Advisory Panel on Clinical Trials Winter 2015 Meeting

Alexandria, VA

January 15, 2015 – 9:30 a.m. to 5:00 p.m. EST

Patient-Centered Outcomes Research Institute

Welcome and Plans for the Day

Bryan Luce, PhD, MBA, 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

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

Today's Agenda

Start Time	Item	Speaker
9:30 a.m.	Welcome and Plans for the Day	B. Luce E. Stuart J. Lantos
9:45 a.m.	PCORI Updates	B. Luce E. Djabali
10:00 a.m.	Reports from Subcommittees	M. Michaels M. Zwarenstein
10:45 a.m.	Break	
11:00 a.m.	Continued Discussion on Methodology Standards for Clinical Trials	S. Goodman
12:00 p.m.	Lunch	
1:00 p.m.	Presentation on PCORnet, the Clinical Trials Task Force and the Ethics and Regulatory Task Force	R. Califf
2:00 p.m.	Subcommittee Proposal Presentation	B. Luce

Today's Agenda (cont.)

Start Time	Item	Speaker
3:00 p.m	Break	
3:45 p.m.	Advisory Panel on Rare Disease Collaboration Updates	J. Connor M. Summar
4:00 p.m.	Open Discussion	
4:45 p.m.	Recap and Next Steps	B. Luce E. Stuart J. Lantos
5:00 p.m.	Adjourn	

Meeting Objectives

- Update CTAP on the work of its subcommittees
- Plan for CTAP to propose new methodology standards for clinical trials to PCORI's Methodology Committee
- Obtain CTAP's input on the creation of trial-specific subcommittees
- Facilitate collaboration between CTAP and PCORnet
- Facilitate collaboration between CTAP and RDAP

PCORI Updates

Bryan Luce, PhD, MBA, Chief Science Officer, PCORI
Emma Djabali, Project Assistant, PCORI

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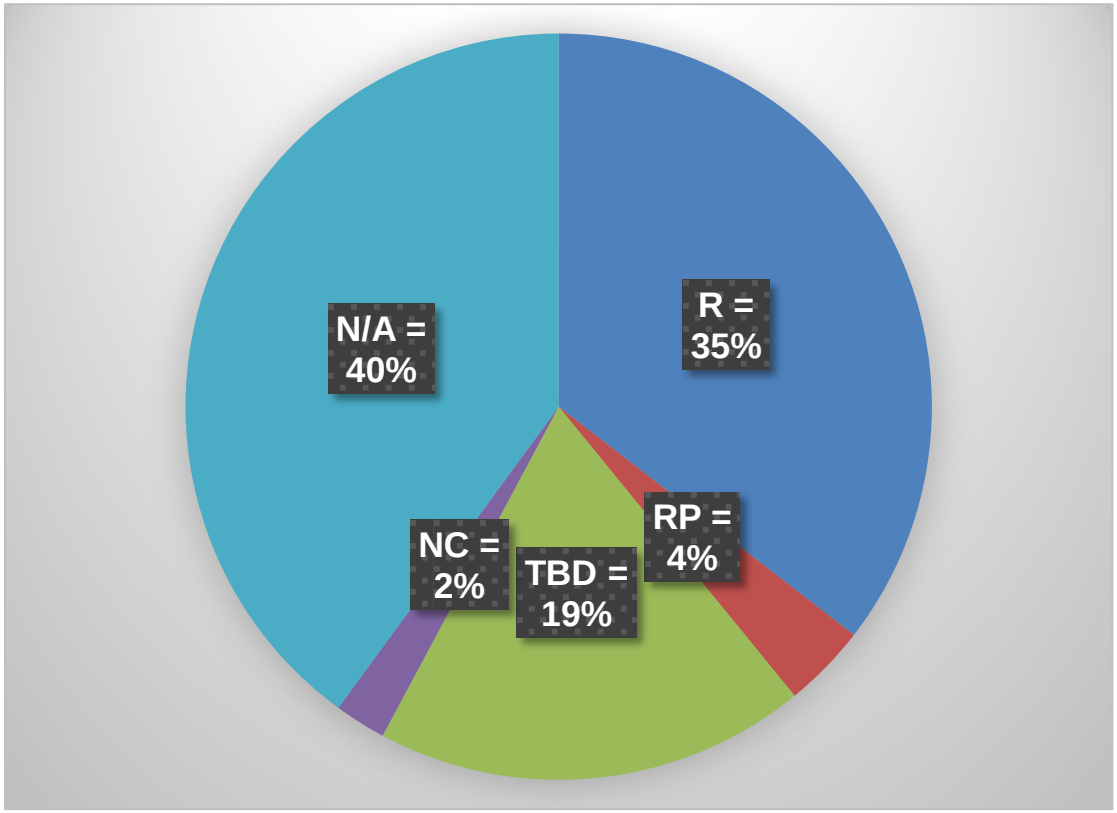
Overview

