Program Success and Evolution

- Common Fund gave support for new ways to think about clinical research and allowed these ideas to take hold by demonstrating feasibility and rigor.

- Successful transition from Common Fund to IC support showed appreciation of the program’s value and uptake among broad group of ICs.

- Integration with NIH HEAL Initiative extended the program’s reach into a major NIH-wide program to address the overdose and pain crisis.

- Informed other NIH initiatives (PMC & IMPACT) using ePCTs to address major health challenges:
  - Pain Management Collaboratory (PMC) in military and Veterans healthcare systems
  - People living with dementia and their care partners (IMPACT Collaboratory)
Program Reach

Supports 32 large-scale, high-impact ePCTs

- 14 NIH Institutes and Centers
- >1400 clinical sites
- >1.2 million patients
- 49 US States and Puerto Rico

No sites in Arkansas
Partnerships

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

- Grand Rounds
- Workshops
- Publications
- Living Textbook
- Tools
- Resources
- Knowledge

COLLABORATION

SHARING
Participants (Total)

Total Subjects

Sex

- Unknown
- Male
- Female

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®
Participant Race and Ethnicity (Total)

Hispanic or Latino

Non-White Race

US population (reference)

US population (reference)
### NIH Collaboratory Trial Populations

<table>
<thead>
<tr>
<th>Participant Age</th>
<th>Health Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 adult</td>
<td>2 healthy</td>
</tr>
<tr>
<td>1 pediatric</td>
<td>10 one chronic condition</td>
</tr>
<tr>
<td></td>
<td>8 multiple chronic conditions</td>
</tr>
<tr>
<td></td>
<td>10 acute</td>
</tr>
<tr>
<td></td>
<td>2 end of life</td>
</tr>
</tbody>
</table>

- **Participant Age:** 31 adults, 1 pediatric
- **Health Condition:**
  - 2 healthy
  - 10 with one chronic condition
  - 8 with multiple chronic conditions
  - 10 acute
  - 2 end of life
# NIH Collaboratory Trial Designs

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Intervention Type</th>
<th>Intervention Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 parallel group with individual randomization</td>
<td>13 therapeutic</td>
<td>21 patient</td>
</tr>
<tr>
<td>13 parallel group with cluster randomization</td>
<td>13 operational/educational</td>
<td>7 clinician</td>
</tr>
<tr>
<td>6 stepped-wedge cluster randomization</td>
<td>6 mix</td>
<td>4 patient and clinician</td>
</tr>
</tbody>
</table>
NIH Collaboratory Trials: Use of EHRs

Eligibility determination: 27 trials

Intervention delivery: 19 trials

Outcome assessment: 31 trials

At least 25 different EHR systems
Ten Trials Completed and Published

- STOP CRC
- TiME
- ABATE Infection
- PROVEN
- LIRE
- TSOS
- PPACT
- SPOT
- EMBED
- ICD-Pieces
Research

Evidence

Care

NIH PRAGMATIC TRIALS COLLABORATORY

Question:
Does daily antiseptic bathing reduce drug-resistant infections in hospitalized (non-ICU) patients?

Pragmatic Trial:
53 hospitals randomized to routine care or intervention

Clinical Impact:
Adopted intervention in all health system hospitals for patients with medical devices
Implementation toolkit published for hospitals

Results:
Negative primary outcome but reduced infections in patients with medical devices

Study Population:
>500,000 patients with 20 million data records

NIH Collaboratory Support:
• Regulatory: Consulted regarding FDA oversight
• Data: Advised on data standardization, cleaning, and sharing
• Engagement: Underscored partnerships between health systems and researchers

Implementing Intervention:
Adopted intervention in all health system hospitals for patients with medical devices
Implementation toolkit published for hospitals

Clinical Impact:
Adopted intervention in all health system hospitals for patients with medical devices
Implementation toolkit published for hospitals

Research

Evidence

Care

NIH PRAGMATIC TRIALS COLLABORATORY

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NIH Collaboratory Support:
• Regulatory: Consulted regarding FDA oversight
• Data: Advised on data standardization, cleaning, and sharing
• Engagement: Underscored partnerships between health systems and researchers
Question: Does an EHR-based outreach program with mailed stool-tests improve rates of colorectal cancer screening?

