Center for Research in Implementation Science and Prevention (CRISP)

Workshop Handbook

Pragmatic TRIALS

www.ucdenver.edu/implementation
A letter from CRISP

Welcome!

Closing the gap between research discovery and clinical and community practice is essential if we are to succeed in improving our nation’s health.

Pragmatic trials are randomized controlled studies whose purpose is to inform decisions about practice. They address questions of major clinical and public health importance and produce results that can be generalized and applied in usual care settings. Because they produce real-world evidence, they help to close the translation gap between discovery and practice.

In this training workshop, we present the PRagmatic-Explanatory Continuous Indicator Summary (PRECIS-2) as a framework for systematically designing and reporting pragmatic trials. The nine PRECIS-2 domains will be discussed in three modules: Study Populations and Setting, Research Design, and Real-World Use. In addition, we will highlight methods for patient and stakeholder engagement, an important component of pragmatic research.

This workbook is designed to be a navigation guide providing key references and online resources to aid you in further study and application.

We are excited about the national pragmatic trial experts who are part of the workshop. We look forward to your feedback and the pragmatic research community we are forging together in Colorado!

Allison Kempe, MD, MPH
Center Director, CRISP

Elaine Morrato, DrPH, MPH
Collaborative Scientific Lead, CRISP

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Planning Faculty: Russ Glasgow, Elaine Morrato, Borsika Rabin and Chase Cameron

Collaborating Agencies:
Center for Research in Implementation Science and Prevention (CRISP)
Colorado Clinical & Translational Sciences Institute (CCTSI)
Ischemic Heart Disease Quality Enhancement Research Initiative,
Veteran Administrations Eastern Colorado Health Care System
CRISP Pragmatic Trials Workshop

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KEY ASPECTS OF PRAGMATIC TRIALS

- Questions from and important to stakeholders;
- Multiple heterogeneous settings
- Diverse populations;
- Comparison conditions are real world alternatives;
- Multiple outcomes important to stakeholders and policy makers.

WHAT PURPOSE DOES PRAGMATIC RESEARCH SERVE?

To evaluate interventions under typical conditions, with typical patients vs. Under ideal conditions with a homogeneous set of selected patients (Explanatory Trials).

What exactly are pragmatic trials and why would we need them when traditional randomized clinical trials have been so important in identifying evidence-based interventions? While traditional trials answer questions about results under ideal conditions, pragmatic trials evaluate interventions under typical conditions.

There are three key reasons to consider and learn about pragmatic trials. First, traditional trials usually take a long time to translate into practice: it takes an average of 17 years for just 14% of research to translate into practice. Second, the conditions under which traditional trials are conducted are often not seen by practitioners as relevant to their practice or patient populations. Finally, although there are over 18,000 RCTs published each year, the vast majority of systematic reviews conclude that there is not enough evidence to inform clinical decisions. Taken together, these data strongly suggest that a different type of practice-based, pragmatic research is needed.

As shown in the table on the right, pragmatic trials have several key characteristics. They address questions important to stakeholders. There are often multiple stakeholders for a given issue, including patients, providers, and administrative decision makers. Pragmatic trials include both multiple, heterogeneous settings and diverse populations that together represent typical settings and typical patients that would receive a given intervention. They also include multiple outcomes that are important to stakeholders, including decision makers. The final important characteristic of pragmatic trials is that they include comparisons of different real world alternatives, rather than placebo or no treatment conditions.

Pragmatic Research: By other names

YOU MAY ALREADY BE FAMILIAR WITH PRAGMATIC TRIALS, THEY HAVE ALSO BEEN CALLED:

Large Simple Trials – Often used to assess the value of therapeutic interventions
Phase IIb-IV Trials – “Periapproval,” studies designed to address commercialization
Community-Based Research – Equitable, community-participatory research
Practical Trials – Include diverse populations, broad range of outcomes & clinical relevance.
Naturallistic Clinical Trials - Prospective “noninterventional” observational studies of phenomena, or retrospective analyses of existing data, studies, follow-up, etc.
As summarized in the table above, there are several differences between pragmatic trials and traditional efficacy or explanatory trials. Some of the key ones are that in pragmatic studies, there is more emphasis on external validity of findings. Thus, stakeholders are involved throughout the study planning, implementation and reporting phases. Measures in pragmatic trials focus on more practical issues such as the reach and costs of an intervention and tend to use existing measures such as data available from electronic health records more than do explanatory trials. In contrast, explanatory trials tend to focus more on investigator-defined outcomes to answer questions about theoretical mechanisms.

