine universal decolonization of intensive care unit (ICU) patients may affect catheter-related bloodstream infections.

Methods. Implementation of universal decolonization—treatment of all ICU patients with chlorhexidine bathing and nasal mupirocin—used a previous version of a publicly available toolkit. Implementation in 136 adult ICUs in 95 acute care hospitals across the United States was supported by planning and deployment tactics coordinated by a central infection prevention team using toolkit resources, along with coaching calls and engagement of key stakeholders. Operational and process measures derived from a common electronic health record system provided real-time feedback about performance. Healthcare-associated central line-associated bloodstream infections (CLABSI), using National Healthcare Safety Network surveillance definitions and comparing the preimplementation period of January 2011 through December 2012 to the postimplementation period of July 2013 through February 2014, were assessed via a Poisson generalized linear mixed model regression for CLABSI events.

Results. Implementation of universal decolonization was completed within 6 months. The estimated rate of CLABSI decreased by 23.0% (95% confidence interval, 9.8%–35.1%; $P < .001$). There was no evidence of a trend over time in either the pre- or postimplementation period. Adjusting for seasonality and number of beds did not materially affect these results.

Conclusions. Dissemination of universal decolonization of ICU patients was accomplished quickly in a large community health system and was associated with declines in CLABSI consistent with published clinical trial findings.

Keywords. universal decolonization, decolonization, healthcare-associated central line-associated bloodstream infections (CLABSI), quality improvement, learning health system.

Toolkit contents

- Introduction and Welcome
- Universal ICU Decolonization Protocol Overview
- Scientific Rationale
- References
- Appendices include training and educational materials

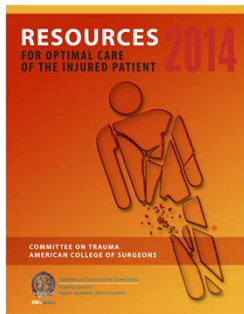
Active Bathing to Eliminate Infection (ABATE) PRECIS-2 wheel



STOP CRC

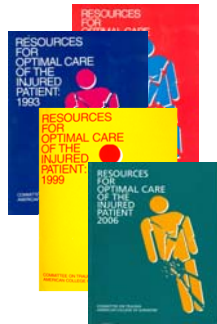


TSOS dissemination

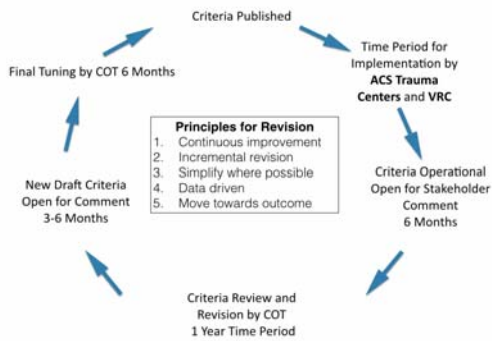


**American College of Surgeons Committee on Trauma
Guideline Dissemination & Verification Process**

- 1976 1st Book
- 2006 “Green Book”
- 2014 “Orange Book”

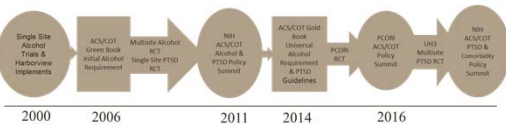


**American College of Surgeons Resources
Guide revision process**



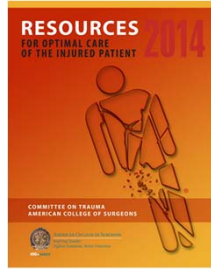
TSOS end-of-study policy summit

Two decades of orchestrated clinical trials & American College of Surgeons policy partnership builds practice change momentum into ePCT design & implementation



American College of Surgeons Resources Guide

PTSD & comorbidity: “The incorporation of routine trauma center–based screening and intervention for PTSD & depression is an area that could benefit from the ongoing integration of emerging data and evolving expert opinion.”



