NIH Collaboratory

Health Care Systems Research Collaboratory

Rethinking Clinical Trials®

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

1	What are ePCTs?
2	Engaging All Stakeholders & Aligning with Healthcare System Partners
3	Designing with Implementation in Mind
4	Design and Analytic Considerations
5	Regulatory and Ethical Challenges of ePCTs
6	Measuring Outcomes
7	Pilot and Feasibility Testing
8	Dissemination of Results
9	ePCT Team Composition
10	Developing a Compelling Application

Learning resource

The NIH Collaboratory's *Living Textbook of Pragmatic Clinical Trials*:
www.rethinkingclinicaltrials.org

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1: What are ePCTs?

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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

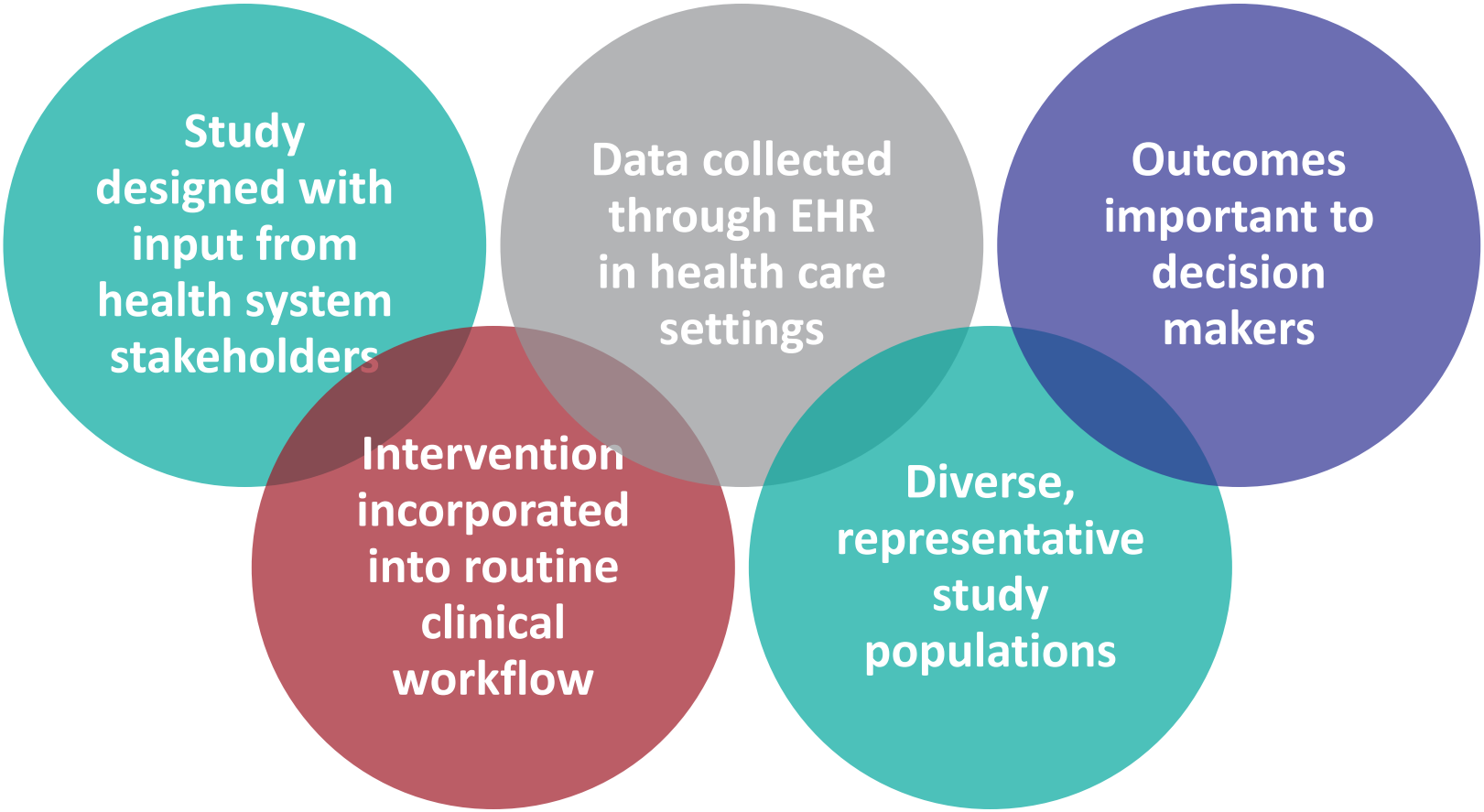
ePCT characteristics

- 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



Key differences between explanatory and pragmatic trials

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

Adapted from Zwarenstein M, Treweek S, Gagnier JJ, et al. BMJ. 2008;337:a2390. doi: 10.1136/bmj.a2390. PMID: 19001484

Common-sense definition

"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."

Califf RM, Sugarman J. Clin Trials. 2015 Oct;12(5):436-41. doi: 10.1177/1740774515598334

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

Resource: What are ePCTs?

[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

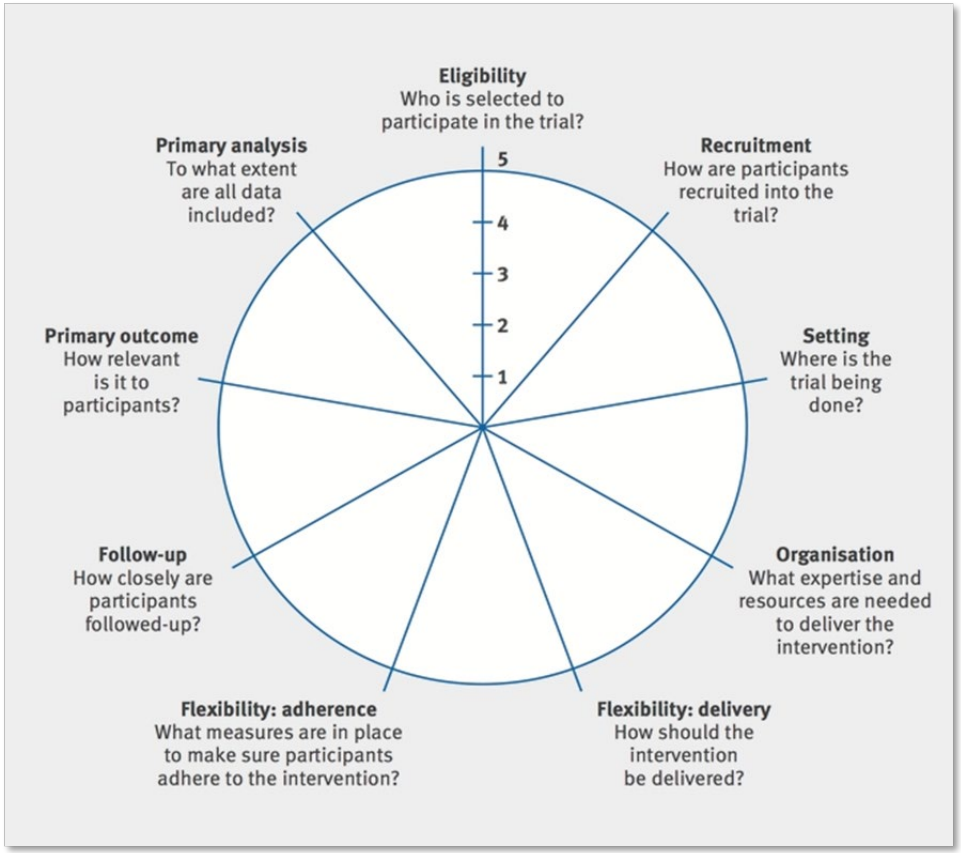
Explanatory — **Pragmatic**

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

Introducing PRECIS-2

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

Pragmatic–Explanatory Continuum Indicator Summary (PRECIS) tool



PRECIS-2 source: Kirsty Loudon et al. BMJ 2015;350:bmj.h2147. Copyright 2015 by British Medical Journal Publishing Group. Used by permission.

PRECIS-2: Eligibility

Who is selected to participate in the trial?

Explanatory — **Pragmatic**

Highly selected patients, strict inclusion criteria

Typical patients, minimal inclusion criteria

PRECIS-2: Recruitment

How are participants recruited into the trial?

Explanatory — **Pragmatic**

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

Recruited in usual healthcare settings; participants may include patients, providers, or health systems

PRECIS-2: Setting

Where is the trial being done?

Explanatory ⟷ **Pragmatic**

Specialist practice or academic medial center

Settings where the trial's results will be applied

PRECIS-2: Organization

What expertise and resources are needed to deliver the intervention?

Explanatory — **Pragmatic**

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

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

PRECIS-2: Flexibility -delivery

How should the intervention be delivered?

Explanatory — **Pragmatic**

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

Details of intervention delivery left to the care provider

PRECIS-2: Flexibility - adherence

What measures are in place to ensure participants adhere to the intervention?

Explanatory — **Pragmatic**

Measures to monitor patient adherence and excludes patients judged not to be adherent

No special measures to enforce intervention engagement or compliance

PRECIS-2: Follow-up

How closely are participants followed up?

Explanatory — **Pragmatic**

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?

Explanatory — **Pragmatic**

Surrogate outcomes or measures distinct from the research question

Outcomes of importance to patients, measured as they would be in usual care

PRECIS-2: Primary analysis

To what extent are all data included?

Explanatory ⟷ **Pragmatic**

Excludes noncompliant participants, dropouts, or practice variability

Intent-to-treat analysis

Resource: Using PRECIS-2

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

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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

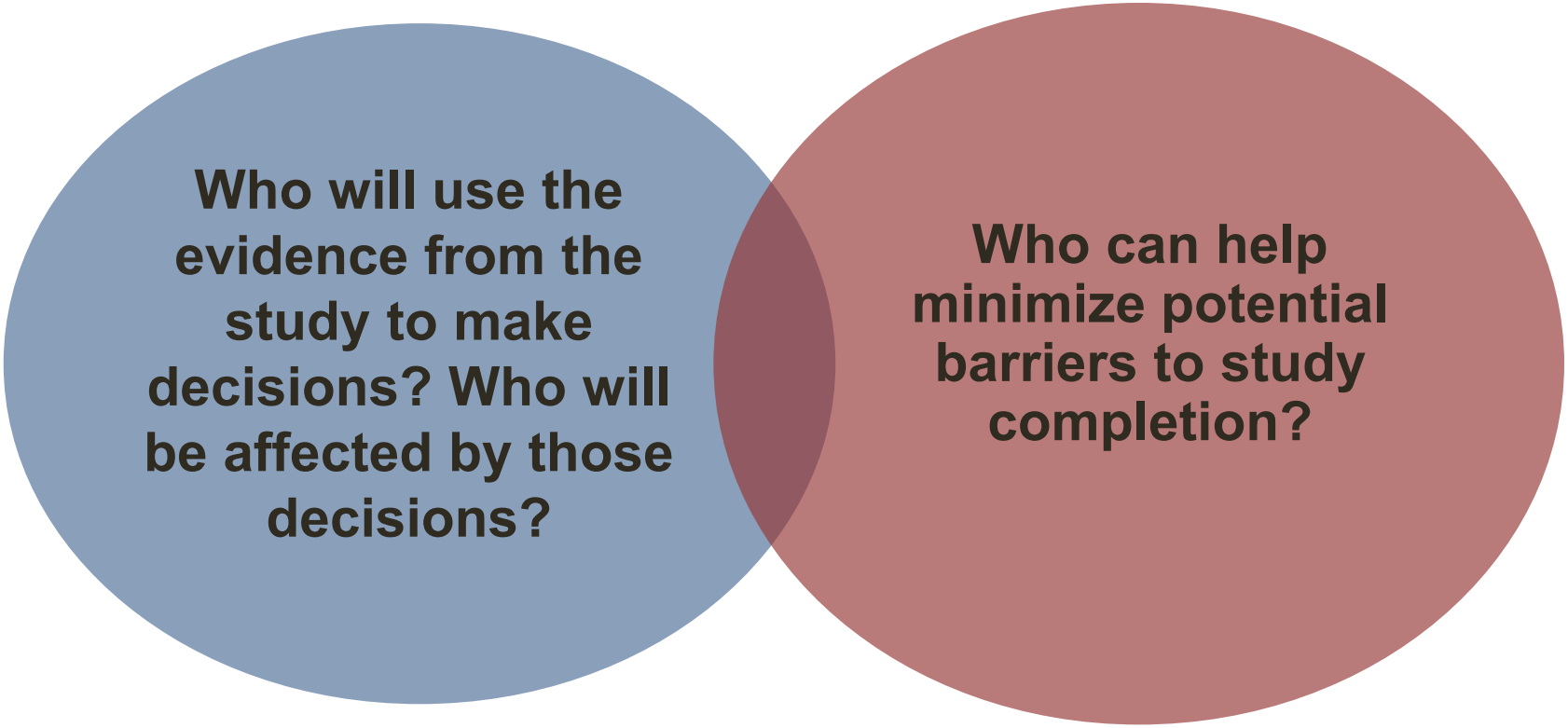
Types of stakeholders

- 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

Important things to do

Determine which stakeholders are important for your trial



Resource: Engaging stakeholders

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 (eg, 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

Challenge	Solution
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

Challenge	Solution
High amounts of **leadership turnover** at medical director and provider levels due to preexisting pressures and challenges inherent in community clinics	Meet regularly with leadership teams and establish an advisory board and other infrastructure to help engage leaders and gatekeepers

Nurturing relationships: challenges and solutions

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

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

Lessons from NIH Collaboratory

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)

Important things to do

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

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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

