Advisory Panel on Clinical Trials Fall 2015 Meeting

Washington, DC

October 26, 2015

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Welcome and Plans for the Day

Hal Sox, MD

Chief Science Officer, PCORI

Elizabeth A. Stuart, PhD, AM (Chair)

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

John D. Lantos, MD (Co-Chair)

Professor of Pediatrics, Children's Mercy Hospital

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Housekeeping

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- Members of the public are invited to listen to this teleconference and view the webinar.
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- Visit www.pcori.org/events for more information.
- Chair Statement on COI and Confidentiality

Today's Agenda

Start Time	Item	Speaker
8:30 a.m.	Welcome and Plans for the Day	H. Sox E. Stuart J. Lantos
8:45 a.m.	"Clinical Trial" Definition	J. Gerson
9:00 a.m.	Reports from Subcommittees • Recruitment, Accrual, and Retention	M. Michaels
10:00 a.m.	Break	
10:15 a.m.	Reports from Subcommittees • Standardization of Complex Concepts and their Terminology • Post-Award Expert Subcommittee	M. Zwarenstein J. Gerson
12:00 p.m.	Lunch	
1:00 p.m.	Methodology Standards for Clinical Trials	E. Stuart
2:00 p.m.	2015 PCORI Annual Meeting Recap: Pragmatic and Large Clinical Studies Summit	A. Trontell

Today's Agenda (cont.)

Start Time	Item	Speaker
2:30 p.m.	Monitoring Large Pragmatic Clinical Trials at PCORI	A. Trontell
3:00 p.m.	Break	
3:15 p.m.	PCORI's Draft DSMP Policy Update	J. Gerson
3:30 p.m.	Clinical Trial Design at PCORI	B. Luce
3:45 p.m.	Recap and Next Steps	E. Stuart J. Lantos A. Trontell J. Gerson
4:00 p.m.	Adjourn	

“Clinical Trial” Definition

Jason Gerson, PhD

Associate Director, CER Methods and Infrastructure, PCORI

Proposed Definition for CTAP Scope

- NIH Definition:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."[1]

1. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html#sthash.o2Lpw7M9.dpuf

Reports from Subcommittees

CTAP Subcommittees

- **Recruitment, Accrual, and Retention**
  - Margo Michaels, MPH, Executive Director/Founder, Education Network to Advance Cancer Clinical Trials
- **Standardization of Complex Concepts and their Terminology**
  - Merrick Zwarenstein, MBBCh, MSc, PhD, Director of the Centre for Studies in Family Medicine, Department of Family Medicine, Western University
- **Post-Award Subcommittee**
  - Jason Gerson, PhD, Associate Director, CER Methods and Infrastructure, PCORI

Recruitment, Accrual, and Retention

Margo Michaels, MPH, Executive Director/Founder, Education Network to Advance Cancer Clinical Trials

Subcommittee on Recruitment, Accrual, and Retention (RAR) – Purpose

- To inform PCORI Funding Announcements and related review criteria
- To guide PCORI monitoring of funded contracts by providing technical assistance and support
- To provide additional direction regarding the engagement of healthcare stakeholders around recruitment, accrual, and retention

Subcommittee on Recruitment, Accrual, and Retention (RAR)

- **Members**
  - CTAP Members
    - Margo Michaels (chair)
    - Sanford Jeames
  - MC Member
    - David Meltzer
  - RDAP Member
    - Kate Lorig, DrPH
  - Outside Experts
    - Clair Meunier
    - Giselle Corbie-Smith, MD, MSc
    - Terrance Albrecht, PhD
    - Deborah Watkins Bruner, PhD, RN, FAAN
    - Consuelo Wilkins, MD, MSCI

Updates

- Methodology Standards
  - Proposed standards for CTAP review and discussion today
- Interim Progress Report and SOP on Project Remediation
  - Subcommittee comments incorporated into final versions

Proposed Standards: Patient-Centered RAR in Clinical Trials – Standard 1

- **If the research is delivered through clinical care, programs, or services, it must be integrated**

OR

- **Ensure research is integrated into the delivery of care, programs, or services**

Proposed Standards: Patient-Centered RAR in Clinical Trials – Standard 2

- **Ensure the proposed study meets unmet needs of those with the disease or condition**

