Lessons Learned from the NIH Health Care Systems Research Collaboratory Demonstration Projects

Lessons Learned as of January 2016

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Introduction

The current healthcare system in the U.S. has been criticized as being overly complex, expensive, and inefficient [1] and pragmatic clinical trials (PCTs) have been lauded as a possible solution that would support a transition to a system in which continual learning is possible [1–3]. These cost-effective, large-scale research studies are designed to address issues that matter to patients, clinicians, and health system workers by comparing interventions in diverse real-world populations [4]. Instead of collecting data through a research-specific, parallel system as in a traditional randomized controlled clinical trial (RCT), data for a PCT are gathered as a part of routine clinical care and harness the data in the electronic health record (EHR). The hope is that PCTs will transform the way the nation gathers information, greatly improve the evidence base, and support the transition to a system of continuous learning for healthcare systems [1,3]. However, use of PCTs is still nascent, and real-word experience with initiating and implementing PCTs is lacking.

Two major initiatives are spearheading the execution of PCTS. First, the Patient-Centered Outcomes Research Institute is a non-profit organization whose mandate is to improve the quality and relevance of evidence available to help stakeholders make informed health decisions. To do this, they fund PCTs for comparative effectiveness research. On October 12, 2015, PCORI posted a funding announcement for pragmatic clinical trials for comparative effectiveness research, improving healthcare system-level approaches to manage care, or eliminating health or healthcare disparities.

Second, to strengthen the national capacity to implement PCTS, the National Institutes of Health (NIH) Health Care Systems Research Collaboratory (Collaboratory) funds Demonstration Projects that support the design and rapid execution of PCTs, address questions of public health importance, include a generalizable population of patients with multiple chronic conditions, and engage healthcare delivery systems as partners [5]. At the Collaboratory Steering Committee meeting in April 2015, those involved with the Demonstration Projects shared their progress and experiences in the Collaboratory. The purpose of this document to share lessons learned to help the future PCT teams, such as those who may apply for PCORI funding, understand the unique challenges of initiating and implementing a PCT.

This document presents problems and solutions for PCT initiation and implementation that were developed by drawing on trial-specific experience in the Collaboratory Demonstration Projects (Table 1). These lessons were shared at the 2015 Collaboratory Steering Committee meeting and based on material from Collaboratory publications.

Table 1. Collaboratory Demonstration Projects

Acronym	Title	Project Goal
PPACT	**P**ain **P**rogram for **A**ctive **C**oping and **T**raining	To coordinate and integrate services for helping patients adopt self-management skills for chronic pain, limit use of opioid medications, and identify factors amenable to treatment in the primary care setting [6].
STOP CRC	**St**rategies and **O**pportunities to Sto**p** **C**olo**r**ectal **C**ancer in Priority Populations	To improve the rates of colorectal-cancer (CRC) screening by mailing fecal immunochemical testing (FIT) tests to patients at Federally Qualified Health Centers (FQHCs). Clinics in the control arm will provide opportunistic CRC screening to patients at clinic visits [7]. Although CRC is 90% curable if caught in time, screening rates are extremely low in patients at FQHCs, which serve nearly 19 million patients annually [8].
SPOT	**S**uicide **P**revention **O**utreach **T**rial	To compare outcomes in patients who receive one of two suicide prevention strategies versus usual care. Strategy 1 is a care management approach, and strategy 2 is an online skills training method designed to help people manage painful emotions and stressful situations [9].
TiME	**Ti**me to Reduce **M**ortality in **E**nd-Stage Renal Disease	To compare hemodialysis sessions of ≥4.25 hours with usual care (no trial-driven approach to dialysis session length). Observational studies indicate that longer hemodialysis session duration is associated with lower mortality, but this has not been evaluated in randomized trials [10].
PROVEN	**P**ragmatic Trial **o**f **V**ideo **E**ducation in **N**ursing Homes	To determine if showing advanced care planning (ACP) videos in nursing homes affects the rates of hospitalization/ person year alive. Patients in nursing homes often have advanced co-morbid conditions, and may get aggressive care that is inconsistent with their preferences. ACP is associated with better palliative care outcomes, but implementation of ACP is inconsistent [11].
LIRE	**L**umbar **I**mage **R**eporting with **E**pidemiology	To determine if inserting epidemiological benchmarks (essentially representing the normal range) into lumbar spine imaging reports reduces subsequent tests and treatments, including cross-sectional imaging (such as magnetic resonance imaging and computed tomography), opioid prescriptions, spinal injections, or surgery. Lumbar imaging frequently reveals incidental findings of disk degeneration that are common in normal, pain-free volunteers [12,13].
ABATE	**A**ctive **Ba**thing **t**o **E**liminate Infection	This study uses antiseptic bathing for all patients and nasal ointments for patients harboring methicillin-resistant *Staphylococcus aureus* (MRSA) to reduce antibiotic resistant bacteria and hospital-associated infections [14].
ICD-Pieces	**I**mproving **C**hronic **D**isease management with **Pieces**	The study uses a novel technology platform (Pieces) to enable use of the electronic health record (EHR) to identify patients with chronic kidney disease (CKD), diabetes and hypertension and to improve care with practice facilitators and within primary care practices or community medical homes [15].
TSOS	**T**rauma **S**urvivors **O**utcomes and **S**upport	Evidence-based treatments for PTSD and comorbidity have not been broadly implemented throughout trauma care systems. This study will use an electronic medical record screen to identify patients; the intervention includes care management, medication and psychotherapy elements [16].

