Advisory Panel on Clinical Trials Fall 2017 Meeting

November 3, 2017
8:30 AM – 3:00 PM ET

Crystal City, VA

Dial-in number (US): 1 877 309 2074

Access code: 551-825-533

Webinar URL:
https://attendee.gotowebinar.com/register/1186740669368206337

Webinar ID: 479-290-875

pcori®

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Welcome and Goals for the Day

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

Elizabeth A. Stuart, PhD, AM (Chair)

Associate Dean for Education & Professor of Mental Health, Biostatistics, and Health Policy and Management,

The Johns Hopkins Bloomberg School of Public Health

Housekeeping

- Today's meeting is open to the public and is being recorded.
- Members of the public are invited to listen to this meeting and view the webinar.
- Anyone may submit a comment through the webinar chat function.
- Visit www.pcori.org/events for more information.
- Chair Statement on COI and Confidentiality

COI Statement

Welcome to the CTAP Fall 2017 Meeting. I want to remind everyone that disclosures of conflicts of interest of members of CTAP are publicly available on PCORI's website and are required to be updated annually. Members of the CTAP are also reminded to update your conflict of interest disclosures if the information has changed. You can do this by contacting your staff representative, Allie Rabinowitz.

If the CTAP will deliberate or take action on a matter that presents a conflict of interest for you, please inform the Chair so we can discuss how to address the issue. If you have questions about conflict of interest disclosures or recusals relating to you or others, please contact your staff representative, Allie Rabinowitz.

Goals for the Meeting

To update CTAP and seek advice and feedback to PCORI on:

- PCORI's Methodology Standards for Complex Interventions and Data Management Plan Standards
- PCORI's Pragmatic Clinical Studies and Issues of Pragmatism in CER
- Issues in Definition and Measurement of Pragmatic Trial Intervention(s)
- Issues in Adherence Planning and Measurement in Pragmatic Trials

Today's Agenda

Start Time (ET)	Item	Speaker
9:00	Welcome, Introductions, and Goals for the Day	E. Stuart/A. Trontell
9:25	Update on PCORI Internship Program	A. Rabinowitz
9:30	PCORI Methodology Standards: Complex Interventions	L. Esmail
10:15	PCORI Methodology Standards: Data Management Plan Standards	J. Gerson
10:35	Break	
10:45	PCORI Pragmatic Clinical Studies and Subcommittee Efforts to Develop a Paper	A. Trontell / E. Stuart
10:55	PCORI Perspectives of Pragmatic Clinical Studies and PRECIS	A. Trontell

Today's Agenda

Start Time (ET)	Item	Speaker
11:20	November 2nd Pragmatic Clinical Studies Workshop: Debrief and Take-Aways	A. Trontell / C. Girman
11:50	Questions for CTAP	A. Trontell
12:00	Lunch	
12:45	Issues in Definition and Measurement of Study Intervention(s)	E. Stuart
1:45	Break	
2:00	Issues in Adherence Planning and Measurement	E. Stuart
2:45	Wrap Up and Next Steps	A. Trontell / E. Stuart
3:00	Adjourn	

PCORI Internships

Allie Rabinowitz, MPH

Office of the Chief Science Officer, PCORI

pcori®

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Internship Information

- Undergraduate, recent graduate, and current graduate student opportunities.
- 10 weeks duration (with possibility for extension).
- 6-10 internship opportunities posted per cycle.
  - Spring Cycle: February – April
    - Posted in late November
  - Summer Cycle: June – August
    - Posted in early February
  - Fall Cycle: September – November
    - Posted in late June
- Both part-time full-time options available in the Fall and Spring; full-time only in the Summer.
- Internship listings (none currently posted): https://pcori-openhire.silkroad.com/epostings/index.cfm?fuseaction=app.welcome&category_id=36339&company_id=16858&version=1&startflag=1&levelid1=36339

Internship Examples

- Examples of past internships:
  - Develop PCORI Funding Announcement (PFA) materials for PCORI's Board and Science Oversight Committee to review.
  - Perform literature reviews and prepare topic briefs to identify key evidence gaps.
  - Aid in creating PCORI's science database by coding PCORI's projects.
  - Video of former interns describing their experiences can be found here: https://www.pcori.org/careers-pcori
- Interns give a formal presentation to the managers and PCORI leadership at the end of the experience, sharing what they have worked on during their time here.

