Advisory Panel on Clinical Trials Spring 2018 Meeting

November 16th, 2018

9:00 AM – 12:30 PM ET

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Welcome and Goals for the Day

Anne Trontell, MD, MPH
Associate Director,
Clinical Effectiveness and Decision Science, PCORI

Kaleab Abebe, MA, PhD (Chair)
Associate Professor,
University of Pittsburgh School of Medicine

Andrea Troxel (Co-Chair)
Professor and Director,
New York University School of Medicine

Housekeeping

- This session of this meeting is open to the public.
- Panelists who were not able to attend in person have access to dial in information.
- Chair Statement on COI and Confidentiality.

COI Statement

Welcome to the CTAP Fall 2018 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

- Discuss aspects of clinical trials associated with “success” to inform
  - PCORI oversight
  - Exploratory analyses of PCORIs clinical trial experience
- Introduce Studies Within A Trial (SWATs) for determining productive clinical trial processes
- Status update on PCORI’s Data Management and Data Sharing Policy

Today's Agenda

Start Time	Item	Speakers
9:00 am	Opening and Introductions	A. Trontell & K. Abebe
9:15 am	Trial Aspects Associated with Success	A. Trontell & CTAP
10:45 am	Break	
11:00 am	Studies Within A Trial (SWATs)	A. Trontell & CTAP
11:30 am	PCORI's Data Management and Data Sharing Policy	A. Rabinowitz
Noon	Wrap Up and Next Steps	K. Abebe & A. Troxel
12:30 pm	Close (Box lunches to go for CTAP)	

Aspects of Clinical Trials Associated with "Successful" Performance

Anne Trontell, MD, MPH
Associate Director,
Clinical Effectiveness and Decision Science, PCORI

PCORI Trial Oversight

- PCORI use contracts with milestones, deliverables, and firm timelines for clinical trial performance
- Can CTAP help PCORI identify & refine aspects of trials associated with high or low risk of 'success': efficient, timely, complete & high quality evidence generation?
  - For internal use to guide award decisions and oversight intensity
  - For possible external guidance or requirements of applicants
- Little scientific literature or systematic study to guide or predict successful clinical trial performance
- Today: Review previously discussed characteristics and explore others of potential value

Factors Considered May 2018 CTAP Meeting

Primary Site

- Principal Investigator
- Support Personnel
- Budgeting

Participating Sites

- Planned numbers and backups
- Existing network or prior collaboration history
- Resource structure to support enrollment
- Feedback & Communications re performance

Design

- Ease to identify eligible participants
- Clinician burden to participate
- Competition for participants with other trials
- Regulatory
- Costs of intervention and comparators
- Pre-work

May 2018 Discussion of Beneficial Characteristics: Primary Site

- The PI is supported by a strong study leadership *team*
- PI is experienced in handling similarly challenging studies
- The PI and team have prior experience working in the study's setting
- A strong central coordinating function is present
  - There is a strong administrative plan
  - An experienced Project Manager is a critical team member

May 2018 Discussion of Beneficial Characteristics: Primary Site Follow-up

How can strength be best determined?

- The PI is supported by a strong study leadership ***team***
- PI is experienced in handling similarly challenging studies
- The PI and team have prior experience working in the study's setting
- A strong central coordinating function is present
  - There is a strong administrative plan
  - A well-experienced Project Manager is part of the team

May 2018 Discussion of Beneficial Characteristics: Study Sites

- Sites are each planned to contribute a meaningful number of participants (avoid many sites with only a few)
- Site champions are present and invested in the study's performance
- The study sites have worked together previously on other studies
- Site compensation combines upfront payment + per capita reimbursement for enrollment

May 2018 Discussion of Beneficial Characteristics: Study Sites Follow-up

How can the extent and reach of champions be assessed?

- Sites are each planned to contribute a meaningful number of participants (avoid many sites with only a few)
- Site champions are present and invested in the study's performance
- The study sites have worked together previously on other studies
- Site compensation combines upfront payment + per capita reimbursement for enrollment

May 2018 Discussion of Beneficial Characteristics: Communications

- Near-continuous communication between the primary and other study sites
- Frequent in-person site visits
- Convene site coordinators frequently by phone to review progress, problem-solve, and share best practices

May 2018 Discussion of Beneficial Characteristics: Design Considerations

- Data collection is parsimonious to minimize burden on providers and participants
- Intervention(s) “fit” within the available capacity of the health system and/or providers to administer them (avoid unnecessary complexity)

Other Potentially Beneficial Study Characteristics or Processes?