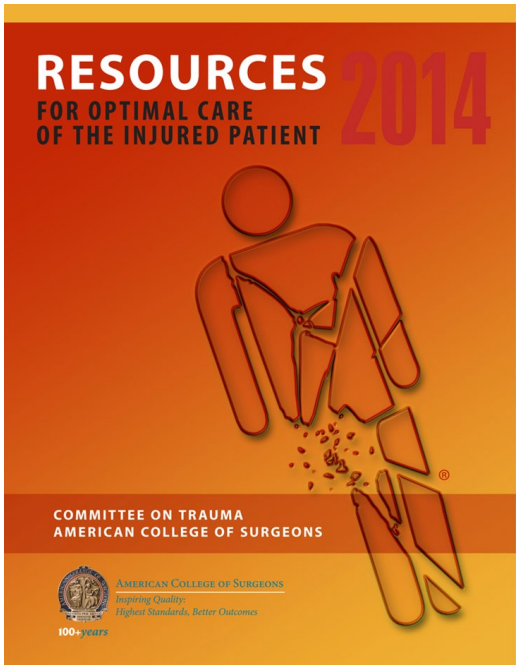
If you build it . . . they will come

Translated to ePCTs:

If you build it
pragmatically …
they will implement

Case study from NIH Collaboratory: Trauma Support and Outcomes (TSOS)

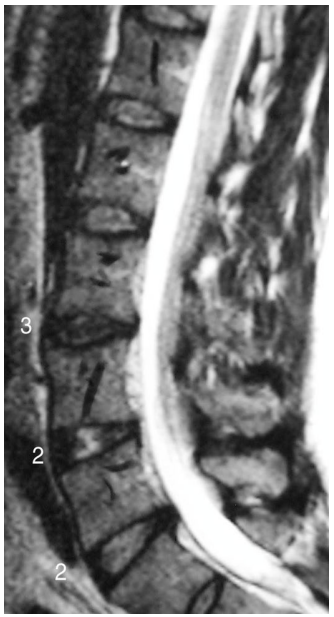
- Effectiveness aim: Reduce PTSD symptoms
- Implementation aim: Influence U.S. trauma center requirements for sustainable PTSD screening and intervention procedures



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

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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

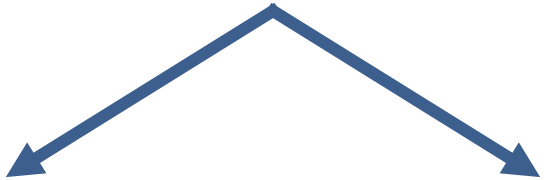
Introduction

and

Statistical Design Considerations

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

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

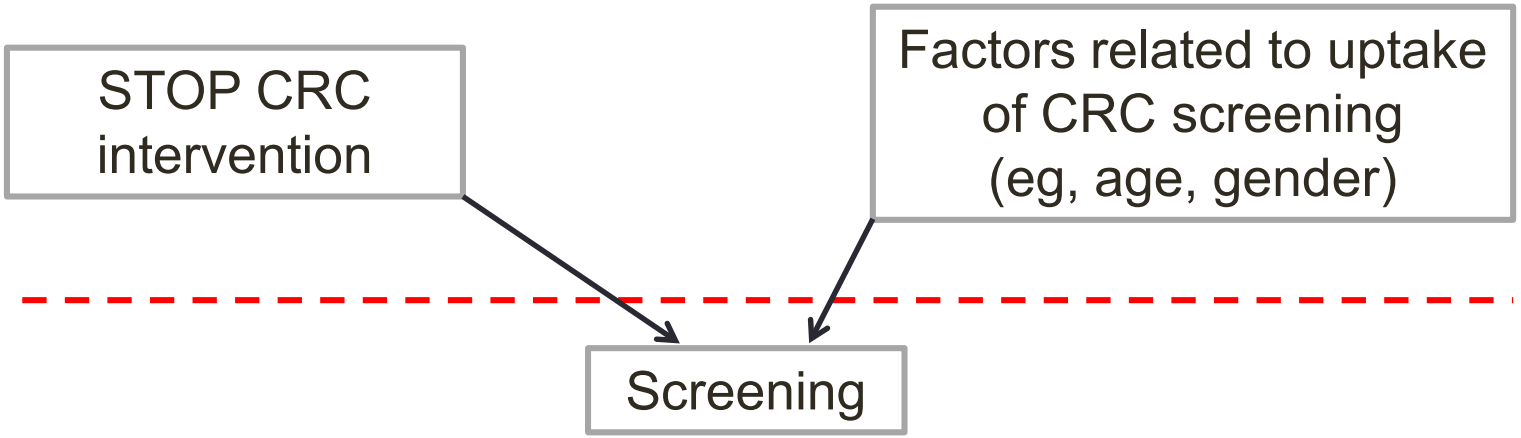
- Target of intervention is a collective instead of an individual
  - For example, comparing 2 protocols for handling in-hospital infections or comparing 12-hour nursing shifts to 8-hour shifts
- Target of intervention is an individual, but there is risk of ***contamination***
  - Contamination occurs 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



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)

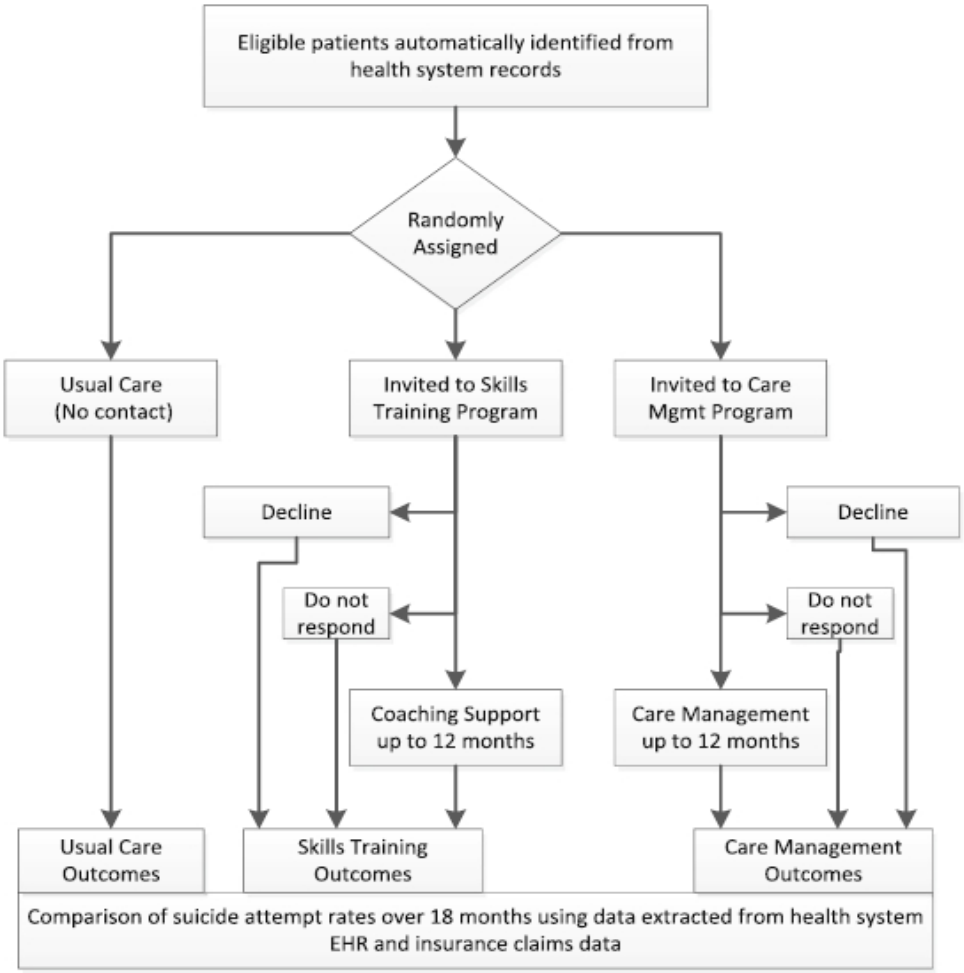
SUICIDE PREVENTION OUTREACH TRIAL

- 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



Simon GE, et al. 2016. Trials. 17:452. doi:10.1186/s13063-016-1566-z. PMID: 27634417

Resources: Randomization schemes

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?

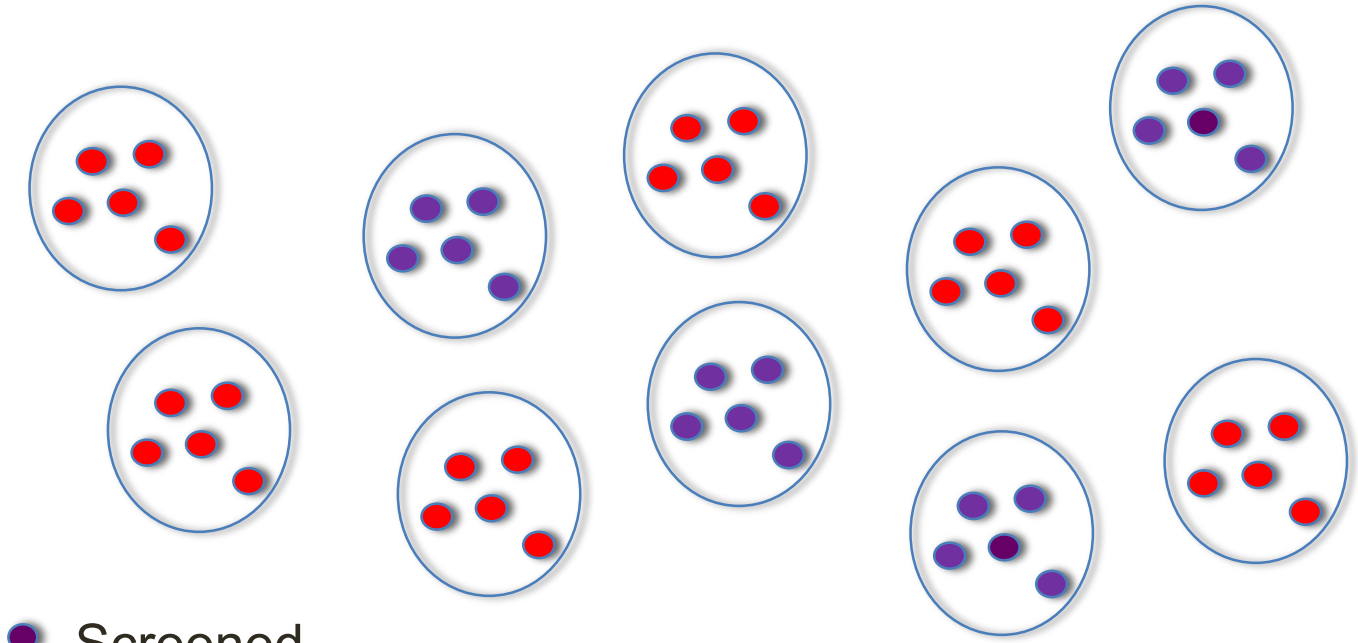
- When unit of randomization is a **cluster** or . . .
- When unit of randomization is an **individual AND** the individual outcomes demonstrate some clustering

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

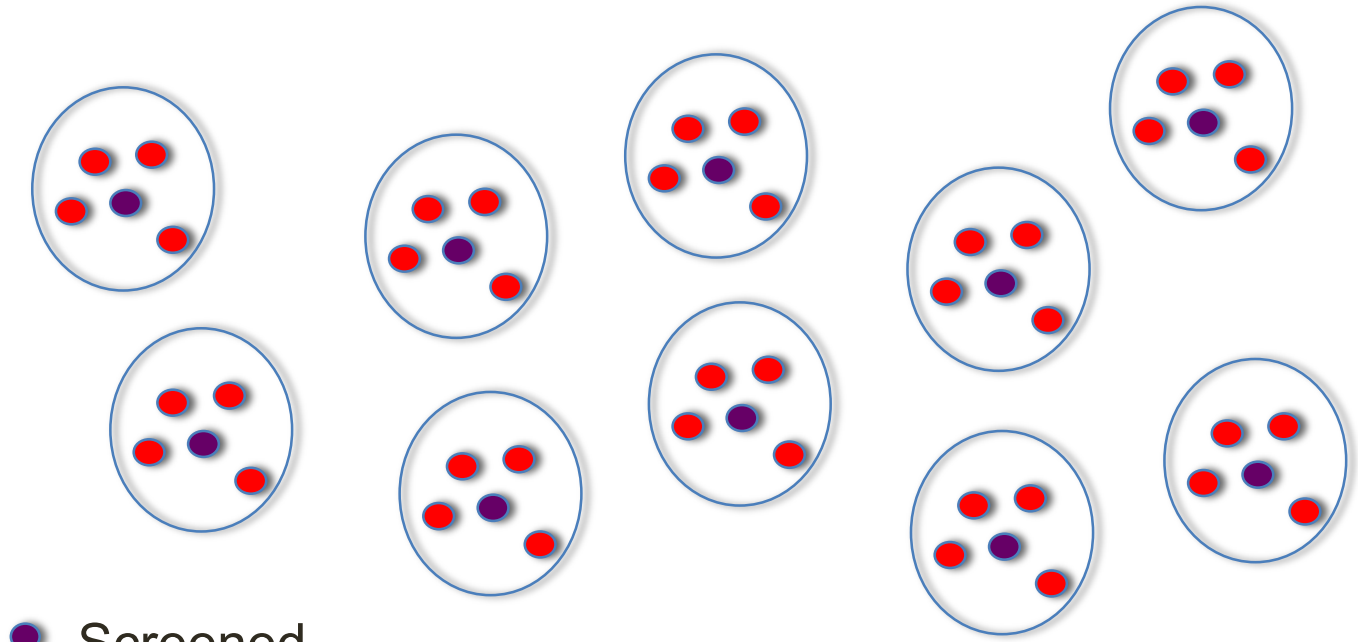
Understanding clustering: complete clustering