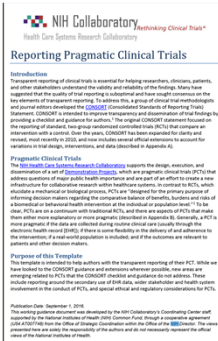
TSOS publications: dissemination aims to “nudge” practice change through regulatory policy

American College of Surgeons guidelines

- Main outcome paper & other publications aim to be cited in College Resources Guide
- End-of-study policy summit aims to integrate findings into College regulatory/verification processes

PCT reporting guidelines

Considerations specific to ePCTs





Important things to know

- Dissemination & implementation science can inform the translation of ePCT results into HCS practice change
- Case examples from NIH Collaboratory trials suggest a number of possible approaches to the dissemination of trial results
- Data sharing can be an essential element of dissemination



Important things to do

- Consider plans for dissemination of ePCT results
- How do these dissemination plans meld with NIH data sharing guidelines?

Collaboratory ePCT Training Workshop

Topic 9

ePCT Team Composition

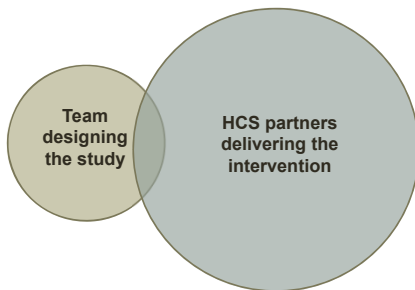
Learning objective	Identify ideal composition and skills needed for an ePCT study team
Instructor	Lesley Curtis
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DISSEMINATION: Intervention Staffing and Training Flexibility• Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial <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">• Health Care Services Research Network website

Topic 9: ePCT Team Composition

Lesley Curtis, PhD
Director, Center for Pragmatic Health Systems
Research, Duke Clinical Research Institute

Collaboratory ePCT Training Workshop

Who is involved?



Potential team members

- Principal investigator, co-investigator
- Health system leader or executive
- Biostatistician
- Lead clinician (eg, epidemiologist, 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
- Professional society leader
- Site champion/liaison
- Practice facilitator
- Research assistant
- Project coordinator
- Research participant, patient, or patient advocate

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?

Tips from the case studies

- Gloria Coronado, STOP CRC
- Doug Zatzick, TSOS



Important things to know

- ePCTs are a team sport
- Necessary expertise depends on the study aims & how the intervention will be implemented



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

Collaboratory ePCT Training Workshop

Topic 10

Developing a Compelling Application

Learning objectives	Part 1: Provide participants with information on how to develop a compelling ePCT application Part 2: Demonstrate learning around how to develop specific aims and study plans for an ePCT
Instructors	Marcel Salive, Kevin Weinfurt
Resources	<p><i>Living Textbook</i> readings</p> <ul style="list-style-type: none">• DESIGN Chapters• Assessing Feasibility: Developing the Trial Documentation• Learning Healthcare Systems <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 <p>Other</p> <ul style="list-style-type: none">• 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

Topic 10: Developing a Compelling Application

Marcel Salive, MD, MPH, National Institute on Aging

Collaboratory ePCT Training Workshop

Outline

- Which Institute?
- Which FOA?
- Strategies for success
- Resources
- Q&A

Understand NIH: find the right fit

Where's the money?

- NIH is made up of **27 institutes and centers** 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



IC mission and priorities

- Focus on a specific disease area, organ system, or stage of life
- Check their website
- Use Matchmaker tool in NIH RePORTER for suggestions
- Speak with program officials
- Consult your mentor & colleagues

NIH RePORTER



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

Matchmaker results



Grant vs 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

Source: PL. 95-224, NIH Manual 4815

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
NIAD	Clayton Huntley	NINR	Jeri Miller
NIAMS	Chuck Washabaugh	ODP	Rachael Ballard
NICHD	Sue Marden		

Which study section?