- U. Penn 8th Annual Conference on Statistical Issues in Pragmatic Clinical Trials
- PCORI funded projects ClinicalTrials.gov registrations
- PCORI Methodology Committee cluster randomization meeting
- CTAP budget

U. Penn 8th Annual Conference on Statistical Issues in Pragmatic Clinical Trials

- Date: April 15, 2015
- PCORI-affiliated speakers:
  - "Statistical Needs for Pragmatic Clinical Trials"
    - Keynote Speaker – Robert Califf, MD, Co-Principal Investigator of the PCORnet Coordinating Center
  - "The Pragmatic Clinical Trial in a Learning Healthcare System" – Roger Lewis, MD
    - Panel Member – John Lantos, MD, CTAP Member
  - "Can Administrative Data Increase the Practicality of Clinical Trials? An example from the Women's Health Initiative"
    - Panel Member – Robert Temple, MD, CTAP Member

PCORI Funded Projects ClinicalTrials.gov Registrations – Breakdown (n=215)



R = Registered: project is registered

RP = Registration Pending: project is registered but the registration is being reviewed by CT.gov (or pending posting to ct.gov listing page)

TBD = Pending: project is a clinical trial, but registration is not required at this time (recruitment has not started)

NC = Non-Compliant: project recruited its first patient and is not yet registered

CTAP Budgeted Activities

- CTAP Work, including In-Person Meetings (3/year), stipend, and travel
- Landscape Reviews (2)
- Work of Subcommittees, including stipends, meetings and travel
- Selected CTAP Presentations at National Conferences

Updates on Subcommittees

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

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 Recruitment, Accrual, and Retention (RAR) – Members

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

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

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

Subcommittee on Recruitment, Accrual, and Retention (RAR) – Kickoff Webinar

- **Date:** December 5th, 2014, 9am-11am
- **Attendees:**
  - Program staff
  - Merit review staff
  - Contracts staff
- **Agenda:**
  - Margo Michael's introduction and Overview of Principles Related to Patient Centered Clinical Trial Recruitment and Retention
  - Discussion with POs:
    - Greatest concerns around RAR in general for your funded contracts?
    - Greatest concerns around RAR for minorities and medically underserved in particular for your funded contracts?

Subcommittee on Recruitment, Accrual, and Retention (RAR) – Kickoff Webinar (cont.)

- Discussion with Merit Review staff
  - How does the current review process identify concerns in applications around recruitment and retention overall, and minority and medically underserved populations in particular?
  - How much attention do reviewers pay to these issues?
  - How much attention to these issues does PCORI allow, in terms of the scoring process and/or the training of reviewers?
  - How often are these concerns raised for highly rated proposals? How are these concerns addressed prior to award?
- Discussion with POs and Contracts:
  - If a contract is struggling around recruitment issues, what kind of assistance is provided?
  - What kind of assistance would you *like* to provide?
  - What kinds of "sticks" could/should be provided if numbers aren't met?

Subcommittee on Recruitment, Accrual, and Retention (RAR) – Potential Activities

- Methodology standards
  - Explore opportunities to vet RAR best practices to "turn them into standards
- PFAs
  - LOIs: propose new section to detail operational capacity/feasibility
  - Propose new section to detail patient-centered RAR practices
  - Propose new questions to indicate how stakeholders engaged in recruitment and feasibility planning

Subcommittee on Recruitment, Accrual, and Retention (RAR) – Potential Activities (cont.)