In summary, pragmatic and explanatory or efficacy studies differ in several ways. It is not that one type of trial is always better than the other, but rather that they answer different questions- about results under optimal (explanatory) versus typical (pragmatic) conditions. To advance science and application, we need answers to both.

REFERENCES:


The most common reason that practitioners give for not applying the results of randomized trials is that they do not see the results as applying to their settings and the patients they see (Rothwell, 2005). Since the mid1960s, a few authors have attempted to argue for trials that would be more broadly applicable, but these papers received relatively little attention.

Pragmatic trials were given a large boost in late 2008 and 2009 when the CONSORT group published both a checklist for recommended elements in pragmatic trials (Zwarenstein et al, 2008), and a tool to help in the design of pragmatic trials (Thorpe et al, 2009). Known as PRECIS for Pragmatic-Explanatory Continuum Indicator Summary, the PRECIS tool has proven extremely valuable.
A key contribution of PRECIS is that breaks down all or none thinking about a trial in terms of being pragmatic or explanatory into series of dimensions or domains, as no trial is completely explanatory or completely pragmatic. PRECIS also includes a summary ‘wheel’ or spoke and hub diagram to visually summarize how pragmatic vs. explanatory a study is across dimensions. As shown in the Figure below, this figure plots each dimension or domain on a 5 point scale with 1 representing a very explanatory trial being very close to the center of the diagram, and 5 representing a very pragmatic score on that dimension, being at the outer edge of the figure. Originally developed to help teams design studies, the original PRECIS criteria and tool proved useful for this purpose as well as for reporting on studies and for evaluating the published literature (Loudon et al., 2013). In the same way that the CONSORT flow diagram is now required by most journals, we recommend that the PRECIS figure be submitted with reports of pragmatic trials.

The PRECIS system has recently been revised to reflect experience and lessons learned into the PRECIS-2 toolkit. Instead of the original 10 dimensions, there are now 9 domains on which studies are rated using the 1-5 point rating system.

Key changes have been to rate all dimensions relative to usual care; to remove ratings of the comparison condition (now one rates only the intervention, or if two or more interventions, the most intensive intervention); and to include recruitment and setting dimensions related to external validity.

PRECIS-2 domains have been used to help us organize most of this workbook. The Table below summarizes the PRECIS-2 domains discussed in each chapter and the specific criteria used to rate each domain are covered in the relevant section of the workbook. More information on PRECIS-2 is available from the international group that developed it at the site below.

https://crs.dundee.ac.uk/precis

REFERENCES:

Rothwell PM. (2005). External validity of randomized controlled trials: To whom do the results of this trial apply?  Lancet, 365, 82-93.


KEY POINTS

- Identify your stakeholders up front and engage them throughout the research process. Focus on working “with” a community, not doing research “on” a community.
- Be open to the possibility that patients and other stakeholders will want to reframe your intervention or study question – in fact you want their active engagement!
- Stakeholder engagement enhances dissemination and implementation of study results.

IDENTIFYING STAKEHOLDERS

The 7Ps Framework to identify stakeholders in patient-centered and comparative effectiveness research (Concannon, et al) can be a useful framework for identifying stakeholders for pragmatic trials.

<table>
<thead>
<tr>
<th>Patients and the Public</th>
<th>Current and potential consumers of patient-centered health care and population focused public health, their caregivers, families and patient and consumer advocacy organizations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providers</td>
<td>Individuals and organizations that provide care to patients and populations.</td>
</tr>
<tr>
<td>Purchasers</td>
<td>Employers, the self-insured, taxpayers and other entities responsible for underwriting the costs of health care or health services</td>
</tr>
<tr>
<td>Payers</td>
<td>Insurers, Medicaid and Medicare, state insurance exchanges, individuals with deductibles, and others responsible for reimbursement of interventions or episodes of care</td>
</tr>
<tr>
<td>Policy makers</td>
<td>The White House, Department of Health and Human Services, Congress, states, professional associations, and other policy-making entities</td>
</tr>
<tr>
<td>Product makers</td>
<td>Electronic health record and related technology companies; drug and device manufacturers; and other affected healthcare product producers</td>
</tr>
<tr>
<td>Principal investigators</td>
<td>Other researchers and funding agencies</td>
</tr>
</tbody>
</table>
HOW ENGAGEMENT INFORMS PRAGMATIC RESEARCH
The Patient-Centered Outcomes Research Institute (PCORI) provides cross-cutting standards for PCOR which cannot be met without engaging patients and stakeholders.