Draft Standards for Studies of Complex Interventions: Overview and Relevance to Pragmatic Studies

Laura Esmail, PhD

Program Officer, Clinical Effectiveness and Decision Science

CTAP Meeting

November 3, 2017

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Objectives of Presentation

- Explain the need for standards on complex interventions.
- Describe the purpose of the PCORI methodology standards.
- Outline the draft standards for studies of complex interventions.
- Summarize issues in relation to pragmatism.
- Discussion.

Comparative Clinical Effectiveness Research

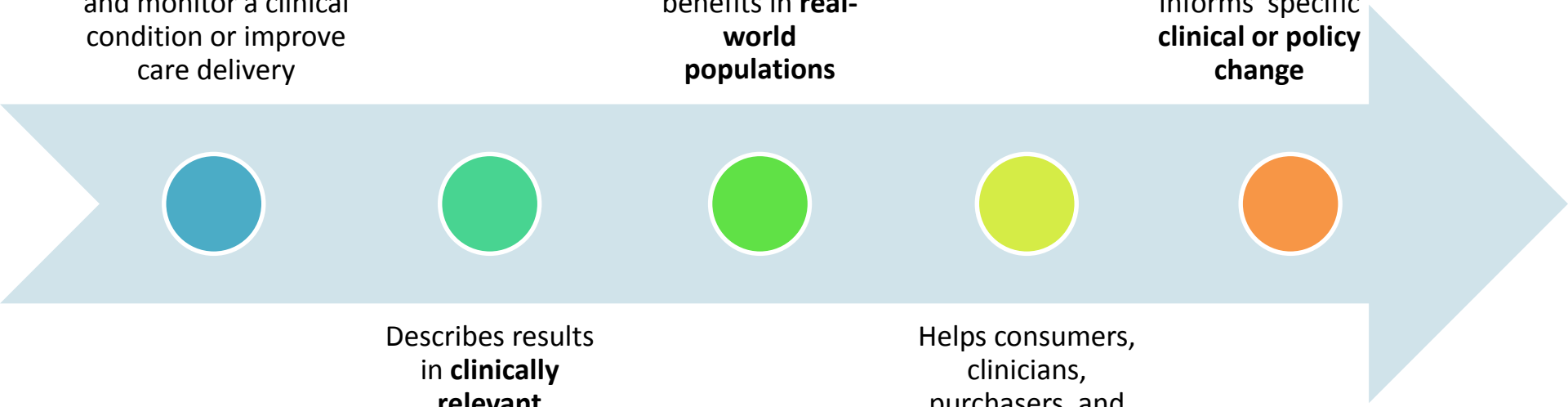
Generates and synthesizes evidence comparing **benefits and harms of at least two different methods** to prevent, diagnose, treat, and monitor a clinical condition or improve care delivery

Describes results in **clinically relevant subpopulations**

Measures benefits in **real-world populations**

Helps consumers, clinicians, purchasers, and policy makers **make informed decisions** that will improve care for individuals and populations

Informs specific **clinical or policy change**



The Need for Standards on Complex Interventions

- Complex interventions are being studied with increased frequency in comparative effectiveness research.
- Frequent applications for PCORI funding.
- Perceived deficiencies in understanding and awareness by the general research community.
- Methodology Committee identified this topic as a priority area for the standards development.

What are Complex Interventions?

- Characterized by one or more of the following:
  - Multiple components that interact.
  - Specified behaviors and activities carried out by healthcare staff.
  - Complex and/or multiple causal pathways.
  - Multiple entities or levels targeted by the intervention.
  - Adaptation or flexibility of the intervention.
  - Contextual factors associated with variation in outcomes.
- Examples include:
  - Health care delivery interventions.
  - Interventions that aim to change knowledge or behavior.
  - Non-pharmacologic interventions.
- For patient centered outcomes research studies, either the intervention, the comparator or both may be complex interventions.

