

Collaboratory fact sheet and white paper on pragmatic trials

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Audience: Health plan and health care system administrators, clinical staff, academic researchers, drug and medical device representatives—people involved in HCS Collaboratory projects who don't know what PCTs are

Objective: Educate about PCTs including what they are; their unique value in translation, implementation, knowledge acquisition and transfer; use of EHRs in planning, execution, measurement; mission of the HCS Collaboratory and features of the 7 demonstration projects; challenges of informed consent

Format: 1) one-page fact sheet; 2) 2200-word and 3-figure white paper with references

Fact Sheet on Pragmatic Trials

- **Traditional clinical trials often do not lead to clinical improvements.**

- Traditional randomized controlled trials (RCTs) study treatment efficacy using idealized populations and conditions.

- But interventions tested in traditional RCTs often show a “voltage drop”—their impact decreases when they are implemented into everyday practice.

- **Pragmatic trials are designed to improve clinical practice.**

- Pragmatic clinical trials (PCTs) compare treatment options in patients getting care in real-world settings (Figure 1).

- The goal of PCTs is evidence to improve practice and policy.

- PCTs often use electronic health records as abundant, inexpensive data sources on diverse people, their treatments, and their outcomes.

- Health plan administrators, patients and families, industry representatives, and clinical staff contribute to the design, conduct, and translation of PCTs.

- **Pragmatic research is on the rise (Figure 2).**

- The Health Care Systems Research Collaboratory is funding large studies with health care delivery organizations as partners.

- Participating health care systems gain practical evidence on how to improve patient health and satisfaction.

- Findings from PCTs are relevant to decision makers so they are likely to be integrated rapidly into practice and policy.

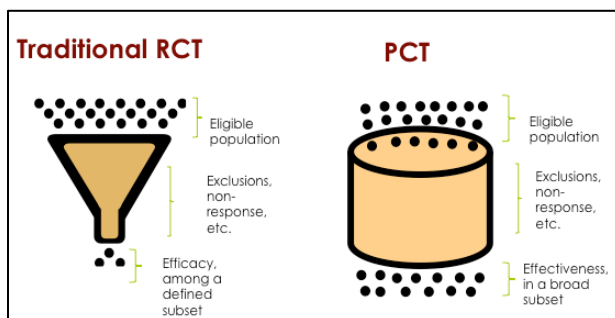


Figure 1. Traditional and pragmatic trials.
Figure from Gloria Coronado, PhD, Kaiser Permanente Center for Health Research.

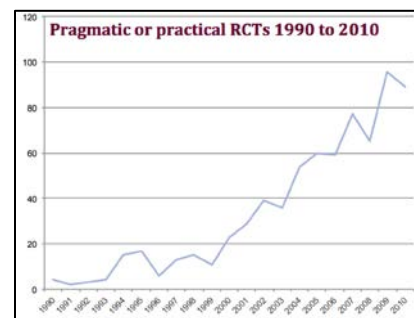


Figure 2. Randomized controlled trials labeled pragmatic or practical, 1990 to 2010.
Figure from Sean Tunis, MD, Center for Medical Technology Policy.

Pragmatic Partnerships to Improve Health Care

This white paper is an overview of pragmatic clinical trials. Find in-depth coverage of pragmatic trial methods, models, and principles in the references.

Through partnerships that capitalize upon our respective strengths, I believe we can work together to achieve our common goal: speeding the movement of scientific discoveries from the lab to patients.

Francis S. Collins, MD, PhD
Director, National Institutes of Health
December 23, 2011¹

Clinical research is more than traditional randomized controlled trials

Clinical research, to many people, means randomized controlled trials (RCTs). In *traditional* RCTs:^{2,3}

- The goals are to determine mechanisms of action, and the causes and effects of treatment;
- The participant population is highly defined and carefully selected and the clinical conditions are tightly controlled to minimize variation;
- Participants are assigned by chance to receive a treatment or a placebo;
- Study protocols are rigid and discourage changes along the way since new data are being collected to test a hypothesis;
- Results are often measured using biological tests such as biomarker changes in blood samples.