- Mostly Institute-specific special emphasis panels
- 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>

2017 NIH RFAs: RM-16-019 AG-17-059

- Demonstration Projects that include an efficient, large-scale pragmatic clinical trial; Alzheimer focus
- Multiple NIH Institutes, topics vs NIA
- Collaborate with 2+ HCS, n/a
- Part of NIH Collaboratory vs standalone
- Mechanism UG2/UH3 vs R21/R33

Review Criteria RFA-RM-16-019

Scored Criteria

- Significance
- Investigators
- Innovation
- Approach
- Environment

Additional Review Criteria

- Milestones
- Resources and Data Sharing Plan
- Software Sharing Plan
- Protection of HS
- Inclusion of Women, Minorities & Children
- Biohazards

All these aspects are considered by reviewers and they do influence the "Overall Impact" score of an application

Several review criteria, as well as the language under the criteria in this FOA, are NOT STANDARD; they are specific for this FOA – READ CAREFULLY

Pragmatic trials of managing multimorbidity in Alzheimer's disease

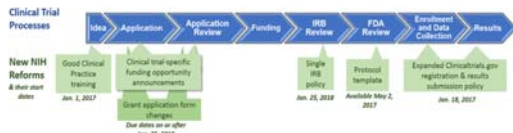
- RFA-AG-18-028
- R01 Clinical Trial Required
- Reissue of RFA-AG-17-059
- Due date: March 26, 2018
- Conduct research involving pragmatic clinical trials into improving the effectiveness of treatment strategies for comorbid conditions that occur frequently in combination with Alzheimer's disease and related dementia (ADRD)
- Phasing is optional
- Uses new clinical trial review criteria

Pragmatic trials for dementia care in long-term services and support settings

- PAR-18-585
- R61/R33 - Clinical Trial Required
- Reissue of RFA-AG-17-065
- Due dates: March 27, 2018; February 20, 2019; and February 20, 2020
- Pragmatic trials for dementia care in LTSS settings designed to address practical comparative questions faced by Alzheimer's disease (AD) and AD-related dementia (ADRD) patients, clinicians and caregivers (both paid and unpaid) and intended to improve quality of care, quality of life, improve cost-effectiveness and reduce disparities
- Pilot research to test the feasibility of implementing and integrating LTSS interventions (R61 phase) that, if successful, can transition to an R33 phase for implementation of large pragmatic trials, using administrative review as basis to advance
- Uses new clinical trial review criteria

NIH clinical trial requirements

- Series of initiatives in 2017-2018 to enhance the accountability and transparency of clinical research
- Clinical Trial-specific Funding Opportunities
- Clinical Trial-specific Review Criteria
- Single IRB requirement



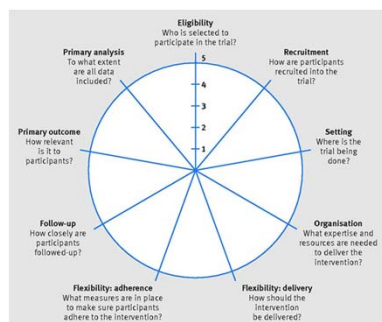
New review criteria—clinical trials

- 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's, 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.

Some real (troubling) summary statement comments ...

“The premise of the study ... is based on weak evidence”

“Data provided did not establish the feasibility of recruitment”

“The differences in anticipated [outcome] rates upon which the study is powered are quite large—larger differences than are seen in other similar trials”

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

“Concerns include the inclusion/exclusion criteria for the study, inadequate power for the study, and whether outcomes of this study would drive a change in [clinical] practices”

“There are no measures of intervention fidelity”

“Investigative team ... had limited experience with multi-systems clinical trials”

“Amount budgeted for a biostatistician is much too low”

Common 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

Strategies for success

- The research question posed must be clear
- The most elegant methods, techniques, and procedure are worthless if you do not convince the reviewer that the study is worth doing
- High tech is no substitute for solid logical planning
- Sell your research plan—highlight the strengths
- Identify weaknesses & explain how you will deal with them
- Tailor your application to the funding agency
- Obtain feedback of your collaborators, consultants & others

Dos and don'ts

DO

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

Source: <https://www.nia.nih.gov/research/blog/2015/01/strengthen-your-research-plan-better-score-dos-and-donts>

Dos and don'ts

DON'T

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

Source: <https://www.nia.nih.gov/research/blog/2015/01/strengthen-your-research-plan-better-score-dos-and-donts>

NIH Research Methods Resources

U.S. Department of Health & Human Services

NIH National Institutes of Health
Advancing Discovery Into Health

Research Methods Resources

Home CRT MCT CRT 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 (PDRAs) 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 IRB 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 to trials that randomize groups or deliver interventions to groups, new methods-related trials and resources will be added in the future. For a guided tour of this website, please refer to a recent blog the Gap website, which presents additional information about its relevance to the new NIH requirements for clinical trial applications, a summary of the methodological issues inherent to recent study designs, and a demonstration of how to use the Group-Randomized Trial (CRT) Sample Size Calculator.