Framework for the design of PCTs

The following framework has been suggested for the design of PCTs: 1) build partnerships, (2) define clinically important questions, (3) assess feasibility, (4) involve stakeholders in study design, and (5) develop study workflows [17]. We will build on this framework to discuss lessons learned from the Collaboratory.

Build Partnerships

The Demonstration Projects required varying levels of engagement with patients, delivery system leaders, IT personnel, clinicians and other frontline providers. According to Jerry Jarvik, the principal investigator (PI) of the LIRE trial, the most important lesson he learned was this: "Work with systems and people that you know and trust and with whom you have good relationships. We had pre-existing, well-established research relationships with the sites, and it helped with engagement with the clinicians, health systems leaders, and with the IRB [18]." Problems and solutions are shown in Table 2.

Table 2. Lessons Learned about Building Partnerships

Project	Problem	Solution
PPACT	Intervention is in the primary care setting where schedules are busy and space is tight.	Teamed with clinicians to understand work flow 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) [4].
STOP CRC	High amounts of leadership turnover at medical director and provider levels due to pre-existing 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.
STOP CRC	Implementation issues and unintended consequences.	Partnered with practice improvement facilitators trained in plan-do-study-act (PDSA), held 1.5-hour in-person meetings with leadership teams from all sites, and asked the sites to submit a PDSA plan for issues and questions with the trial. For example, when there were too many fecal kits submitted without a collection date, the "Plan" was to test new materials that prompted patients to write the collection date on the kits. PDSA cycles empowered clinics to identify and address local problems and provided information about implementation challenges.
ICD-Pieces	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 did, and Stakeholder B could not approve the study before Stakeholder A.	Facilitated in-depth discussions of the project with all the relevant stakeholders on the phone at the same time. Prior history of collaboration among investigators and support from senior officers in the healthcare systems was instrumental in obtaining approval.

Define Clinically Important Questions

Because all healthcare systems have finite financial resources and institutional energy, it is important to align research with organizational goals and performance improvement initiatives [19]. Researchers can work in partnership with administrators, clinicians, practice-based research networks, QI personnel, payers and patients to identify clinically relevant study questions [20]. The Collaboratory Demonstration Projects were specifically chosen because of their high-impact clinical importance and the pragmatic nature of the studies. However, with high-priority questions, it is important to be cognizant of what makes a question timely and relevant: there may be a lack of existing services or there may be services in the healthcare system that may or may not meet the needs of existing patients (Table 3). Alternatively, if a PCT is testing an intervention that addresses a high-priority question, and the intervention is associated with better outcomes, then clinics in the control arm are likely to want to use that intervention with their patients.

