NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Lessons From the First Decade of the NIH Pragmatic Trials Collaboratory

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Housekeeping

- All participants will be muted
- Enter **all questions** in the Zoom **Q&A/chat box** and send to Everyone
- Moderator will review questions and ask them at the end
- Want to continue the discussion? Associated podcast released about 2 weeks after Grand Rounds
- Visit impactcollaboratory.org
- Follow us on Twitter & LinkedIN:

 @IMPACTcollab1 https://www.linkedin.com/company/65346172

Learning Objectives

Upon completion of this presentation, you should be able to:

- Understand the goals of the NIH Pragmatic Trials Collaboratory
- Describe the state of the science of pragmatic trials based on experiences from the Collaboratory's first decade
- Identify opportunities for advances in pragmatic trials methodology

Today's Presentation

10 Years of the NIH Pragmatic Trials Collaboratory

- Why We Started
- Where We've Been
- What We've Learned
- What Lies Ahead

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Why We Started

Millions

Patients **walk through the doors** of hospitals and clinics each year **with questions** about their health and their care.

?

How do we **study their experiences** to **find answers** and **create solutions** that **change care** and **improve outcomes**?

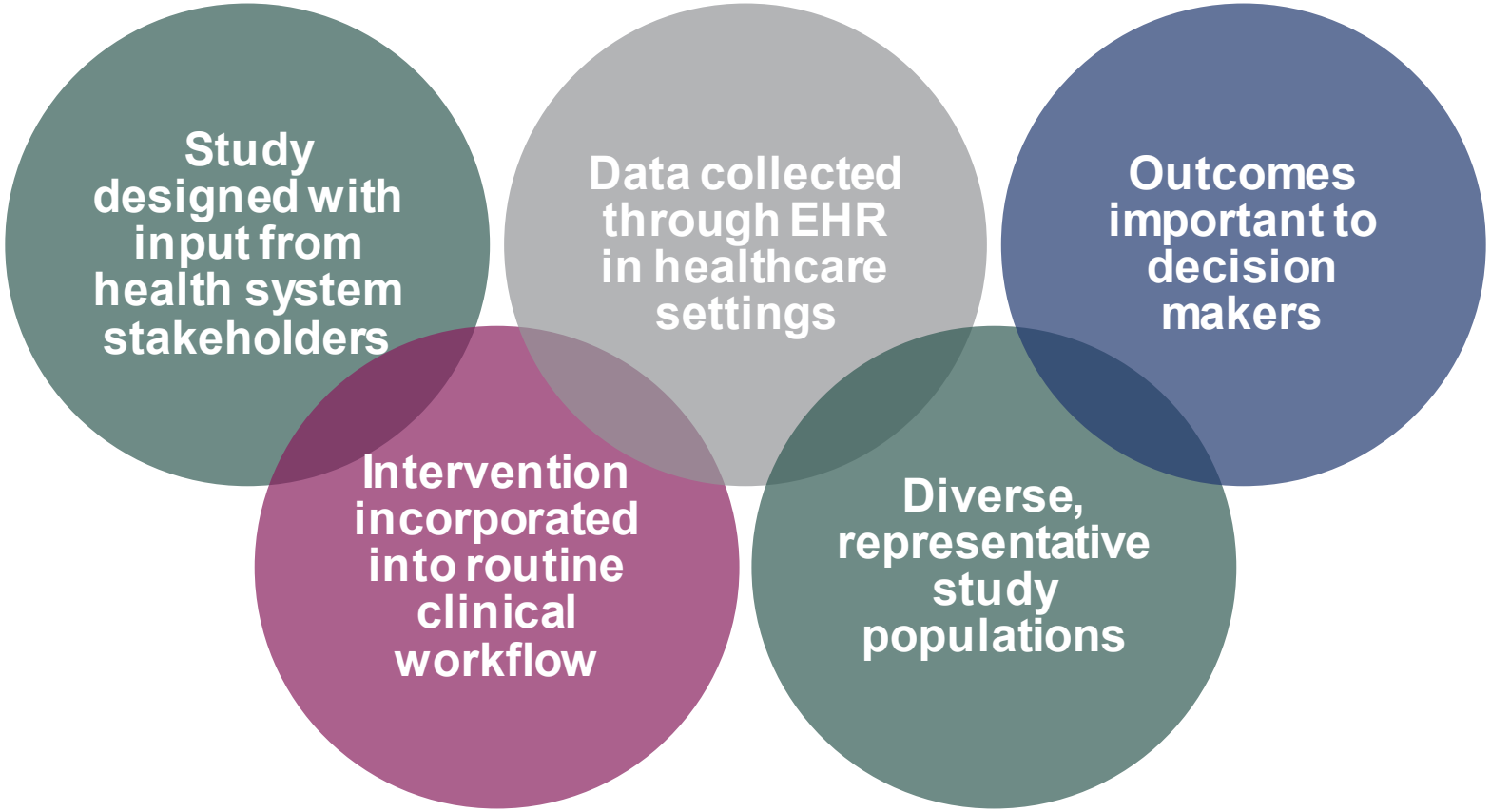
Our Story

Initiated through the NIH Common Fund in 2012

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

Vision: Support the design and execution of innovative pragmatic clinical trial Demonstration Projects to establish best practices and proof of concept

Embedded PCTs Bridge Research Into Clinical Care



NIH Pragmatic Trials Collaboratory

- Amazing opportunity to use new information and clinical learning to inform and change the system
- Program provides a fascinating vantage point for the transformation
  - Tremendous progress and opportunity
  - Show how to overcome the hurdles or speed bumps

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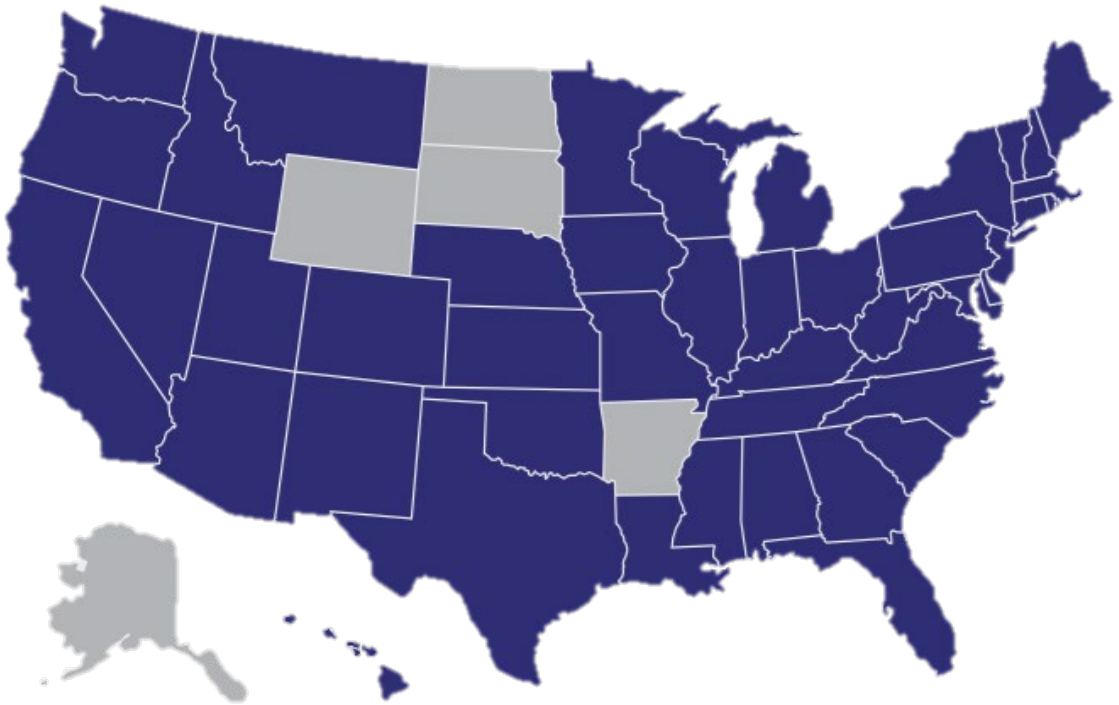
Where We've Been