- Merit Review
  - Propose evaluation criteria for new section/questions as above
  - Provide criteria for RAR plan evaluation in general and with minority and medically undeserved populations in particular
- Contract Negotiation
  - Serve as reviewers to make specific recommendations for change
- Post-Award Monitoring
  - Review (selected) recruitment monthly reports and propose changes
  - Serve as advisors for struggling contracts
  - Develop “red flag” list, including recruitment speed
  - Develop Recruitment Tool Kit for PIs

Seven Operational Principles for Patient Centered Recruitment, Accrual and Retention

- Trials are normalized throughout institution through effective patient communication by all staff / providers
- 100% of patients beginning new treatment will be effectively pre-screened for trial eligibility
- 100% of those (who appear) eligible will be offered trial participation
- Clinical trials selected for local implementation will more appropriately meet needs of local patients
- All interested will have their information, knowledge and behavior needs met throughout the consent process
- All enrolled participants will receive adequate support to ensure their compliance and retention throughout the trial
- Trials are normalized in the community to increase referrals and inquiry

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) – SOW

- 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’
  - ‘usual care’
  - ‘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) – Principles

- Its work should not contradict any work already done by PCORI
- Its work should be coherent with the work done in the literature
- It will collaborate with the MC and vet its work through the committee
- Its first step will be to get consensus on terminologies included in PCORI materials (PFAs, Methodology report, …etc.) to provide clearer definitions to potential applicants for PCORI funding

Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – PCORI Methodology Standards

- The terms tackled by this subcommittee to produce definitions will not necessarily lead to new PCORI Methodology Standards.
- The MC is open to the CTAP recommending new methodology standards. CTAP could have a lot of work in drafting standards for clinical trials, and standards on pragmatic clinical trials could be a subset of those.
- Potential possibility of including a “Definition” portion to the PCORI Methodology Report in a second edition of it.
- The subcommittee should not plan around these two future possibilities for the time being.

Subcommittee on Monitoring of Funded Clinical Trials (MFCT)

- Chair: Craig Nichols
- SOW:
  - PCORI Data Safety Monitoring Board (DSMB) policy
  - Training materials for DSMB members, including non-traditional DSMB members, like patients and stakeholders, who may be less familiar with the role of DSMBs
  - Monitoring of PCORI's large pragmatic clinical trials

Break

10:45 – 11:00 a.m. EST

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Continued Discussion on Methodology Standards for Clinical Trials

Steve Goodman, MD, MHS, PhD

Methodology Committee (Vice Chair), PCORI

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Lunch

12:00 – 1:00 p.m. EST

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PCORnet, the Clinical Trials Task Force and the Ethics and Regulatory Task Force

Robert Califf, MD
Vice Chancellor, Clinical and Translational Research
Director, Duke Translational Medicine Institute
Professor of Medicine, Division of Cardiology, Duke University Medical Center

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Trial-Specific Subcommittee Proposal

Bryan Luce, PhD, MBA
Chief Science Officer, PCORI

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Purpose of Presentation

- Obtain CTAP input on all aspects of the proposal
- Review the approach for specific trials (obesity and aspirin)
- Determine frequency and nature of subcommittee reports
- Determine next steps for future subcommittees

Background

- Per its charter, a CTAP subcommittee, as appropriate, will coordinate with PCORI staff to review awarded applications and provide input on study design and methodology.
- This review and input will help ensure that the study design and methodology are appropriate and consistent with the standards generated by the PCORI Methodology Committee.
- CTAP subcommittee(s) are intended to address specific methodological designs of awarded applications that have already undergone PCORI's merit review process, with the purpose of providing technical advice to the Program staff monitoring the trials.

Overview

- Creation of trial-specific subcommittees for three large PCORI funded clinical trials:
  - Two Obesity Trials
  - PCORnet's Aspirin Trial
- These trial-specific subcommittees will report back to the CTAP's three overarching subcommittees and to the full CTAP to inform their broad guidance to PCORI.

Process and Management of Trial-Specific Subcommittees

- **Communication:** All communication between the CTAP subcommittee and the investigators of a project will go through program staff.

- **Nature of Advice:** Each Science Program will determine what the guidance needs are. The nature of advice solicited from the CTAP subcommittee could include, but is not limited to, issues associated with:
  - Statistical inference
  - Confounding
  - Complex methods
  - 'Usual care'
  - Sample size power
  - Alignment of trial components for cross-study analyses
  - Recruitment, accrual, and retention
  - Patient engagement
  - Review of DSMB reports

- **Member Selection:** To select subcommittee members, program staff are encouraged to ask the CTAP as well as other PCORI staff for recommendations.

Obesity Trials

- The Louisiana Trial to Reduce Obesity in Primary Care
  - Principal Investigator: Peter T. Katzmarzyk, PhD
  - Project Budget*: $9,997,107
  - Project Period*: 5 Years
- Midwestern Collaborative for Treating Obesity in Rural Primary Care
  - Principal Investigator: Christie Befort, PhD
  - Project Budget*: $9,999,962
  - Project Period*: 5 Years

The Louisiana Trial to Reduce Obesity in Primary Care

Engagement

- Patient community, and other stakeholder boards will be involved in project governance and oversight, in addition to ad hoc focus groups and interviews with patients and stakeholders to inform study components

Potential Impact

- Project, designed to be scalable to large patient populations , could influence the obesity treatment options that are offered to patients in the primary care setting

Methods

- Cluster randomized controlled trial

Compares two approaches for managing obesity patient-centered comprehensive, multicomponent intervention
delivered by health coaches in a primary care setting that aims to improve physical activity and diet to current fee-for-service obesity treatment reimbursed by Medicare.