Trials that Randomize Groups or Deliver Interventions to Groups

Source: <https://researchmethodsresources.nih.gov>

Discussion questions

- Non-disease vs disease-specific institute?
 - Consult program officers for both
- Single vs multiple PI? Suitability for assist mechanism (U)?
- What materials would be good for training reviewers?
- Other individual questions that might be of more general interest



Important things to know

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



Important things to do

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

For further information, contact

Marcel Salive, MD, MPH
301-496-5278
Marcel.Salive@nih.gov

Next steps for your project



Worksheet: Next Steps for Your Project

Aims/Significance (Topics 1 & 2)

Decisions the trial is intended to inform

In what setting

Who are the stakeholders?

Research question/aims

A large, empty rectangular box with a thin black border, intended for the user to write their answers to the questions listed above.

Design (Topic 4)

Unit of randomization? (e.g., individual patient, provider, clinic)


Parallel groups, stepped-wedge?



Participants (Topic 1)

Who is eligible? (e.g. should anyone be excluded for safety reasons)

How will they be identified?

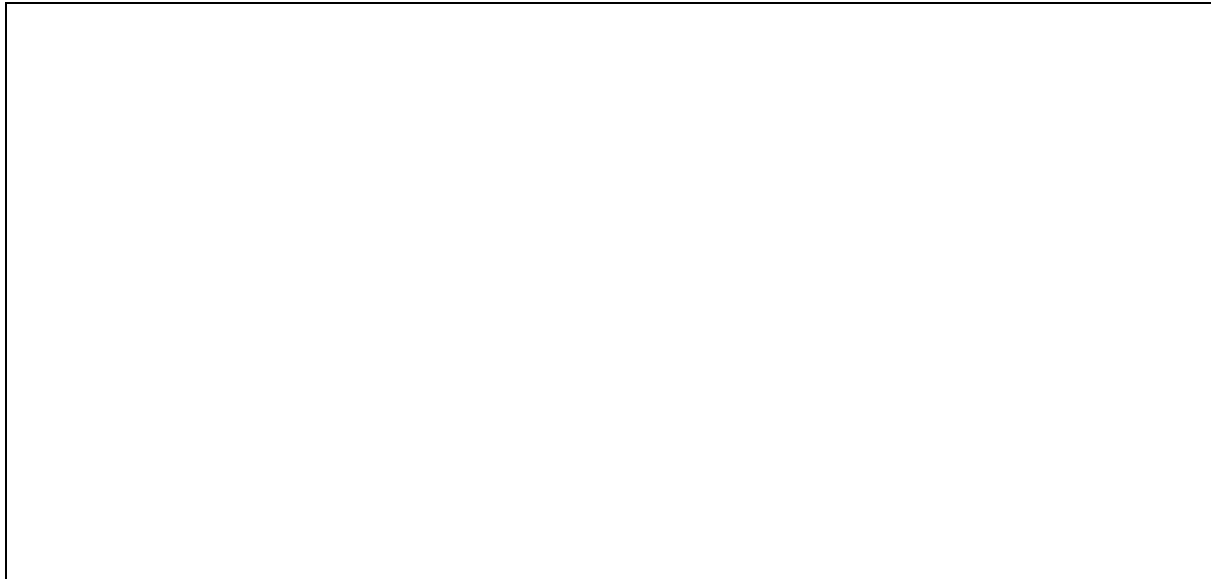


Interventions (Topics 1 & 3)

Organization: what kind of expertise is needed to deliver?

Flexibility in how intervention is delivered?