Demonstration Projects

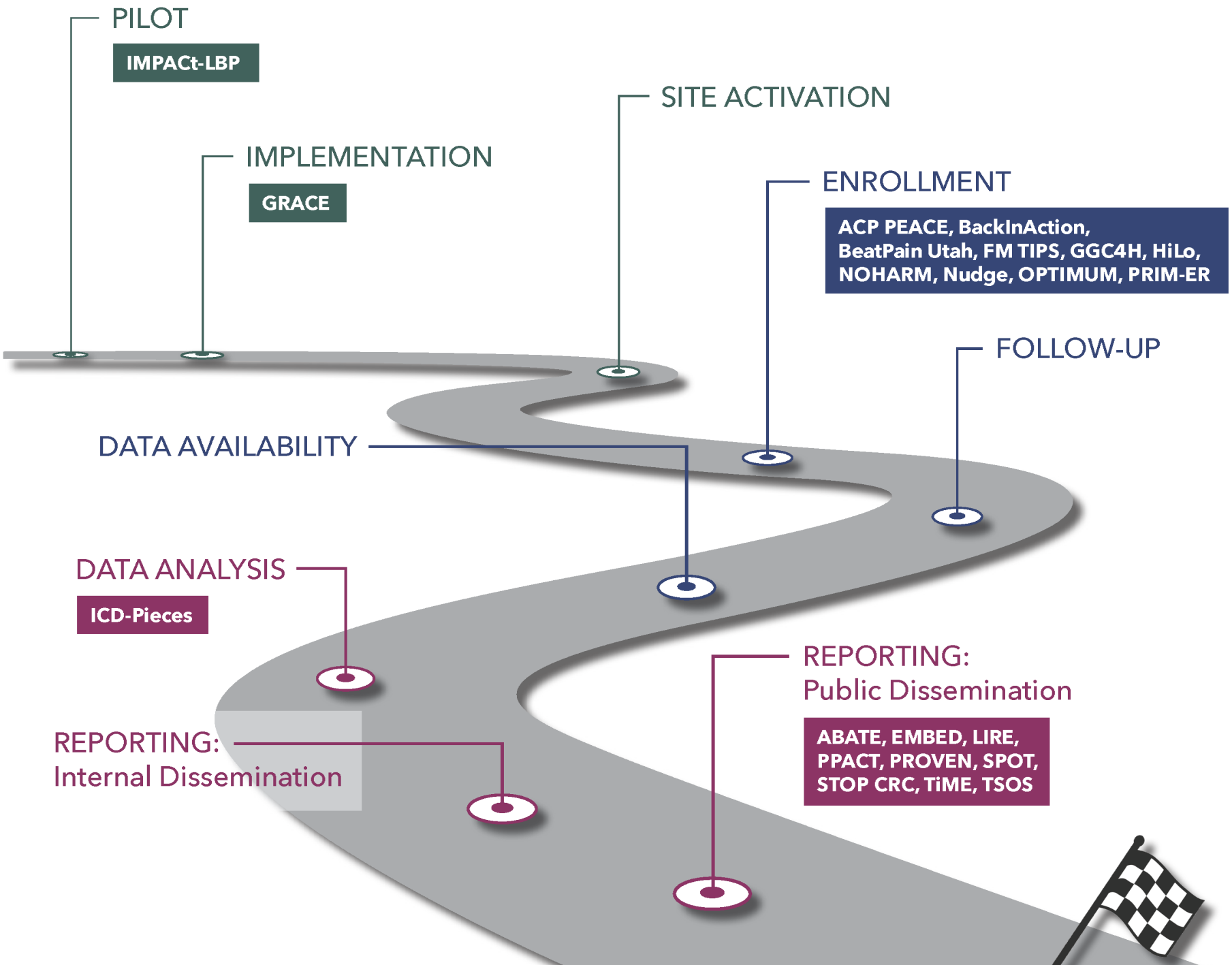
- Pragmatic trials embedded in healthcare systems to address questions of major public health importance
- Projects span multiple NIH Institutes, Centers, and Offices
- Projects have 1-year planning phase followed by implementation phase

Reach of Demonstration Projects

>1,100 clinical sites across 90% of the United States



Over 752,000 active subjects


PILOT
IMPACt-LBP
IMPLEMENTATION
GRACE
SITE ACTIVATION
ENROLLMENT
ACP PEACE, BackInAction, BeatPain Utah, FM TIPS, GGC4H, HiLo, NOHARM, Nudge, OPTIMUM, PRIM-ER
FOLLOW-UP
DATA AVAILABILITY
DATA ANALYSIS
ICD-Pieces
REPORTING: Internal Dissemination
REPORTING: Public Dissemination
ABATE, EMBED, LIRE, PPACT, PROVEN, SPOT, STOP CRC, TiME, TSOS