- Screened
- Not screened

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

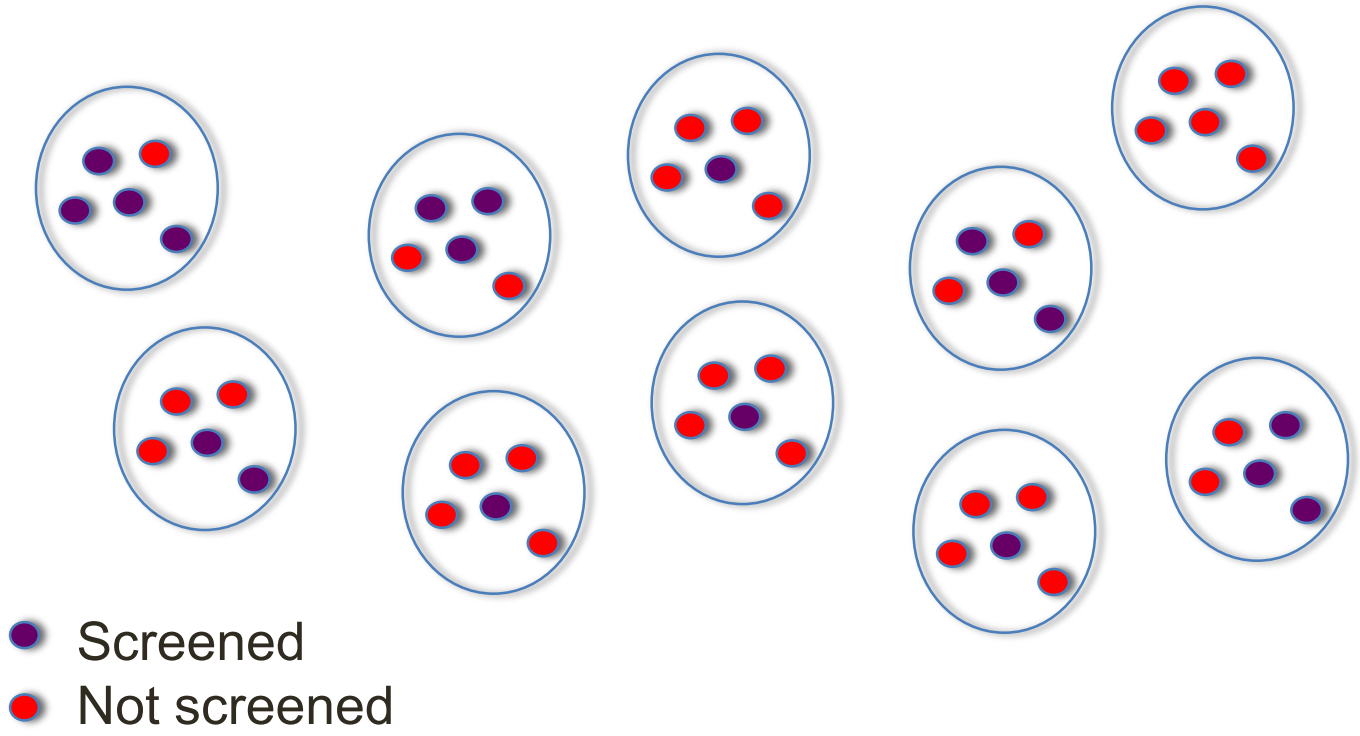
Understanding clustering: no clustering



- 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 μ is overall mean of outcome

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

Resource: Design and analysis

Analysis Plan

and

Intraclass Correlation

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Analytic approaches for clustered data

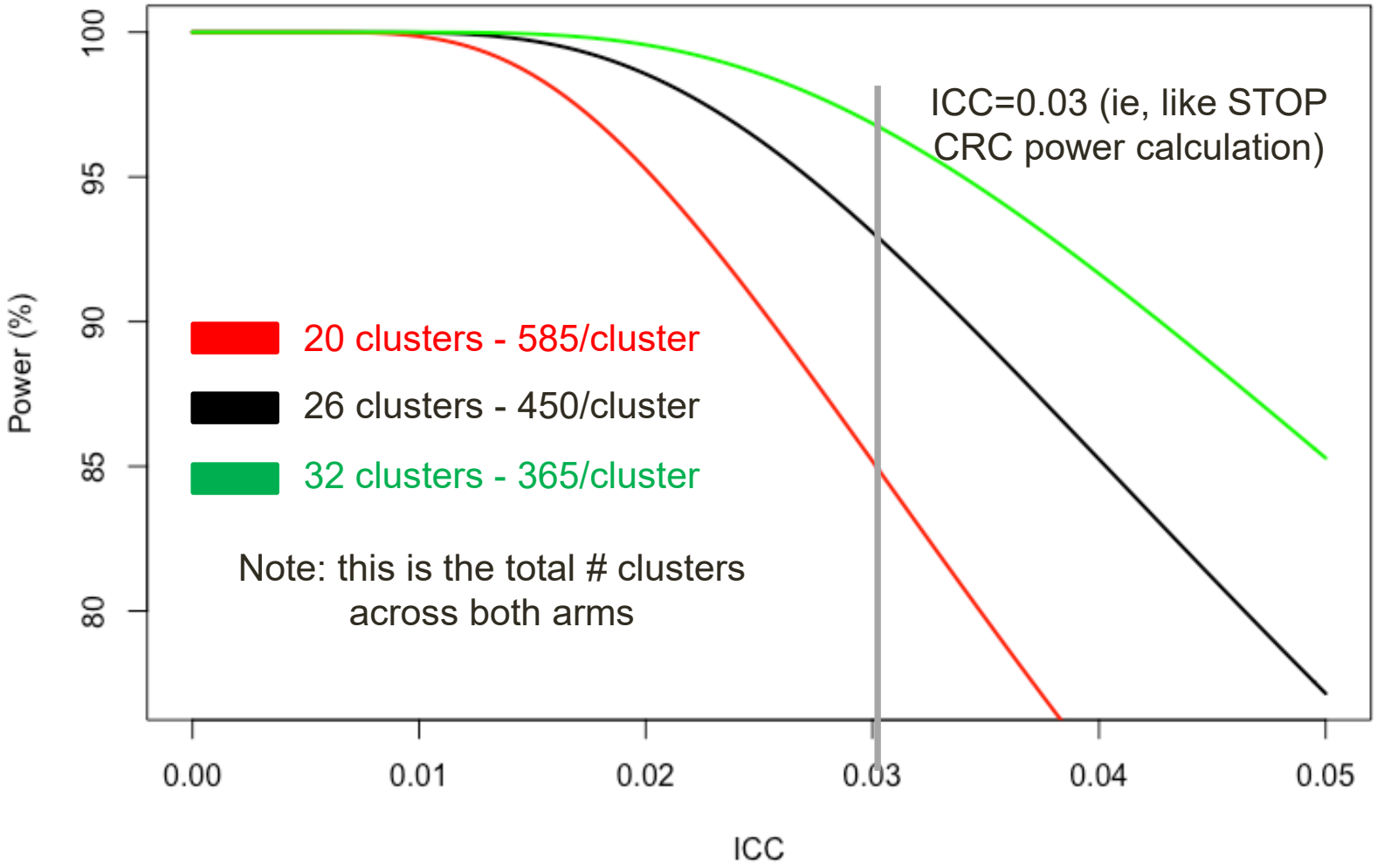
- Typically use regression-type models of individual-level data
  - Random effects/mixed effects models
  - Generalized estimating equations
- **Important:** Work with a statistician to ensure correct accounting for clustering

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)



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

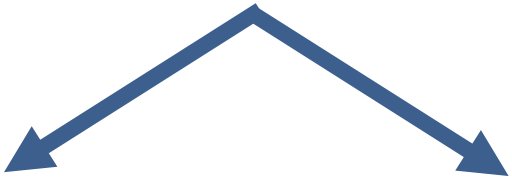
"Assumed equal numbers of subjects per clinic and equal numbers of clinics (n = 13) per group. In practice, the clinic sizes will not be equal, but since almost all clinics have at least 450 active age-eligible patients, we conservatively use this figure for all sites. We based our calculations on the 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."

Coronado GD, et al. 2014. Contemp Clin Trials. 38:344-349. doi:10.1016/j.cct.2014.06.006. PMID: 24937017

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?

Resource: Randomization methods

Randomization Methods

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

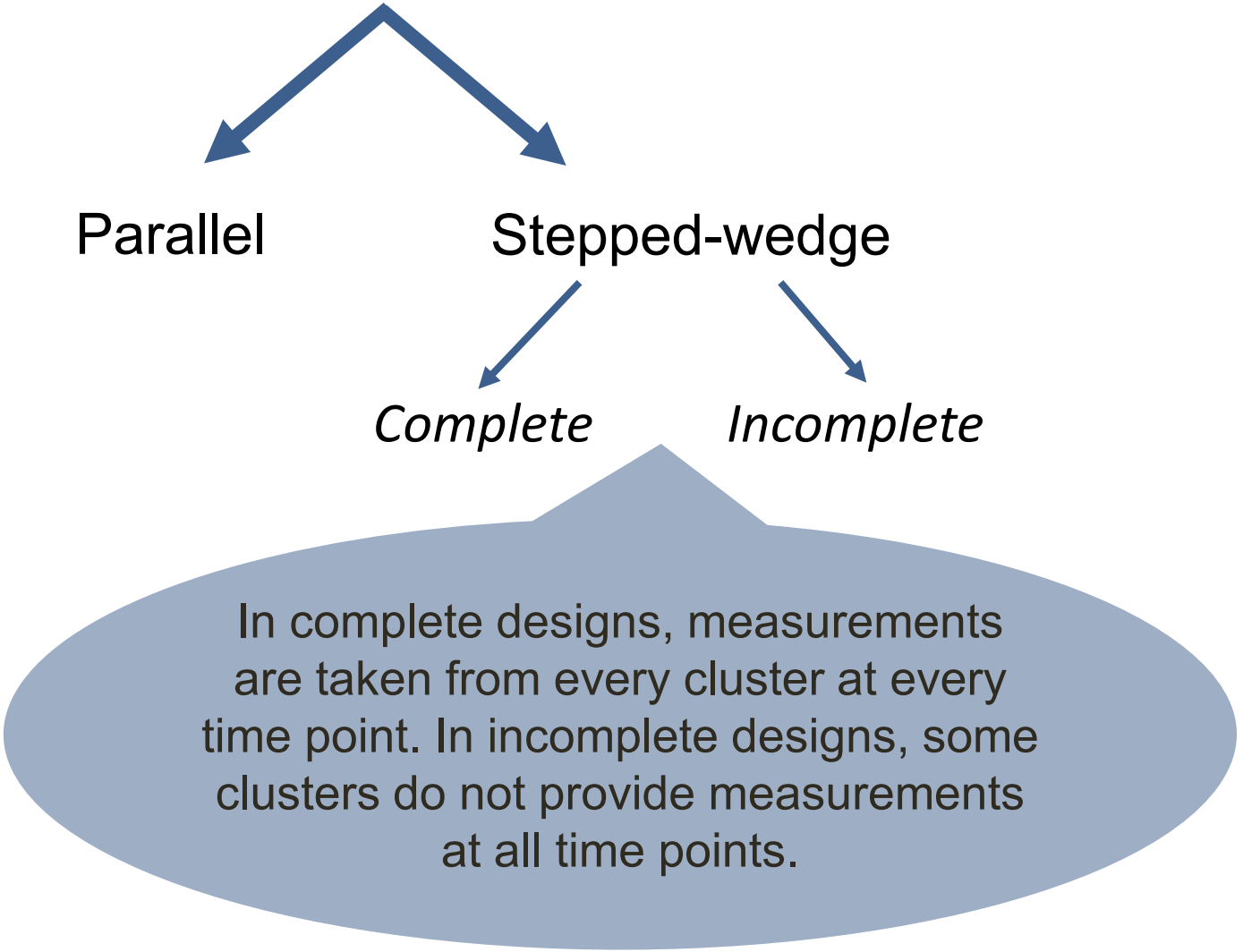
Number of clusters: *How low can you go?*