Results: Significantly improved screening rates

 NIH Collaboratory Support:
- Biostatistics: Extensive support to modify analysis, develop secondary analysis
- Data: Helped team learn and implement standards and methods for validating EHR code
- Overall: Knowledge sharing, troubleshooting

Clinical Impact:
Adopted intervention in at least 150 clinics

Implementation materials published to support uptake

Study Population:
>40,000 patients and ~6,300 mailed stool-tests

FQHC, federally qualified health center
**Question:** Can an interdisciplinary intervention improve chronic pain among patients receiving long-term opioid therapy?

**Results:** Improved pain, disability, and care satisfaction; no change in opioid use

**Study Population:** 850 patients

**Pragmatic Trial:** 273 PCPs randomized to routine care or intervention

**Clinical Impact:** Intervention partially sustained in many clinics

**App for patients developed by managed care organization**

**NIH Collaboratory Support:**
- **Regulatory:** Facilitated conversations with IRBs
- **Engagement:** Discussed challenges and strategies for working with providers, clinic leaders
- **Patient-centered outcomes:** Learned from researchers in other fields

**NIH PRAGMATIC TRIALS COLLABORATORY**

**PCP, primary care provider**
Sharing Trial Data and Resources

**STUDY TOOLS**
- Protocols
- Consent forms
- Implementation tools
- Site materials
- Questionnaires
- Toolkits
- Ethics and regulatory documentation

**DATASETS AND DOCUMENTATION**
- Data dictionaries
- Public use datasets
- Analytic code
- Computable phenotypes
- Data quality manuals
- Data request forms
- Data sharing checklists

77 study tools

17 datasets and documentation
Core Working Groups
Impact of Cores

>225 trial consultations

>150 publications & products

>1,000 Core meetings

PI Testimonials

“Take the Biostats Core Working Group advice seriously—get it early and act on it early.”

“The CC helped greatly with the selection of our secondary outcome measures.”

“Have as many key members of your team work closely with Collaboratory Cores.”

“Having adjusted our strategy prior to IRB submission based on input from the Core was likely a major reason the IRB review went so smoothly.”
Biostatistics and Study Design Core: Impact Highlights

Key products

- Living Textbook chapters on study designs and analysis plans
- Intraclass Correlation Coefficient Cheat Sheet
- Statistical Analysis Plan Checklist for Addressing COVID-19 Impacts
- “Design and Analysis of ePCTs” workshop and Grand Rounds series

Major achievements

- Consultations had a direct impact on many NIH Collaboratory Trials, resulting in revised:
  - Statistical analysis plans
  - Sample sizes
  - Trial designs
- Substantial contributions to literature on design and analysis of group-randomized trials
Biostatistics and Study Design Core: Key Publications

- An evaluation of constrained randomization for the design and analysis of group-randomized trials
- Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: an overview
- Designing three-level cluster randomized trials to assess treatment effect heterogeneity
Cluster randomization

Stepped-wedge designs

Missing data

Extracting usable data from EHRs

Intraclass correlation

Variable cluster sizes and heterogeneous treatment effects
Electronic Health Records Core: Impact Highlights

Key products

- Living Textbook chapters on using real-world data and EHR-based phenotyping
- Assessing Data Quality guidance document
- Data and resource sharing information and checklists
- Workshop series on advances in digital health, EHRs, and ePCTs

Major achievements

- Developed data and resource sharing materials to help the NIH Collaboratory Trials identify their sharing plans and promote posting of materials at closeout
- Established the NIH Collaboratory’s Distributed Research Network and executed data queries
Clinical phenotyping in selected national networks: demonstrating the need for high-throughput, portable, and computational methods

Collecting patient-reported outcome measures in the EHR: lessons from the NIH Pragmatic Trials Collaboratory

Potential bias and lack of generalizability in EHR data: reflections on health equity from the National Institutes of Health Pragmatic Trials Collaboratory
Electronic Heath Records Core: Evolution of Topics

- **Computable phenotypes**
- **Acquiring real-word data**
- **Data sharing**


- **Data meaning and quality**
- **Assessing fitness for use of real-world data**
- **Potential bias and lack of generalizability in EHR data**
Ethics and Regulatory Core: Impact Highlights