A Bird’s-Eye View of Our Demonstration Projects

Trial Designs

Parallel Groups With Individual Randomization	Parallel Groups With Cluster Randomization	Stepped-Wedge Cluster Randomization
BackInAction	ABATE Infection	ACP PEACE
BeatPain Utah	EMBED	LIRE
GRACE	FM-TIPS	NOHARM
HiLo*	GGC4H	PRIM-ER
Nudge	ICD-Pieces	TSOS
OPTIMUM	IMPACt-LBP	
SPOT	PPACT	
	PROVEN	
	STOP CRC	
	TiME	

* HiLo switched from cluster randomization to individual randomization after recruitment began.

Approaches to Notification/Authorization

Design	Waiver of Consent	Individual Consent	Notification or Opt-Out
Parallel groups with individual randomization	SPOT	BackInAction BeatPain Utah GRACE IMPACt-LBP OPTIMUM	Nudge
Parallel groups with cluster randomization	ABATE Infection EMBED PROVEN STOP CRC	FM-TIPS GGC4H HiLo PPACT	ACP PEACE ICD-Pieces TiME
Stepped-wedge cluster randomization	LIRE NOHARM PRIM-ER TSOS		

Severity and Intervention Type

Baseline Severity	Therapeutic Intervention	⟷	Operational or Educational Intervention
End of life			PROVEN
Metastatic cancer			ACP PEACE
Acute	TSOS ABATE Infection	EMBED SPOT	NOHARM PRIM-ER
Multiple chronic conditions	BackInAction HiLo TiME		ICD-Pieces Nudge
One chronic condition	BeatPain Utah FM-TIPS GRACE OPTIMUM PPACT	IMPACt-LBP	LIRE
Healthy		STOP CRC	GGC4H

Severity, Intervention Type, and Target

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Target of intervention = patient; clinician; or patient and clinician.

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Age of Patients

Adults		Adolescents	Younger Children
ACP PEACE	NOHARM	GGC4H	
ABATE Infection	Nudge		
BackInAction	OPTIMUM		
BeatPain Utah	PPACT		
EMBED	PRIM-ER		
FM-TIPS	PROVEN		
GRACE	SPOT		
Hi-Lo	STOP CRC		
ICD-Pieces	TiME		
IMPACt-LBP	TSOS		
LIRE			

Uses of Electronic Health Records

Trial	Eligibility Determination	Intervention Delivery	Outcome Assessment
ACP PEACE	■		■
ABATE Infection	■	■	■
BackInAction	■		■
BeatPain Utah	■		■
EMBED	■	■	■
FM-TIPS			■
GGC4H	■		■
GRACE			■
Hi-Lo	■	■	■
ICD-Pieces	■	■	■
IMPACt-LBP			■
LIRE	■	■	■
NOHARM	■	■	■
Nudge	■		■
OPTIMUM	■		■
PPACT	■	■	■
PRIM-ER		■	
PROVEN			■
SPOT	■	■	■
STOP CRC	■	■	■
TiME	■	■	■
TSOS	■	■	■

Completed Demonstration Projects

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

- Intervention: EHR-embedded tool to identify patients overdue for colorectal cancer screening and mail a fecal immunochemical test kit to them
- Results
  - Higher screening rates overall in intervention clinics compared with control clinics
  - Low and highly variable implementation rates among participating clinics

STOP CRC

Challenge	Solution
Inadequate capacity at some clinics to immediately activate EHR tool	Regular teleconferences with clinic and data coordinating center representatives
Analysis challenges due to system-level HER upgrades and clinic-level delays	Consultation with Biostatistics and Study Design Core to modify statistical analysis and develop secondary analysis
Lack of reliable data on colonoscopies	Validation of available colonoscopy codes and chart audits
Difficulty motivating clinic staff to learn new technology and process	Frequent contact with clinics; offers of training and support; advisory board of clinic staff with quarterly conference calls, annual meetings

ABATE Infection *Active Bathing to Eliminate Infection*

- Intervention: Decolonization with universal chlorhexidine and targeted nasal mupirocin in non–critical-care units