Under these idealized conditions, traditional RCTs can detect maximal possible effects and explore the causes and effects of a therapy. Because of this mechanistic focus, traditional RCTs are called *explanatory trials*.^{4,5}

Explanatory RCTs are particularly useful in drug discovery or to fulfill regulatory requirements. However, their idealized conditions mean their results are difficult to translate to the real world. Interventions tested in explanatory trials under controlled clinical settings might be difficult to implement in community clinics or large hospitals with diverse populations. Sometimes, results from traditional RCTs can't be implemented: for example, studies of weight-loss or smoking-cessation interventions often test programs that, even if they get results, are too intensive and costly to be made widely available.⁶

This disconnect between traditional clinical research and routine clinical practice might explain the “voltage drop” from research to practice: Treatments that are highly

efficacious under controlled research conditions often lose power in everyday practice.⁷ This voltage drop might explain our evidence paradox in which 18,000 traditional, explanatory studies are published annually, yet systematic reviews consistently find that we don't have enough evidence to make clinical recommendations.^{8,9}

Enter *pragmatic clinical trials* (PCTs). PCTs are a clinical research model that suits learning health care systems^{2,10} (Fig. 1), in which evidence from research improves clinical practice and in turn, issues raised in practice motivate research. Our current national efforts to rapidly improve clinical care, focus on patient priorities, and boost cost effectiveness are drawing growing attention to learning health care systems and pragmatic trials (Fig. 1).

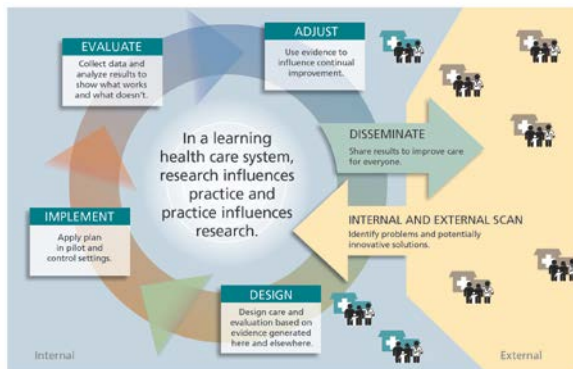


Figure 1. Learning health care system.¹⁰ Figure from Group Health Research Institute.

Pragmatic trials are practical

PCTs can be as varied in topic, method, and design as traditional, explanatory RCTs. PCTs use comparators and controls, but usually compare real-world options instead of a placebo. Randomization occurs in the process of normal health care operations. For example, PCT participants might be randomly assigned to different real-world treatment options, therapeutic strategies or policies. Some basic principles of PCTs are:¹¹⁻¹³

- The primary goal is improving clinical practice;
- The topics are important to people who are affected by the results and who can implement findings: patients, providers, insurers, policymakers, health system administrators;
- Criteria for participants and clinical settings are inclusive so that results are broadly applicable (Fig. 2);
- Comparisons are between existing options in real-world conditions—also known as comparative effectiveness research (CER);
- Results might include measurements of reach, effectiveness in actual clinical practice, and sustainability, including cost comparisons;

- Reports include how successful interventions can be implemented, including conditions under which the intervention works and does not work;
- Measurements are reported in ways that are meaningful to patients, clinical staff, payers, policy makers, and health care system administrators;
- Protocols can adapt to changes at learning health care systems and a dynamic health care environment;
- The explicit purpose “is to be most informative to decision makers.”³

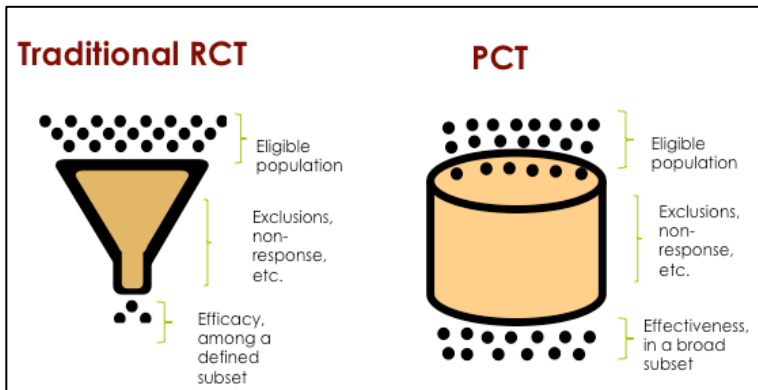


Figure 2. Differences between traditional and pragmatic trials. Figure provided by Gloria Coronado, PhD, Kaiser Permanente Center for Health Research.

Pragmatic trials have a not-so-secret weapon

PCTs study diverse populations of people getting care in real-world settings. For this reason, they often use electronic health records (EHRs or electronic medical records), which contain data on patient care as it is actually practiced.^{2,11} PCTs might collect new data, or they might use only existing data from EHRs or administrative claims. PCTs still have controls or comparators and all this is possible with EHR data.

EHRs can give PCTs a speed advantage over explanatory trials because enrollment is less complicated: data might already be available in EHRs. For studies that recruit participants, EHRs can streamline identification of eligible patients, facilitate communication with participants through EHR secure messaging features, and allow followup data collection that might not require additional in-person contact.