STANDARDS FOR FORMULATING RESEARCH QUESTIONS
Identify specific populations and health decision(s) affected by the research
To produce information that is meaningful and useful to people when making specific health decisions, research proposals and protocols should describe: 1) the specific health decision the research is intended to inform; 2) the specific population for whom the health decision is pertinent; and 3) how study results will inform the health decision.

Measure outcomes that stakeholders notice and care about
Identify and include outcomes the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform an identified health decision. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria.

Provide information that supports the selection of outcomes as meeting the criteria of “patient-centered” and “relevant to decision makers,” such as patient and decision-maker input from meetings, surveys, or published studies. Select outcomes based on input directly elicited from patient informants and people representative of the population of interest, either in previous studies or in the proposed research.

STANDARDS ASSOCIATED WITH PATIENT-CENTERDNESS
Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context
People representing the population of interest include individuals who have the condition or who are at risk of the condition and, as relevant, their surrogates or caregivers. Other relevant stakeholders may include clinicians, administrators, policy makers, or others involved in healthcare decision making.

Stakeholders can be engaged in the processes of:

- Formulating research questions;
- Defining essential characteristics of study participants, comparators, and outcomes;
- Identifying and selecting outcomes that the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform decision making relevant to the research topic;
- Monitoring study conduct and progress; and
- Designing/suggesting plans for dissemination and implementation activities.

When applicable, research proposals should describe how these stakeholders will be identified, recruited, and retained. If engagement is not necessary or appropriate, explain why.

Boot Camp Translation:
A community-based approach in which community members, organizations, and primary care practices are brought together to address health problems … and a locally developed method of engagement (Norman, et al (2013).

CRISP seminar series lecture available at:
www.ucdenver.edu/academics/colleges/medicalschool/programs/crisp/training/Documents/CRISPSeminarPresentationNease091613.pdf
ENGAGING STAKEHOLDERS
The Centers for Disease Control and the Agency for Toxic Substances and Disease Registry defined community engagement as:

… the process of working collaboratively with groups of people who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being. (CDC, 1997)

The Clinical and Translational Science Awards Consortium has stated that “community engagement is a blend of science and art”.

- **Scientific principles of engagement** are derived from the disciplines of sociology, psychology, social work, organizational development, and political science. Organizing concepts are described in the scientific literature on community participation, community mobilization, constituency building, community psychology, and cultural influences.

- **The art of engagement** comes from the understanding, skill and sensitivity used to apply and adapt the science in order to meet the interests of the community and the purpose for the engagement.

*Principles of Community Engagement (2nd Edition)* is an excellent guide for understanding definitions and organizing concepts of community engagement. It provides an excellent resource for researchers wanting to incorporate engagement into the research process. Engagement can be labor-intensive, requiring dedicated resources including: time, funding, and people with the appropriate skills. This primer also provides guidance for managing organization support for community engagement.

DEVELOPING AN ENGAGEMENT PLAN
PCORI has published general guidance regarding engagement in the conduct of PCOR research. The Engagement Plan instructs applicants, merit reviewers, awardees and engagement/program officers.

The PCORI Engagement Rubric contains 4 Core Components:

1. **Planning the Study**: Describe how patient and stakeholder partners will participate in study planning and design
2. **Conducting the Study**: Describe how patient and stakeholder partners will participate in the study conduct.
3. **Disseminating the Study Results**: Describe how patient and stakeholder partners will be involved in plans to disseminate study findings, and ensure that findings are communicated in understandable, usable ways.
4. **Using PCOR Engagement Principles**:
   - Reciprocal Relationships in decision-making
   - Co-learning through training and educational opportunities
   - Partnership where value is reflected in fair financial compensation and time commitment
   - Trust, Transparency, Honesty
LOCAL and NATIONAL RESOURCES

The Colorado Clinical and Translational Sciences Institute (CCTSI) has a core which facilitates Community-Based Participatory Research, educates and connects investigators and communities, develops programs to improve relationships and build trust between academicians and communities, and makes funds available for community engagement and research.