- Results
  - No overall reduction in methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE) clinical cultures
  - In post hoc analyses of patients with medical devices, significant reductions in all-cause bloodstream infections and MRSA/VRE clinical cultures

ABATE Infection

Challenge	Solution
Concurrent quality improvement initiatives competing with study intervention	Monthly tracking and review; encouragement to delay, limit competing initiatives
Changes in site leadership, trial unit names for identifying site locations	Study champions asked to disclose changes during monthly coaching calls
Need for data cleaning, standardization greater than anticipated	Increased programming effort budgeted for data cleaning and standardization
Requirement for dedicated ethical oversight for any prisoner admitted to non-ICU area during trial	Identification of participating site with prisoner on IRB to provide oversight

TiME *Time to Reduce Mortality in End-Stage Renal Disease*

- Intervention: Minimum hemodialysis session duration of 4.25 hours for patients with end-stage renal disease beginning maintenance hemodialysis
- Results
  - Trial discontinued early due to insufficient difference in mean hemodialysis session duration between intervention and usual care groups
  - No observed reduction in mortality or hospitalization rate in either group

TiME

Challenge	Solution
Difficulty implementing intervention due to lack of on-site research staff, implementation by clinicians rather than researchers	Use of multiple approaches to engage facility personnel and participating patients during all stages of trial design and conduct
Incomplete ascertainment of patient-reported outcome already being used routinely in clinical practice	Adding processes to those already being used in clinical practice

LIRE *Lumbar Imaging With Reporting of Epidemiology*

- Intervention: In lumbar spine imaging reports, insertion of age-appropriate prevalence data for common imaging findings in individuals without back pain

- Results
  - No reduction in spine-related healthcare utilization
  - In prespecified secondary analyses, slight reduction in subsequent opioid prescriptions, and lower spine-related healthcare utilization among patients for whom computed tomography was the imaging modality

LIRE

Challenge	Solution
Harmonizing data across multiple healthcare systems	Distributed standard data dictionary and iteratively addressed discrepancies between sites, communicating frequently with regular conference calls involving key personnel
Changes in personnel over time	Strong local leadership in site PI who was an engaged and proactive partner in helping to recruit and replace study personnel
Accounting for temporal trend of opioid decrease as confounder due to the stepped-wedge design	Modeling to account as much as possible for this potential confounder

PROVEN *Pragmatic Trial of Video Education in Nursing Homes*

- Intervention: Delivery of short advance care planning videos to nursing home residents or their proxies on admission and every 6 months

- Results
  - No reduction in hospital transfers, no decline in burdensome treatment use, and no increase in hospice enrollment among long-stay nursing home residents with or without advanced illness
  - Low level of intervention fidelity highlights challenges of implementing new programs in nursing homes

PROVEN

Challenge	Solution
Low implementation fidelity	High level of buy-in from frontline staff responsible for implementing the program, and strong endorsement from healthcare system leadership
Healthcare system interactions	Strong relationships with healthcare systems before the study; study-specific project manager in each healthcare system to oversee the project and serve as liaison between research team and healthcare system

TSOS *A Policy-Relevant US Trauma Care System Pragmatic Trial for PTSD and Comorbidity*

- Intervention: Collaborative care consisting of evidence-based medication, cognitive behavioral therapy, and case management among adults with traumatic injury and high levels of distress

- Results
  - Significant PTSD symptom reductions at 6 months, but not 3 or 12 months
  - Greater treatment effects among patients with greater baseline risk for PTSD and centers with good or excellent protocol implementation

TSOS

Challenge	Solution
Multiple site-level factors that influenced intervention quality and treatment outcomes (such as variability in site leadership stability) yet were not captured in baseline structured assessments	Development of Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE) method for capturing pragmatic trial implementation processes, allowing for secondary analyses that assess associations between site implementation processes and individual-level treatment effects
Biostatistics and study design issues	Working with the lead statistician and the Biostatistics and Study Design Core to avoid significant barriers
Lag time between publication of pragmatic trial results and integration of research findings into US trauma care systems	End-of-study policy summit to ensure integration of trial findings into American College of Surgeons Committee on Trauma policy