**Key products**
- Foundational scholarship on ethics and regulatory issues in ePCTs
- Data Monitoring Committee Charter
- Points to Consider in Data Monitoring for ePCTs
- 8 Living Textbook chapters
- Documentation of ethics and regulatory consultations with NIH Collaboratory trials

**Major achievements**
- Consulted with each NIH Collaboratory Trial on ethical and regulatory issues
- Organized workshops on ethical and regulatory aspects of ePCTs
- Conducted substantial empirical research on stakeholder perspectives on ePCTs
Ethics and Regulatory Core: Key Publications

- Special issue of 12 articles exploring ethical and regulatory issues in pragmatic clinical trials
- Toward meeting the obligation of respect for persons in pragmatic clinical trials
- Post-trial responsibilities in pragmatic clinical trials: fulfilling the promise of research to drive real-world change
Ethics and Regulatory Core: Evolution of Topics

Relation between pragmatic trial interventions and standard of care

- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020
- 2021
- 2022
- 2023
- 2024

Data monitoring

- Consent, waiver, and notification
- Privacy and confidentiality
- Responsibility to participate in research

FDA-regulated products

- Research payments

FDA-regulated products

- Posttrial responsibilities

Data sharing

- Certificates of Confidentiality

Data sharing

Certificates of Confidentiality

- Data sharing
Health Care Systems Interactions Core: Impact Highlights

Key products

- Collaborated in planning and delivering annual workshops on design and conduct of embedded pragmatic trials
- Collaborated in Living Textbook chapters on:
  - Building successful partnerships
  - Dissemination approaches for different stakeholders
  - Adapting to unexpected events

Major achievements

- Created and maintained a comprehensive issues tracker with challenges and resolutions shared by the NIH Collaboratory Trials
- Developed a typology of trial interactions with health systems
- Shared lessons about building and sustaining trusting partnerships between research teams, health system leaders, clinicians, and staff
Health Care Systems Interactions Core: Key Publications

A guide to research partnerships for pragmatic clinical trials

Accounting for quality improvement during the conduct of embedded pragmatic clinical trials within health care systems: NIH Collaboratory case studies

A value proposition for pragmatic clinical trials
Health Care Systems Interactions: Evolution of Topics

- Minimizing burden on healthcare systems
- Building partnerships

- Value proposition for PCTs
- Healthcare leadership perspectives

- Implementation and sustainment
- Engaging diverse participants

Health Equity Core: Impact Highlights

Key products
- Equitable Language Cheat Sheet
- Fellowship curriculum to increase diversity of ePCT researchers
- Adapted DUSON checklist for integrating a health equity lens in pragmatic trials

Major achievements
- Consulted with NIH Collaboratory Trials to understand how they are incorporating a health equity lens in their research, and offer tools and strategies
Health Equity Core: Key Publications

Potential bias and lack of generalizability in EHR data: reflections on health equity from the National Institutes of Health Pragmatic Trials Collaboratory
Health Equity Core: Evolution of Topics

Core formed in 2022

2022

2023

2024

Diversifying ePCT participants and workforce

Structural barriers to healthcare systems

Defining health equity in ePCTs
Implementation Science Core: Impact Highlights

Key products

- Review of implementation-related data collection within the NIH Pragmatic Trials

Major achievements

- Supported NIH Collaboratory Trial teams in considering appropriate implementation science theories, models, and frameworks
- Researched factors affecting posttrial sustainment or de-implementation of ePCT interventions
Factors affecting post-trial sustainment or de-implementation of study interventions: a narrative review

Post-trial responsibilities in pragmatic clinical trials: fulfilling the promise of research to drive real-world change
Implementation Science Core: Evolution of Topics

Core formed in 2022

- Sustainment vs de-implementation decisions
- Implementation frameworks and measures
- Posttrial responsibilities

2022 2023 2024
Patient-Centered Outcomes Core: Impact Highlights

Key products

- Roundtable report on capturing patient-reported health data
- Contributed to Users Guide for Integrating Patient-Reported Outcomes in EHRs
- Patient-Reported Outcomes Living Textbook chapter
- Toolkit to support the capture of PROs in diverse study populations