Through national collaborations, researchers can combine data from the EHRs of different health care systems for PCT results that represent diverse populations of people, their treatments, and their outcomes. Of course, this raises challenges that are still being resolved about informed consent requirements using EHRs. As more PCTs are conducted, researchers and institutional review boards will develop acceptable solutions that respect patient privacy and right to consent while facilitating research.

Pragmatic trials drive health care system improvements

Why pragmatic trials now? Traditional research is slow, taking years from proposal to funding to analysis to dissemination. The world is fast, with emerging infectious

diseases, aging populations, rapidly rising conditions such as obesity, new technology (e.g., cancer screening techniques), skyrocketing health care costs, and ever-changing health care policy. PCTs are responsive and might change trial protocols to accommodate technological advances, changes in health system needs, or improvements implemented by care delivery systems.¹⁴

Of particular relevance to health care systems, PCTs advance the efficiency of knowledge acquisition and knowledge transfer. PCTs are conducted in pragmatic settings such as community clinics and hospitals where everyday health care takes place. These are the settings where PCT results will be applied to improve care. Since the site of the research is also the target for implementation of results, and health system management and clinical staff collaborate in the projects, translation is likely to be rapid and effective.¹⁵

Because of their speed, flexibility and potential for translation, PCTs are a priority of policy makers and the medical and research communities. In 2003, the National Institutes of Health (NIH) Roadmap for Medical Research called for moving research results more quickly into practice.¹⁶ The 2009 American Recovery and Reinvestment Act strongly supported CER, signaling US research funding priorities.³ And health care systems and policy makers are striving to apply clinical evidence to eliminate variability in care—not the variation that results from personalized medicine, but from non-evidenced-based treatment and overtreatment that are a danger to patients and lead to unnecessarily high health care expenditures. The fundamental premise of PCTs is to address practical, everyday clinical problems with evidence-based interventions—and funding for them is now available.

If we want more evidence-based practice, we need more practice-based evidence.

Lawrence W. Green, DrPh
University of California, San Francisco¹⁵

Powering up pragmatic trials: the Health Care Systems Research Collaboratory

Practical research is a standing priority of NIH Director Francis Collins, MD, PhD. Dr. Collins was instrumental in establishing the Health Care Systems (HCS) Research Collaboratory, funded by \$11.3 million for its inaugural year from the NIH Common Fund.¹⁷ The HCS Research Collaboratory is engaging health care delivery organizations as research partners in large-scale studies that are relevant to health care practice.

The Collaboratory “will move us beyond traditional methods of participant-level randomized clinical trials to more broad-based, real-world settings,” said Dr. Collins in a 2012 NIH announcement. “Partnerships with health care systems offer an opportunity to transform research and ultimately improve America’s health.”¹⁸ To demonstrate this vision, seven initial projects on a range of public health issues were funded in 2012.¹⁹

- *Strategies and Opportunities to Stop Colon Cancer in Priority Populations*, headed by Gloria Coronado, Kaiser Foundation Research Institute, with the Oregon Community Health Information Network.

This study tests an evidence-based approach to increase colorectal cancer screening in minority and low-income populations. The approach is a health care system-based program tailored for medically underserved populations. The project is a partnership with a community-based network of Federally Qualified Health Centers with a common, integrated EHR.

- *Collaborative Care for Chronic Pain in Primary Care*, led by Lynn DeBar, Kaiser Foundation Research Institute, with Kaiser Permanente Georgia, Northwest, and Hawaii.

In this project, primary care clinical staff are involved in testing a team-based program to help patients manage chronic pain. The study involves more than 250 primary care providers and their diverse patient populations in Georgia, Hawaii, and the Pacific Northwest and addresses a common problem for primary care providers.

- *Pragmatic Trials in Maintenance Hemodialysis*, with Laura Dember, University of Pennsylvania, as principal investigator, and partners Fresenius Medical Care North America and DaVita, the dialysis services division of DaVita HealthCare Partners.

To improve survival and quality of life for patients with kidney failure, a diverse team of health services researchers, academic scientists, and dialysis providers is collecting data from multiple EHRs. Outcomes are based on importance to health care systems and kidney disease patients.

- *Decreasing Bioburden to Reduce Healthcare-Associated Infections and Readmissions*, led by Susan Huang, University of California Irvine, with Hospital Corporation of America and Harvard Pilgrim Health Care.

This project evaluates the effectiveness of antiseptic soap and nasal antibiotic ointment for reducing multidrug-resistant organisms and health care-associated infections during hospitalization. Studies in intensive care units showed this intervention was highly effective. This study extends the investigation to less critically ill patients. The problem addressed is common and costly, with serious consequences for patients.