- 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

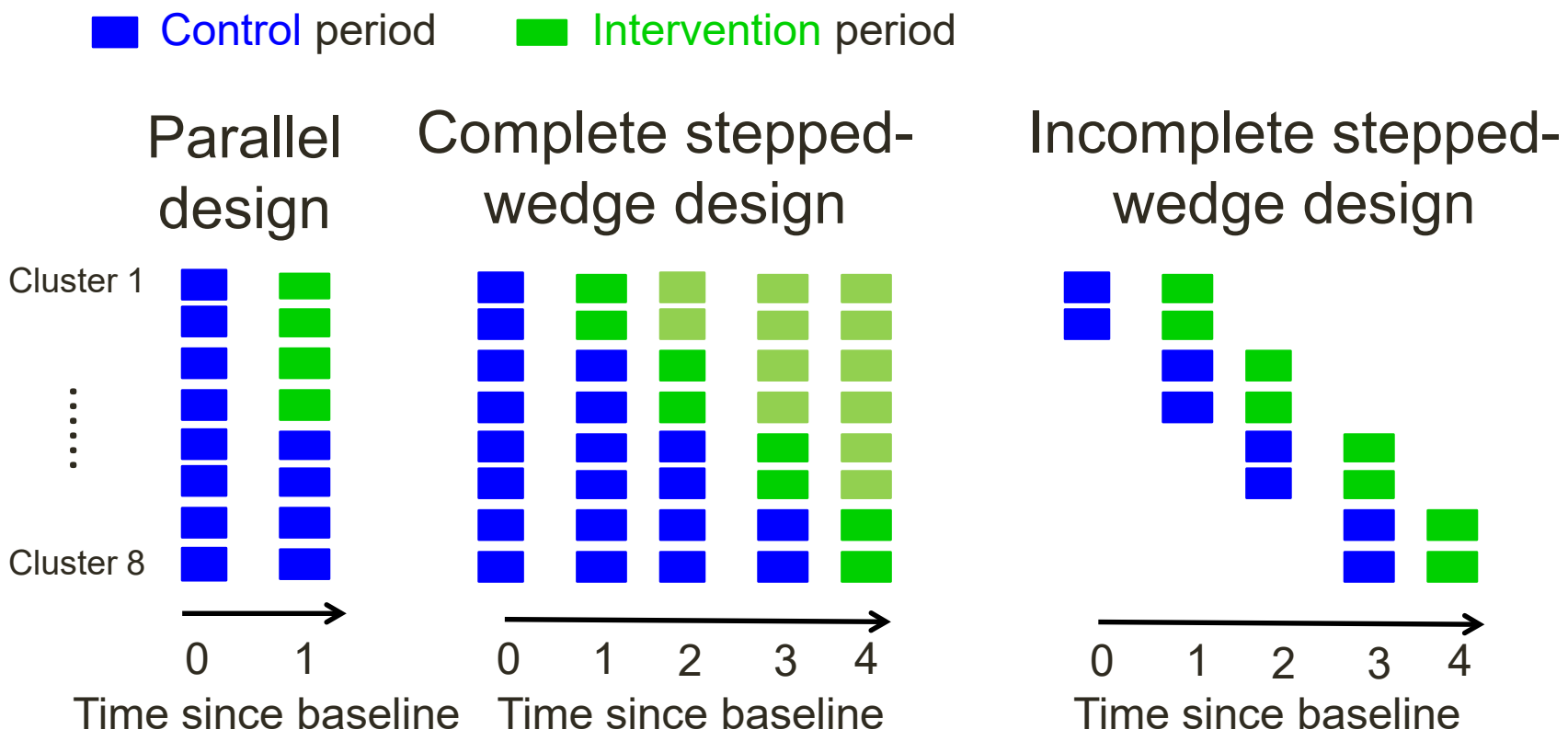
1. Parallel CRT
2. Stepped-wedge CRT

Two types of CRT designs



Types of CRT designs

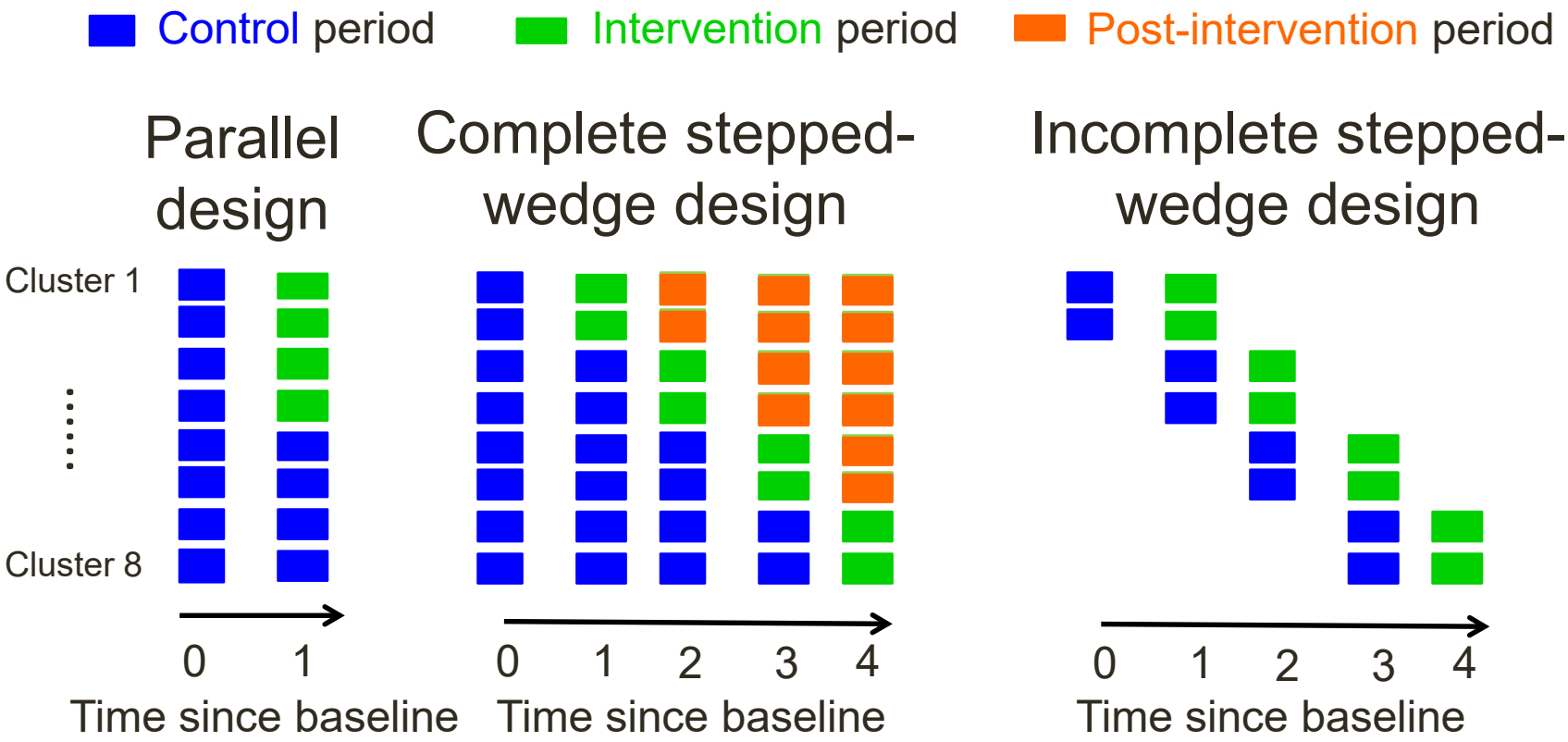
Examples with 8 clusters: 1-year intervention



Based on: Hemming K, Lilford R, Girling AJ. 2015. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Stat Med. 34:181-196. doi:10.1002/sim.6325. PMID: 25346484

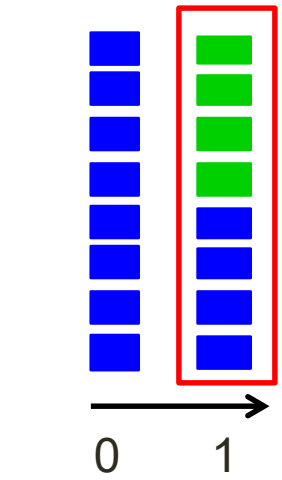
Types of CRT designs

Examples with 8 clusters: 1-year intervention



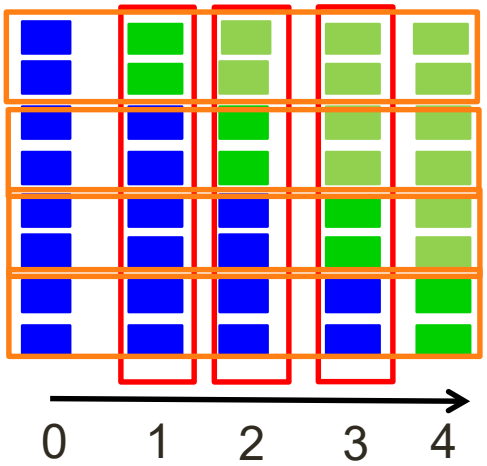
CRT analysis: treatment effects

Estimated (primarily) using between- cluster ie, **vertical** information



Parallel design

Estimated using both **vertical** & **horizontal** (ie, within-cluster) information



Complete SW design

Control period Intervention period

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

Consider …

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

Resources: Other design considerations

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

Select design features with analysis in mind

Collaborate early with a statistician

Choose individual randomization, but only if possible

Weigh statistical choices vs implementation challenges

Write & publish a protocol paper

Resource: ePCT design and analysis

Additional Resources

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

NIH Collaboratory

Health Care Systems Research Collaboratory

Rethinking Clinical Trials®

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

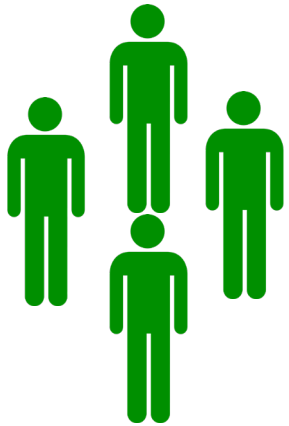
ePCTs are motivated by ethical imperatives

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

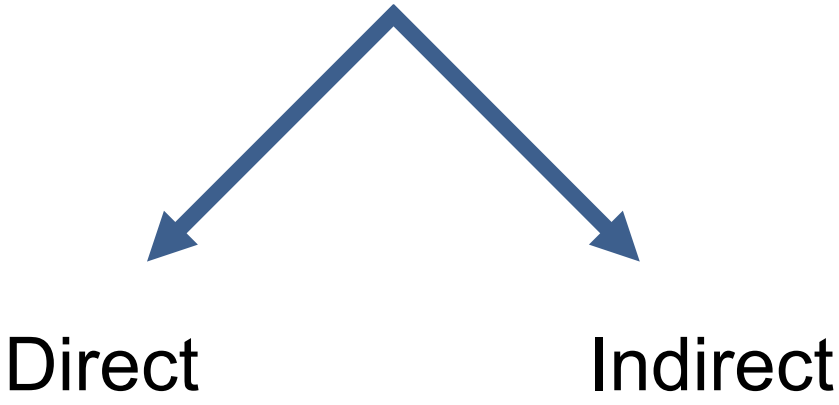
Informed Consent

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Current ethics/regulatory in flux

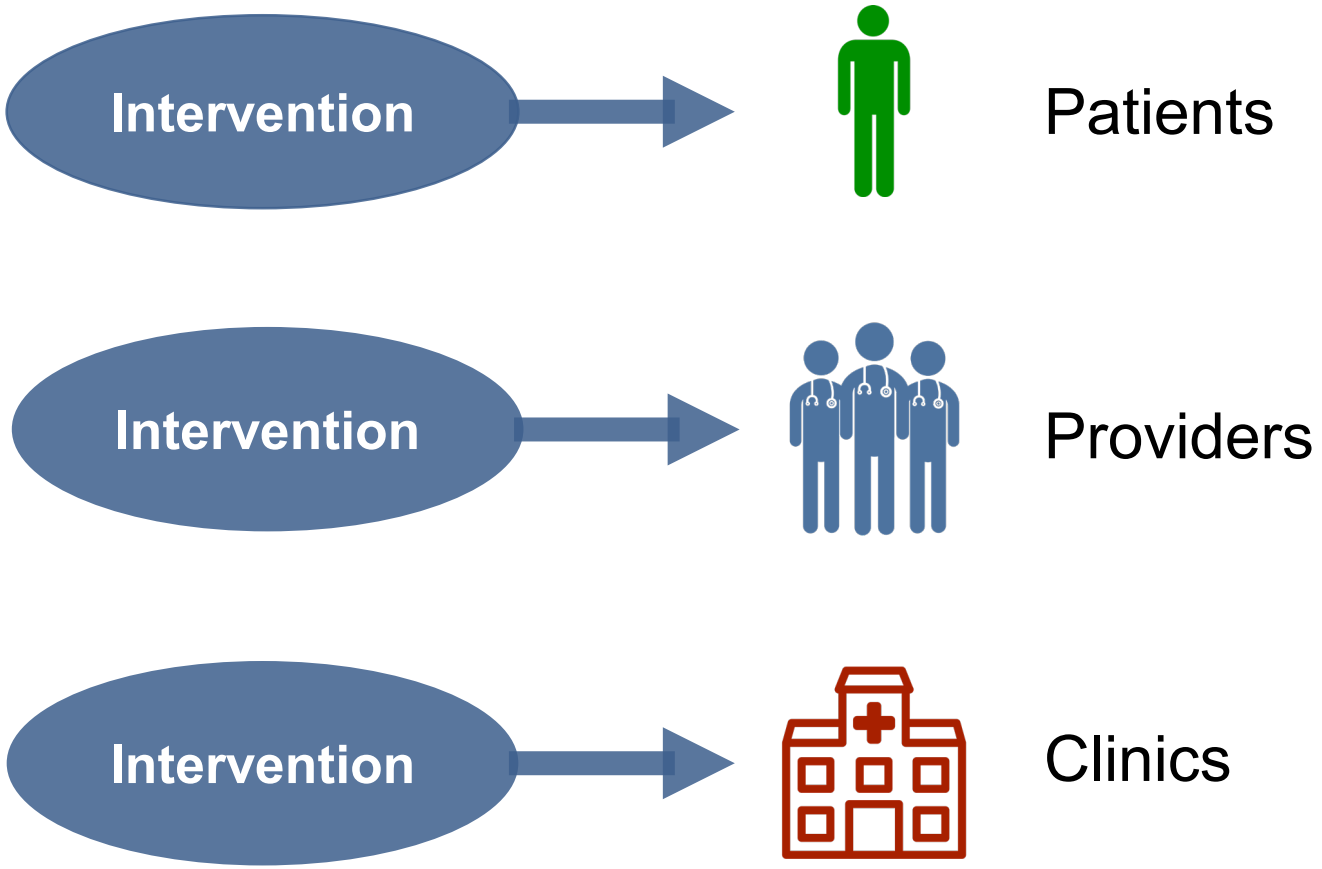
Delayed compliance date of revised final Common Rule