The CCTSI Core is called the Partnership of Academicians and Communities for Translation (PACT). Don Nease, MD (Donald.Nease@ucdenver.edu) and Montelle Tamez (Montelle.Tamez@ucdenver.edu) direct this program. Cornerstones of the program include their annual Colorado Immersion Training and Pilot Grant Awards.

At the national level, the PCORI Engagement Awards program to advance patient-centered outcomes research. The program provides targeted funding to groups of patients, clinicians and others across the healthcare community. There are three award categories:

- **Knowledge Awards** – background papers, landscape reviews, development of mechanisms to share PCOR results
- **Training and Development Awards** – including, Pipeline to Proposal Awards
- **Implementation Awards** – support disseminating PCOR evidence and best practices for engagement patients and other stakeholders.

For more information, see: Pipeline to Proposal Awards and Eugene Washington PCORI Engagement Awards.

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REFERENCES:


Partnership of Academicians and Communities for Translation (PACT). See: http://cctsi.ucdenver.edu/CommunityEngagement/PACT/Pages/default.aspx


Study Population and Setting

KEY POINTS

- A critical characteristic of pragmatic trials is the inclusion of diverse populations from multiple, heterogeneous settings.
- PRECIS-2 identifies two domains related to Study populations (i.e., eligibility and recruitment) and two domains related to Settings (i.e., setting and organization).
- Pragmatic studies:
  - Have fewer exclusion criteria than explanatory ones and include population that is characterized to be similar to individuals with the given condition;
  - Use recruitment approaches that build on exiting care procedures;
  - Are conducted in multiple settings similar to the ones in usual care;
  - Deliver the intervention via providers who interact with participants with the condition in usual care, require little or no additional resources, and line up the delivery of the intervention with exiting care delivery processes as closely as possible.

Pragmatic trials call for the inclusion of diverse populations from multiple, heterogeneous settings. PRECIS-2 identifies two domains related to Study populations and two domains related to Settings.

The Study populations domains are concerned with the questions of “Who is selected to participate in the study?” (Eligibility) and “How participants are recruited into the study?” (Recruitment). In the context of PRECIS-2, “participants” include patients or other individual recipients of an intervention, and/or providers of the intervention. This may include individual participants and/or one or more levels of clusters. For example, in a trial of a continuing education intervention, participants may be health professionals and trained instructors and the trial may be randomized into clusters at the level of the instructor.

<table>
<thead>
<tr>
<th>Precis Domain: Eligibility</th>
<th>Precis Domain: Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who is selected to participate? - to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?</td>
<td>How are participants recruited? - how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients?</td>
</tr>
</tbody>
</table>

ELIGIBILITY

To assess the Eligibility domain, we want to evaluate to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care.

Explanatory studies tend to have more exclusion criteria than pragmatic ones. Typical reasons for exclusion include: (1) excluding participants not known/shown to be highly compliant to the interventions under study; (2) excluding participants not known/shown to be at high risk for the primary trial outcome (3) excluding participants not expected to be highly responsive to the experimental intervention. The goal of these exclusions is typically to exclude participants who are less likely to respond to the intervention (Thorpe, 2009).

RECRUITMENT

The Recruitment domain refers to the amount of extra effort that is made to recruit participants over and above what that would be used in the usual care setting to engage with patients?
The **Settings** domains are concerned with the questions of “Where is the study being done?” (Setting) and “What expertise and resources are needed to deliver the intervention? (Organization).

<table>
<thead>
<tr>
<th>PRECIS-2 Domain: Setting</th>
<th>PRECIS-2 Domain: Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where is the trial being done? - how different is the setting of the trial and the usual care setting?</td>
<td>What expertise and resources are needed? - how different are the resources, provider expertise and the organization of care delivery in the intervention arm of the trial and those available in usual care?</td>
</tr>
</tbody>
</table>

**SETTING**
The Setting domain in PRECIS-2 assesses how different is the setting of the study from the usual care setting. Pragmatic trials encourage the selection of multiple, diverse settings in which the intervention would be delivered. More explanatory trials would be characterized by fewer or a single source for the participants (Thorpe, 2009).