Table 3. Lessons Learned from Defining Clinically Important Questions

Project	Problem	Solution
PPACT	Need to understand not only the "what" but also "how" this is a clinically important question.	The researcher, as an outsider, needs to understand whether the intervention is intended to replace poorly functioning existing services or to fill a gap in available care; implications are different for how to involve clinical and operational stakeholders in the process of ensuring smooth implementation.
TiME	Because observational data suggest better outcomes with longer dialysis sessions, dialysis units, including some of those randomized to usual care, have increased session durations for their patients.	In many PCTs, the control group is usual care and is "not controlled". This may require larger sample sizes and a design that allows for rapid completion of the trial.
ICD-Pieces	There was some debate during the planning period about considering as primary outcome all-cause hospitalization versus hospitalizations directly related to the three chronic conditions.	Using de-identified sample data, it was possible to determine that the difference in the number of patients with disease-specific vs. all-cause hospitalizations was small in the study healthcare systems. Ascertainment of all-cause hospitalization required minimal adjudication of the EHR data.

Assess Feasibility

Because of the pragmatic nature of the Demonstration Projects, many of the PIs began by assessing feasibility of using existing data in the EHR. Use of available data is a way to reduce cost and burden and a key feature of a PCT. Greg Simon, PI of the SPOT trial was initially skeptical about using EPIC for population management, but stated at the Collaboratory Steering Committee Meeting that his impression dramatically changed. They used data from EPIC to simulate the trial, perform power calculations, and determine sample size. The head of one of the IT units helped automate the process. Other projects were able to assess feasibility with existing data as well. The PIs from the PROVEN project

were able to check the adequacy of randomization before enrollment. The investigative team of the ABATE project used data from the health system's corporate data warehouse to ensure balance of key variables in randomization. When assessing feasibility using EPIC, it is almost as important to be aware of what is *missing* as what is available (Table 4). Teams also faced challenges with linking EHR systems.

Table 4. Lessons Learned from Assessing Feasibility

Project	Problem	Solution
PPACT	Patient-reported outcomes, such as the Brief Pain Inventory, were not embedded into the system to allow extraction from EPIC.	Build infrastructure, add resources and processes to the system, and use the healthcare system's infrastructure to ensure it was feasible and sustainable within regular clinical workflow.
ICD-Pieces	The investigators did not anticipate some of the delays associated with data validation.	Reallocate funds for additional IT and data analyst efforts.
PROVEN	The team faced challenges linking data from acute care settings and nursing homes. Because the primary outcome is hospitalization rate/person day-alive, the data needed to be matched between nursing homes and hospitals.	Added additional IT resources to help link the systems.
SPOT	Identifying patients at increased risk for suicide attempt is only possible in health systems where providers routinely administer the PHQ9 questionnaire.	At one potential study site, the rate of use of the PHQ9 was low enough that recruitment was not feasible.
TSOS	The study is randomizing 24 level 1 trauma centers across the U.S. Capabilities of the EHR systems are varied, and there is no single administrative database.	The investigative team asked all level I and II trauma centers to complete a survey regarding EHR capabilities and found that while some sites will be able to automate PTSD screening, other sites will need to screen manually [21]. They worked with the Collaboratory's Phenotypes, Data Standards, and Data Quality Core to develop methods that will allow them to work with all sites regardless of capability. They developed a 10 domain EHR screen for risk factors for PTSD and other comorbid conditions.
TSOS	The initiative aims to longitudinally follow trauma patients who are at risk for PTSD and coordinate care from the acute setting to the primary care setting. However, approximately 40% of patients may not have primary care physicians, and this coordination may require re-designing trauma center workflow.	At one pilot site they hired a dedicated person to follow patients from acute to primary care. At another site, they developed a team-based design. They found that the site with a dedicated person was better able to link patients to appropriate care.