Types of participants in an ePCT

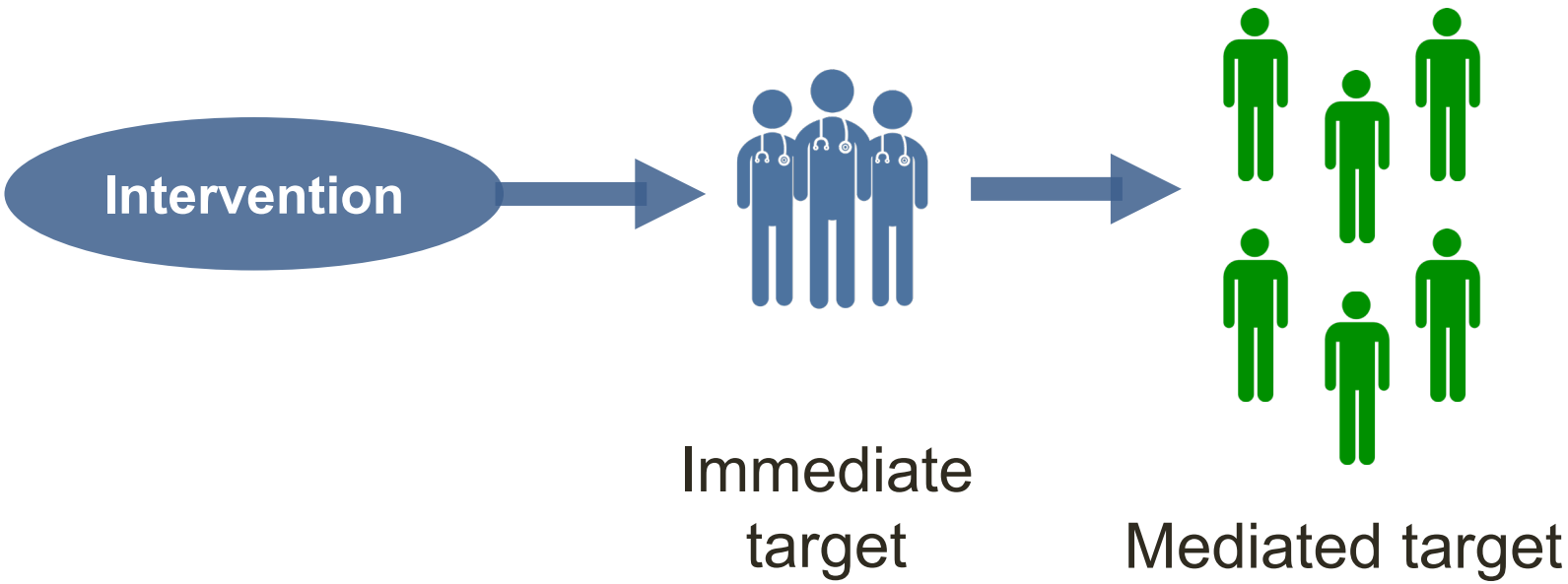


Direct participants

Immediate or mediated targets of the intervention

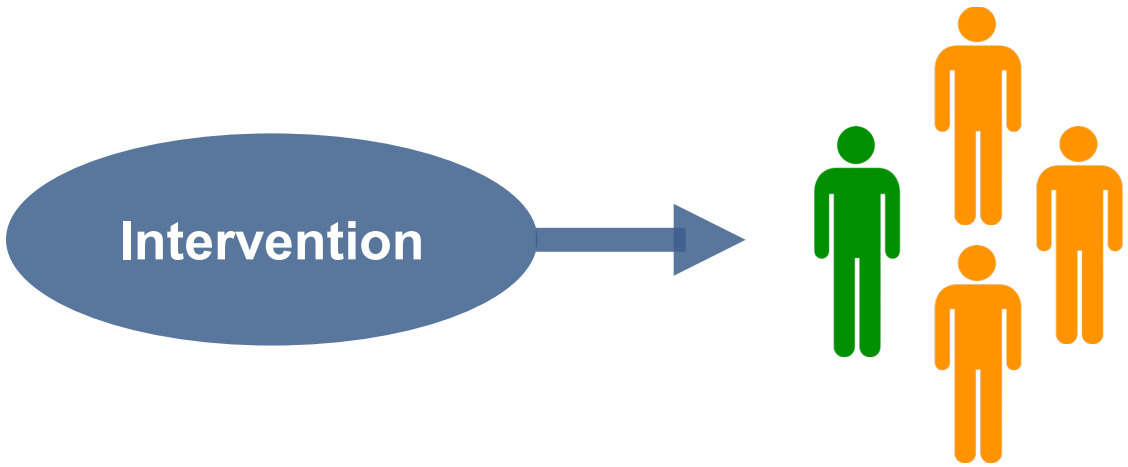


Direct participant



Indirect participants

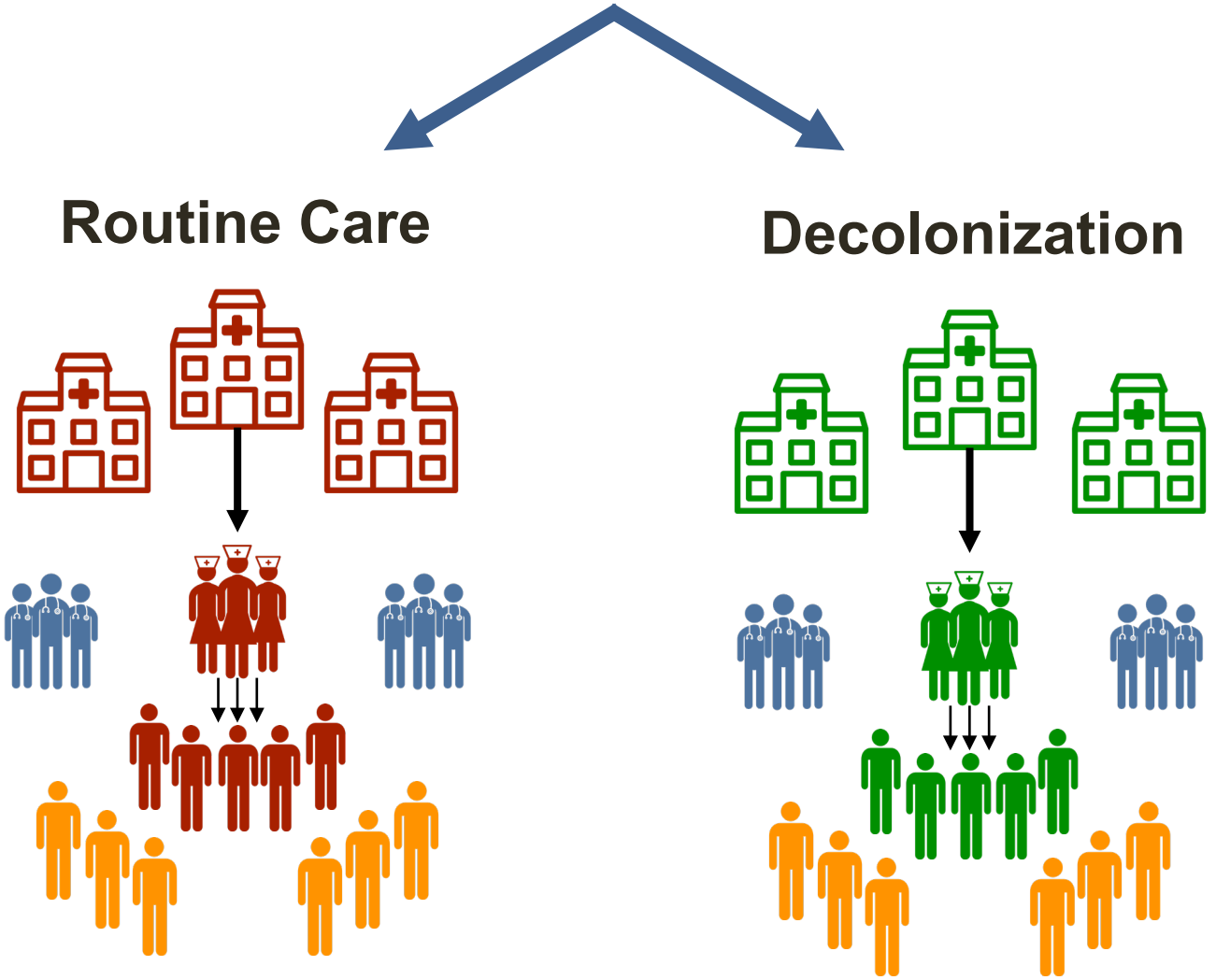
People affected by routine exposure to the environment (eg, family/caregivers)



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 …

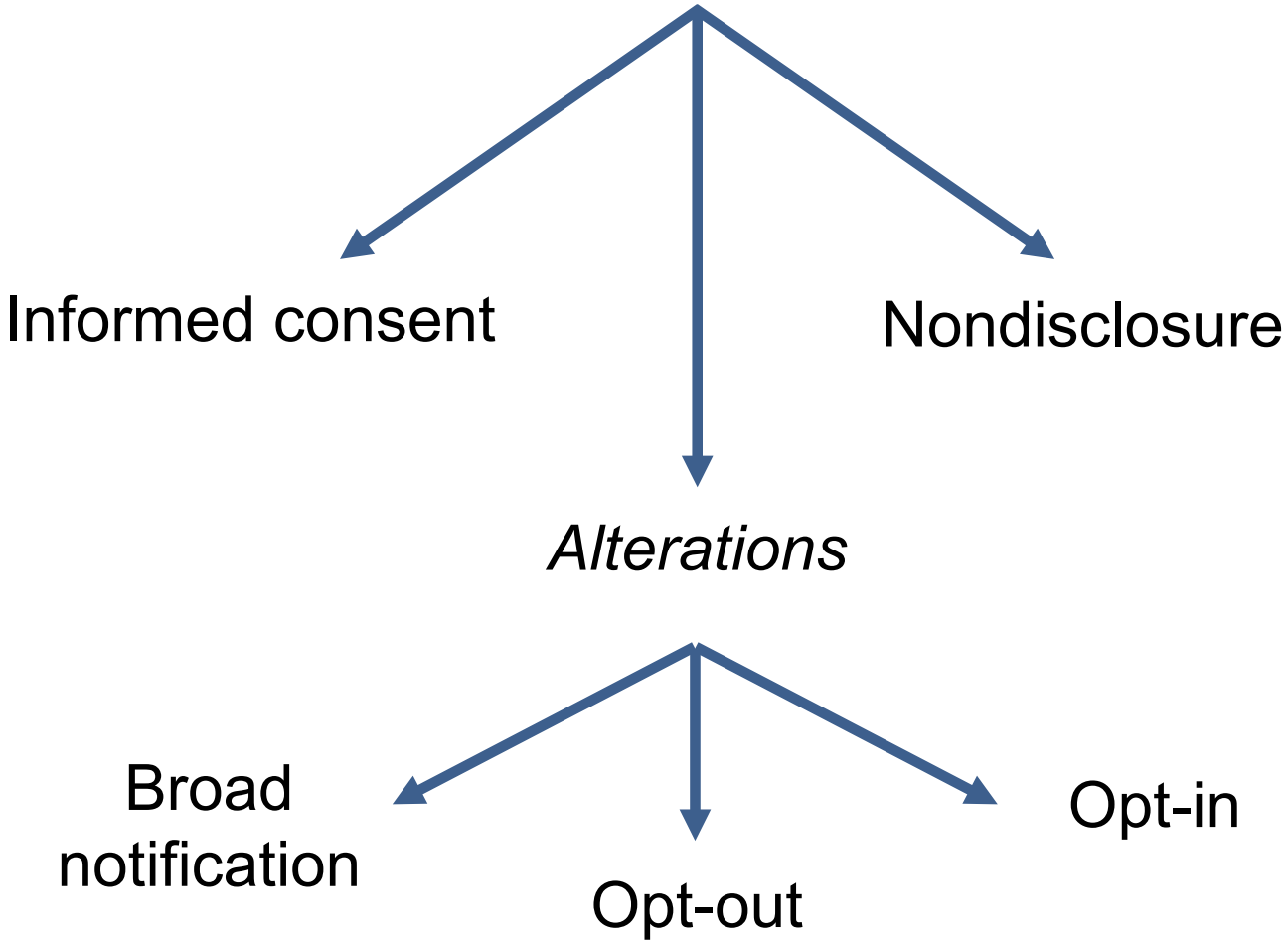
- Who are the direct and indirect participants for your study?
- What are the potential risks and benefits for each?

Resource: Alternative approaches

Alternative Approaches to Disclosure and Authorization

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Approaches to notification & authorization



Conditions for waiver of consent

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)."

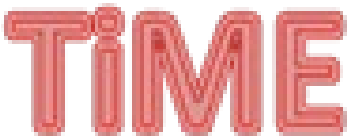
Common Rule: CFR 46.111 (a)(2)

"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

Some debate here!!!

