Introduction to ePCTs

10 self-paced learning modules on how to design, conduct, and disseminate embedded pragmatic clinical trials (ePCTs)
Objectives

1. Provide investigators with an introduction to the design and conduct of ePCTs
2. Identify important things to know
3. Identify important things to do
4. Point to key resources to advance learning
# Learning modules

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What are ePCTs?</td>
</tr>
<tr>
<td>2</td>
<td>Engaging All Stakeholders &amp; Aligning with Healthcare System Partners</td>
</tr>
<tr>
<td>3</td>
<td>Designing with Implementation in Mind</td>
</tr>
<tr>
<td>4</td>
<td>Design and Analytic Considerations</td>
</tr>
<tr>
<td>5</td>
<td>Regulatory and Ethical Challenges of ePCTs</td>
</tr>
<tr>
<td>6</td>
<td>Measuring Outcomes</td>
</tr>
<tr>
<td>7</td>
<td>Pilot and Feasibility Testing</td>
</tr>
<tr>
<td>8</td>
<td>Dissemination of Results</td>
</tr>
<tr>
<td>9</td>
<td>ePCT Team Composition</td>
</tr>
<tr>
<td>10</td>
<td>Developing a Compelling Application</td>
</tr>
</tbody>
</table>
Learning resource

The NIH Collaboratory’s *Living Textbook of Pragmatic Clinical Trials:*

[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
1: What are ePCTs?

Contributing authors:
Lesley Curtis, PhD, Duke Center for Pragmatic Health Systems Research
Gloria Coronado, PhD, Kaiser Permanente Center for Health Research
Doug Zatzick, MD, University of Washington School of Medicine
Learning goals

• Identify key characteristics in the rationale and design of ePCTs
• Identify key differences between explanatory and pragmatic trials
• Provide an understanding of the PRECIS-2 tool and its ability to assist teams in the design of an ePCT
Important things to know

- ePCTs are designed to answer important, real-world clinical questions
- Broad stakeholder engagement and support are essential from beginning to end
- Tradeoffs in flexibility, adherence, and generalizability are inevitable
ePCT characteristics

- Conducted within healthcare systems
- Use streamlined procedures and existing infrastructure
- Answer important medical questions
Why conduct ePCTs?

ePCTs have the potential to inform policy and practice with high-quality evidence at reduced cost and increased efficiency compared with traditional clinical trials.
ePCTs bridge clinical care and research

- Study designed with input from health system stakeholders
- Intervention incorporated into routine clinical workflow
- Data collected through EHR in health care settings
- Diverse, representative study populations
- Outcomes important to decision makers
## Key differences between explanatory and pragmatic trials

<table>
<thead>
<tr>
<th></th>
<th>EXPLANATORY</th>
<th>PRAGMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research question</strong></td>
<td>Efficacy: Can the intervention work under the best conditions?</td>
<td>Effectiveness: Does the intervention work in routine practice?</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Well-resourced “ideal” setting</td>
<td>Routine care settings including primary care, community clinics, hospitals</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Highly selected</td>
<td>More representative with less strict eligibility criteria</td>
</tr>
<tr>
<td><strong>Intervention design</strong></td>
<td>Tests against placebo, enforcing strict protocols &amp; adherence</td>
<td>Tests 2 or more real-world treatments using flexible protocols, as would be used in routine practice</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Often short-term surrogates or process measures; data collected outside of routine care</td>
<td>Clinically important endpoints; at least some data collected in routine care</td>
</tr>
<tr>
<td><strong>Relevance to practice</strong></td>
<td>Indirect: Not usually designed for making decisions in real-world settings</td>
<td>Direct: Purposely designed for making decisions in real-world settings</td>
</tr>
</tbody>
</table>

“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.”

Balancing relevance and efficiency

- Achieving both relevance and efficiency is a goal of pragmatic trials, yet high relevance to real-world decision-making may come at the expense of trial efficiency.

- For example, a trial measuring outcomes that matter most to patients and health systems may not be able to rely exclusively on information from the EHR, and instead need to assess patient-reported outcomes, which is more expensive and less efficient.
Why Are We Talking About Pragmatic Clinical Trials?

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
PRECIS-2: Designing trials fit for purpose

Tool assesses trial across 9 domains

Explanatory

- Eligibility
- Recruitment
- Setting
- Organization
- Flexibility: delivery
- Flexibility: adherence
- Follow-up
- Primary outcomes
- Primary analysis

Pragmatic
Introducing PRECIS-2

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

WHO IS SELECTED TO PARTICIPATE IN THE TRIAL?

HIGHLY SELECTED PATIENTS, STRONG INCLUSION CRITERIA

TYPICAL PATIENTS, MINIMAL INCLUSION CRITERIA
How are participants recruited into the trial?

**Explanatory**

Uses methods and resources outside of, or in addition to, what is typical

**Pragmatic**

Recruited in usual healthcare settings; participants may include patients, providers, or health systems
Where is the trial being done?

Explanatory

Specialist practice
or academic
medial center

Pragmatic

Settings where
the trial’s results
will be applied
PRECIS-2: Organization

What expertise and resources are needed to deliver the intervention?

Changes to clinical delivery and resources are minimal, easy to implement in usual care after the trial

Changes the workflow, adds equipment or staff training, or affects how care is typically delivered

Explanatory

Pragmatic
How should the intervention be delivered?

**Explanatory**

Highly specified, protocol-driven with timing of intervention tightly defined

**Pragmatic**

Details of intervention delivery left to the care provider
What measures are in place to ensure participants adhere to the intervention?

- Measures to monitor patient adherence and excludes patients judged not to be adherent
- No special measures to enforce intervention engagement or compliance
How closely are participants followed up?

- Frequent follow-up visits scheduled outside of clinical encounters, extensive data collection
- Few follow-up visits, outcome data obtained through EHR, questionnaires, or other data sources
PRECIS-2: Primary outcome

How relevant is it to participants?