Complex Interventions in Relation to Pragmatism

- Studies of complex interventions are particularly vulnerable to compromise.
  - Multiple sources of potential variation in their conduct.
- The characteristics that define them as complex also make them more challenging to study rigorously.
- Standards are one step to encouraging :
  - Replicability; and
  - Internal validity.

PCORI Methodology Standards

- Required by PCORI's authorizing legislation.
- Reflect minimal standards for the conduct and reporting of sound science.
- Provide guidance for *thinking* about how to design, conduct, and analyze a study to answer a CER question.
- Used to assess the scientific rigor of applications, monitor the conduct of funded research, and evaluate the final research report.

2017 PCORI Methodology Standards

The 48 standards can be grouped into 2 broad categories and 12 topic areas.

Cross-Cutting Standards

- Formulating Research Questions
- Patient Centeredness
- Data Integrity & Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects

Design-Specific Standards

- Data Registries
- Data Networks
- Causal Inference Methods*
- Adaptive & Bayesian Trial Designs
- Studies of Medical Tests
- Systematic Reviews
- Research Designs Using Clusters

The first standard for Causal Inference Methods (CI-1) is considered cross-cutting and applicable to all PCOR/CER studies.

Draft Standards for Studies of Complex Interventions

- SCI-1: Fully describe the intervention and comparator and define their core functions.
- SCI-2: Specify the hypothesized causal pathway and its theoretical basis.
- SCI-3: Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.
- SCI-4: Describe planned data collection and analysis.

SCI-1: Fully Describe the Intervention and Comparator and Define Their Core Functions

- Core functions
  - Intended purpose or goals of the interventions
- Form(s)
  - Modes of delivery, who delivers, materials/tools, dose, frequency/intensity

Example: Functions Versus Form

Example of alternative ways to standardise a whole community intervention to prevent depression in a cluster trial*

Principle of intervention	Type of standardisation	
	By form	By function
To educate patients about depression	All sites distribute the same written patient information kit	All sites devise ways to distribute information tailored to local literacy, language, culture, and learning styles
To improve detection, management, and referral of patients in primary care	All sites hold a series of three in-service training workshops for general practitioners with preset curriculums	Local health authorities are provided with materials and resources to devise in-service training tailored to local schedules, venues, and preferred learning methods
To involve local residents and decision makers in order to increase uptake, effectiveness, and sustainability of the intervention	A local intervention steering committee is convened in each site with representatives of pre-specified organisations	Mechanisms are devised to engage local key agencies and consumers in decision making about the intervention. Suggested options: steering committee, consultations, surveys, website, phone-ins
To harness and facilitate material, emotional, informational, and affirmational support across social networks of people in particular life stages	All mothers of new babies are invited to join discussion and mutual support groups. People moving into nursing homes receive three friendly visits from a designated resident	Methods to alter network size, network diversity, contact frequency, reciprocity, or types of exchanges are tailored to subgroup preferences

* Hypothetical example drawing on published studies[13-16] and reflecting a sample of principles depending on the intervention theory.

Hawe P, Shiell A, Riley T. Complex interventions: how “out of control" can a randomised controlled trial be? *BMJ.* 2004 Jun 26; 328(7455):1561.

SCI-2: Specify the Hypothesized Causal Pathways and Their Theoretical Basis

- Describe hypothesized causal pathways.
- Depict how each intervention function generates the hypothesized effects on the pre-specified patient outcome(s).
- Contextual factors that may influence the impact of the intervention should be included in the causal model so that their hypothesized relationships are made explicit.
- Describe the theoretical and/or empirical basis.

Example: Logic Model

Table 1 The logic model of *Continuum of care for frail elderly persons, from the emergency ward to living at home* intervention

Core inputs	Immediate Impacts	Short-Term Impacts	Impacts	Health Outcomes
Geriatric assessment at emergency department,	Contact between emergency department and community case manager,	Community care will have increased information regarding the needs of the older person, increased contact between emergency healthcare and community social care,	Possibilities for earlier discovery of problems, earlier care and rehabilitation efforts and changes in care and rehabilitation plans, better uptake of older people's viewpoints	Maintained functional ability, increased life satisfaction, reduced number of visits to the emergency department,
Case manager and multi-professional team at the community care,	Case manager has early contact with older person at hospital, continuous contact between case manager and older people, early contact with older peoples' families			Reduced number of stays in hospital wards, higher satisfaction with community care and rehabilitation
Care planning after hospital discharge at older person's home		Older people will have more knowledge of whom to contact when they need help, increased participation opportunities for older people and their families in care planning		

Hasson H. Systematic evaluation of implementation fidelity of complex interventions in health and social care. *Implementation Science.* 2010 Sep 3; 5(1):67.