Flexibility in degree of adherence tolerated?



Outcome(s) (Topic 6)

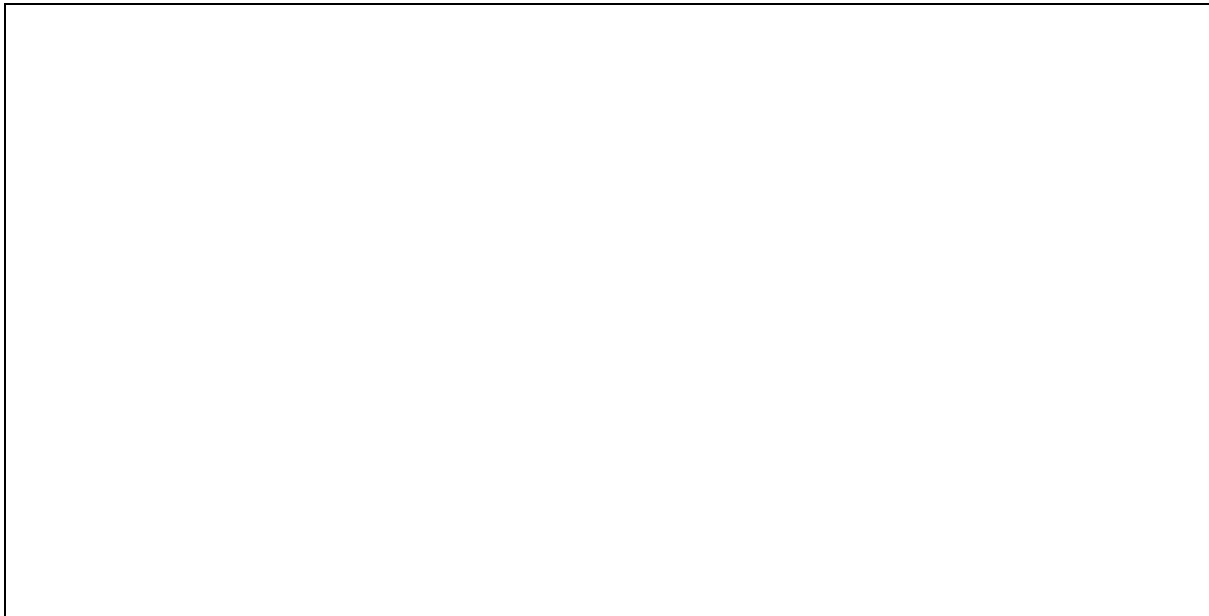
How will it be ascertained? (e.g., passive or active data collection?)

Relevance to stakeholders?



Sample Size (Topic 4)

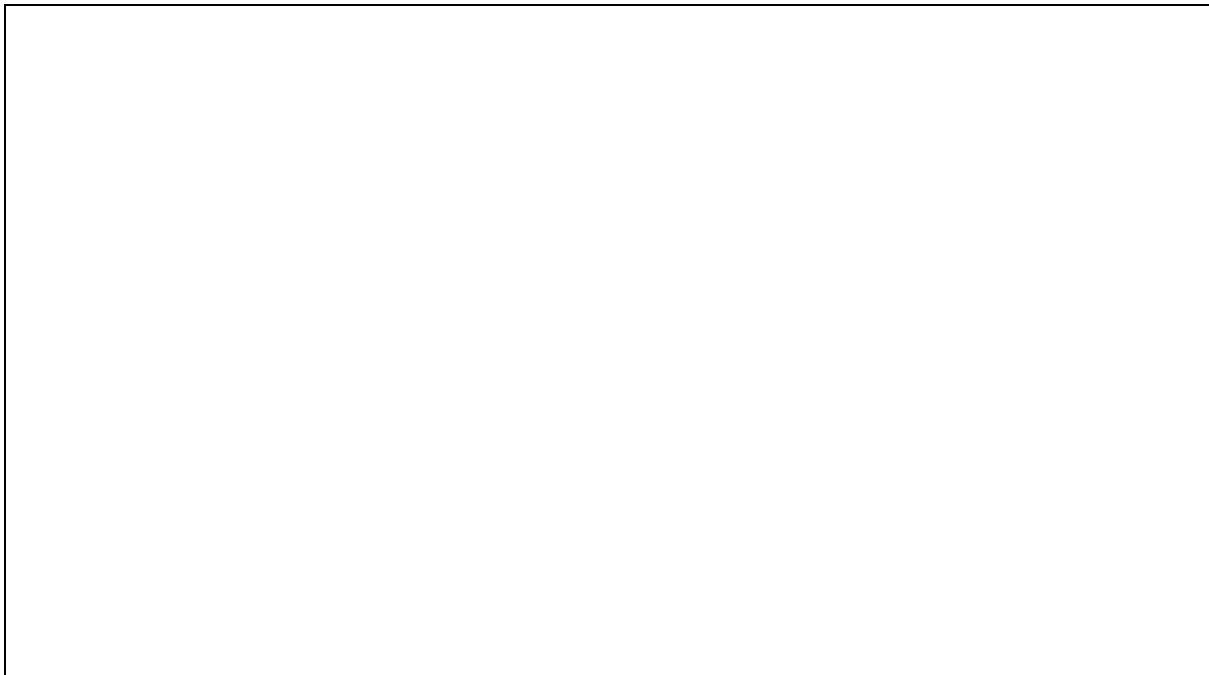
If cluster randomized, estimate of ICC?