Surrogate outcomes or measures distinct from the research question

Outcomes of importance to patients, measured as they would be in usual care
To what extent are all data included?

**Explanatory**
- Excludes noncompliant participants, dropouts, or practice variability

**Pragmatic**
- Intent-to-treat analysis
Pragmatic Elements: An Introduction to PRECIS-2

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Important things to do

• For each domain of PRECIS-2, determine the approach along the pragmatic-explanatory continuum that is most appropriate for answering your research question
• Remember that trials may have some elements that are more pragmatic and some that are more explanatory
2: Engaging Stakeholders & Aligning with Healthcare System Partners

Contributing author:
Leah Tuzzio, MPH, Kaiser Permanente Washington Health Research Institute
Learning goals

• Understand the range of stakeholders to engage and how to partner with them through all phases of the trial
• Identify strategies for understanding the priorities and perspectives of health system leaders and obtaining their support
Important things to know

• Be patient: relationships take time to build and nurture
• Get to know your stakeholders, their values, priorities, and expectations
• Consider whether your intervention will add long-term value to the health system and its patients
• Assess the capacity and capabilities of your health system partners
• Engage across all trial phases: design, conduct, and dissemination
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)
What’s the value of engagement?

- Identifies priorities and perspectives early and throughout the research continuum
- Defines relevant questions and selects high-priority outcomes
- Improves efficiency and diversity of participant enrollment
- Continuously helps improve methods and overcome challenges
- Reduces missing data and loss to follow-up
- Increases the uptake and impact of research
Who are ePCT stakeholders?

- Potential stakeholders have varied priorities, values, work cultures, and expectations:
  - Healthcare delivery organization leaders
  - Clinicians
  - Operational personnel
  - Patients, caregivers, patient advocacy groups
  - Payers, purchasers
  - Policymakers, regulators
  - Research funders
  - Researchers
  - Product manufacturers
Types of stakeholders

- The wider community of stakeholders is needed to define the question and design the intervention
  - “We really want to know what you need”
- Local stakeholders are essential to implementing the ePCT at sites
  - “We really need your help to get this done”

Source: Greg Simon, MD, MPH
Determine which stakeholders are important for your trial.

Who will use the evidence from the study to make decisions? Who will be affected by those decisions?

Who can help minimize potential barriers to study completion?
Deciding Who To Engage
and
Stakeholder Engagement Throughout the PCT Life Cycle

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Engagement strategies in the design phase

- Carefully choose the research question
- Design the intervention for sustainability
- Select meaningful outcome measures
- Design the protocol to minimize burden on patients and clinicians
- Promote and support the study
Engagement strategies in the conduct phase

- Develop recruitment strategies
- Promote and assess compliance with study requirements (e.g., regulatory)
- Engage study champions at each site
- Solve problems and remove barriers
- Consider privacy and data sharing issues
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

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
</table>
| Intervention is in the **primary care setting** where schedules are busy and space is tight | Team with clinicians to understand workflow and schedule study-related patient visits during slower clinic periods  

Hold patient visits in less conventional ways (eg, after hours, meet in lobby spaces) |
## Nurturing relationships: challenges and solutions

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>High amounts of leadership turnover at medical director and provider levels due to preexisting pressures and challenges inherent in community clinics</td>
<td>Meet regularly with leadership teams and establish an advisory board and other infrastructure to help engage leaders and gatekeepers</td>
</tr>
</tbody>
</table>
## Nurturing relationships: challenges and solutions

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leadership approval of the study is delayed because different departments within a single healthcare system are unable to initiate approval before another department does</td>
<td>Hold in-depth discussions of the project with all relevant stakeholders attending in person or by phone or web</td>
</tr>
<tr>
<td></td>
<td>A prior history of collaboration among investigators and health system leadership can be instrumental in obtaining approval</td>
</tr>
</tbody>
</table>
Engagement strategies in the dissemination phase

- Determine key messages for different stakeholder groups
- Identify avenues for dissemination
- Assist with the development of manuscripts and other dissemination materials
- Share findings via professional networks and social media
- Support implementation or de-implementation of intervention
- Consider changes to policies and guidelines
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)
Prepare a brief, clear abstract that includes:

- Reasons to invest in intervention
- Alignment with organizational priorities
- Impact on workflows
- Downstream implications
- Potential harms or liability issues
- Alignment with policy makers
- Sustainability plans
Resource: Engaging stakeholders

Engaging Stakeholders and Building Partnerships to Ensure a Successful Trial

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
3: Designing with Implementation in Mind

Contributing author:
Doug Zatzick, MD, University of Washington School of Medicine
Learning goal

Consider how to design ePCTs so findings can be successfully implemented and sustained in real-world healthcare settings
Important things to know

- Pragmatic trials can simultaneously address effectiveness and implementation aims
- Health systems vary in how they change practice based on evidence from a clinical trial
- Methods that integrate pragmatic trials and implementation science frameworks are in development
Consider implementation early

To design the trial with implementation and sustainability in mind:

- Consider how your intervention fits with the target patient population and setting
- Think about whether your intervention can be delivered in a variety of healthcare settings
Resource: Upfront design considerations

Key Considerations

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
If you build it . . . they will come

Translated to ePCTs:

If you build it *pragmatically* …
they will implement
Case study from NIH Collaboratory: Trauma Support and Outcomes (TSOS)

- Effectiveness aim: Reduce PTSD symptoms
- Implementation aim: Influence U.S. trauma center requirements for sustainable PTSD screening and intervention procedures
Some TSOS implementation tasks

- Embed implementation team in the health system
- Spend time in clinical context of trauma care system
- Conduct participant observations
- Record field notes and key informant interviews
- Review and document themes related to trial roll-out and sustainable implementation
Case study from NIH Collaboratory: Lumbar Imaging with Reporting of Epidemiology (LIRE)