- *A Pragmatic Trial of Lumbar Image Reporting with Epidemiology (LIRE)*, headed by Jeffrey Jarvik, University of Washington, with Kaiser Permanente Northern California, Group Health Cooperative, the Mayo Clinic, and Henry Ford Health System.

Using readily available data in EHRs, this trial tests the effects of using imaging benchmarks to improve interpretation of diagnostic tests for lower back pain. This simple, inexpensive method could lead to fewer unnecessary tests and less overtreatment of patients.

- *Nighttime Dosing of Anti-Hypertensive Medications: A Pragmatic Clinical Trial*, from Gary Rosenthal, University of Iowa, with Duke University.

This project is developing EHR methods and Web-based means for obtaining informed consent, as well as testing a simple, inexpensive way of possibly improving the effectiveness of medication for high blood pressure.

- *Pragmatic Trial of Population-based Programs to Prevent Suicide Attempt*, led by Gregory Simon, Group Health Research Institute, with Group Health Cooperative, HealthPartners Research Foundation, Kaiser Permanente Colorado, and the University of Pittsburgh Medical Center.

This CER trial builds on recent developments in identifying people at risk for suicidal behavior and providing programs that reduce suicide risk. Two suicide prevention programs are being compared for effectiveness under real-world conditions.

All projects are conducted by teams that, in addition to health services researchers and academic scientists, include partners from health care systems, provider organizations, community health centers, or other multidisciplinary collaborators. The projects use EHRs as efficient and inexpensive tools for recruitment, participant communication and monitoring, data collection, and followup. Randomization is usually at the clinic level rather than the individual level. While diverse in the topics they tackle, all projects work on problems that, if solved, would give health care systems effective, timely, and feasible ways to keep their patients healthier.

In addition to the NIH HCS Collaboratory, pragmatic research has long been funded by individual NIH Institutes and Centers, the Veterans Health Administration, the federal Agency for Healthcare Research and Quality, foundations such as the Robert Wood Johnson Foundation, and internationally, for example by the World Health Organization.

A new, independent agency, the Patient-centered Outcomes Research Institute (PCORI), has about \$3.5 billion through September 2019 to fund patient-focused research, which is often conducted through pragmatic trials. Patient-centered research and pragmatic research share the principle of making the results relevant by involving patients, providers, practitioners, payers, and other stakeholders in study design, conduct of research, and implementation of results. A specific area funded by PCORI is developing methods for patient-centered research, much of which uses EHRs, which will further advance pragmatic research.²⁰⁻²²

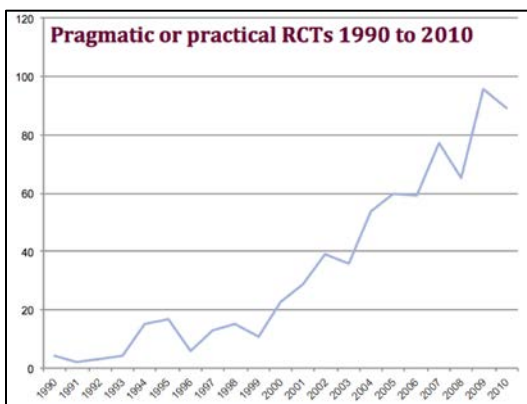


Figure 3. Randomized controlled trials labeled pragmatic or practical, 1990 to

2010. Figure from Sean Tunis, MD, Center for Medical Technology Policy⁹.

Pragmatic trials: watch this space

Pragmatic trials are increasingly part of our rapidly changing health care environment (Fig. 3)^{2,9}. They are relevant to:

- Current federal funding priorities that emphasize CER;
- A focus on patients and shared decision making driven by our increasing capacity for personalized medicine;
- A growing realization that evidence-based guidelines can improve health care and patient safety while containing costs;
- The move towards learning health care systems and other US health care reforms.

Clinical staff, physicians, health plan managers, and care delivery system administrators now have the opportunity to contribute to PCTs by commenting on research priorities and questions, guiding study designs, participating in trials, and helping implement results in ways that improve clinical practice. Current clinical research in general and PCTs in particular emphasize collaboration, so other participants include medical industry representatives, insurers, and patients and their families.

Summary

Results from PCTs help patients, providers, payers, and policy makers choose among real-world clinical alternatives. PCTs are increasingly common. The inclusive, practical, translation-oriented research model of PCTs fits our national priorities of improving clinical care, focusing on patient priorities, and increasing cost effectiveness through evidence-based clinical practice.

Participation in research is an essential dimension of the social compact among the health care delivery system, health care providers, the public, and the scientific enterprises that serve them.

Robert Califf, Duke University Medical Center; Gary Filerman, Atlas Health Foundation; Richard Murray, Merck & Co., Inc.; and Michael Rosenblatt, Merck & Co., Inc.²

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