Case study from NIH Collaboratory: Time to Reduce Mortality in End-Stage Renal Disease (TiME)

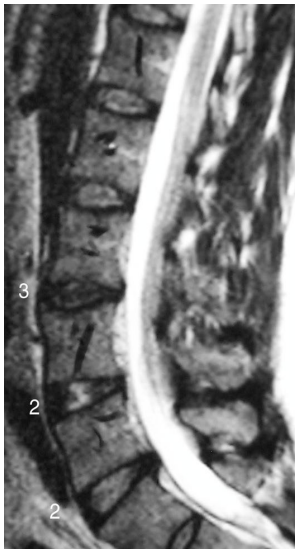


- CRT testing whether a longer hemodialysis session can improve survival and quality of life for patients with kidney failure who require chronic treatment with dialysis
- 256 clinical sites
- 7053 patients

Consent process: TiME example

- 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

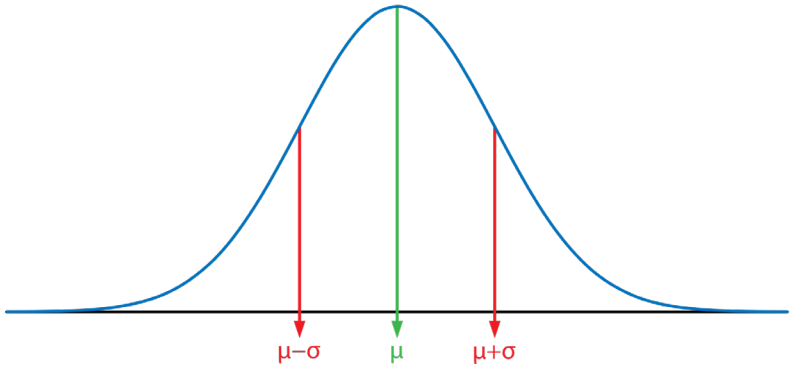
Consent process: LIRE example

- 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

ORIGINAL ARTICLE

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

Weinfurt KP, et al. Med Care. 2017 Nov;55(11):970-978. doi: 10.1097/MLR.0000000000000762

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

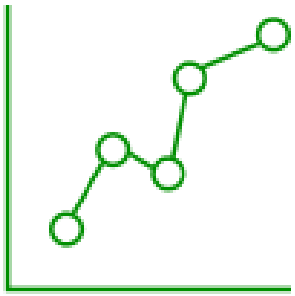
Group of experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial

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

NIH Collaboratory

Health Care Systems Research Collaboratory

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6: Measuring Outcomes

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

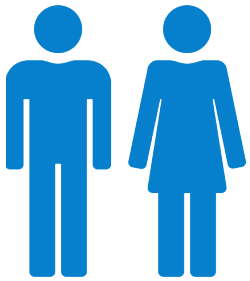
Learning goal

Describe methods for measuring study outcomes using data sources such as electronic health records (EHRs) and patient-reported outcomes (PROs)

Important things to know

- 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?

Resource: Endpoints and outcomes

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

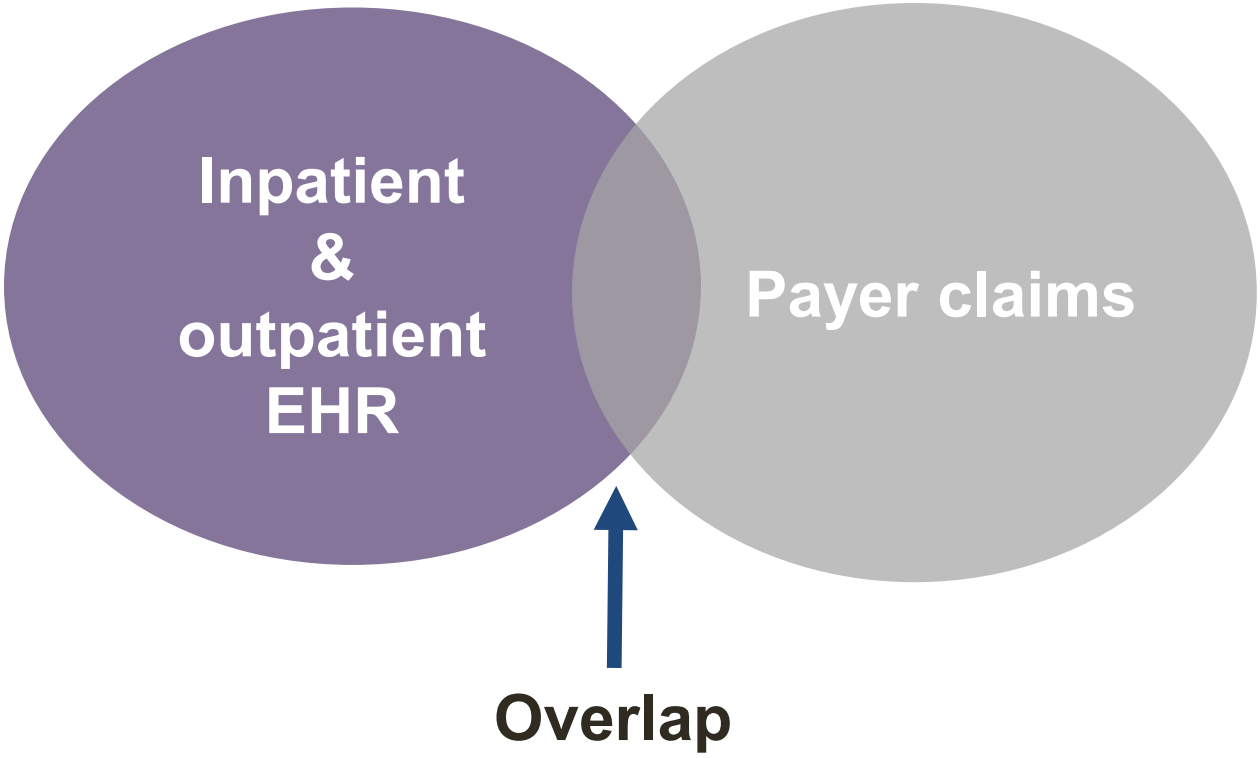
Choosing and specifying endpoints

- Acute MI
- Broken bone
- Hospitalization

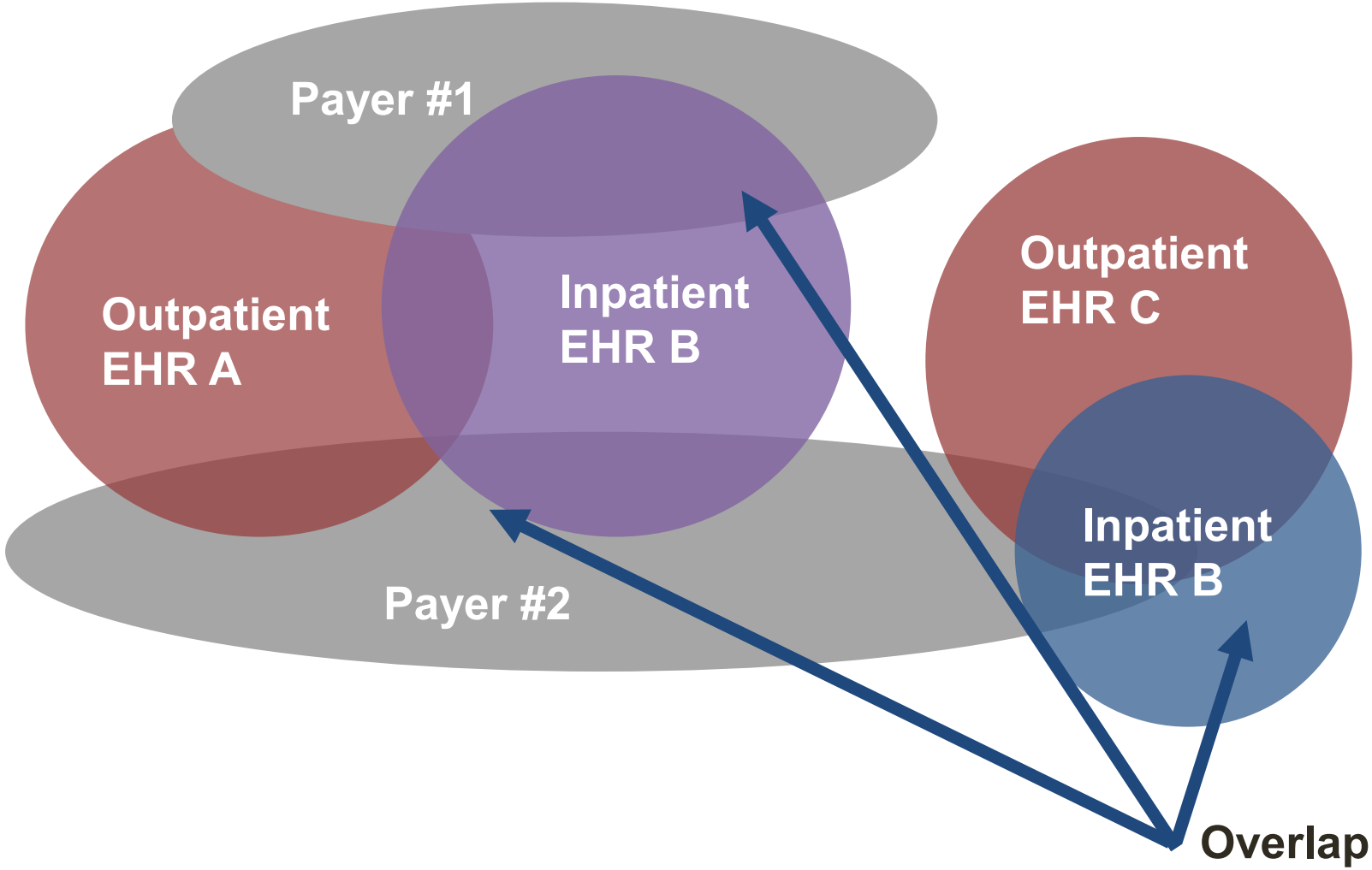
- Suicide attempts
- Gout flares
- Silent MI
- Early miscarriage

Where is the signal?

- EHR (laboratory values, treatments, etc)
- Claims data (does the event generate a bill?)



Reality is not straightforward

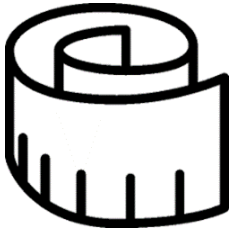


Simon G, Group Health Research Institute

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

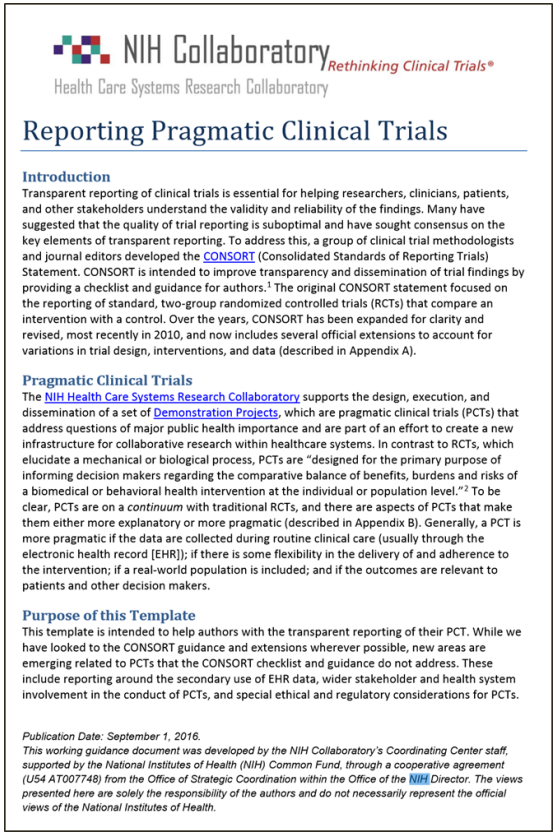
- PROs are often the best way to measure quality of life
- Challenge is that PROs are not routinely or consistently used in clinical care and not regularly recorded in the EHR
- Need a mechanism to collect PROs

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

Consider ePCT reporting 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



NIH Collaboratory *Rethinking Clinical Trials®*
Health Care Systems Research Collaboratory

Reporting Pragmatic Clinical Trials

Introduction

Transparent reporting of clinical trials is essential for helping researchers, clinicians, patients, and other stakeholders understand the validity and reliability of the findings. Many have suggested that the quality of trial reporting is suboptimal and have sought consensus on the key elements of transparent reporting. To address this, a group of clinical trial methodologists and journal editors developed the CONSORT (Consolidated Standards of Reporting Trials) Statement. CONSORT is intended to improve transparency and dissemination of trial findings by providing a checklist and guidance for authors.[1] The original CONSORT statement focused on the reporting of standard, two-group randomized controlled trials (RCTs) that compare an intervention with a control. Over the years, CONSORT has been expanded for clarity and revised, most recently in 2010, and now includes several official extensions to account for variations in trial design, interventions, and data (described in Appendix A).

Pragmatic Clinical Trials

The NIH Health Care Systems Research Collaboratory supports the design, execution, and dissemination of a set of Demonstration Projects, which are pragmatic clinical trials (PCTs) that address questions of major public health importance and are part of an effort to create a new infrastructure for collaborative research within healthcare systems. In contrast to RCTs, which elucidate a mechanical or biological process, PCTs are "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."[2] To be clear, PCTs are on a *continuum* with traditional RCTs, and there are aspects of PCTs that make them either more explanatory or more pragmatic (described in Appendix B). Generally, a PCT is more pragmatic if the data are collected during routine clinical care (usually through the electronic health record [EHR]); if there is some flexibility in the delivery of and adherence to the intervention; if a real-world population is included; and if the outcomes are relevant to patients and other decision makers.

Purpose of this Template

This template is intended to help authors with the transparent reporting of their PCT. While we have looked to the CONSORT guidance and extensions wherever possible, new areas are emerging related to PCTs that the CONSORT checklist and guidance do not address. These include reporting around the secondary use of EHR data, wider stakeholder and health system involvement in the conduct of PCTs, and special ethical and regulatory considerations for PCTs.