- LIRE tests effectiveness of a simple, inexpensive intervention: Epidemiologic benchmarks inserted into lumbar spine imaging reports
- Total patient N ~250,000
- Rated highly pragmatic using PRECIS-2 tool
- Stepped-wedge design leaves intervention “turned on” after study completion
Some LIRE implementation challenges

- A few providers/radiologists/clinics:
  - Adopted the intervention before the start of the trial
  - Selectively removed the intervention from reports
  - Temporarily discontinued the intervention during the trial
- Can potentially contaminate comparison groups and interrupt sustainability
- Requires communication between study team and system leadership to find practical solutions
Upfront considerations

• What are the needs of those who will use the research findings to make decisions?
• Who is able to deliver the intervention?
• Build in tests of training, support, and adherence/fidelity
• During trial roll-out, remove barriers to high-quality, sustainable intervention delivery
Important things to do

Plan for:

- How the trial addresses sustainable implementation
- How the trial addresses effectiveness
- How the health system learns
- Key policy or practice changes to enhance sustainable implementation
Resource: Designing with implementation in mind

**Designing with Implementation and Dissemination in Mind**

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
4: Design and Analytic Considerations

Contributing authors:
Liz Turner, PhD, Duke University School of Medicine
Liz DeLong, PhD, Duke University School of Medicine
Learning goals

• Determine which randomization scheme makes sense for your ePCT
• Understand special considerations with clustered data
• Recognize the analytical challenges of cluster-randomized and stepped-wedge study designs
Important things to know

- Question drives design, design drives analysis
- Randomization
  - Individual preferred for statistical reasons
  - But cluster often needed (cluster-randomized [CRT] design)
  - Avoiding informed consent is not a reason to favor a CRT design
- Considerations in both design and analysis
  - Must account for clustering (if CRT design)
  - Best to account for baseline imbalance
- Good design is difficult but critical
  - Need input from diverse team, including statistician
  - Analysis may not be able to overcome design flaws
Resources: Introduction to experimental designs

Introduction and Statistical Design Considerations

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Deciding on the level of randomization

**Individual**
- Examples: patient, caregiver
- Often used in explanatory trials

**Cluster**
- Examples: clinic, hospital, region
- Often used in pragmatic trials
When the unit of randomization is a cluster, the trial is called . . .

Cluster-randomized trial (CRT)
or group-randomized trial
or community-randomized trial
Reasons to randomize clusters instead of individuals

- Target of intervention is a collective instead of an individual
  - For example, comparing 2 protocols for handling in-hospital infections or comparing 12-hour nursing shifts to 8-hour shifts
- Target of intervention is an individual, but there is risk of **contamination**
  - Contamination occurs when aspects of an intervention are adopted by members of the group that was randomized to not receive that intervention
  - For example, physicians randomized to a new educational program might inadvertently share lessons learned from the program with physicians in their practice that were randomized to control
  - Contamination reduces the observed treatment effect
- Logistically easier to implement intervention by cluster
Cluster-level randomization in an NIH Collaboratory study: Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC)

- STOP CRC is a CRT testing a culturally tailored, health system–based program to improve CRC screening rates in community-based collaborative network
  - 26 clinical sites
  - 40,000+ patients
STOP CRC cluster randomization levels

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

- STOP CRC intervention
- Factors related to uptake of CRC screening (eg, age, gender)

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
Individual-level randomization in an NIH Collaboratory study: Suicide Prevention Outreach Trial (SPOT)

- SPOT is a collaborative care model testing treatments intended to reach large groups of adult patients who have serious thoughts of suicide
  - 4 clinical sites
  - 16,000 expected patients
SPOT individual randomization

- Two active arms
  - Both interventions are individual-level
  - Intervention contact mostly through electronic health record, so low risk of contamination is expected
SPOT study flow

Eligible patients automatically identified from health system records

Randomly Assigned

Usual Care (No contact)

Invited to Skills Training Program

Invited to Care Mgmt Program

Decline

Do not respond

Coaching Support up to 12 months

Usual Care Outcomes

Skills Training Outcomes

Care Management Outcomes

Comparison of suicide attempt rates over 18 months using data extracted from health system EHR and insurance claims data

Cluster-Randomized Trials
and
Choosing Between Cluster and Individual Randomization

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
When are special statistical analyses needed to accommodate clustering?

- When unit of randomization is a *cluster* or . . .
- When unit of randomization is an *individual AND* the individual outcomes demonstrate some clustering

*What does it mean to say that an outcome is clustered?*
Clustering of a particular outcome

- Suppose 10 clinics
- Each with 5 age-eligible patients: ie, are not up to date with colorectal cancer (CRC) screening
- Outcome
  - Binary outcome: refused screening (Y/N)
  - No screening within year of enrollment
Understanding clustering: complete clustering

>1 participant/clinic gives no more information than a single participant/clinic since every participant in a given clinic has the same outcome.
Understanding clustering: no clustering

- Screened
- Not screened

20% uptake of CRC screening in each clinic
No structure by clinic; more like a random sample of eligible participants
Understanding clustering: some clustering

A more typical situation: proportion screened ranges from 0% - 80%
Measure of clustering: intraclass correlation coefficient (ICC)

ICC, ρ:
- Most commonly used measure of clustering
- Ranges: 0-1; 0=no clustering; 1=total clustering
- Typically <0.2; commonly around 0.01 to 0.05
- Ratio of between-cluster variance of outcome to the 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* and *within-cluster* variance
Measure of clustering: ICC & coefficient of variation (CV)

- Need measure of clustering for sample size
- CV is an alternative to ICC:

\[ k = \frac{\sigma_B}{\mu} \]

where \( \mu \) is overall mean of outcome

- Multiple definitions of ICC for binary outcomes (some authors prefer CV for binary)
Analysis Plan

and

Intraclass Correlation

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Analytic approaches for clustered data