- **For discussion: Is this standard duplicative of the following?**
  - **PCORI funding requirement:** "PCORI research seeks to address questions or concerns that are important to patients and other stakeholders. […] Investigators applying for PCORI funding must make the case that the study addresses a clinical choice and decisional dilemma faced by patients and healthcare providers. As part of the justification for the importance of the study, investigators should describe how the interventions being studied are currently used in clinical practice for the diagnosis, treatment, or management of the condition, both in terms of how widely they are used and any particular clinical and population considerations."
  - **PCORI methodology standard RQ-6:** "Measure outcomes that people representing the population of interest 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."

Proposed Standards: Patient-Centered RAR in Clinical Trials – Standard 3

- Address (potential) participants' knowledge and behavior needs throughout the accrual and recruitment process

Proposed Standards: Patient-Centered RAR in Clinical Trials – Standard 4

- **Provide adequate support to encourage ongoing participation and retention throughout the trial**

Proposed Standards: Patient-Centered RAR in Clinical Trials – Standard 5

- **Form partnerships to increase referrals and inquiry**

Discussion

- Methodology standards to be proposed to the Methodology Committee?
- Incorporation into PCORI Funding Announcements?
- Other uses for these standards?

Break

10:00 – 10:15 a.m.

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Standardization of Complex Concepts and their Terminology

Merrick Zwarenstein, MBBCh, MSc, PhD, Director of the Centre for Studies in Family Medicine, Department of Family Medicine, Western University

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Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Purpose

- The CTAP Subcommittee on SCCT will provide guidance, as requested, on topics relating to the standardization of complex concepts and their terminology, which may include, but are not limited to:
  - "Pragmatic"
  - "Mixed methods"
  - Ideal level of detail with which investigators should describe their interventions and comparison conditions

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **Members**
  - CTAP Member
    - Merrick Zwarenstein, MBBCh, MSc, PhD (chair)
  - MC Members
    - Robin Newhouse, PhD, RN
    - Mary Tinetti, MD
  - Outside Experts
    - Philip Posner, PhD
    - Sean Tunis, MSc, PhD
    - Jerry Krishnan, MD, PhD

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **Update: Defining/Characterizing "Pragmatic" Clinical Trials**
  - Full subcommittee meeting (1/13): Introductions and going through SOW
  - Full subcommittee meeting (2/25): Introductions and going through SOW (for absentees at first meeting)
  - Review of sources (2/25 – 4/6)
  - Merrick meeting with PCORI staff (4/6): Workgroup on compiling sources
  - First version of the document drafted (4/6 – 4/23)
  - Full subcommittee meeting (4/23): Going over document with full subcommittee and comments incorporated into version 2 of the document
  - Document circulated to several PCORI staff and comments incorporated into version 2 of the document
  - Merrick presentation at Spring CTAP meeting + document circulated for further comments after CTAP meeting (May 2015)
  - Merrick incorporated comments into version 3 presented today for discussion

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved comments

- **"pRCTs should be conducted in all settings where the interventions under evaluation are expected to be delivered as part of usual care."**
  - **Bryan Luce:** The term "usual care" is a bit of worry at PCORI because it has been used as if it is a defined intervention. Suggest changing to: "routine clinical and/or health care". Could use the term "community care"

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved comments

- **Regarding size: "Because modest gains, even among subgroups, might be important to patients and decision makers, pRCTs may often be large in size to produce robust and precise estimates."**
  - **Bryan Luce:** Size is also a function of the "noise", that is the likely extensive variation due to heterogeneity of patients, practice patterns, adherence rates, and heterogeneity of community sites, etc.
  - **Merrick Zwarenstein:** In eRCTs "noise" is eliminated by exclusions and tight trial procedures for delivery of care. In pRCT design these variations are not seen as "noise". They are real world delivery of care, to which trial results must be applicable, and so size is increased.