Publication Date: September 1, 2016.
This working guidance document was developed by the NIH Collaboratory's Coordinating Center staff, supported by the National Institutes of Health (NIH) Common Fund, through a cooperative agreement (U54 AT007748) from the Office of Strategic Coordination within the Office of the NIH Director. 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.

Resource: Reporting secondary use of EHR data

General Considerations

and

PCT Reporting Template

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Perspective

Pragmatic (trial) informatics: a perspective from the NIH Health Care Systems Research Collaboratory

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JAMIA
A SCHOLARLY JOURNAL OF INFORMATICS IN HEALTH AND BIOMEDICINE

- 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

Richesson RL, et al. 2017. J Am Med Inform Assoc. 24:996-1001. doi:10.1093/jamia/ocx016. PMID: 28340241

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

NIH Collaboratory

Health Care Systems Research Collaboratory

Rethinking Clinical Trials®

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?

Resource: Health system partnerships

Establishing Close Partnerships with Healthcare Systems Leaders and Staff

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Aspects of feasibility that can be piloted

Verify that target population can be identified via the EHR

Test phenotypes needed for sample identification

Validate data collection & extraction methods

Test data sample for quality & accuracy

Coordinate processes with local champions

Test the training materials for frontline providers & staff

Evaluate informed consent materials

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)

SUICIDE PREVENTION OUTREACH TRIAL

- 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

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

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

Resource: Trial readiness criteria

Implementation Readiness Checklist

From the *Living Textbook of Pragmatic Clinical Trials*
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

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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

NIH Dissemination and Implementation Research in Health PAR-16-238

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

NIH Dissemination and Implementation Research in Health PAR-16-238

Resource: Dissemination and implementation

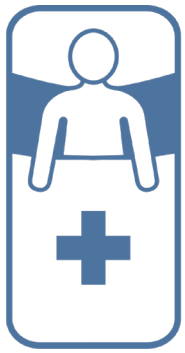
D&I Introduction

From the *Living Textbook of Pragmatic Clinical Trials*
www.rethinkingclinicaltrials.org

Dissemination and implementation together: Case study

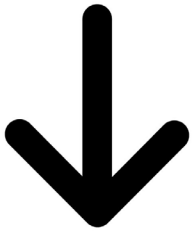
Randomized evaluation of decolonization versus universal clearance to eliminate methicillin-resistant staphylococcus aureus (REDUCE MRSA)

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

REDUCE MRSA manuscript

Clinical Infectious Diseases

MAJOR ARTICLE

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

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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.

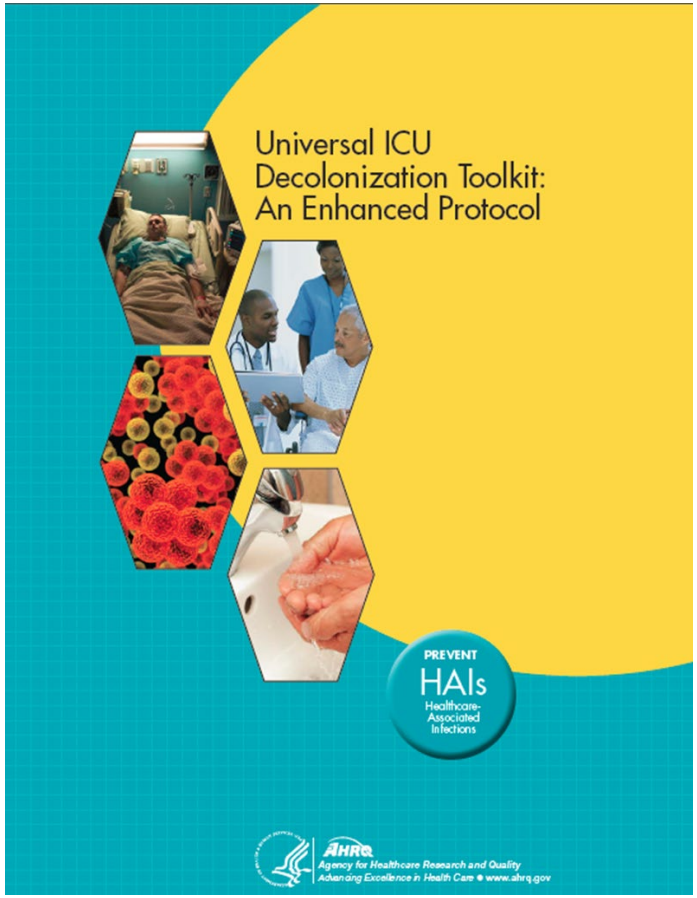
Methods. Implementation of universal decolonization—treatment of all ICU patients with chlorhexidine bathing and nasal mupirocin—used a prerelease version of a publicly available toolkit. Implementation in 136 adult ICUs in 95 acute care hospitals across the United States was supported by planning and 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 (CLABSIs), 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

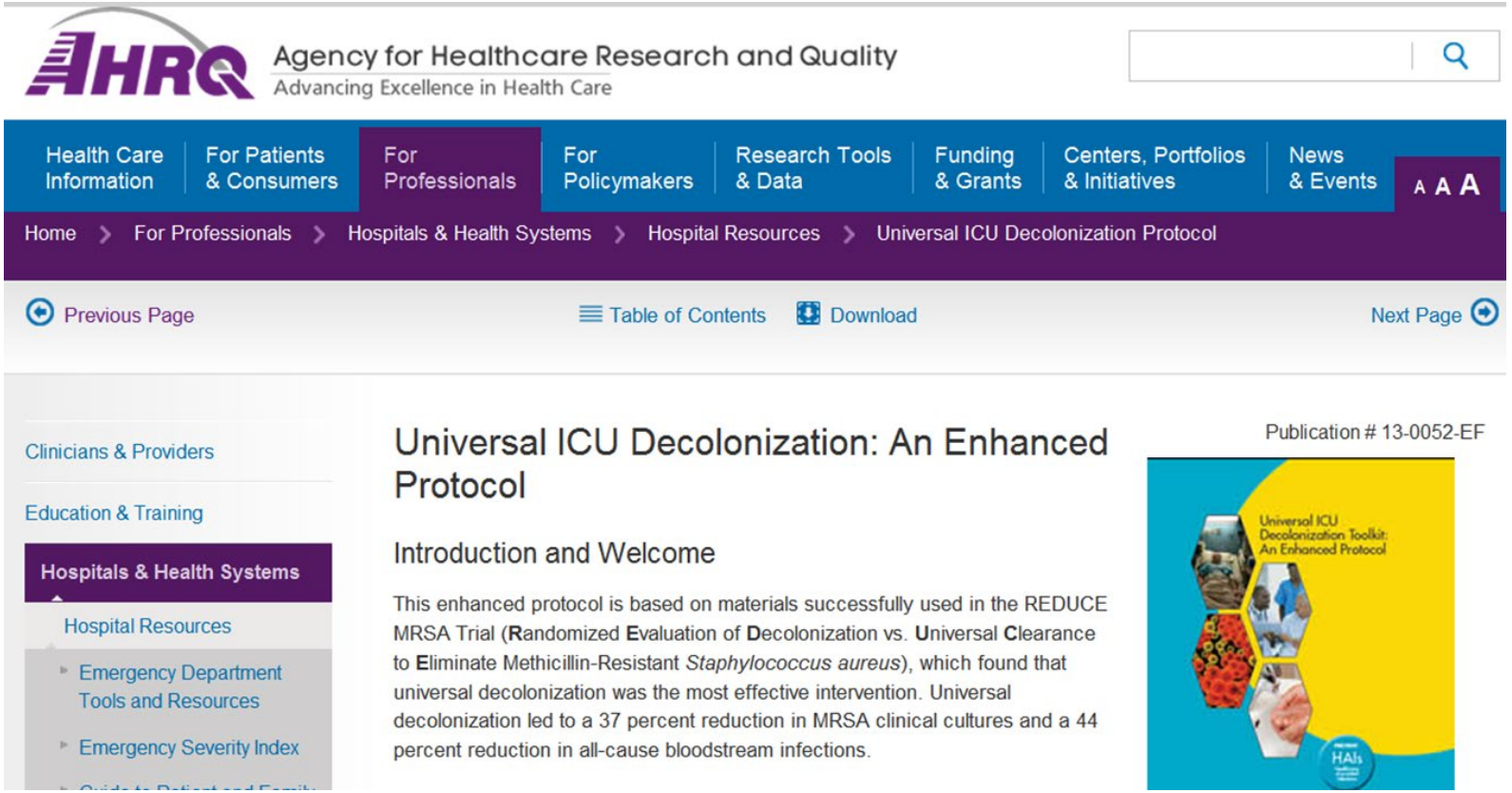


Created for clinicians by clinicians, the toolkit is designed to serve as a roadmap for hospital champions and frontline staff

Toolkit contents

- Introduction and welcome
- Universal ICU decolonization protocol overview
- Scientific rationale
- References
- Appendices include training and educational materials

REDUCE MRSA toolkit available on AHRQ website



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

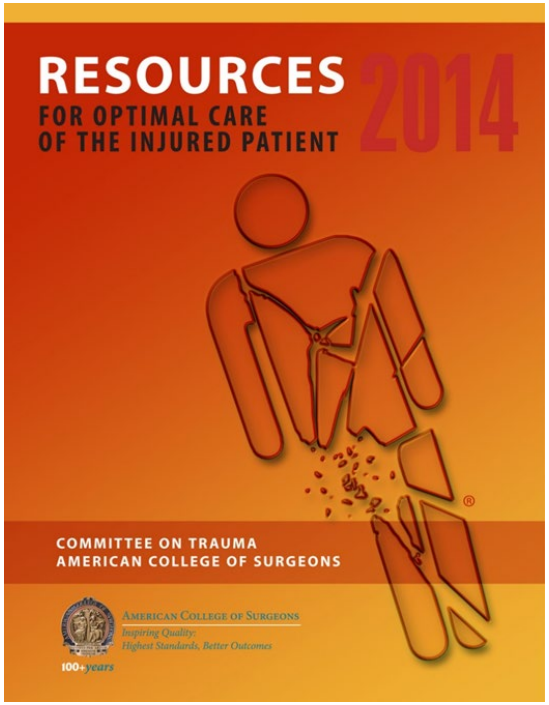
TSOS dissemination aims to “nudge” practice change through regulatory policy

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

American College of Surgeons Resources Guide

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

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9: ePCT Team Composition

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

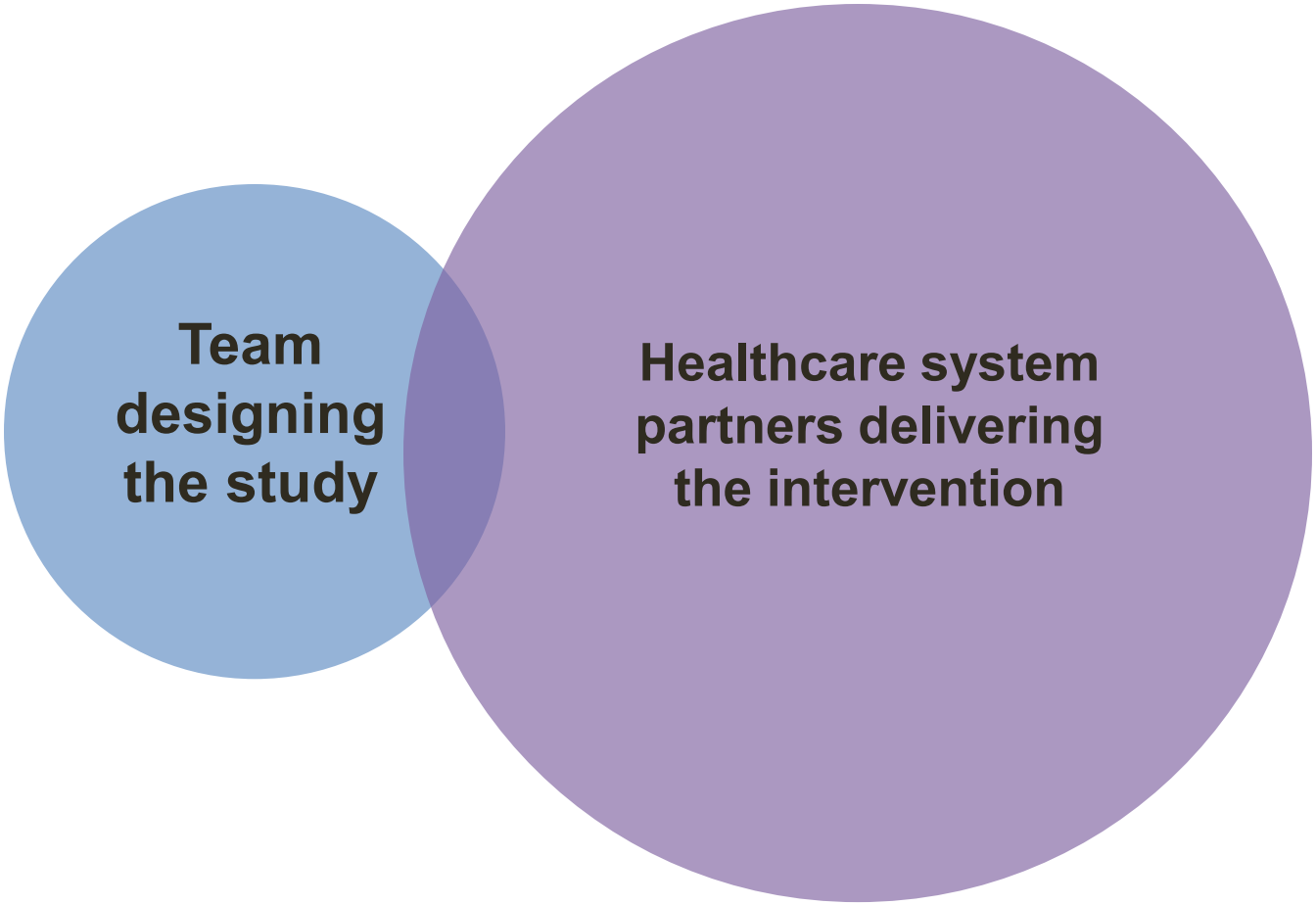
Learning goal

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?