- Typically use regression-type models of individual-level data
  - Random effects/mixed effects models
  - Generalized estimating equations
- **Important:** Work with a statistician to ensure correct accounting for clustering
Adjustment for clustering in the analysis will require larger sample size to have adequate power

- Power is affected by . . .
  - Strength of the clustering effect (eg, size of ICC)
  - Number of clusters
  - Number of patients per cluster
Higher ICCs and fewer clusters = lower power (so need to increase sample size to compensate)

ICC=0.03 (ie, like STOP CRC power calculation)

Note: this is the total # clusters across both arms
Accounting for clustering in design

- Power and sample size
  - Account for anticipated clustering
  - Inflate RCT sample size
  - Work with statistician to do 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**
Estimating ICC to plan study

- How to get good initial estimate of ICC for a particular outcome?
  - It depends on outcome and study characteristics
  - CONSORT statement on reporting of CRTs recommends ICC reported
  - Look at other articles with similar settings
- Be cautious when using pilot data from small study
  - The ICC might have a wide confidence interval
Design considerations: clustering in STOP CRC

“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.”

Special consideration for CRTs: Greater potential for imbalance on baseline covariates

- Pragmatic CRTs often enroll small # of clusters (<40)
- Randomization may not balance baseline covariates
- Baseline covariate imbalance threatens internal validity; ie, comparability of treatment arms
  - There may be confounding due to non-comparability of treatment arms
Addressing imbalance in baseline covariates

- Prevent imbalance at design stage
  - Recommended
  - Restricted randomization

- Adjust for imbalance at analysis stage
  - Not recommended
Using restricted randomization

- Use restricted randomization if
  - Total # clusters <40, and . . .
  - Know which baseline covariates are predictive of outcome
- Multiple approaches possible
  - Pair-matching
  - Stratification
  - Covariate-constrained randomization
  - *Consult a statistician to choose!*
- Analysis must account for whatever type of restricted randomization is used in design
Consider …

- If you are planning a cluster-randomized design, what cluster-level covariates might be important to balance on?
Randomization Methods

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Number of 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 many more than 8 clusters in total in a 2-arm trial!
- Remember: # clusters drives the power of trial more than # participants
- CRTs require a lot of time and effort
  - Consider a pilot trial to get procedures in place
2 major types of CRT

1. Parallel CRT
2. Stepped-wedge CRT
Two types of CRT designs

Parallel

Stepped-wedge

Complete

Incomplete

In complete designs, measurements are taken from every cluster at every time point. In incomplete designs, some clusters do not provide measurements at all time points.
Types of CRT designs

Examples with 8 clusters: 1-year intervention

- **Parallel design**
- **Complete stepped-wedge design**
- **Incomplete stepped-wedge design**

Types of CRT designs

Examples with 8 clusters: 1-year intervention
CRT analysis: treatment effects

Estimated (primarily) using between-cluster information

Estimated using both \textit{vertical} \& \textit{horizontal} (ie, within-cluster) information

Parallel design

Complete SW design

\begin{itemize}
\item Control period
\item Intervention period
\end{itemize}
Choosing the right type of CRT

- Arguments **for** stepped-wedge CRT:
  - Cannot immediately implement intervention in half the clusters
  - Pragmatic research: plan to eventually implement in all clusters
  - Have few clusters and might gain power

- Arguments **against** stepped-wedge CRT:
  - Risk confounding treatment effect with time effect
  - Could do staggered-start parallel CRT if cannot start implementation in half the clusters immediately
    - Roll out to all clusters at end of evaluation, if effective
Recommendations for CRT Design

- Use a parallel CRT design if you can
- If not, plan for time effects in designing and analyzing stepped-wedge CRT
- Work with statistician to account for clustering in design and analysis of both designs
If you are planning a cluster-randomized design, what are the pros and cons of using a parallel versus stepped-wedge design for your trial?
Other considerations for ePCTs

- Intent-to-treat (ITT) versus per-protocol analysis
- Concealment and blinding
- Monitoring and managing unexpected changes
Intent-to-treat vs per protocol analysis

• Pragmatic nature → ITT commonly used
• Per protocol 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
Concealment and blinding

- 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
Managing unanticipated 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

• Careful planning and monitoring are needed
Concealment and Blinding
and Unanticipated Changes

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org
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 and is familiar with the PRECIS-2 tool
• Has experience with using EHR data
• Has experience with CRT design and analysis (if using a clustered design)
Important things to do

- Focus on research question
- Collaborate early with a statistician
- Weigh statistical choices vs implementation challenges
- Select design features with analysis in mind
- Choose individual randomization, but only if possible
- Write & publish a protocol paper
Resource: ePCT design and analysis

Additional Resources

From the *Living Textbook of Pragmatic Clinical Trials*

[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
5: Regulatory and Ethical Challenges

Contributing author:
Kevin Weinfurt, PhD, Duke Clinical Research Institute
Learning goal

Learn about the regulatory and ethical considerations specific to conducting ePCTs
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 the part of patients, providers, IRBs, and DSMBs
ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions
Evolving understanding of unique ethical/regulatory issues for ePCTs

- Informed consent
- Data monitoring
- Defining minimal risk
- Research/quality improvement distinction
- Vulnerable subjects
- IRB harmonization

- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
Regulatory & ethical challenges of ePCTs

Ethical, not regulatory, question:

*Whose rights and welfare need to be protected?*
Resources: Regulatory & ethical challenges of ePCTs

Introduction

and

Informed Consent

From the *Living Textbook of Pragmatic Clinical Trials*  
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Current ethics/regulatory in flux