Major achievements

- Conducted surveys and interviews on cultural/linguistic adaptation and acceptability/burden of PROs
- Led workshop to help clinicians implement NIH PROMIS
- Consulted with NIH Collaboratory Trials on selection and collection of PROs
- Convened policy meeting to discuss getting PROs into the EHR
Patient-Centered Outcomes Core: Key Publications

Assessing the value of patient-generated data to comparative effectiveness research

Clarifying the meaning of clinically meaningful benefit in clinical research: noticeable change vs valuable change

Collecting patient-reported outcome measures in the electronic health record: Lessons from the NIH Pragmatic Trials Collaboratory
Patient-Centered Outcomes Core: Evolution of Topics

- Initiating and implementing PRO measures
- Collecting PROs in the EHR
- PROs as a surrogate for patient engagement
- PRO instruments
- Cultural and linguistic adaptation
- PROs and health equity

Years:
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020
- 2021
- 2022
- 2023
- 2024
Disseminating Knowledge and Best Practices
Living Textbook Content and Reach

- 30+ chapters
- >75,000 visitors/year
- >100 contributors

TOPICS INCLUDE:

Design
- Developing a Grant
- Experimental Designs
- Building Partnerships
- Patient Engagement
- What Is a Pragmatic Trial
- Endpoints & Outcomes
- Using EHR Data
- Intervention Complexity

Data, Tools, and Conduct
- Assessing Feasibility
- Acquiring & Assessing Real-World Data
- Study Startup
- Participant Recruitment
- Monitoring Fidelity
- Clinical Decision Support
- Patient-Reported Outcomes
- Mobile Health

Dissemination
- Data Sharing
- Dissemination
- Implementation

Ethics and Regulatory
- Privacy
- Consent, Waiver, & Notification
- Collateral Findings
- Data & Safety Monitoring
- Single IRB
Living Textbook Growth

Pageviews (Cumulative)

Chapters
Living Textbook Users Over Time

Users (Cumulative)

- 2018
- 2019
- 2020
- 2021
- 2022
- 2023

- 0
- 100,000
- 200,000
- 300,000
- 400,000
- 500,000
## Living Textbook: Most Popular Topics

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Pageviews in 2023</th>
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<tbody>
<tr>
<td>Cluster Randomized Trials</td>
<td>12,429</td>
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<tr>
<td>Endpoints and Outcomes</td>
<td>7599</td>
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<tr>
<td>What Is a Pragmatic Trial?</td>
<td>6585</td>
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<tr>
<td>Intraclass Correlation</td>
<td>4598</td>
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<tr>
<td>Stepped-Wedge Designs</td>
<td>2536</td>
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<tr>
<td>Real-World Data Sources</td>
<td>1758</td>
</tr>
<tr>
<td>Clinical Decision Support</td>
<td>1665</td>
</tr>
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</table>
Publications*

**TOTAL PUBLISHED**

>315

**CITATIONS**

>8,300

**JOURNALS**

>120

*As of May 15, 2024*
Publications Over Time

>315 total peer-reviewed publications*

*As of May 15, 2024
Where We Published Most

- Clinical Trials
- Journal of General Internal Medicine
- eGEMs: The Journal for Electronic Health Data and Methods
- JASN: Journal of the American Society of Nephrology
- Trials
- JAMIA
- JAMA: The Journal of the American Medical Association
- JN: Internal Medicine
- The American Journal of Bioethics
- Contemporary Clinical Trials: Design, Methods, and Analysis
- Statistics in Medicine
- Translational Behavioral Medicine: Practice, Policy, Research
- NIH Pragmatic Trials Collaboratory: Rethinking Clinical Trials
Is Learning Worth the Trouble? — Improving Health Care System Participation in Embedded Research

Think Pragmatically: Investigators’ Obligations to Patient-Subjects When Research Is Embedded in Care

Do Clinicians Have a Duty to Participate in Pragmatic Clinical Trials?

Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH Health Care Systems Collaboratory

Two weights make a wrong: Cluster randomized trials with variable cluster sizes and heterogeneous treatment effects

Data Sharing and Embedded Research
NIH Relative Citation Ratio (RCR)

- Measure of an article’s influence
- Citation rate normalized by field and time, benchmarked to a value of 1.0

**NIH Relative Citation Ratio (RCR)**

- **RCR = 5.6**
- This article from the TSOS trial has received 5.6 times as many citations per year as the median NIH-funded article in its field.
# Impact of NIH Collaboratory Trial Publications

## All Papers (N = 297)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Mean RCR</td>
<td>3.0</td>
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<tr>
<td>Median RCR</td>
<td>1.2</td>
</tr>
<tr>
<td>Weighted RCR</td>
<td>792.4</td>
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</tbody>
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*As of May 15, 2024

## Main Outcomes (N = 9)

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<th>Value</th>
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<tbody>
<tr>
<td>Mean RCR</td>
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<tr>
<td>Median RCR</td>
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<tr>
<td>Weighted RCR</td>
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## Study Design (N = 18)

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<tbody>
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<td>Median RCR</td>
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<tr>
<td>Weighted RCR</td>
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</tr>
</tbody>
</table>

*As of May 15, 2024*
Training Activities

11 workshops

600 attendees

46 presenters

73 hours of presenter-led training

AUDIENCES REACHED

- Academic researchers
- Funding agencies
- Investigators
- Health system leaders
- Healthcare practitioners
- Other ePCT partners
Training Resources

24 learning modules

55 videos in library

253 workshop materials (slides, recordings, summaries, etc)

19 resources (handouts, checklists, etc)
Rethinking Clinical Trials® Grand Rounds

>500 total Grand Rounds webinars

>83,600 total attendees

48 podcast episodes

19,200 total plays
# Rethinking Clinical Trials® Grand Rounds: Highest Attended Sessions

<table>
<thead>
<tr>
<th>All Time</th>
<th>Past Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>870</strong> May 1, 2020</td>
<td><strong>313</strong> August 4, 2023</td>
</tr>
<tr>
<td><strong>650</strong> March 20, 2020</td>
<td><strong>310</strong> February 10, 2023</td>
</tr>
<tr>
<td>Clinical Trials in the Time of COVID-19 (Susanna Naggie, Adrian Hernandez, Eric Perakslis)</td>
<td>Informing and Consenting: What Are the Goals? (Pearl O’Rourke, David Wendler, Miguel Vazquez, Mike Ho)</td>
</tr>
<tr>
<td><strong>605</strong> May 8, 2020</td>
<td><strong>309</strong> January 26, 2024</td>
</tr>
<tr>
<td>Advances at the Intersection of Digital Health, Electronic Health Records, and Pragmatic Clinical Trials: Real World Evidence: Contemporary Experiences and Future Directions (Patrick Heagerty, Jacqueline Corrigan-Curay, Joshua Denny)</td>
<td>Advancing the Safe, Effective and Equitable Use of AI in Healthcare (Mark Sendak, Suresh Balu)</td>
</tr>
<tr>
<td>All Time</td>
<td>Past Year</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>1044 Podcast 40:</td>
<td>479 Podcast 45: From Observational Studies</td>
</tr>
<tr>
<td>Survivor Corps:</td>
<td>to Pragmatic Clinical Trials: Research in</td>
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<tr>
<td>Long-Term COVID-19 Patient</td>
<td>PCORnet</td>
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<td>Engagement</td>
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<td>957 Podcast 42:</td>
<td>455 Podcast 47: BeatPain Utah</td>
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<tr>
<td>FDA Draft Guidance on Real-World Evidence</td>
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<tr>
<td>721 Podcast 41:</td>
<td>443 Podcast 46: All of Us Research Program</td>
</tr>
<tr>
<td>Searching for a</td>
<td></td>
</tr>
<tr>
<td>Unicorn: Selecting Outcomes for Outpatient Trials</td>
<td></td>
</tr>
</tbody>
</table>
Videos

Views (cumulative)

682 total videos
68,000 total plays
Email Newsletter

>1700 subscribers

>70 editions

>36% average open rate, consistently higher than industry benchmarks

>24,000 reads
Social Media

LinkedIn

Launched August 2023

>320 followers

>100 total posts

5.6% average engagement rate (past 90 days)

X (formerly Twitter)

>2250 followers

4.6% average engagement rate (past 90 days)