Human Subjects Protection (Topic 5)

Who are the participants and how should they be protected?

Is written informed consent required of any participants?

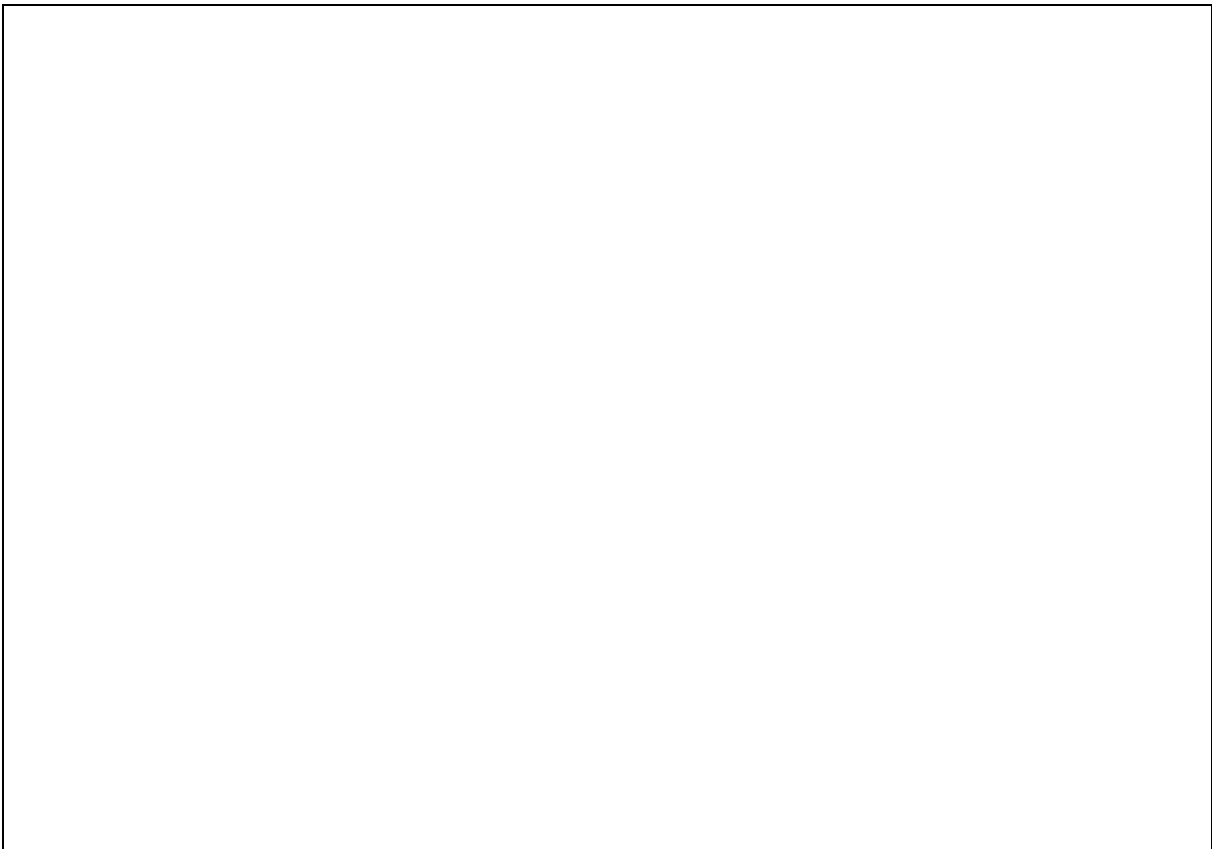


Analysis (Topic 4)