Delayed compliance date of revised final Common Rule

Your dedicated ethics/regulatory liaison
Types of participants in an ePCT

Direct

Indirect
Direct participants

Immediate or mediated targets of the intervention

- **Intervention** → **Patients**
- **Intervention** → **Providers**
- **Intervention** → **Clinics**
Direct participant

Intervention

Immediate target

Mediated target
Indirect participants

People affected by routine exposure to the environment (eg, family/caregivers)
Case study from NIH Collaboratory: Active Bathing to Eliminate (ABATE) Infection

- Cluster trial comparing 2 quality improvement strategies to reduce multidrug-resistant organisms and healthcare-related infections in non-ICU population
- 53 hospitals
- 331,584 patients
Indirect participants: ABATE example
Consider …

- Who are the direct and indirect participants for your study?
- What are the potential risks and benefits for each?
Alternative Approaches to Disclosure and Authorization

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Approaches to notification & authorization

- Informed consent
- Nondisclosure

Alterations

- Broad notification
- Opt-out
- Opt-in
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*
Case study from NIH Collaboratory: Time to Reduce Mortality in End-Stage Renal Disease (TiME)

• CRT testing whether a longer hemodialysis session can improve survival and quality of life for patients with kidney failure who require chronic treatment with dialysis
• 256 clinical sites
• 7053 patients
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.
Case study from NIH Collaboratory: Lumbar Imaging with Reporting of Epidemiology (LIRE)

- Tests effectiveness of an intervention that inserts epidemiologic benchmarks into lumbar spine imaging reports
- Goal of intervention is to reduce subsequent diagnostic and therapeutic interventions
- 98 clinical sites
- 246,289 patients
Consent process: LIRE example

- 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
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
What do data suggest about different approaches?
Resource: Comparison of approaches

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

1. Difficulty understanding aspects of pragmatic trials of accepted medical practices

2. Nontrivial consent bias, but it’s the same for all approaches to notification and authorization

3. Less active approaches to notification and authorization 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
Working with human subjects oversight bodies

- Institutional review boards (IRBs)
- Data monitoring committees (DMCs)
  - Data safety and monitoring boards (DSMBs)
Major issue: single IRB review

- NIH policy on single IRB 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
Case study from NIH Collaboratory: Trauma Support and Outcomes (TSOS)

- Stepped-wedge CRT testing innovative intervention for patients with PTSD and comorbidity
- 25 level 1 trauma centers
- 960 expected patients
“Single” IRB experience: TSOS example

• At the time of study initiation, the University of Washington IRB did not have capacity for “centralization”
• Western IRB 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)
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 adverse events still be monitored?
• Limited or delayed access to study outcomes during study conduct
• Are interim analyses actionable?

Adapted from Greg Simon, PCT Grand Rounds, December 8, 2017
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
Resource: Regulatory and ethical challenges of ePCTs

Consent, Disclosure, and Nondisclosure

From the *Living Textbook of Pragmatic Clinical Trials*  
www.rethinkingclinicaltrials.org
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
Resource: Additional readings on regulatory/ethical considerations

Special Issue of Clinical Trials

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
6: Measuring Outcomes

Contributing authors:
Rachel Richesson, PhD, Duke University School of Nursing
Lesley Curtis, PhD, Duke Clinical Research Institute
Learning goal

Describe methods for measuring study outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)
• In pragmatic research, endpoints and outcomes need to be available as part of routine care
• Endpoints and outcomes should be
  • Meaningful to providers and patients
  • Relatively easy to collect
• Researchers do not control the type or format of data collected in EHR systems
Endpoints and outcomes

• An **endpoint** usually refers to an analyzed parameter (eg, change from baseline at 6 weeks in mean PROMIS Fatigue score)
• An **outcome** usually refers to a measured variable (eg, peak volume of oxygen or PROMIS Fatigue score)
Key questions for choosing endpoints

- Is the outcome medically significant such that a patient would seek care?
- Does it require hospitalization?
- Will it be medically attended?
- Is the treatment generally provided in inpatient or outpatient settings?
Choosing and Specifying Endpoints and Outcomes

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org
Data sources for endpoints in ePCTs

“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.”

Weber GM, et al. JAMA. 2014;311(24):2479-2480. doi:10.1001/jama.2014.4228 (Figure 1)
Data sources for endpoints

- EHR or ancillary health information systems
- Patient report
- Patient measurement
Choosing and specifying endpoints

- Acute MI
- Broken bone
- Hospitalization

- Suicide attempts
- Gout flares
- Silent MI
- Early miscarriage
Where is the signal?

- EHR (laboratory values, treatments, etc)
- Claims data (does the event generate a bill?)
Reality is not straightforward
Longitudinal data linkage

• To fully capture all care—complete longitudinal data—linking research and 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
More pragmatic outcomes

- Are meaningful to providers and patients
  - Myocardial infarction vs MACE
  - Clinical event vs blood test
- Are captured reliably as part of routine clinical care
- Do not require central adjudication
Less pragmatic outcomes

• Are surrogate outcomes mainly important to providers (eg, blood test)
• Are composite outcomes less important to patients
• Involve tests not used in usual care or are outcomes that require central adjudication
• Are shorter term outcomes for a condition in which patients are more concerned about longer term outcomes
Key questions for using data in research

- What is the phenomenon you are trying to identify or measure?
- What are the sources of error, and how can you reduce the error?
Assessing data quality

- Identify variation between populations at different sites or study groups
- Recommend formal assessment of accuracy, completeness and consistency for key data
- Data quality should be described, reported, and informed by workflows
Case study from NIH Collaboratory: Collaborative Care for Chronic Pain in Primary Care (PPACT)

- Mixed-methods cluster trial evaluating integration of multidisciplinary services within the primary care environment to improve chronic pain management
  - 3 regional health systems
  - 2000 expected patients
PPACT data challenges