Engagement with the study

- Clinicians implementing the study intervention(s)
  - Specialty care, primary care, procedure-based practitioners
  - Incentives to recruit
- Participants or patients
  - Communication avenues and materials
  - Handling of participation burdens (transportation, parking, childcare)
  - Compensation or incentives for additional time spent on study
  - Retention and long-term engagement

Other Potentially Beneficial Study Characteristics or Processes?

- In person kick-off meetings of primary and participating sites
- Minimal % FTE of Primary site PI
- Contingency plans that should be put in place
- Extent or nature of pre-work or pilot work
- Other

Potential Next Steps

- Future focused discussion
  - Recruitment and enrollment
  - Retention
  - Missing data
- Analyses of the PCORI portfolio to suggest or illuminate these or other factors associated with study performance?
- Case studies of performance outliers from PCORI portfolio analyses?

Break

10:45 – 11:00

Studies Within A Trial (SWATs) To Inform Trial Processes
The Trial Forge Initiative

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

The Trial Forge Initiative and SWATs

- Trial Forge: An initiative coordinated by the Health Services Research Unit at the University of Aberdeen. More information at www.trialforge.org
- Purpose: To increase the evidence base for decision-making about processes used in clinical trial conduct
- SWAT definition: A self-contained research study embedded within a host trial with the aim of evaluating or exploring alternative ways of delivering a trial process.
  - Generally low cost and easy to implement
  - https://trialsjournal.biomedcentral.com/track/pdf/10.1186/s13063-018-2535-5 (Trial Forge Guidance 1 on SWATs)

Key Features
Studies Within A Trial (SWATs)

- Seek to resolve important uncertainties about the processes used in trials
- Are embedded within a host trial
- Must not affect the scientific integrity of the host trial, its rationale or outcome measures
- Should have a formal protocol, just like the host trial
- Can be evaluated in a single trial or be run across multiple host trials in sequence or at the same time
- Provide data to inform the design and conduct of future trials and possibly inform the ongoing host trial as well

Example of a SWAT from Trial Forge Guidance 1

- Test of Patient Information Leaflets (PIL)
  - Used to tell potential participants about a trial, help recruitment (and perhaps retention) while adhering to ethical standards.
  - SWAT done in multiple trials with coordination and analysis by the START Programme (Systematic Techniques for Assisting Recruitment to Trials)
- Randomized comparison of the impact of two PILs upon patient recruitment
  - A bespoke, tailored and user-tested PIL
  - Standard PIL
- Meta-analysis done of all trials encompassing 6600 patients