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved Comments

- **"To the extent possible, standardization of procedures, and masking of treatment assignment should be maintained."**
  - **Frank Rockhold:** If blinding is needed to yield a useful result then it will help patients.
  - **Anne McTiernan:** Blinding patients, caregivers reduces bias in some endpoint determinations.
  - **Merrick Zwarenstein:** Blinding may render the results inapplicable by changing context, physician and placebo effects. Shifts away from usual care, where patients and providers are fully aware of the intervention they are choosing. Masking and standardization make the trial less relevant to decision makers and patients. Standardization defeats the goal of evaluating under real world conditions where variability is usual.
  - **Emily Evans:** Actively incorporate placebo effects into merits of intervention or just not go out of our way to isolate placebo effect? Masking does not necessarily make results inapplicable. By discouraging masking we reduce rigor in pragmatic RCTs.

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved comments

- **"pRCT analyses focus power on minimizing the probability of preferring the inferior treatment reducing sample size requirements. This ~~distinguishes a superior intervention but does not differentiate between equivalence and inferiority~~ excludes choosing the inferior intervention without distinguishing between equivalence and superiority."**
  - **Merrick Zwarenstein:** This comes from Schwartz and Lellouch, and may be an idea before its time. Is this is a parallel idea to non inferiority analysis, which does not distinguish between a superior and an equivalent outcome?
  - **Frank Rockhold:** Simply not correct. NI trials actually do distinguish between superiority and equivalence. Delete last sentence which is incorrect.
  - **Emily Evans:** A general explanation of relevant analytical methods is needed. This language suggests that we are trying to distinguish between non-inferiority trial design and non-inferiority analysis.

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved Comments

- **"Inclusion of economic outcomes in clinical trials provides information that has significant impact on clinical and policy decisions."**
  - **Merrick Zwarenstein:** I'm uncertain of whether the document can say this because PCORI is mandated to not fund cost effectiveness studies—may have to reframe this as patient cost burden.
  - **Penny Mohr:** I think it is important to leave in, we probably want to say measuring the cost of implementing the intervention may be important too.
  - **Danielle Whicher:** I would delete this text.
  - **Emily Evans:** Agreed.

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved Comments

- **"Data collection should be minimized and integrated into normal clinical data collection [...] rather than being collected exclusively for research. Where data is collected exclusively for research, inexpensive and unobtrusive mobile and web technologies can be used to collect data, such as patient reported outcomes, from individuals including remotely. Participant consent needs to be efficiently obtained, and still meet ethical and legal requirements which are currently under debate. Innovative approaches should be explored to collect, store and utilize biological specimens."**
  - **Danielle Whicher:** It seems important to mention here that a notable exception to this is PROs, which are an important component of many PCORI projects.
  - **Merrick Zwarenstein:** In Ontario, every single patient in the province with cancer fills out a PROM on wellbeing at every visit.
  - **Anne McTiernan:** If you have to develop applications for electronic data collection and analyses, it's not inexpensive!

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Unresolved Comments

- **"While they are designed to be conducted at lower cost due to the lower intensity of data collection from and contact with participants, and with less time invested per patient compared to traditional randomized clinical trials, pragmatic trials may cost as much in total due to their large sample sizes and longer follow-up, unless designed with simplicity and economy in mind."**
  - **Sarah Greene:** Do we really want to wade into discussion of costs? I tend to think we do not. Price tag of our trials, out of context, will seem high.

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Discussion

- **Is this proposed definition in accordance with PCORI's policies and methodology standards?**
- **How might such a document be used? Circulated? Incorporated?**
  - 4 potential uses for the document:
    - Incorporation into current Pragmatic Clinical Studies PFA
    - Present and propose to the Methodology Committee:
      - Minimal standard
      - Guidance document
    - Continue refining the document as a white paper/standalone thought piece that could be published in the literature and on PCORI's website
    - PCORI blog
- **Has this activity been useful or would another format be more effective?**

Post-Award Subcommittee

Jason Gerson, PhD

Associate Director, CER Methods and Infrastructure, PCORI

Post-Award Subcommittee

- **Purpose**
  - Address specific methodological concerns for funded projects in the post-award phase
  - Provide technical advice to the program staff monitoring the trials
  - Help ensure that the study design and methodology are appropriate and consistent with the standards generated by the PCORI Methodology Committee
- **Process Overview**
  - Functions as a pool of experts available to PCORI staff on an ad hoc basis
  - Reports back, when appropriate, to the CTAP's two overarching subcommittees and to the full CTAP to inform their broad guidance to PCORI