• Patient-reported outcomes (PROs) were needed but were not standardly collected across diverse regions
• Study team worked with national healthcare system to create buy-in for a common instrument
• Local IT team built instrument within each region
• A multi-tiered approach supplemented the clinically collected patient-reported data at 3, 6, 9, and 12 months
• Study team needed a follow-up phone call to maximize data collection at each time point
Resource: Methods of measuring outcomes

Via Electronic Health Record

Via Direct Patient Report

Via Mobile Devices

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Caveats when using EHR data for research

- Data may be transformed/coded for purposes other than research and clinical care
- Data captured in clinical notes may not be available
- EHRs are often highly customized
- EHRs may present multiple sources of similar data
- EHRs often do not tell a complete story
Direct patient report

- PROs are often the best way to measure quality of life
- Challenge is that PROs are not routinely or consistently used in clinical care and not regularly recorded in the EHR
- Need a mechanism to collect PROs
Mobile devices

- Smartphones, tablets, 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 ePCTs for passive or active surveillance
Visit the ePCT guidelines when choosing outcomes

- Clearly define primary and secondary outcome measures
- Report methods used to enhance the quality of measurements
- Explain how selected outcomes and length of follow-up are important to stakeholders
Resource: Reporting secondary use of EHR data

General Considerations

and

PCT Reporting Template

From the *Living Textbook of Pragmatic Clinical Trials*

[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
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 Smerek,7 Erik G Van Eaton,8 Meredith Zozus,9 W Ed Hammond,2 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 and research activities into EHR functions

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
7: Pilot and Feasibility Testing

Contributing author:
Wendy Weber, ND, PhD, MPH, National Center for Complementary and Integrative Health (NCCIH)
Learning goal

Identify approaches to evaluate the capabilities and challenges of the partner healthcare system and test key elements of the intervention
Important things to know

- Pilot testing the ePCT methods increases likelihood of completing the trial and can prevent 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, and consider scalability of your intervention
ePCTs are not efficacy trials

- ePCTs bridge research into clinical care
- Intervention is integrated into a real-world healthcare settings
During the pilot phase

- Establish close partnerships with healthcare system (HCS) personnel
- Test and validate EHR data collection and extraction
- Assess how well the intervention can be integrated into the clinical workflow
- Identify local champions at each study site
Build partnerships

- Is the intervention aligned with the priorities of the partner HCS?
- How ready is the partner?
  - 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 use existing HCS infrastructure?
- If the intervention proves successful, what adaptations would be needed to implement it in other healthcare settings?
Establishing Close Partnerships with Healthcare Systems Leaders and Staff

From the *Living Textbook of Pragmatic Clinical Trials*  
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Aspects of feasibility that can be piloted

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verify that target population can be identified via the EHR</td>
<td>Test phenotypes needed for sample identification</td>
</tr>
<tr>
<td>Test data sample for quality &amp; accuracy</td>
<td>Coordinate processes with local champions</td>
</tr>
<tr>
<td>Validate data collection &amp; extraction methods</td>
<td>Test the training materials for frontline providers &amp; staff</td>
</tr>
<tr>
<td>Evaluate informed consent materials</td>
<td></td>
</tr>
</tbody>
</table>
Quantify feasibility for pilot study aims

- Eligibility
- Recruitment
- Randomization
- Adverse events
- Retention
- Missing data
- Intervention fidelity
Quantifying 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.
Quantifying example 2

- Determine whether the intervention can be delivered with reasonable feasibility, defined as 70% of the enrolled participants engage in the intervention.
Quantifying example 3

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

- If cluster randomization is involved, collect data to confirm estimate of intraclass correlation (ICC) for power calculations
Resource: Pilot and feasibility testing

Pilot Testing
and
Feasibility Scenarios

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Case study from NIH Collaboratory: Suicide Prevention Outreach Trial (SPOT)

- Collaborative care model to test treatments intended to reach large groups of adult patients who have serious thoughts of suicide
- 4 clinical sites
- 16,000 expected patients
Pilot testing in SPOT

• An NIH Collaboratory Demonstration Project in UH3 phase
• Gregory Simon, MD, MPH, Principal Investigator, Kaiser Permanente Washington Health Research Institute
• Watch the 9-minute webinar (on Vimeo)
In the end, it’s about

- Avoiding silly mistakes
- Maximizing acceptability
- Maintaining affordability
- Remembering scalability
Resource: More feasibility examples

Spotlight on Four Demonstration Projects

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Ensuring trial readiness

- Troubleshooting and iterative testing
- Flexibility to accommodate local conditions and changes over time
- Continuous engagement with healthcare system
- Readiness tasks
  - Recruitment plans are finalized
  - Ethical/regulatory aspects are addressed
  - Intervention is fully developed and finalized
  - Data collection methods are adequately tested
  - Budget and timeline are realistic and feasible
# Readiness checklist

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruitment plans are finalized</strong></td>
<td></td>
</tr>
<tr>
<td>All sites identified (documentation of site commitment)</td>
<td></td>
</tr>
<tr>
<td>Methods for accurately identifying participants validated</td>
<td></td>
</tr>
<tr>
<td>All agreements for necessary subcontracts in place</td>
<td></td>
</tr>
<tr>
<td><strong>Ethical/regulatory aspects are addressed</strong></td>
<td></td>
</tr>
<tr>
<td>Coordinated IRB oversight in place</td>
<td></td>
</tr>
<tr>
<td>Finalized plans for informed consent or waiver of informed consent</td>
<td></td>
</tr>
<tr>
<td>Finalized data and safety monitoring plan</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention is fully developed and finalized</strong></td>
<td></td>
</tr>
<tr>
<td>Finalized intervention (including materials and training at sites) ready for site implementation</td>
<td></td>
</tr>
<tr>
<td>Finalized protocol is IRB approved (informed consent and data collection forms, if applicable)</td>
<td></td>
</tr>
<tr>
<td><strong>Data collection methods are adequately tested</strong></td>
<td></td>
</tr>
<tr>
<td>Validated methods for the electronic health record information</td>
<td></td>
</tr>
<tr>
<td>Validated study surveys, interviews, or other data collection modes</td>
<td></td>
</tr>
<tr>
<td>Demonstrated quality assurance and harmonization of data elements across healthcare systems/sites</td>
<td></td>
</tr>
<tr>
<td>Statistical and data analysis methods have been adequately developed</td>
<td></td>
</tr>
<tr>
<td><strong>Budget is realistic, feasible, and accounts for potential changes</strong></td>
<td></td>
</tr>
</tbody>
</table>
Resource: Trial readiness criteria