PPACT *Collaborative Care for Chronic Pain in Primary Care*

- Intervention: Primary care–based interdisciplinary behavioral intervention among patients receiving long-term opioid therapy for chronic pain
- Results
  - Modest but statistically significant and sustained reductions in pain impact, pain-related disability, and benzodiazepine use
  - No significant difference in opioid use between groups

PPACT

Challenge	Lesson
Competing change initiatives and quality improvement efforts	Adopt systems and processes native to the healthcare system, and partner with quality improvement managers
Patient-reported outcomes not embedded into system in a way that enabled pulling data from EHR	Build infrastructure, processes, and additional resources into system ahead of time to gather this information
Intervention was challenging because it required different clinical skill set to harmonize support of patients' self-care efforts with traditional treatments	Close work with clinicians and other stakeholders to sustain healthcare system investment in intervention

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What We've Learned

Spirit of Openness Fuels Progress

- Program's success depends on willingness of investigators to share their challenges in real time with the rest of the network, including NIH staff
- In many research enterprises, investigators feel motivated to present an image of perfection to everyone outside their project and especially sponsors
- Good faith, generosity, and candor of NIH Collaboratory investigators allows transformation of challenges into lessons that can be shared with the broader community

Planning Phase Is Essential

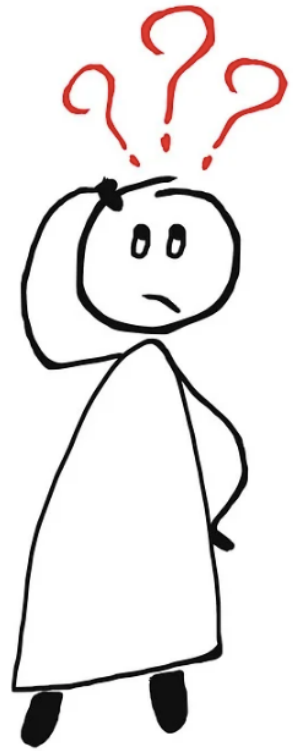
- Nothing is “plug and play” in a PCT within a healthcare system
- Planning phase allows further engagement with stakeholders, consultation with other experts, and collection of pilot data
- Resulted in important protocol changes in all Collaboratory trials
- Despite planning, challenges often arise during execution requiring midcourse corrections

Early and Ongoing Engagement Is Critical

- With healthcare systems
  - Need strong and trusting partnerships
  - Align research and organizational goals
- With clinicians
  - Ensure intervention can be added into existing workflows as seamlessly and with as little burden as possible

Uncertainty of Ethics and Regulatory Frameworks

- Ambiguity about how best to protect rights and welfare of participants in pragmatic trials context
  - How to define “minimal risk” in high-risk populations
  - Appropriate reporting of adverse events
  - Challenges applying standard ethics and regulatory frameworks



Unanticipated Changes Can Occur

- In conventional randomized controlled trials, it is possible to exert significant control over what happens in the study arms
- In pragmatic trials, investigators can face:
  - Competing initiatives at study sites
  - Provider resistance due to burden
  - Poor implementation fidelity due to staff turnover

- Careful monitoring of study sites can help investigators prevent, or at least describe, changes that might affect the study comparison

Leveraging EHRs Adds Complexity

- Challenges include
  - Need for cross-site data standardization
  - Site-level differences in preferred methods for implementing standardized assessment tools
  - Integration of study-related data elements into EHRs optimized for clinical practice or billing

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What Lies Ahead

Implementation Science and Hybrid Designs

- Traditionally, trials that examine effectiveness are followed by trials that study implementation
- Research that examines both intervention effectiveness and successful implementation could
  - Accelerate advances in practice
  - Provide better information for decision makers
  - Make changes smoother and more effective

Addressing Health Equity

- Pragmatic trials well positioned to reduce barriers to research participation that have historically limited diversity in trials
- However, barriers to care mean patients who access healthcare systems not always representative of larger community
- Collaboratory poised to explore methods for
  - Diversifying research sites
  - Engaging with stakeholders to improve diversity, equity, and inclusion in research

Conclusions

- Take advantage of continued interest in real-world evidence and learning health systems
- Multiple lessons learned from rethinking research integrated with practice
- Cost-effective, large-scale research is possible, and we have the charge to scale it…
  - By learning, sharing, and helping the ecosystem evolve

Questions?