Involve stakeholders in study design

Involving healthcare leaders, clinicians, clinical staff, payers, and patients in the design of ta PCT will help align projects with clinical and patient priorities [20]. Ensuring the inclusion of patient perspectives is becoming increasingly important, and organizations such as PCORI require patient and stakeholder engagement in a majority of the research initiatives and projects that it funds [22]. Although not required, patient and stakeholder engagement have been important aspects of Collaboratory Demonstration Projects, and the Stakeholder Engagement Core has provided a forum for a variety of stakeholders to provide feedback on study design and implementation issues of the Demonstration Projects. Patient engagement was crucial to the design of the SPOT trial (Table 5).

For TSOS, the prioritization of the study came in part from the regulatory body that establishes trauma center requirements—the American College of Surgeons Committee on Trauma (ACS/COT). In the most recent guideline from trauma center care, PTSD and depression screening and treatment have been recommended, but not mandated. TSOS will test the feasibility of screening, intervention and referral procedures. The results of the pragmatic trial will be disseminated through the American College of Surgeons; a policy summit with the College is included as part of the UH3 dissemination plan in the final year of the award.

Quality improvement (QI) departments, clinicians, frontline staff, and heath system leaders can provide native processes and resources for PCTs. Lynn DeBar, the PI of PPACT recommends: "Adopt systems and processes that are native to the healthcare system whenever you can. At the various Kaisers, there are systems, processes, and project managers for change initiatives and quality improvement, and I wish we had substantively partnered with them earlier on in the process [23]."

Table 5. Lessons Learned from Involving Stakeholders

Project	Problem	Solution
PPACT & SPOT	Navigating local systems was challenging.	Next time, they will tap the QI infrastructure for their trials. QI project managers are embedded in healthcare systems can guide projects.
SPOT	They had to find the right balance —between assertive and intrusive—for their outreach, but there is no way to understand what level of engagement is necessary until they have the results of the PCT.	The team partnered with people with lived experience of suicidal ideation and self harm to develop and refine their outreach messages and "reduce the chances of getting it all wrong" [24]. They iterated language carefully, borrowing extensively from motivational interviewing and using first-person content for their skills program.

Develop Study Workflows

Each project requires different approaches to the development of study workflows. One of the recurring lessons from the demonstration projects is that everything is more complicated than expected, and workflows at every site are different.

Table 6. Lessons Learned from Developing Study Workflows

Project	Problem	Solution
LIRE	In LIRE, epidemiological benchmarks are inserted into the radiology reports of lumbar images. One of the sites dynamically rendered the information so that when someone looked at the report the benchmark information would pop up. But because of the rendering, there was no way to track whether the information was actually being inserted.	Fixing the problem created another problem: the team inserted the text permanently into the report, but the text was linked to date of viewing instead of date of imaging, although the date of imaging was the desired date for the analysis [25].
TiME	A small change to work flow or the IT system is often viewed as a large change by health system personnel.	More activity than expected was required at the local level and with individual practitioners and administrators to engage the personnel at the facilities.
ICD-Pieces	The study team initially planned for structured, step-wise electronic tools that were time consuming to use but would provide a detailed therapy plan.	After discussing the tool with medical directors and physicians, they developed more user-friendly, less burdensome tools.
ICD-Pieces	Management of multiple chronic conditions varies across different healthcare systems.	Study facilitators developed different workflows to accommodate the variations in resources at every site. These were roles in the healthcare systems and required more multidisciplinary review of the proposed workflows.

An additional obstacle for the LIRE team was the difficulty they had in paying the health system IT programmers. In certain systems, it wasn't initially possible to transfer money to the appropriate departments, and this may have made their intervention less of a priority.

Consider IRB and Regulatory Issues

Some of the biggest lessons learned had to do with Institutional Review Board (IRB), regulatory and policy issues.