Implementation Readiness Checklist

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Important things to do

- Conduct a pilot or feasibility study of the ePCT intervention
- Work with a great biostatistician and an informatician (if needed)
- Develop a partnership approach to working with your healthcare system
- Identify local champions for all your sites
- Anticipate, identify, and make a plan to address changes in the healthcare system
8: Dissemination of Results

Contributing author: Doug Zatzick, MD, University of Washington School of Medicine
Learning goal

Identify considerations and approaches for dissemination of study results
Important things to know

- Dissemination and implementation (D&I) science can inform the translation of ePCT results into healthcare system practice change
- Case examples from NIH Collaboratory demonstration projects suggest a number of possible approaches to the dissemination of trial results
Dissemination research

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
Implementation research

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.
Resource: Dissemination and implementation

D&I Introduction

From the *Living Textbook of Pragmatic Clinical Trials*
[www.rethinkingclinicaltrials.org](http://www.rethinkingclinicaltrials.org)
Dissemination and implementation together: Case study

Randomized evaluation of decolonization versus universal clearance to eliminate methicillin-resistant staphylococcus aureus (REDUCE MRSA)
REDUCE MRSA

- Large-scale cluster trial conducted in hospital intensive care units (ICU)
- Tested whether targeted decolonization of MRSA carriers versus universal decolonization of all ICU patients was the most effective intervention
REDUCE MRSA findings

Universal decolonization led to:
• 37% reduction in MRSA clinical cultures
• 44% reduction in bloodstream infections
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 Septimus, Jason Hickok, Julia Moody, Ken Kleinman, Taliser R. Avery, Susan S. Huang, Richard Platt, and Jonathan Perlin

1Hospital Corporation of America, Nashville, Tennessee; 2Texas A&M Health Science Center College of Medicine, Houston; 3Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; and 4University of California, Irvine Health School of Medicine

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 prerelease 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 23.5% (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.
REDUCE MRSA toolkit

Created for clinicians by clinicians, the toolkit is designed to serve as a roadmap for hospital champions and frontline staff.
Toolkit contents

- Introduction and welcome
- Universal ICU decolonization protocol overview
- Scientific rationale
- References
- Appendices include training and educational materials
Universal ICU Decolonization: An Enhanced Protocol

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 Methicillin-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.
Resource: Dissemination and implementation

Dissemination Approaches For Different Stakeholders

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Case study from NIH Collaboratory: Trauma Support and Outcomes (TSOS)

- Effectiveness aim: Reduce PTSD symptoms
- Implementation aim: Influence U.S. trauma center requirements for sustainable PTSD screening and intervention procedures
TSOS dissemination aims to “nudge” practice change through regulatory policy

American College of Surgeons guidelines
• Main outcome paper and other publications aim to be cited in College Resources Guide
• End-of-study policy summit aims to integrate findings into College regulatory/verification processes
PTSD and 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.”
Resource: Dissemination and implementation

Changes to Policies and Guidelines

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
Important things to do

• Consider plans for dissemination of your ePCT results
• Data sharing can be an essential element of dissemination
• How do your dissemination plans align with NIH data sharing guidelines?
Resource: Dissemination and implementation

Data Sharing and Embedded Research

From the Living Textbook of Pragmatic Clinical Trials
www.rethinkingclinicaltrials.org
9: ePCT Team Composition

Contributing author:
Lesley Curtis, PhD, Duke Clinical Research Institute
Learning goal

Identify ideal composition and skills needed for your ePCT study team
Important things to know

- ePCTs are a team sport
- Necessary expertise depends on the study aims and how the intervention will be implemented
Who is involved?

Team designing the study

Healthcare system partners delivering the intervention
Potential team members

- PI/Co-PI
- Clinical staff
- HCS leader or executive
- Lead clinician
- Biostatistician
- Professional society leader
- Information technology specialist
- Site champion
- Research assistant
- Practice facilitator
- Communications specialist
- Patient or patient advocate
- Project coordinator
Consider

- 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?
Important things to do

- Identify the types of expertise needed for your trial
- Recruit team members during the planning phase and engage them for the duration of the trial
10: Developing a Compelling Application

Contributing author:
Marcel Salive, MD, MPH, National Institute on Aging
Learning goal

Provide trainees information on how to develop a compelling ePCT application
Important things to know

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

- NIH is made up of 27 institutes and centers (IC)
- 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
Understand NIH: find the right fit

IC mission and priorities

• Focus on a specific disease area, organ system, or stage of life
• Use Matchmaker tool in NIH RePORTER for suggestions
• Talk to program officials
• Consult your mentor and colleagues
Use Matchmaker to find similar projects

Enter abstracts or other scientific text and Matchmaker will return a list of 100 similar projects from RePORTER. These matches are based on the terms and concepts used in the submitted text. Up to 15,000 characters are permitted.

Enter your Text:

Terms will be weighted by frequency of appearance in the text above. The process is automated and confidential. The Matchmaker system does not track and store submitted text.

Characters left: 15000

Submit  Clear

https://projectreporter.nih.gov/reporter_matchmaker.cfm
Matchmaker results

Matchmaker Results

100 projects similar to concepts from the entered text. (100 maximum).
Click on chart labels to filter search results by the Institute/Center or Activity Code or Study Section.