SCI-3: Specify How Adaptations to the Form of the Intervention and Comparator Will be Allowed and Recorded

- Researchers should specify:
  - Allowable adaptations in form and/or function.
  - A description of how planned and unplanned adaptations will be managed, measured and reported over time.
- Any planned adaptations should
  - Have a clear rationale.
  - Ideally be supported by theory, evidence, or experience.
  - Maintain fidelity to the core functions of the intervention.
- Upon study conclusion, researchers should provide guidance on:
  - Allowable adaptations; or,
  - Unproductive adaptations.

SCI-4: Describe Planned Data Collection and Analysis

- Outline plans to test and refine causal pathway and explain how the results will be used to draw inferences about both effectiveness (i.e., patient outcomes) and the processes of care (i.e., process outcomes).
- Process evaluations should measure, document, analyze and report:
  - Fidelity (and adaptations)
  - Quantity/dose
  - Reach
  - Mechanisms of action
  - Contextual factors (moderators)
- Quantitative and/or mixed methods to process evaluation.

SCI-4 Aims to Address the Components in Blue

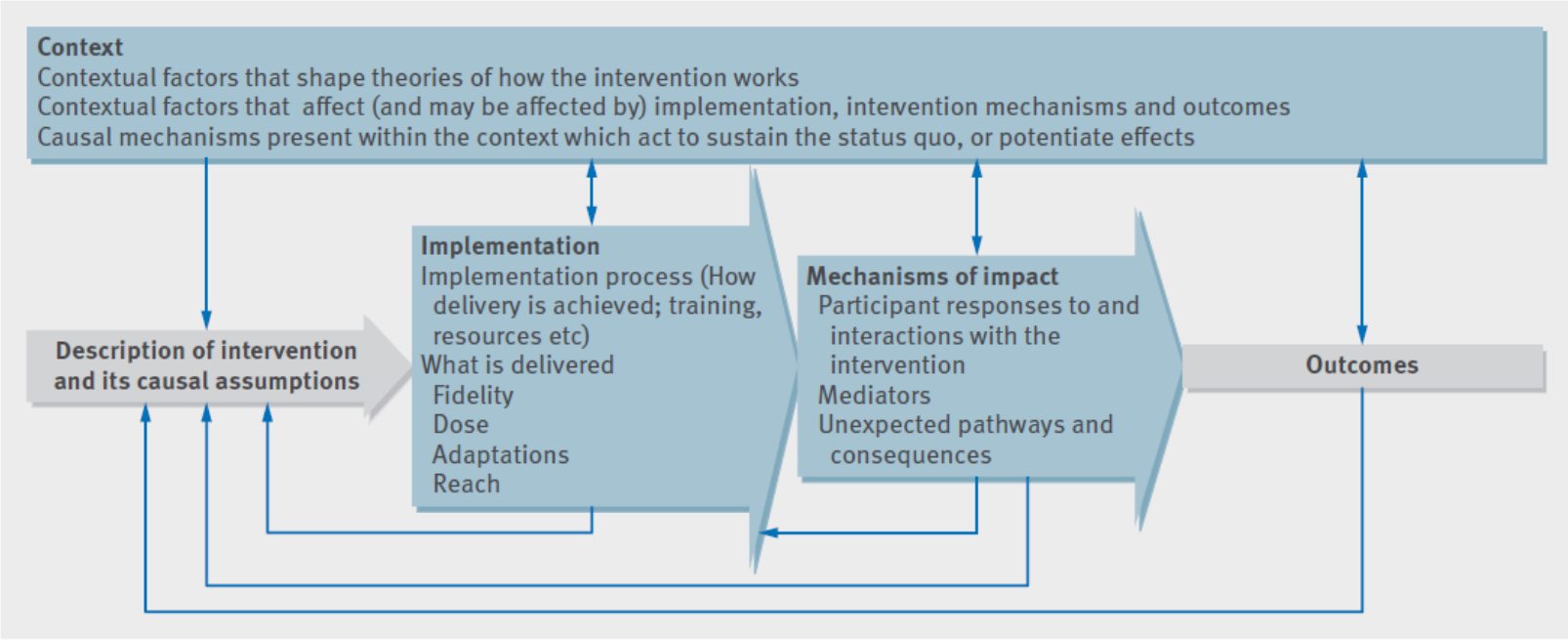


Fig 1 | Key functions of process evaluation and relations among them (blue boxes are the key components of a process evaluation. Investigation of these components is shaped by a clear intervention description and informs interpretation of outcomes)

Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015 Mar 19;350:h1258.

Summary

- Complex Interventions standards aim for:
  - A well-defined intervention
  - Causal pathway and mechanisms of action hypothesized (at a minimum)
  - Explicit consideration about adaptations *a priori*
  - Study execution with explicit consideration of fidelity and potential adaptations
  - Judicious monitoring and tracking of intervention fidelity and adaptations
    - Analysis needs to take these into account to be able to say something about intervention effect (and hopefully causal pathway)
  - Clear replicability and generalizability
- Requires investigators to appreciate the primacy of internal validity.

Next Steps for Standards Development

- CTAP members are encouraged to submit individual comments:
  - https://www.pcori.org/webform/standards-studies-complex-interventions-sci
- Public comment period
  - The new standards are posted on the PCORI website for public comment by all stakeholders for 60 days.
  - All comments will be reviewed by staff and MC members and will inform revisions to the standards.
- Methodology Committee and Board Approval of Final Standards
  - Once revisions based on the public comments are complete, the standards will be reviewed and approved by the Methodology Committee and PCORI Board.