Post-Award Subcommittee – Members

- **35 total (including 5 CTAP members)**

Name	Employer
Methods Consultants	
Daniel Merenstein, MD	Georgetown University
Daniel Sargent, PhD	Mayo Clinic
Charles McCulloch, PhD	University of California, San Francisco School of Medicine
Shelley Tworoger, PhD	Harvard University School of Public Health
Ronald Chen, MD, MPH	University of North Carolina Chapel Hill
Peter Peduzzi, PhD	Yale University School of Public Health
Jason Roy, PhD	University of Pennsylvania Perelman School of Medicine
Abdus Wahed, PhD	University of Pittsburgh School of Public Health
Soko Setoguchi-Iwata, MD	Duke University Clinical Research Institute
John Wong, MD	Tufts University Medical Center
Tom Louis, PhD	Johns Hopkins Bloomberg School of Public Health
James O'Malley, MS, PhD	Dartmouth Institute for Health Policy and Clinical Practice
Eloise Kaizar, MS, PhD	Ohio State University
CTAP Members	
Sanford Jeames, DHA	Eastside Memorial High School
Frank Rockhold, PhD	GlaxoSmithKline
Jason Connor, PhD	Berry Consultants
Merrick Zwarenstein, PhD	Western University
Margo Michaels, MPH	Self-employed

Name	Employer
Methodology Committee Members	
Adam Wilcox, PhD	Intermountain Healthcare
Outside Experts	
Elizabeth A. Chrischilles, PhD	University of Iowa College of Public Health
Constantine Gatsonis, PhD	Brown University School of Public Health
Kert Viele, PhD	Berry Consultants
Roger Lewis, PhD	University of California Los Angeles School of Medicine
Leslie Curtis, PhD	Duke University
William Crown, PhD	Optum Labs
David Kent, MD	Tufts University Medical Center
Ravi Varadhan, PhD	Johns Hopkins University
Lisa Salberg	HCMA - Hypertrophic Cardiomyopathy Association
Ralph B. D'Agostino Jr., PhD	Comprehensive Cancer Center, Wake Forest University School of Medicine
Bibhas Chakraborty, PhD	Duke-NUS Graduate Medical School
Asheley Cockrell Skinner, PhD	University of North Carolina, Gillings School of Global Public Health
Deepak L. Bhatt, MD, MPH	Brigham and Womens Hospital, Harvard Medical School
Pamela Tenaerts, MD, MBA	Clinical Trials Transformation Initiative and Duke University
Nancy Puziferri, MD	University of Texas Southwestern Medical Center
Tammy Beaumont, BSN, RN, CBN	Patient Representative - N/A

Post-Award Subcommittee

- **Areas of expertise include, but are not limited to:**
  - Pragmatic trials
  - Missing data
  - Bayesian methods
  - Adaptive designs
  - Decision analysis
  - Screening
  - Generalizability
  - Sequential analysis
  - Rare events
  - Recruitment, accrual, and retention
  - Operational capacity
  - Interim analysis and the oversight of clinical trials (and DSMBs)
  - Data linkage methods
  - Heterogeneity of treatment effect/subgroup analysis
  - Ethical issues in research

Survey Sent to PCORI Program Officers

- Summary of need for the consultation:
  - Description of issue(s) that motivated the consultation
  - Maturity of project at time of consultation request
  - Specific expertise sought
- Description of the consultation process:
  - Number and type of experts involved
  - Whether consultation was one-time/iterative, written/verbal
  - How feedback was conveyed to the awardee
- Summary of resulting recommendations:
  - Summary of consultant recommendations
  - Program staff agreement with the suggestions
  - Awardee receptivity
- Description of the impact of the consultation:
  - Changes to the study design, analytic plan, etc.

Survey Sent to PCORI Program Officers (cont.)

- Staff feedback on the consultation process:
  - What aspects of the consultation process worked well for you?
  - What actions facilitated implementing changes with the awardee?
  - What barriers, if any, were faced in negotiating the recommended changes?
  - Do you have any suggestions for ways to improve the consultation process in the future?
  - How valuable was the consultation process for you and your team? Why?