Table 7. IRB and Regulatory Lessons Learned

Project	Problem	Solution
SPOT	The process took an additional 9 to 10 months 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 appropriate consent was a challenge [24].
TiME	Fundamental questions about minimal risk also arose for TiME—a trial that enrolls a high-risk population (patients with end-stage renal disease) and has an outcome of mortality.	The incremental risk of the research was considered minimal both from a medical standpoint and because treating physicians and patients maintain autonomy with respect to intervention implementation.
STOP CRC	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.
TSOS	The DSMB charged with study oversight initially suggested that the team to report every hospitalization as a serious adverse event, but in their cohort of people who are at risk for PTSD, approximately 15-20% are re-hospitalized for non-emergent reasons.	Negotiation was required.
TSOS	DSMB members suggested that the study team ensure that every site distributes a suicide hotline number to patients at baseline. However, only one of the 24 sites routinely gives a suicide hotline number; therefore, the study team did not implement this suggestion.	As in all PCTs, the usual care condition is not malleable, and the goal is to compare to usual care.
ICD-Pieces	It was unclear whether the study would require informed consent; the study would not be feasible if traditional informed consent was required.	The study met minimal risk criteria and a waiver of consent was granted. In addition, information about the study is available to patients at all participating sites, and a process was put in place to honor any request from patients to have their data removed from the study.

Consider Potential Issues with Biostatistics and the Analytic Plan

The STOP CRC team partnered with Federally Qualified Health Centers (safety net clinics) to try to improve colorectal screening rates in underserved populations. They needed to develop an analytic plan that was flexible enough to account for the use of real-time EHR tools and adaptable enough for community healthcare settings, where patient populations are generally in flux for a variety of reasons. Updates in real-time with the use of the EHR meant that the lists of eligible and active patients at the clinics were continuously changing, which caused discordance between the lists that had been gathered for research purposes [26]. Specifically, it caused the research denominator to be greater than the clinic denominator, meaning the effect size would be underestimated. This problem resulted from the pragmatic design, was unexpected and not accounted for in the original analytic plan. The team worked with the Biostatistics and Study Design Core to resolve the issue. Although the primary analytic plan needed to stay the same for the integrity of the research, the core suggested a secondary analysis. The primary outcome will be based on the rate of fecal testing 12 months after a patient is identified as *eligible*, and the secondary outcome will be based on any CRC screening 12 months after the *intervention,* using screening rates calculated via Uniform Data Systems.

Table 8. Biostatistical Lessons Learned

Project	Problem	Solution
STOP CRC	Updates in real-time with the use of the EHR meant that the lists of eligible and active patients at the clinics were continuously changing, which caused discordance between the lists that had been gathered for research purposes [26].	The team worked with the Biostatistics and Study Design Core and added a secondary analysis; see above for details.
PROVEN	They did not want to recruit facility leadership to participate in the study and then be told that they were assigned to control since the partners felt that all facilities would want to have the videos.	They chose to "pre-randomize" by first applying eligibility criteria to existing data on all of the partner facilities and then gave them the opportunity to exclude other facilities based on recent leadership changes, etc. They then divided facilities into a priori strata and randomly selected the 120 treatment facilities from the pool, leaving the rest as controls. In this way, no facilities that wanted to participate were "disappointed," and the partners were confident that they would have a high participation rate.
ICD-Pieces	Initial sample size was based on broad estimates of the prevalence of multiple chronic conditions across the healthcare systems, and was limited by lack of cluster-level detailed information.	In the planning phase, the cluster units were re-defined from individual practitioners to practice sites. The team queried EHR systems with the new cluster definition and collaborated with biostatisticians at the NIH and the Biostatistics and Study Design Core to establish appropriate sample size.

Summary

Initiating and implementing PCTs requires resiliency, flexibility, and problem-solving skills. All the Demonstration Projects met with unforeseen challenges, and the overarching lesson learned is that nothing is a simple as one thinks it will be. To succeed the project team needs to build partnerships, identify clinically relevant questions, assess feasibility, involves stakeholders in study design, and develop study workflows.

Appendix A: Resource Materials

Clinical Trials Transformation Initiative (CTTI): Advancing the use of central IRBs for multicenter clinical trials

Toolkit for designing multi-center cluster randomized trials.

A Guide to Research Partnerships for Pragmatic Clinical Trials

Karin Johnson Slide Presentation: Introduction the Pragmatic Clinical Trials

Living Textbook Chapters: Regulatory Issues and Informed Consent.

Patient-Centered Outcomes Research Institute (PCORI)

National Patient-Centered Clinical Research Network (PCORnet)

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