Discussion

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Methodology Standards for Data Management Plans

Jason Gerson, PhD

Senior Program Officer, Science

CTAP Meeting

November 3, 2017

pcori®

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Rationale for Data Management Plans (DMPs) Standards

- The cross-cutting Methodology Standard (CC-3) for Data Integrity and Rigorous Analyses (IR) is silent about data management.
- Good data management is fundamental to ensuring the scientific integrity of clinical research.
  - Salutary effect for open science: Ensuring that good data management plans are in place at the outset of a study will facilitate data sharing at its conclusion.
- Many organizations (incl. most federal funders) now require DMPs, and others that have articulated "best practices." Including a Standard re: DMPs is, therefore, non-controversial.
- We propose adding IR-7: **In your study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.**

Overview: DMP Standard Summary Document

- Full text of the standard
  - Basic definition of the standard
  - Brief descriptions of the components

- Justification for the standard
  - Articulates the ways in which the proposed standard promotes scientific rigor and transparency
  - Emphasizes importance of an accurate and complete DMP
  - Any and all changes to the DMP should be traceable and should be explained, if necessary (e.g., via an audit trail)

Elements of a Data Management Plan

- How the data will be obtained or collected.
- How the individual data items will be described.
- How the data will be safely organized, stored, and preserved.
- Who will have access to the data set.
- Who will have permission to make edits or changes to the data.
- What mechanisms you will use at the end of your project to share the data.

- The DMP is a living document and should be reviewed periodically (or any time your research plans change) to ensure that it remains suitable for the research being conducted.

Next Steps

- After several iterations with the Methodology Committee's feedback, the draft standards have been declared ready for public comment.
- On 10/30/2017, PCORI Board of Governors approved releasing document for public comment.
- Document will be posted this week and remain available for public comment for a period of 60 days, until December 29, 2017. Comment page: https://www.pcori.org/engagement/engage-us/provide-input/comment-proposed-new-pcori-methodology-standards-2017.

- Once the public comment period ends, PCORI staff and MC will review the collected comments and consider further revisions.
- The revised standards & updated report will be presented to the MC for approval and then sent to the Board for adoption.

Break

10:35 – 10:45 a.m.