Survey Results (include 4 funded projects)

- **What triggered the need for the consultation:**
  - Finalize/refine/amend proposed protocol
  - Project remediation due to project being behind timeline
- **Expertise needed:**
  - Clinicians
  - Patients
  - Researchers
  - Informaticians
  - Biostatistician
- **Consultation frequency:**
  - One year with regular check-ins
  - Episodic (as needed)
  - One-time consultation (by phone)

Survey Results (cont.)

- **Substantive concerns identified by consultants included:**
  - Concerns with validity of endpoints, feasibility of recruitment, and generalizability
  - Customization of evaluation needed
  - Need to document specificity of what works and doesn't work with data at each site
- **Recommendations included:**
  - Truncated intervention design (because it allows for timely completion of the study without compromising statistical rigor)
  - Requiring two sets of outcomes for controls and interventions: one set of analyses using the same follow-up period for all sites; and a second set of outcomes based on varying lengths of follow-up

Survey Results (cont.)

- **Benefits of consultation:**
  - Identified specific problems and provided concrete, actionable recommendations
  - Investigators generally appreciative of opportunity to have leading methodologists provide technical expertise in support of their project
  - Allowed for thoughtful discussion between POs and awardees about options
- **Proposed process improvements:**
  - Need to clarify roles of consultants and communicate that to the investigators at the outset of any consultation activity
  - Define number of hours expected per consultation activity

Discussion

- Was this report useful for overseeing and monitoring the work of the subcommittee?
- Was any information missing?
- Should any further questions be added to the survey sent to Program Officers?
- When should the subcommittee be called upon? What activates it other than PCORI staff concerns/questions?
- Any further questions/comments?

Lunch

12:00 – 1:00 p.m.

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New Methodology Standards for Clinical Trials

Elizabeth A. Stuart, PhD, AM (Chair)

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

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Goal of Discussion

- Wrap up the “blinding” topic
- Prioritize other topics for standard development
- Finalize scope of work for the other prioritized topics
- Propose which existing PCORI methodology standards are of particular importance to the conduct and analysis of clinical trials
- Propose other existing standards to be endorsed by the PCORI Methodology Committee (survey results)

Blinding: Important Issues for Standard Development

- Definitions of different types of blinding and their appropriateness for different types of trials (advantages and disadvantages), in particular when dealing with PROs
  - Single
  - Double
  - Triple
  - Patient
  - Practitioner
  - Data analyst
  - Outcome assessment of individual who is blinded to treatment assignment
  - Other or combinations
- Disadvantages to take into consideration and address when planning and interpreting a clinical trial
  - Cost/feasibility/complexity
  - Disruption of medical therapy
  - Deviation from “usual care,” reducing real-world relevance of results
- The management of blinding for complex interventions, studies in community-based settings, in cluster trials, and other unusual settings or situations (i.e., variations on traditional blinding that can be used)

Potential Areas for Standard Development

- Data management plans
- Issues of consent: assessing risk of participation in trials
- Guidance on the issue of justifying the inclusion/exclusion criteria used in a trial
- Handling noncompliance
- Recruitment, accrual, and retention
- Criteria for determining “equivalence” criteria
- Methods to look at safety issues
- Benefit to risk modeling
- Key elements of data management plans
- Heterogeneity
- Use of networks
- Illustrations of useful Bayesian design/analyses

Other Existing Standards to be Proposed for MC Endorsement

- What are some current existing methodology standards developed by other organizations that the CTAP could encourage the Methodology Committee to endorse?

Existing PCORI Methodology Standards of Particular Importance to Clinical Trials – Survey Results

Standard	Very Important	Somewhat Important	Not Important
RQ-1	83.3 %	16.7 %	0.0 %
RQ-2	100.0 %	0.0 %	0.0 %
RQ-3	100.0 %	0.0 %	0.0 %
RQ-4	83.3 %	16.7 %	0.0 %
RQ-5	83.3 %	16.7 %	0.0 %
RQ-6	83.3 %	16.7 %	0.0 %
PC-1	83.3 %	16.7 %	0.0 %
PC-2	100.0 %	0.0 %	0.0 %
PC-3	66.7 %	33.3 %	0.0 %
PC-4	83.3 %	16.7 %	0.0 %
IR-1	66.7 %	33.3 %	0.0 %
IR-2	33.3 %	66.7 %	0.0 %
IR-3	100.0 %	0.0 %	0.0 %
IR-4	83.3 %	16.7 %	0.0 %
IR-5	66.7 %	33.3 %	0.0 %
IR-6	83.3 %	16.7 %	0.0 %