Meta-Analysis
Three Evaluations of PIL SWAT

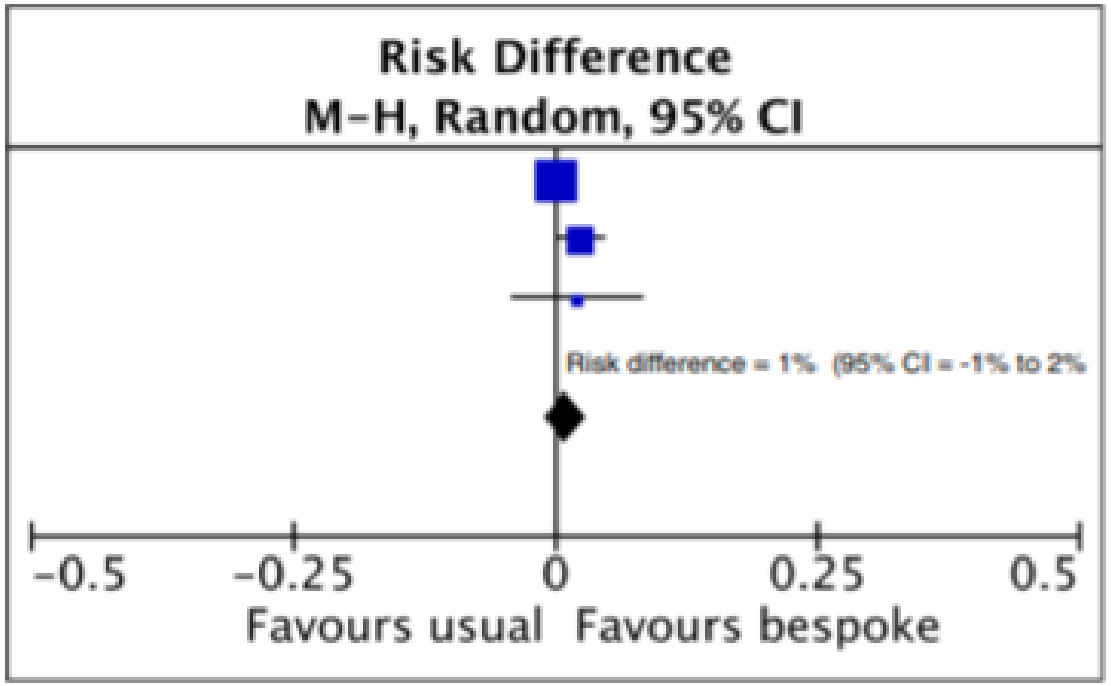


Fig. 1 Meta-analysis of three evaluations of the effect on trial recruitment of a bespoke, tailored and user-tested method of developing a Participant Information Leaflet

- Bespoke showed improvement of 1% (95% CI: -1% – 2%) over standard PIL
- Little or no effect upon recruitment despite additional expense of customization

SWATs: Opportunities and Questions

- Potential trial processes for comparative effectiveness study via SWATs
  - Engagement strategies of sites, participants, providers
  - Different communication means or methods on participant recruitment, accrual, and retention (RAR)
  - Financial or other incentives on participant RAR
  - Site engagement practices
  - Data collection methods on data completeness/missingness
- Questions
  - Downstream impact of heterogeneous processes upon PICOTS – heterogeneity, effect sizes, study power
  - Suitability of use with cluster-randomized host studies

SWATs in PCORI Studies?

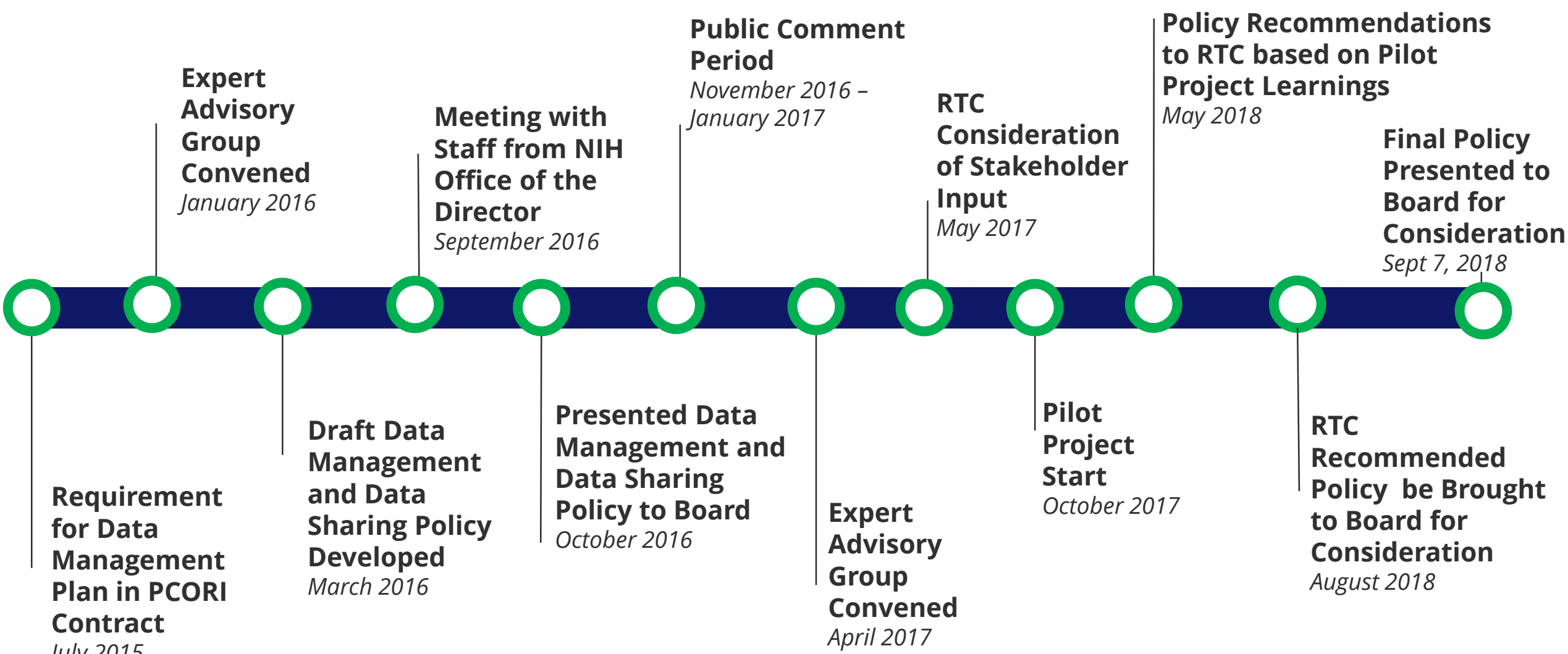
- Might SWATs be useful for PCORI to investigate further?
- What additional information does PCORI need to determine whether SWATs are appropriate in clinical CER?
- What trial processes appear most promising for potential PCORI SWAT analyses?