PCORI Pragmatic Clinical Trials in Comparative Effectiveness:

Guiding Balanced Choices in Design and Study Execution

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Outline

- PCORI goals in funding pragmatic clinical trials of comparative effectiveness.
- Efforts of PCORI & CTAP to define pragmatic clinical trials.
- PCORI requested features of pragmatic clinical studies.
- Overview of Pragmatic Explanatory Continuum Indicator Summary (PRECIS).
- Questions for CTAP discussion and input on pragmatic trials:
  - Defining & measuring flexibility in interventions.
  - Adherence by participants.
  - Eligibility criteria and randomization (time permitting).

PCORI Goals in funding Pragmatic Clinical Trials

- Robust and 'real-world' evidence about the comparative effectiveness of known efficacious interventions.
- To inform decisions by patients & multiple stakeholders in choosing between or amongst competing treatment options.
- Studies designed and conducted under conditions which reflect the decisional context of stakeholders.
  - Patients, interventions, settings, and other key factors which strive to mimic the actual use conditions under which the intervention would be applied.
- To speed dissemination, implementation, and uptake in US health care practice.

Pragmatism and Comparative Effectiveness

- PCORI focuses upon comparison of 2 or more active and efficacious interventions currently being used in health care
  - Not efficacy or effectiveness testing of a new intervention for potential introduction into the health care system
- PCORI funded studies to date
  - Head to head comparison of medication treatments is relatively uncommon
  - Many interventions are complex in the number and nature of their components which themselves are subject to variability

PCORI Pragmatic Clinical Studies (PCS)

- PCORI has articulated the features it seeks in pragmatic trials in its Funding Announcements (PFAs) for Pragmatic Clinical Studies (PCS).
- The PCS PFAs allow both randomized trials and non-randomized or observational studies.
- PCORI nonetheless seeks real world comparative effectiveness research in **ALL** of its funded studies and trials, not solely in its PCS portfolio.

Efforts to Define Pragmatic Clinical Trials

- PCORI Funding Announcements for Pragmatic Clinical Studies from 2014 to present:
  - States desirable, undesirable, and some required features of PCORI pragmatic studies.
  - PRECIS publications are referenced but not required.
- CTAP Subcommittee on Complex Concepts and Terminology (SCCT) charged to write a paper about pragmatic clinical trials.
  - Multiple authors led by Merrick Zwarenstein.
- Current plan to clarify pragmatic trial characteristics for PCORI applicants and awardees:
  - Develop PCORI guidance.
  - Separate scientific publication authored by Dr. Zwarenstein.

Urgency of Defining "Pragmatism"

- Bring substantial SCCT efforts to closure.
- Clarify what PCORI seeks for applicants and awardees.
- Address questions and challenges raised by investigators in carrying out their PCORI-funded pragmatic trials.
  - Of 28 respondents (70% of surveyed) 25 noted $\geq$ 1 challenge/question (avg=4).
  - Study execution questions arising after protocol is finalized (13).
  - Degree of definition/flexibility allowed in applying the study intervention (11).
  - If/how to assess practitioner adherence to study protocol (7).
  - If/how to assess participant adherence with the intervention (8).
- Explore ambiguities and different interpretations of expectations as described by PCORI and PRECIS publications.

Potential *Misperceptions* with Pragmatic Clinical Trials

- *Making more study domains extremely pragmatic is always better.*
  - Latest PFA requests explicit consideration of tradeoffs of PRECIS domains and states absolute pragmatism is NOT the ideal.
- *Generalizability (external validity) requires a trade off with internal validity.*
  - Internal validity is foundational and cannot be sacrificed.
- *Being 'pragmatic' implies uncontrolled trial conduct or "anything goes" due to the variability of real world clinical practice.*
  - Real world variability in care practices and in adherence in pragmatic studies should be anticipated with plans for judicious measurement of fidelity and adherence.

PCORI PFA Expectations for Pragmatic Clinical Trials or Studies

- Stakeholder-driven, patient-centered comparative effectiveness question about choices of available interventions.
- Populations
  - Must involve broadly representative and diverse patients.
  - Should be specified with broad and simple eligibility criteria.
  - Should use standardized inclusion and exclusion criteria.
- Settings
  - Conducted within typical, routine, real-world clinical care and community settings.
- Follow-up
  - Minimize participant visits for study-assessment purposes to minimize disruptions to routine.