Existing PCORI Methodology Standards of Particular Importance to Clinical Trials – Survey Results

Standard	Very Important	Somewhat Important	Not Important
MD-1	66.7 %	33.3 %	0.0 %
MD-2	83.3 %	16.7 %	0.0 %
MD-3	50.0 %	33.3 %	16.7 %
MD-4	66.7 %	33.3 %	0.0 %
MD-5	50.0 %	50.0 %	0.0 %
HT-1	80.0 %	20.0 %	0.0 %
HT-2	80.0 %	20.0 %	0.0 %
HT-3	40.0 %	40.0 %	20.0 %
HT-4	40.0 %	60.0 %	0.0 %
DR-1	16.7 %	33.3 %	50.0 %
DR-2	16.7 %	33.3 %	50.0 %
DR-3	50.0 %	16.7 %	33.3 %
DN-1	33.3 %	33.3 %	33.3 %
DN-2	33.3 %	33.3 %	33.3 %
CI-1	66.7 %	33.3 %	0.0 %
CI-2	83.3 %	16.7 %	0.0 %

Existing PCORI Methodology Standards of Particular Importance to Clinical Trials – Survey Results

Standard	Very Important	Somewhat Important	Not Important
CI-3	66.7 %	16.7 %	16.7 %
CI-4	50.0 %	16.7 %	33.3 %
CI-5	33.3 %	16.7 %	50.0 %
CI-6	16.7 %	33.3 %	50.0 %
AT-1	83.3 %	0.0 %	16.7 %
AT-2	83.3 %	0.0 %	16.7 %
AT-3	83.3 %	0.0 %	16.7 %
AT-4	66.7 %	33.3 %	0.0 %
AT-5	50.0 %	16.7 %	33.3 %
DT-1	66.7 %	0.0 %	33.3 %
DT-2	66.7 %	0.0 %	33.3 %
DT-3	66.7 %	16.7 %	16.7 %
DT-4	60.0 %	20.0 %	20.0 %
DT-5	50.0 %	33.3 %	16.7 %
SR-1	83.3 %	16.7 %	0.0 %

Next Steps

- Highlight current PCORI methodology standards that are of particular importance to the conduct and analysis of clinical trials?
- Existing methodology standards for clinical trials to be proposed to PCORI's Methodology Committee for endorsement?
- PCORI to develop standards around blinding and other prioritized topics
- Standards to be presented to CTAP in 2016
- Following CTAP endorsement, new standards to be proposed to PCORI's Methodology Committee

2015 PCORI Annual Meeting Recap: Pragmatic and Large Clinical Studies Summit

Anne Trontell, MD, MPH

Senior Program Officer, Clinical Effectiveness Research, PCORI

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Overview

- Attendees and session topics
- Questions and issues raised by investigative team participants
- Advice about ongoing forum and CTAP involvement

Invited Attendees

Principal investigators, team members, and stakeholders

- 14 studies awarded under 3 cycles of pragmatic studies PFA
- 2 PCORI-funded studies being administered by NIA (STRIDE) and AHRQ (COMPARE-UF)
- 2 targeted obesity studies
- PCORnet ADAPTABLE trial

PCS Summit Sessions

- Open public session – focus on clinical study conduct/operations
  - Ken Getz, CSDD: Drug Development Challenges and Choke Points
  - Margo Michaels: Integration of Study RAR into Clinical Care
  - Kate Deans: Fostering Genuine Stakeholder Engagement
- Closed session of investigative teams only
  - To foster a collaborative community of practice to optimize the conduct of large and pragmatic clinical studies
  - Investigator-driven topic discussion (engagement, study start-up, with small group exercise using proposed standards for patient-centered RAR in clinical trials)

Initial Discussion Points

Start-up issues with multiple study sites

- Recruiting sites to participate
- Ways to speed up/manage subcontracts most efficiently
- Securing IRB approval
- Ways of facilitating training and on-boarding of site personnel