Peter Katzmarzyk, PhD, FACSM, FAHA
Pennington Biomedical Research Center
Baton Rouge, LA

Addressing Disparities Research Project, awarded September 2014

Midwestern Collaborative for Treating Obesity in Rural Primary Care

Engagement

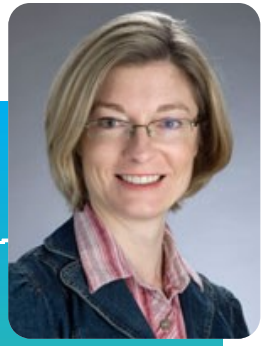
- Patient advisory panel shaped treatment approaches and defined outcomes, and local, state, and national stakeholders will be engaged at every stage of the study from implementation to dissemination

Potential Impact

- Primary care practices could fill an important gap in treating obesity in rural America because of their access to this population

Methods

- Cluster randomized controlled trial



Compares two new approaches for managing chronic diseases—patient-centered medical home and disease management—to the traditional fee-for-service model for treating obesity in rural primary care practices in the Midwest.

Christie Befort, PhD
University of Kansas Medical Center
Kansas City, KS

Addressing Disparities Research Project, awarded September 2014

Timeline

Item	Date
Create CTAP trial-specific subcommittee	March 15 to April 30,2015
Potentially invite other individuals with appropriate expertise to serve on the subcommittee	April 1 to April 30, 2015
Schedule subcommittee meetings based on needs	February 3, 2015
Contract execution	TBD/as needed

Aspirin Trial

- Topic approved by Board July 29th 2014
- Be a **proof of concept** for the type of research that PCORnet will be able to support on large scale in the near future
- **Optimal aspirin dosage** is not known and the evidence is contradictory: this question matters to patients and clinicians
- 53.6% of US patients with CAD **(15.4 million patients)** are on high-dose aspirin, which is associated with higher rates of GI bleeding
- A large **multi-center trial** would provide the necessary evidence
  - To establish whether low dose aspirin is safer, but as effective as high-dose aspirin
  - Definitively change clinical care
  - Improve health outcomes for patients
- Trial **"flexes" the use of the EHR in innovative ways**

Background

- A limited competition funding announcement was released to the network in October 2014

- Applications from the network will be reviewed through PCORI merit review
  - Selection made on a single trial
  - Anticipate funding to be awarded in Spring 2015

Timeline

Item	Date
Release funding announcement	October 27, 2015
Application deadline	January 30, 2015
Preliminary review by merit review panel	February 3, 2015
In-person review by merit review panel	March 6, 2015
PCORI selects application and begins contract negotiation	Mid-March
Board of Governors meeting	April 2015
CTAP trial-specific subcommittee creation	March/April 2015
Protocol refinement with CTAP trial-specific subcommittee	March/April 2015
Contract execution	TBD

Aspirin Trial Subcommittee Members

- It will be important to infuse continuity by inviting the **merit reviewers** (including patients, stakeholders, outside experts and 2 CTAP members), one expert from each of the 3 overarching CTAP subcommittees, and adding CTAP members and/or external experts as appropriate to form a CTAP trial-specific subcommittee.

Break

3:30 – 3:45 p.m. EST

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Advisory Panel on Rare Disease Collaboration Updates

Jason Connor, PhD, Director and Senior Statistical Scientist, Berry Consultants

Marshall Summar, MD, (RDAP Chair), Division Chief, Genetics and Metabolism, Margaret O'Malley Chair in Genetic Medicine, Medical Director, Clinical Research Center, and Vice-Chair External Affairs, Children's National Medical Center, Professor of Pediatrics, George Washington Medical College

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Recap and Next Steps

Bryan Luce, PhD, MBA
Chief Science Officer, PCORI
Elizabeth A. Stuart, PhD
Chair, Advisory Panel on Clinical Trials, PCORI
John D. Lantos, MD
Co-Chair, Advisory Panel on Clinical Trials, PCORI

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Adjourn

Thank you for your participation!