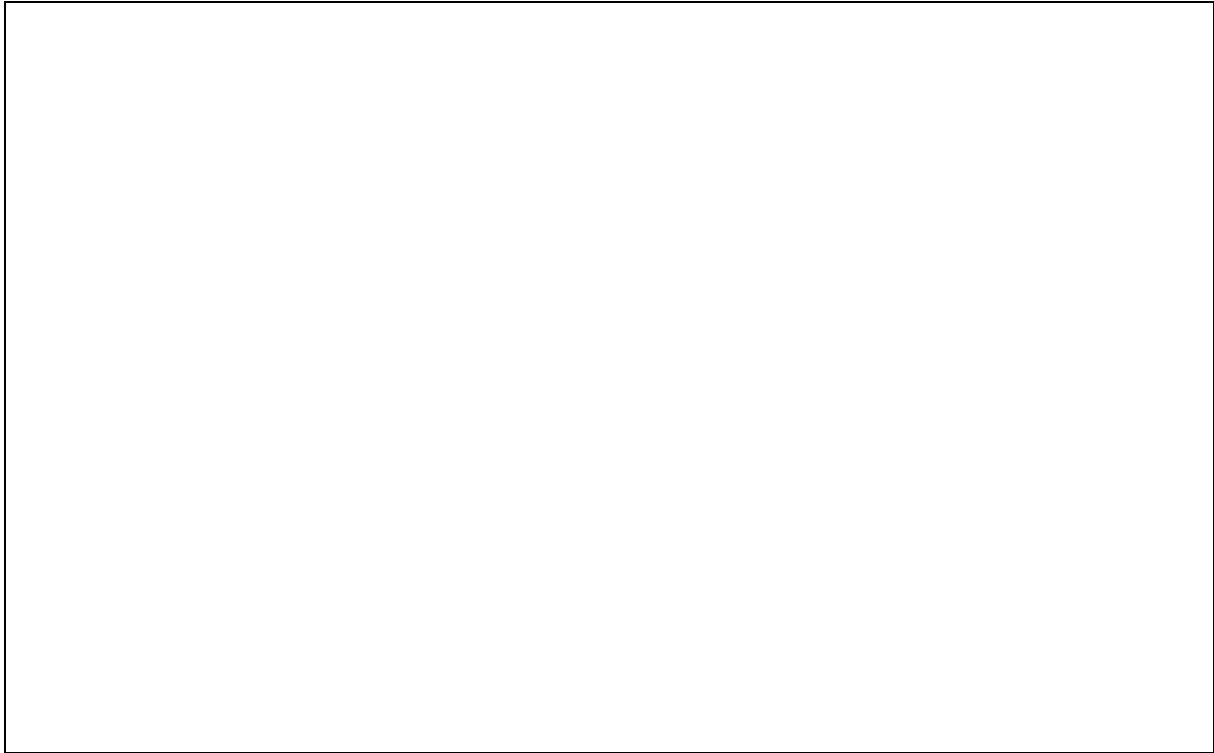
Are all observations included? (Intent-to-Treat)



Pilot/feasibility testing: What needs to be done? (Topic 7)



Dissemination/Implementation Strategy? (Topics 3 & 8)



Weaknesses and how you will manage them?