Engagement

- Ways to engage community partners, health plans, and systems not directly involved in the study conduct
- Effective models and practices of engagement at different stages of a study
- Maintaining enthusiasm of patients and stakeholders once the study is funded and underway
- Bridging local and national stakeholder and patient organizations

Additional Issues and Questions

- Appropriateness of different approaches to recruitment
- Central IRBs
- Federal and commercial payers' coverage of treatments
- Study site contracting models to achieve flexibility & incentivize
- Pragmatism – how much is enough?
  - Control of intervention fidelity
  - Internal validity vs. generalizability
  - Handling research data collection in clinical care

Follow-Up Options to Sustain Interactions

- Additional face-to-face meetings
- Webinar series
- Secure online collaborative forum or listserv
  - User subgroups (PIs, project managers, CRCs, data managers, analysis)
  - Topic subgroups (RAR, analysis, engagement, business/contracting, HSP)

We will resurvey attendees for suggestions and volunteers to pilot test approaches

Questions for CTAP

- What feedback or reporting would be most informative or beneficial to CTAP?
- What is CTAP's interest or role in involving this community of pragmatic researchers?
- How might CTAP assist in addressing questions arising from investigators?

Thank You

Monitoring Large Pragmatic Clinical Trials at PCORI

Anne Trontell, MD, MPH

Senior Program Officer, Clinical Effectiveness Research, PCORI

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In Evolution…

- Which PCORI-funded studies are included
  - Pragmatic clinical studies
  - Large, targeted clinical studies
  - Observational studies and registries?
- Clarification of scope, roles, and responsibilities of OCSO staff vs. individual Science Department Program staff
- OCSO staffing, roles, and resources

Opportunities of Program-Wide Oversight

- Foster communication and collaboration across Science Programs
- Review diverse practices and approaches of different programs
  - Share knowledge & develop best practices, quality approaches
  - Standardize monitoring and reporting
- Develop new knowledge on the optimal conduct of clinical studies
- Develop, train, and mentor PCORI staff regarding clinical study conduct and oversight

Activities to Date

- Bimonthly meetings of Science and Engagement staff
  - Data monitoring systems and procedures for funded projects
  - Intercomparison of approaches, SOPs
- Common approaches under development
  - Kickoff meeting preparation for PCORI staff
  - DSMB participation by patient stakeholders
  - Compensation challenges with IRBs concerning patient partners
  - Communications policies in acknowledging PCORI funding support
- Organization and support of PCS Summit at PCORI Annual Meeting

Activities to Date

- Exploration of a common data management system
  - In-depth exploration of external CTMS providers
  - Development in conjunction with PCORI of end-to-end IT infrastructure
  - Adaptation of existing programmatic tracking systems
- Development of simple cross-study tracking spreadsheet

Formative Policies and Processes

- "Red flags" to watch out for in the budgetary review of large, multi-site studies
- Candidate attributes to be tracked in studies
- Core and ancillary milestones for large and pragmatic clinical studies
- Informal policy/recommendations
  - PCORI staff attendance of study kickoff meeting of investigative staff
  - Monthly progress reporting on study recruitment progress for sites, patients

Future Plans

- Provide dashboard and other study progress & status reports to CTAP and PCORI governing bodies
- Bring challenging or intractable questions to CTAP or its subcommittees for advice and solutions
- Nominate topics for CTAP to consider for development of guidance or standards

Future Plans: CTAP Questions

- Provide dashboard and other study progress & status reports to CTAP and PCORI governing bodies
- Bring challenging or intractable questions to CTAP or its subcommittees for advice and solutions
- Nominate topics for CTAP to consider for development of guidance or standards

- Does CTAP agree with these plans?
- Any additional suggestions or requests?

Thank You

Break

3:00 – 3:15 p.m.