PCORI's Policy for Data Sharing and Data Management

Jason Gerson, PhD
Senior Program Officer,
Clinical Effectiveness and Decision Science, PCORI

Allie Rabinowitz, MPH
Program Associate, Office of the Chief Science Officer, PCORI

Timeline of Policy



Features of the Policy

- Articulates expectations for data management and data sharing to Awardees
- Specifies data and data documentation to be shared
- Provides funding to support Awardees' time and effort to prepare data
- Specifies when data would be made available for third-party requests
- Describes third-party data request review process

Data Deposition: Overview

- Deidentified data only in accordance with the HIPAA Privacy Rule (45 C.F.R. § 164.514(b)).
- Full Data Package: Analyzable Data Set, Full Protocol, metadata, data dictionary, full statistical analysis plan, and analytic code
- Data will be hosted by designated repository(ies), not PCORI

Data Deposition: Expectations for Research Awardees

Targeted and Pragmatic Clinical Studies Funding Announcements	PCORnet Funding Announcements	Broad Funding Announcements
• Deposit full data package (or required data elements, as applicable) in a PCORI-designated repository	• Deposit applicable data elements, such as the full protocol, analytic code used to query PCORnet data, and aggregate level datasets in a PCORI-designated repository	• Maintain full data package for 7 years • PCORI may notify Awardee of its intent to provide funds for the deposition of the full data package in a PCORI-designated repository

Timeframe for Data Availability

- The full data package will be made available for third-party requests only when the

Final Research Report is made available on PCORI's website

- OR -

One of the research project's primary results papers is published in a peer-reviewed journal

<u>WHICHEVER COMES FIRST</u>

Data Requests: Review Process

- Independent review committee to ensure data request has scientific merit by evaluating that:
  - Scientific purpose is clearly described
  - Data requested will be used to develop or contribute to generalizable knowledge to inform science, medicine and/or public health
  - Proposed research can be reasonably addressed using the requested data
  - Requestor team has the appropriate expertise to conduct the proposed research
- Approved requestors will enter into a Data Use Agreement (DUA) with a PCORI-designated repository. DUA specifies the terms and conditions of data use, as well as the responsibilities and obligations of data requestors.

Data Requests: Independent Review Committee

- All data requests will be reviewed by an independent committee. Committee will be comprised of 5 individuals:
  - Representative from the PCORI-designated repository
  - Data scientist
  - Clinical researcher with expertise germane to the data request
  - PCORI staff member
  - Patient representative
- A member of the Awardee research team that generated the requested data will be invited to attend the review as a non-voting participant

Next Steps: Policy Implementation

- PCORI plans to implement the specific requirements of this Policy in stages
- We'll work one-on-one with Awardees to facilitate compliance with the Policy
  - Assessment of data types and current informed consent forms
  - Negotiation/execution of contract modifications
- PCORI Town Hall for awardees on 11/7/2018
- FAQs available on PCORI's website
  - https://help.pcori.org/hc/en-us/sections/360000257660-Data-Management-and-Data-Sharing-Policy
- Submit questions to: OpenScience@pcori.org.

Questions?

Wrap Up and Next Steps

Kaleab Abebe, MA, PhD (Chair)
Associate Professor,
University of Pittsburgh School of Medicine

Andrea Troxel (Co-Chair)
Professor and Director,
New York University School of Medicine

Anne Trontell, MD, MPH
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Thank you!