**ORGANIZATION**
The Organization domain explores the difference between the resources, provider expertise and the organization of care delivery in the intervention arm of the study and those available in usual care. Increased resource needs, specialized provider expertise and deviance from usual care delivery processes pushes the study to the more explanatory end of the continuum. For example providers delivering the intervention can be restricted to ones with (1) some defined experience in working with the subjects like the ones to be enrolled in the study; (2) specialty certification relevant to the given intervention; (3) experience with the actual intervention (Thorpe, 2009).

**EXAMPLE IN PRACTICE:**
Krist and colleagues in their pragmatic study of the implementation of the My Own Health Report (MOHR) identified 18 sites to participate. Each collaborating research team identified one or two pairs of primary care practices within their network that were similar with respect to practice type (e.g., FQHC or PBRN, family practice or internal medicine), practice ownership, geographic region, EHR infrastructure, and patient population served. Practice pairs were purposefully selected to represent the diversity of primary care settings and populations to ensure greater generalizability of results (Krist, 2013).
### APPLYING PRECIS-2 DOMAINS: POPULATION AND SETTING

<table>
<thead>
<tr>
<th>PRECIS – 2 DOMAIN</th>
<th>More pragmatic . . .</th>
<th>More explanatory . . .</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>Identical to those in usual care.</td>
<td>Include a number of exclusions (e.g. those who don’t comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care.</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Use usual appointments or clinic</td>
<td>Use targeted invitation letters, advertising in newspapers, radio plus incentives and other routes that would not be used in usual care.</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Use identical settings to usual care</td>
<td>Selection of a single center or specialized or academic centers.</td>
</tr>
<tr>
<td><strong>Organization</strong></td>
<td>Allows for the delivery of the intervention by any provider treating study participants in the usual care setting, requiring no additional resources than the ones utilized in usual care, and delivering the intervention using existing care delivery channels</td>
<td>Limits the delivery of the intervention to providers with specialized training/expertise, would require additional resources (e.g., increased staff time), and require deviation from /additional steps to the usual care process.</td>
</tr>
</tbody>
</table>

### REFERENCES:

KEY POINTS

- Pragmatic trials often involve randomizing randomize groups (cluster randomization) vs. individuals to avoid contamination across individuals, or spill-over, of the intervention.
- Some participants may demand that everyone gets the intervention, for example in quality improvement studies. In this situation, a stepped wedge design can be very useful.
- In pragmatic trials,
  - Primary outcome measures are relevant to the participants (and to the users of the research findings).
  - Measurement and follow-up intensity reflect usual care (or what could be accomplished under typical practice conditions)
  - The primary analysis includes everyone who was randomized (an intention-to-treat analysis), regardless of their adherence to the intervention.

STATISTICAL CONSIDERATIONS – TRIAL DESIGNS

Cluster randomization:

Cluster randomization trials randomize groups of individuals to receive different interventions. Groups can be clinics, hospital, worksites and entire communities. This trial design has become increasing popular in public health and clinical trial research.

In the context of pragmatic trials, the benefits of increased efficiency and decreased risk of experimental contamination often outweigh the resulting loss in statistical precision from the effects of variance inflation.

Special Considerations: Identifying the unit of inference based upon the level of cluster randomization selected. There is potential for imbalance between groups when randomizing a relatively small number of clusters. Assessing the value of the intra-cluster correlation (ICC) may be difficult when planning the trial size.

<table>
<thead>
<tr>
<th>PRECIS-2 Domain: Primary Outcome</th>
<th>PRECIS-2 Domain: Follow-Up</th>
<th>PRECIS-2 Domain: Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>To what extent is the trial's primary outcome relevant to participants?</td>
<td>How different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care?</td>
<td>To what extent are all data included in the analysis of the primary outcome?</td>
</tr>
</tbody>
</table>
**Stepped wedge**

Stepped wedge randomized trial designs involve sequential roll-out of an intervention to participants (individuals or clusters) over a number of time periods.

By the end of the study, all participants will have received the intervention, although the order in which participants receive the intervention is determined at random.

The design is particularly relevant where it is predicted that the intervention will do more good than harm (thereby, making a parallel design, in which certain participants do not receive the intervention unethical or unattractive to participants) and/or where, for logistical, practical or financial reasons, it is difficult to deliver the intervention simultaneously to all participants.

*Special Consideration:* Stepped wedge trials are vulnerable to time varying confounding. They work best when the desired effect on individuals is achieved within a short period of time.

**Effectiveness - Implementation Hybrid**

This design strategy involves blending design components of clinical effectiveness and implementation research and is described by 3 hybrid types:

1. testing clinical effectiveness, while gathering information on implementation;
2. dual testing of clinical effectiveness and implementation interventions/strategies; and
3. testing of an implementation strategy, while gathering information on clinical effectiveness

*Special Consideration:* Traditional clinical and implementation research have not shared many design features – for example, unit of analysis, typical unit of randomization, outcome measures, and targets of the intervention being tested. Hybrid designs are new and the field is still evolving on how best to blend these design components. However, the information they provide could speed the translation of research findings into routine practice.

**STATISTICAL CONSIDERATIONS – ANALYSES**

**Intention-to-Treat (ITT)**

ITT analysis includes every subject who is randomized according to their treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. In this regard, it reflects usual care practices.

*Special Consideration:* Addressing patient drop-out (data missingness) is particularly critical when using ITT in longitudinal studies. Thus, a natural tension exists between ensuring protocol adherence and minimizing follow-up burden.

**Contextual Factors**

Characteristics of the setting can affect implementation and effectiveness of interventions. Analyses should explore potential moderators (effect modifiers) that are present at baseline using multilevel modeling with time x treatment x moderator interactions.

*Special Consideration:* Ensuring that data on possible contextual factors are collected.
APPLYING PRECIS-2 DOMAINS: RESEARCH DESIGN

<table>
<thead>
<tr>
<th>PRECIS-2 Domain</th>
<th>More pragmatic …</th>
<th>More explanatory …</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Of obvious importance to participants</td>
<td>Uses a surrogate, physiological outcome in which the direct relevance to participants is not clearly evident</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Participant burden is no more than usual care</td>
<td>More frequent or longer visits compared to usual follow-up</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>Intention-to-Treat using all available data (all participants count)</td>
<td>Excludes ineligible post-randomization participants</td>
</tr>
</tbody>
</table>

**Perspective: NECESSARY PRAGMATIC RESEARCH TRIAL INFRASTRUCTURE**

An important challenge is the need to develop infrastructure to support pragmatic clinical trials, which compare interventions in usual practice settings and subjects.

The NIH Clinical and Translational Science Awards Consortium reported on five recommendations related to strengthening the research infrastructure for pragmatic clinical trials (Concannon, et al 2013).

<table>
<thead>
<tr>
<th>Develop a Learning Network</th>
<th>Share research opportunities across diverse funding agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Share key lessons learned</td>
</tr>
<tr>
<td>Support Community and Stakeholder Engagement</td>
<td>Establish a standing infrastructure for routinely engaging communities, practices, and stakeholders in trial development, implementation, and dissemination activities</td>
</tr>
<tr>
<td>Address Regulatory Challenges</td>
<td>Modify IRB process to support joint approvals</td>
</tr>
<tr>
<td></td>
<td>Develop strategies to streamline multi-institutional contracting</td>
</tr>
<tr>
<td>Provide Information Technology Solutions</td>
<td>Implement secure, standards-based, interoperable information systems across sites and institutions</td>
</tr>
<tr>
<td></td>
<td>Develop a comprehensive dictionary of data elements across data platforms</td>
</tr>
<tr>
<td>Expand Research Methods</td>
<td>Focus method development on study design and analytical approaches that help measure and interpret treatment, site, and patient (subject) heterogeneity</td>
</tr>
</tbody>
</table>
**PRAGMATIC TRIALS vs. PRE-POST OBSERVATIONAL STUDIES**

Pragmatic trials involve randomization of the treatment or the intervention. Pre-post evaluations are one form of pragmatic research that does not involve randomization. Different statistical considerations are necessary to account for selection biases using observational study designs.

See the following resources for guidance on best-practices in observational comparative effectiveness research:

AHRQ (2013): Developing a Protocol for Observational Comparative Effectiveness Research

PCORI (2012): Standards for Causal Inference Methods

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**REFERENCES**


Dreischulte T, Grant A, Donnan P, Guthrie B. Pros and cons of the stepped wedge design in cluster randomised trials of quality improvement interventions: two current examples. Trials 2013 14 (Suppl 1):O87


Resolving the tension between intervention fidelity and adaptation is often the key to success in a real world application.

**KEY POINTS:**

- Two issues addressed by PRECIS 2;
  - Flexibility delivery - this relates to staff or program delivery;
  - Flexibility adherence, which relates to the adherence of participants (patients);
- Key is balance between assuring implementation of core components of intervention while allowing adaptation of non-essential components.
- How to achieve this balance is a challenge and ongoing issue - Main Approaches include;
  - Data from prior implementation - aspects most strongly associated with outcomes;
  - In absence of this, theory of the intervention;
- One approach that has been used is to standardize what needs to be done (for example, the 5 A’s), but to allow flexibility in how and to some extent who does this.

**CHALLENGES IN REAL-WORLD APPLICATION AND IMPLEMENTATION Addressed**

There are many challenges in real world application and pragmatic research on implementation of evidence based interventions and guidelines. This section will focus on the tension between rigorous fidelity to validated intervention components and what is feasible in real world, and especially low resource settings. On one hand, the most common reason for failure to replicate positive intervention findings is failure to deliver the intervention as intended (Allen et al, 2012). On the other hand, as discussed earlier, many settings do not have the resources, training or time to deliver interventions as evaluated in efficacy research.

Often, satisfactorily resolving this tension between intervention fidelity and adaptation to specific settings and conditions is key to success in real world use (Cohen et al, 2008). PRECIS 2 addresses this in two categories: flexibility delivery and flexibility adherence. Flexibility delivery refers to how different flexibility in how the intervention is delivered is in the trial than in usual care. For example, if there is a strict protocol with close monitoring and frequent feedback to staff, this would be considered an explanatory trial and rated a 1 or 2 on the 5 point PRECIS scale.

<table>
<thead>
<tr>
<th>PRECIS- 2 Domain: Flexibility (delivery)</th>
<th>PRECIS-2 Domain: Flexibility (adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How different is the flexibility in how the intervention is delivered and the flexibility likely in usual care?</td>
<td>How different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care?</td>
</tr>
</tbody>
</table>
Parallel issues are relevant at the participant or patient adherence level, called flexibility adherence in PRECIS-II. An intervention that closely monitors patients and has mechanisms to improve adherence, or even removes patients from the study because of non-adherence would be rated as very explanatory (1), whereas one that involves no more than usual encouragement that would be in usual care would be rated as very pragmatic (5).

One recommended approach for achieving balance between fidelity and adaptation has been to assure implementation of ‘core’ components of an intervention while allowing for customization of non-essential components (e.g., often the way a program is presented or what it is called).

Achieving the desired level of balance is admittedly a challenge and an ongoing issue throughout a trial. Ideally, one would have data on the components of an intervention most strongly associated with outcomes to provide guidance. In the absence of this, relying on the theory of the intervention can be used to identify core components. For example, in working with different healthcare systems to implement the 5 As model of self-management (Glasgow et al, 2003), we have emphasized the importance of delivering each of the 5 As (Ask, Advise, Agree, Assist, Arrange) as core components, but that the specific forms used to counsel patients and how these elements are integrated into patient flow can be customized to the practice.

**APPLYING PRECIS-2 DOMAINS: REAL-WORLD USE**

<table>
<thead>
<tr>
<th>PRECIS – 2 DOMAIN</th>
<th>More pragmatic . . .</th>
<th>More explanatory . . .</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility (Delivery)</td>
<td>Identical flexibility to usual care</td>
<td>Has a strict protocol monitoring and measures to improve compliance</td>
</tr>
<tr>
<td>Flexibility (Adherence)</td>
<td>No more than usual care encouragement to adhere</td>
<td>Exclusions based on adherence Measures to improve adherence if suboptimal</td>
</tr>
</tbody>
</table>

**REFERENCES:**


BACKGROUND and CONTEXT
Vaccination is recognized as one of the greatest public health achievements of the 20th century. Notably, incidence of major childhood infectious diseases has declined by 98% since childhood immunizations began.