Click on the column header to sort the results.

T: Application Type; Act: Activity Code; Project: Admin IC,Serial No.; Year: Support Year/Supplement/Amendment.

Score | Act | Project | Year | Sub # | Project Title | Contact PI | Organization | FY | Admin IC | Funding IC | FY Total |
------|-----|---------|------|-------|---------------|------------|--------------|----|----------|-----------|---------|
3046  | U10 | MH160338 04 | A POLICY RELEVANT TRAUMA CARE SYSTEM PRAGMATIC TRIAL | ZATZICK, DOUGLAS F | UNIVERSITY OF WASHINGTON | 2017 | NIMH | $219,246 |

Click here to view detailed Charts
1 of 4 Next Last
Grant versus 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.
## NIH Research Collaboratory: RFA-RM-16-019

### Scientific contacts from participating NIH Institutes and Centers

<table>
<thead>
<tr>
<th>NIH Institute</th>
<th>Contact Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCIH</td>
<td>Robin Boineau</td>
</tr>
<tr>
<td>NCI</td>
<td>Erica Breslau</td>
</tr>
<tr>
<td>NHLBI</td>
<td>Barbara Wells</td>
</tr>
<tr>
<td>NIA</td>
<td>Marcel Salive</td>
</tr>
<tr>
<td>NIAAA</td>
<td>Brett Hagman</td>
</tr>
<tr>
<td>NIAID</td>
<td>Clayton Huntley</td>
</tr>
<tr>
<td>NIAMS</td>
<td>Chuck Washabaugh</td>
</tr>
<tr>
<td>NICHD</td>
<td>Sue Marden</td>
</tr>
<tr>
<td>NIDA</td>
<td>Sarah Duffy</td>
</tr>
<tr>
<td>NIDCR</td>
<td>Dena Fischer</td>
</tr>
<tr>
<td>NIDDK</td>
<td>Andy Narva</td>
</tr>
<tr>
<td>NIMH</td>
<td>Jane Pearson</td>
</tr>
<tr>
<td>NINDS</td>
<td>Robin Conwit</td>
</tr>
<tr>
<td>NINR</td>
<td>Jeri Miller</td>
</tr>
<tr>
<td>ODP</td>
<td>Rachael Ballard</td>
</tr>
</tbody>
</table>
Common application 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
Avoid receiving these summary statement comments!

- Data provided did not establish the feasibility of recruitment
- The premise of the study is based on weak evidence
- No adequate description of how activities in the planning phase would inform activities in the implementation phase
- Concerned whether outcomes of this study would drive a change in clinical practice
- Amount budgeted for a biostatistician is much too low
Strategies for success

- Pose a clear research question
- Convince the reviewer your study is worth doing
- Sell your research plan—highlight the strengths
- Identify weaknesses and explain how you will deal with them
- Tailor your application to the funding agency
- Obtain feedback from your collaborators, consultants, and others
Application dos

• Justify the research
• Include pilot data
• Reduce complexity
• Ensure aims are capable of advancing the field
• Choose appropriate expert personnel
• Link data collection and analysis to aims
• Justify use of multiple sites and sample size
Application don’ts

- Skip any steps (e.g., literature review)
- Use dense or confusing writing style
- Use appendix inappropriately
- Include untestable aims
- Include non-relevant aims or fishing expeditions
- Assume that prior collaboration is irrelevant
NIH research methods resources

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 (FORMS-E) 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 in trials that randomize groups or deliver interventions to groups, new methods-related topics and resources will be added in the future. For a guided tour of this website, please refer to a recent Mind the Gap webinar, which presents additional information about its relevance to the new NIH requirements for clinical trials applications, a summary of the methodological issues inherent in nested study designs, and a demonstration of how to use the Group-Randomized Trials (GRT) Sample Size Calculator.

Trials that Randomize Groups or Deliver Interventions to Groups

https://researchmethodsresources.nih.gov
Important things to do

• Read relevant Funding Opportunity Announcement multiple times
• Identify program staff at your target NIH Institute/Center and review your Specific Aims and any questions with them
• Obtain adequate feedback on the Research Plan from the entire team
Worksheet to help study teams get started

Download from the Living Textbook (PDF)
More learning resources ...

Demonstration Projects

The NIH Collaboratory is designed in part to support the design and rapid execution of several pragmatic clinical trial Demonstration Projects. These projects address questions of major public health importance and engage healthcare delivery systems in research partnerships. The data, tools, and resources produced by the Demonstration Projects will be made available to the greater research community to facilitate a broadened base of partnerships with healthcare systems. A U24U2C is a cooperative agreement that supports the development of exploratory or innovative research activities (considered a pilot phase for feasibility assessments), and a U1U1 award provides support for the second phase of research activities initiated with the U24U2C.

Dr. Lesley Curtis, Arthur Hernandez, and Catherine Meyers share their enthusiasm for the 6 early U24U2C demonstration projects, which include new areas of expertise, such as pediatrics, new digital technologies, and the Collaboratory’s first A/B trial.

ePCT Training Resources

Welcome to your source for training materials on how to design, conduct, and disseminate embedded pragmatic clinical trials (ePCTs). These materials reflect the knowledge, insight, and best practices acquired by the NIH Collaboratory program and its ePCT Demonstration Projects. The resources are being shared with the research community to provide guidance about building partnerships with health systems and overcoming the challenges of conducting pragmatic research. We hope you find this information useful in implementing ePCTs.

From the Living Textbook of Pragmatic Clinical Trials

www.rethinkingclinicaltrials.org
Funding Statement

The National Institutes of Health (NIH) Health Care Systems Research Collaboratory Coordinating Center is supported by the NIH Common Fund, through a cooperative agreement from the Office of Strategic Coordination within the Office of the NIH Director (Grant # 1U24AT009676-01). The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.