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Clinical Trial Design at PCORI

Bryan Luce, PhD, MBA

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Background

- PCORI's Methodology Standards report includes a standard for adaptive trials
- PCORI's funding announcements encourage the submission of pragmatic trials with adaptive designs, but to date….
  - …we have received little to no submissions
- We surmise that:
  - Many PCT applications may benefit from considering novel trial designs
  - There may be a dearth of trialists/statisticians with such experience and/or expertise
  - Investigators with expertise may be reluctant to submit because of concern PCORI merit review may not fully appreciate the technical approach

Types of Design Issues Under Consideration

- Trial design simulation
  - May be particularly useful for power estimation of complex designs or trials with high uncertainty across multiple key parameters
- Adaptive designs
  - For example, trials with 3 (or greater) arm trials; likely new innovations and/or changing practice patterns during trial
- Response-adaptive platform designs
  - When the issue is “what works best for whom under what circumstances?” across a condition (e.g., diabetes) of interest, as opposed to which of two interventions to employ
  - May be particularly applicable for certain PCORnet studies

PCORI Trial Design Initiative

- More explicitly encourage the previously noted designs (in PFAs)
- Recruit a cadre of trial design experts: PCORI Adaptive Trial Expert Research Network "PATERN"
- Integrate PATERN with the PCORI Methods Consultation experts
- Evaluate (employing PATERN) highly scoring, traditionally designed submissions as possible candidates for a "redesign phase"
- Work with selected PIs to consider a re-design phase while…
  - …offering to fund the consultation and redesign effort, including providing extra time (e.g., 6 months)

Questions?
Comments?
Discussion?

PCORI's Draft DSMP Policy Update

Jason Gerson, PhD

Associate Director, CER Methods and Infrastructure, PCORI

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Background and Context

- Draft policy was developed by PCORI staff in consultation with legal, IRB, and other human subjects protection experts.
- Policy does not usurp the role of Institutional Review Boards (IRBs) or other monitoring or regulatory bodies with jurisdiction over a particular research study.
- Already studies underway that have DSMPs—policy will not require existing DSMPs to be changed.

PCORI as Funder – Not Sponsor – of Research

- Awardees are responsible for the conduct of the research study, including fulfilling applicable regulatory requirements (e.g., FDA) and requirements of the IRBs.
- PCORI awardees should ensure that PCORI's role as a funder of the research study is accurately described.
- Awardee institution is responsible for ensuring that PCORI, as funder of the research study, is informed in timely manner of all recommendations/decisions/steps taken emanating from DSMP activities.

Overview of PCORI's DSMP Policy

- PCORI requires awardee institution to ensure there is a DSMP for the research study commensurate with the study's potential risks, nature, size, and complexity.
- DSMP for PCORI-funded research must be approved by the applicable IRB.
- Policy articulates minimal requirements for DSMP to: (1) identify who is responsible for monitoring study, and (2) describe DSM procedures (e.g., minimizing research-associated risk; protecting confidentiality of data; reporting adverse events and unanticipated problems)

New in the Updated Draft

- Based on the CTAP's comments and on additional internal PCORI discussions about expected reporting and existing mechanisms of monitoring, we updated the draft policy.

- Updated draft policy includes a separate section addressing reporting to PCORI and continues to make clear that the awardee institutions must meet applicable reporting obligations to the sponsor, IRB, DSMB, and any regulatory or other oversight bodies such as the FDA.

- Updated draft also provides direction about DSMP-related information that should be included by the awardee institution in each PCORI Interim Report and recognizes that accelerated reporting to PCORI is appropriate relating to serious unanticipated problems. The draft takes into account terminology utilized by IRBs and the FDA, while recognizing that PCORI itself is not in the role of an IRB, FDA, or sponsor.

DSMB Membership

- Updated policy makes clear that every member of the DSMB is expected to be independent and that training for DSMB members is appropriate (including for any DSMB member who is an independent patient or family member).

DSMB Meetings and PCORI Program Staff

- Updated policy reflects a presumption that PCORI staff not attend closed and executive sessions of any DSMB. CTAP members expressed their concern that NHLBI's approach of leaving it to the discretion of the DSMB chair typically results in inappropriate participation by staff representatives of funders.

Unmasked Data

- Updated policy recognizes that as a DSMB deems appropriate, it should have access to unmasked data.

Recap and Next Steps

Elizabeth A. Stuart, PhD, AM (Chair)

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

John D. Lantos, MD (Co-Chair)

Professor of Pediatrics, Children's Mercy Hospital

Anne Trontell, MD, MPH

Senior Program Officer, Clinical Effectiveness Research, PCORI

Jason Gerson, PhD

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Thank You!

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