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

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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

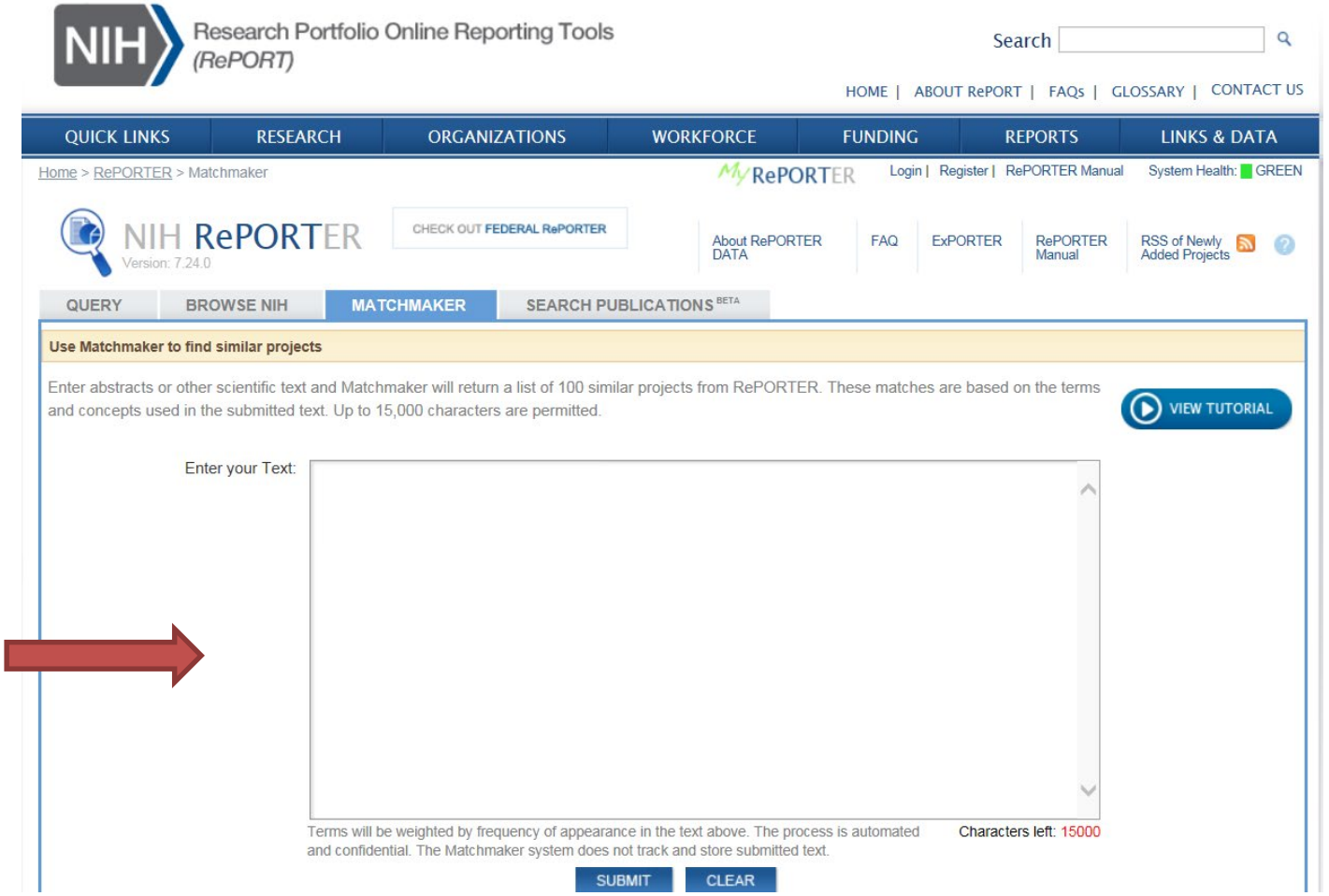
- NIH is made up of 27 institutes and centers (IC)
- ICs award >80% of the NIH budget each year
- Each IC has a budget and a director, and typically their own review for large trials

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

NIH RePORTER



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

Matchmaker results

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

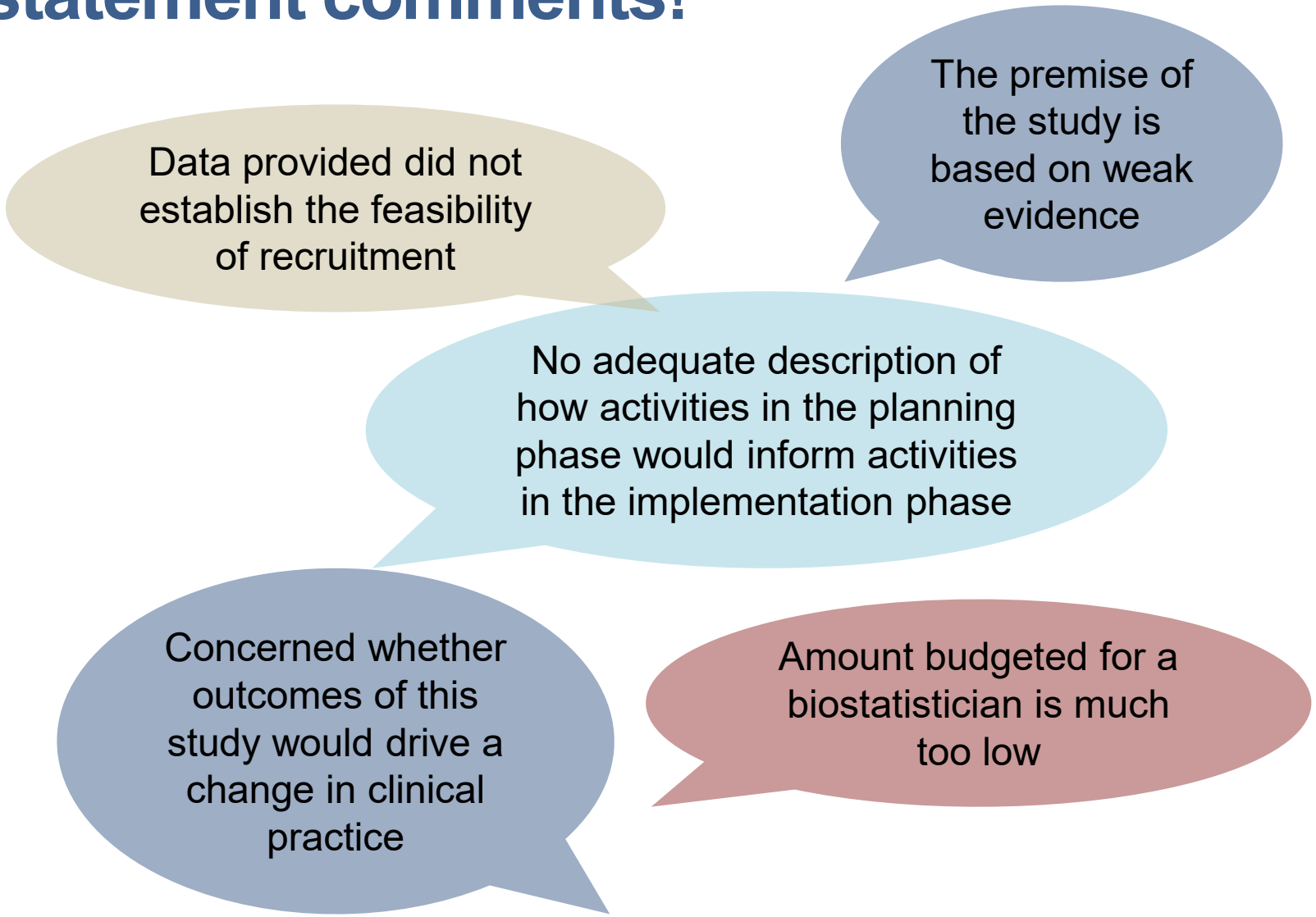
Scientific contacts from participating NIH Institutes and Centers

NCCIH	Robin Boineau	**NIDA**	Sarah Duffy
NCI	Erica Breslau	**NIDCR**	Dena Fischer
NHLBI	Barbara Wells	**NIDDK**	Andy Narva
NIA	Marcel Salive	**NIMH**	Jane Pearson
NIAAA	Brett Hagman	**NINDS**	Robin Conwit
NIAID	Clayton Huntley	**NINR**	Jeri Miller
NIAMS	Chuck Washabaugh	**ODP**	Rachael Ballard
NICHD	Sue Marden		

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!



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 (eg, 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

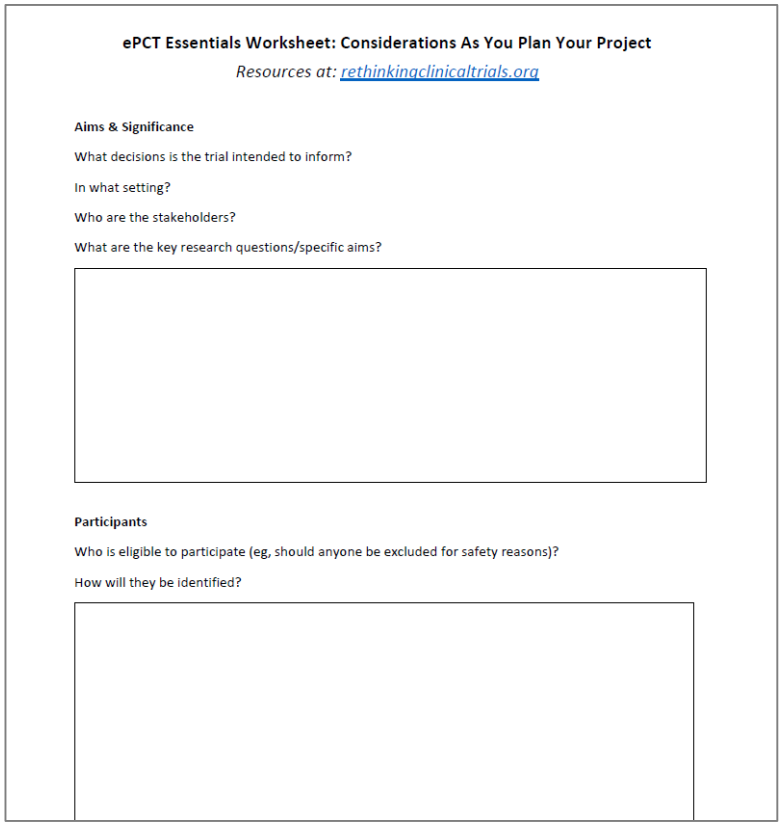
https://researchmethodsresources.nih.gov

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)



ePCT Essentials Worksheet: Considerations As You Plan Your Project

Resources at: rethinkingclinicaltrials.org

Aims & Significance

What decisions is the trial intended to inform?

In what setting?

Who are the stakeholders?

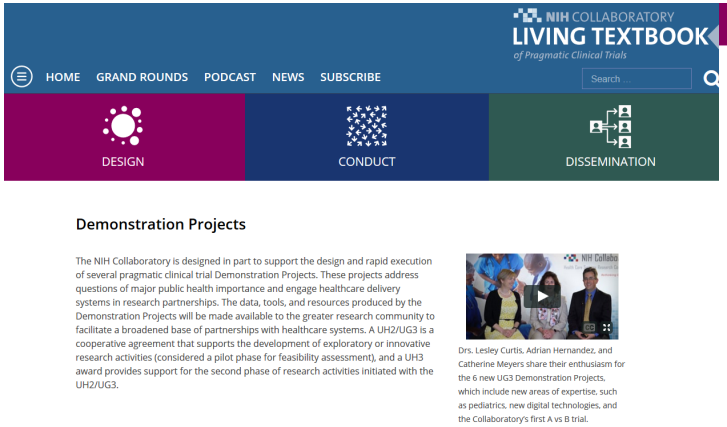
What are the key research questions/specific aims?

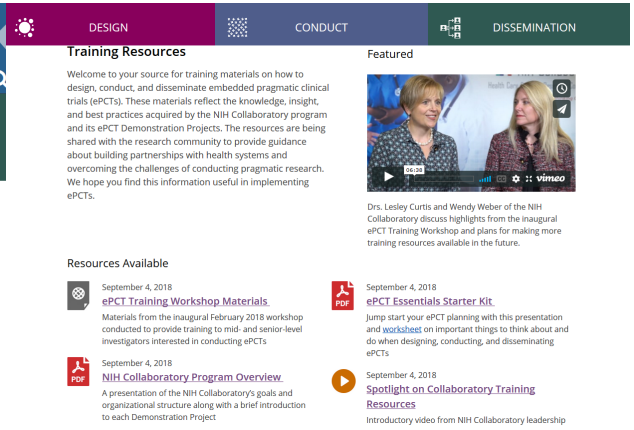
Participants

Who is eligible to participate (eg, should anyone be excluded for safety reasons)?

How will they be identified?

More learning resources …





[Demonstration Projects](#) [ePCT Training Resources](#)

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.