PCORI PFA Expectations for Pragmatic Clinical Trials or Studies

- Sample Size
  - Large enough to enable precise estimates of small yet important difference in effect sizes.
  - Must support testing of *a priori* hypotheses related to potential differences in effectiveness among relevant patient subgroups (Heterogeneity of Treatment Effect, or HTE).
- "Usual care" as a comparator
  - Strongly discouraged as an inappropriate comparator due to considerable variation and difficulty in quantifying
  - If used, must be justified, described in detail, coherent, and the nature of its measurement in each patient explained

PCORI PFA Expectations for Pragmatic Clinical Trials or Studies

Intervention flexibility and variability

- Addressed explicitly in most recent PFA (Cycle 3 2017)
- Notes interventions should be standardized to correspond to the specific research question(s) and the underlying inferences of which factors contribute causally to outcomes
- Acknowledges the need for some degree of intervention flexibility
- Requires sufficient definition of interventions so as to be replicable in their dissemination and implementation in US health care

PCORI PFA Expectations for Pragmatic Clinical Trials or Studies

Adherence Considerations

- "Discuss [the] capacity to measure such factors as differential adherence to chosen treatments (or participation in intervention programs) that could create or explain apparent differences in the effectiveness of the alternative interventions being compared in clinical populations.
  - Adherence includes both provider and participant adherence
  - 'Capacity to measure' implies adherence be ascertained in some way
- Adherence to how an intervention is applied or delivered may be particularly challenging, yet important, in PCORI studies
  - Interventions in PCORI studies are frequently complex
  - Multiple components may independently contribute to outcomes

Pragmatic Explanatory Continuum Indicator Summary - PRECIS

- Intended to guide trialists in study design so they are “fit for purpose” of the decision-makers who will use the evidence
  - Explanatory or mechanistic studies of “Does it work under ideal conditions?”
  - Pragmatic studies of “Will it work in actual practice?”
- Developed with international input, review, and validation
- Defines trial domains (initially 10, revised to 9 in PRECIS-2) to capture the degree that a trial is pragmatic or explanatory
  - For each domain choice, envision explanatory and pragmatic extremes to then score each domain on a scale of 1 – 5 based on position between extremes
  - Spidergram with domain spokes having most explanatory at the center and most pragmatic at the periphery

Nine Domains of PRECIS-2

- Flexibility (delivery)—does it mimic what is anticipated in usual care?
- Flexibility (adherence)—Does monitoring, encouragement to adhere similar to usual care
- Organization—Do resources, provider expertise, and organization of care delivery differ from usual care?
- Recruitment—Does effort to recruit participants exceed patient engagement in usual care?
- Follow-up—Is intensity of measurement & follow-up typical in usual care?
- Eligibility—are participants similar to those who would receive this intervention outside of the trial?
- Primary outcome—To what extent is it relevant to participants?
- Primary analysis—Are all data included?
- Setting—How different are settings the usual care setting?

PRECIS Focus on Pragmatism

- Overall goal is to minimize the distortions that clinical trials can introduce in determining effectiveness of an intervention once it is put into real world practice environments and patients
  - Tightly controlled patients, practitioners, practice parameters, and measurement efforts can modify behaviors and outcomes
  - Lowest possible intensity of trial operations preferred
  - 'Usual care' represents care option(s) with no/minimal modifications introduced by trial conduct
- Encourages stakeholder input but with an orientation to systems decisions about whether the introduction of a new intervention will improve outcomes over usual care

PCORI & PRECIS Perspectives

- Close alignment in recommended features of pragmatic trials
  - Patient populations are broadly representative and diverse with few excluded
  - Settings reflect real-world care as offered in typical practice environments
  - Protocols are less complex & intrusive to integrate with routine clinical operations and to minimize disruption to participants' daily routines
  - Large samples often required to distinguish differences

PCORI & PRECIS Perspectives

- Divergent approaches with PRECIS advocating less control
  - Degree of standardization and allowable flexibility of study interventions
  - Use of usual care as a comparator
  - Level of attention in ascertaining adherence effects
    - At practitioner and patient levels