However, only 68% of children aged 19-35 months receive all recommended vaccines in 2012. A Healthy People 2020 goal is to increase the proportion of children aged 19-35 months who receive all recommended doses of childhood vaccines to 80%

The Community Preventive Services Task Force recommends the use of reminder/recall for increasing immunization rates. Reminder/recall consists of: notification for upcoming immunizations (reminders) and recall notices for overdue immunizations (recall).

Practice-based reminder/recall has been proven efficacious in multiple RCTs; however, few providers are conducting reminder/recall for immunizations.

An alternative public-health based approach working in collaboration with regional or state immunization information systems can facilitate reminder/recall because such systems can identify children who need immunizations and generate reminder postcards or electronic data for centralized messaging.

RESEARCH QUESTION: Which is more effective at increasing immunizations among preschool children: practice-based reminder/recall or population-based reminder/recall conducted centrally by health departments using a regional or state immunization information system?


PRECIS-2: Health Informatics Centre (University of Dundee) https://crs.dundee.ac.uk/precis
Module: Engagement

Which stakeholders (individuals and/or organizations) would you engage?

When in the research process, and how, would you engage these stakeholders?
Module: Study Population and Setting

**ELIGIBILITY:** What criteria will you use to select participants for your study? How might this choice affect the generalizability of your findings?

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

**RECRUITMENT:** What typed of approach will you use to recruit study participants? How much effort will be made to recruit them?

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

**SETTING:** Where should the trial be conducted? What criteria will you use to select sites for the study? How might this affect the generalizability of your findings?

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________
ORGANIZATION: What expertise and resources will be required to deliver the intervention? How might this affect the generalizability of your findings?


Module: Research Design

RESEARCH DESIGN: What trial design will you use? Why?


OUTCOME MEASURE: What measures are relevant for your study participants? For other stakeholders who will be using the results of the study?


FOLLOW UP INTENSITY: How often will you collect data? How similar is this approach to usual care? What data source(s) will you use? Are they valid and reliable?

PRIMARY ANALYSIS: Will you use an intention-to-treat analysis? Why or why not?

Module: Real-World Use

FLEXIBILITY (delivery): To what degree will you monitor and enforce intervention fidelity? How would this compare with flexibility allowed in usual care?
FLEXIBILITY (adherence): To what degree will you monitor and encourage adherence to the intervention by study participants? How would this compare with practices employed in usual care?

Other Notes...
The contributors of this workbook recommend the following resources for current funding opportunities, tips for applicants, information about funding processes, priorities and trends.

**Patient-Centered Outcomes Research Institute**

PCORI helps people make informed health care decisions, and improves health care delivery and outcomes, by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers and the broader health care community. Their online resources include:

- Funding opportunities
- National Priorities and Research Agenda:
- Applicant Training:
- Meetings and Events:

**NIH Collaboratory**

A paragon of collaborative health systems research, The NIH aims to achieve the rapid integration of scientific evidence, practice and policy, with the ultimate goal of improving the effect of research on outcomes and promoting health across individual, organizational and community levels. The NIH website is a comprehensive resource for

- Interactive tools;
- Funding opportunities;
- Conferences and Trainings;
- Publications and presentations.
- Collaboration Spaces

**Centers for Disease Control and Prevention**

The CDC website offers D&I resources in a variety of specific areas including violence protection, chronic disease prevention, tobacco cessation, and cancer control. The website also has extensive information on health communication, social media and marketing
The AHRQ site contains a variety of resources for patients and consumers, healthcare professionals, policy makers, and researchers. AHRQ offers toolkits, funding opportunities, other information on:

- Patient education;
- Preventive care;
- Quality and patient safety.

The CCTSI is a collaborative enterprise between University of Colorado Denver | Anschutz Medical Campus, University of Colorado Boulder, Colorado State University, six affiliated hospitals and health care organizations, and multiple community organizations with a goal to accelerate the translation of research discoveries into improved patient care and public health. Resources include:

- Protocol submission reviews
- Information on Financial Support Policies
- Regulatory knowledge and support
- Forms, tools, checklists, and templates

QUERI was launched in 1998 as part of a system-wide transformation aimed at improving the quality of healthcare for Veterans. Their mission is to improve care using research evidence to improve clinical practice.