- Areas of divergence represent the leading surveyed questions and challenges of PCORI Principal Investigators conducting pragmatic clinical trials

November 2nd Pragmatic Clinical Studies Workshop: Debrief and Take-Aways

Cynthia Girman, DrPH, FISPE

Ex-Officio CTAP Member from the PCORI Methodology Committee

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Questions for CTAP about Pragmatic Trials

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

pcori

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Discussion Points

Study Interventions – Definition and Flexibility

- How can PCORI best guide the appropriate definition and allowable flexibility of how practitioners apply study interventions?
- How might the Complex Intervention Standards help define what is allowable and what is inviolate in an intervention?
  - Delineation of core components or "active ingredients" considered critical to CER
  - Characterization of key "drivers" of implementation per protocol
- How to distinguish "allowable" variations vs. significant departures (e.g. variable application of the intervention vs. not applying it at all)
- Does the PCORI description of usual care offer a model for guidance?

Discussion Points

Study Interventions – Ascertainment of Variability

- How can PCORI best guide appropriate measurement of variability in how practitioners apply study interventions?
- How can assessment be done without undue burden or distortion of intervention delivery?
  - To measure practitioner practices that deviate from protocol
  - To capture reasons for practitioner deviation from protocol
  - Might methods of practice/quality improvement or health services accounting aid in assessment?

Discussion Points

Adherence of Participants

- Are there best practices, considerations, or criteria to assist in determining the most appropriate monitoring of participants' (often patients') adherence to an intervention?
- What methods of adherence measurement are least burdensome or intrusive upon patient behaviors being measured?

Lunch

12:00 – 12:45 p.m.

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Issues in Definition and Measurement of Pragmatic Study Intervention(s)

Elizabeth A. Stuart, PhD, AM (Chair)

Associate Dean for Education & Professor of Mental Health, Biostatistics, and Health Policy and Management,

The Johns Hopkins Bloomberg School of Public Health

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Intervention Definition and Flexibility

- How can PCORI best guide the appropriate definition and allowable flexibility of how practitioners apply study interventions?
- How might the Complex Intervention Standards help define what is allowable and what is inviolate in an intervention?
  - Delineation of core components or "active ingredients" considered critical to CER
  - Characterization of key "drivers" of implementation per protocol
- How to distinguish "allowable" variations vs. significant departures (e.g. variable application of the intervention vs. not applying it at all)
- Does the PCORI description of usual care offer a model for guidance?

Intervention Ascertainment of Variability

Study Interventions – Ascertainment of Variability

- How can PCORI best guide appropriate measurement of variability in how practitioners apply study interventions?
- How can assessment be done without undue burden or distortion of intervention delivery?
  - To measure practitioner practices that deviate from protocol
  - To capture reasons for practitioner deviation from protocol
  - Might methods of practice/quality improvement or health services accounting aid in assessment?

Break

1:45 – 2:00 p.m.

pcori®

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Issues in Adherence Planning and Measurement in Pragmatic Trials

Elizabeth A. Stuart, PhD, AM (Chair)

Associate Dean for Education & Professor of Mental Health, Biostatistics, and Health Policy and Management,

The Johns Hopkins Bloomberg School of Public Health

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Adherence of Participants

- Are there best practices, considerations, or criteria to assist in determining the most appropriate monitoring of participants' (often patients') adherence to an intervention?
- What methods of adherence measurement are least burdensome or intrusive upon patient behaviors being measured?

Optional Questions

(Time Permitting)

Questions Arising in Pragmatic Trial Execution

- How can pragmatic eligibility criteria best handle informed clinician judgment about the suitability of a patient to be randomized?
  - Uncertainties in equipoise can arise due to unspecified patient characteristics affecting likelihood of benefits or harms or anticipated challenges in cooperation, reliability, or other
  - Should clinician judgement be an allowed exclusion criterion? If yes, how should this be captured?
- What are realistic expectations and means for PCORI applicants to characterize an expected/acceptable range of clinical care practices underlying their research question?

Wrap Up and Next Steps

Elizabeth A. Stuart, PhD, AM (Chair)

Professor of Mental Health and Biostatistics, The Johns Hopkins Bloomberg School of Public Health

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

Thank You!

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE