Advisory Panel on Clinical Trials Spring 2018 Meeting

May 7th, 2018
9:30 AM – 3:30 PM ET

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Welcome and Goals for the Day

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

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

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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 Spring 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

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

- Drafted PCORI Guidance on Pragmatic Clinical Studies
- Estimands Commentary Publication by Hernan & Scharfstein
- Factors to Predict Clinical Trial Challenges or Success
- Future Directions for CTAP

Today's Agenda

Start Time (ET)	Item	Speaker
9:30	Welcome, Introductions, and Goals for the Day	E. Stuart/A. Trontell
9:45	New Panelist Introduction	K. Weinfurt
10:00	CTAP Feedback on PCS Guidance	A. Trontell
11:00	Break	
11:15	Estimands in Clinical Trials	E. Stuart/A. Troxel
12:15	Lunch	
12:45	Recognition of Departing Panelists & Chair	
1:00	Factors to Predict Clinical Trial Challenges or Success	E. Stuart/A. Trontell
2:30	Break	
2:45	Update from the CSO	E. Whitlock
3:15	Closing and Next Steps	E. Stuart/K. Abebe
3:30	Adjourn	

Introduction to NIH Collaboratory

Kevin Weinfurt, PhD

Professor and Vice Chair for Research,
Department of Population Health Sciences,
Duke University School of Medicine

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PCORI Guidance on Pragmatic Clinical Trial Design Features

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

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Background

CTAP Subcommittee on Communicating Complex Topics undertook an effort to develop a PCORI document on pragmatic trials

- Leadership by Merrick Zwarenstein
- Delayed due to uncertainties about purpose and audience
- Resolved to develop a PCORI guidance and an independent peer-reviewed publication from SCCT efforts

Draft Guidance on Pragmatic Trials

- Modeled after a similar document on clinical trials in rare diseases arising from the Rare Disease Advisory Panel
- Informed by PCORI's now extensive experience in funding 310 randomized clinical trials employing pragmatic designs
- Built upon discussions with PCORI investigators and advice and feedback from the CTAP in November 2017
- Preliminary draft shared with CTAP members
- Plan to refine and vet within PCORI and with the Methodology Committee prior to publication on the PCORI Website

Key Points in the Draft Guidance

- Virtually all PCORI trials are “pragmatic”
  - Broadly inclusive of all types of patients
  - Reflect the complexities of real world clinical practice vs. research settings
- PCOR focus directly compares 2 or more health care alternatives
- PCOR pragmatic clinical trials (PPCT) have similarities to PRECIS
  - Fit for purpose of answering stakeholder-driven questions
  - Similar domain interests as PRECIS
    - Patient population
    - Study settings
    - Minimally burdensome data collection

Key Points in the Draft Guidance

- Distinctive features of PCOR pragmatic trials
  - Meet PCORI Methodology Standards
  - "Usual care" comparators used only if well-defined and coherent
  - Anticipate real world conditions of use and application
  - Judicious attention & monitoring of intervention fidelity and adherence.
    - Purposeful rather than laissez-faire conduct
  - Careful balancing required
    - Internal and external validity
    - Controlled study conduct and real-world flexibility

Break

11:00 – 11:15 a.m.

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Estimands in Clinical 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

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

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Background

- An estimand is the quantity of interest in an analysis—the thing that is being estimated
- Examples of estimands include the ITT effect, and a per protocol effect
- Key questions about any estimand include
  - 1) is it meaningful,
  - 2) can we estimate it, and
  - 3) what assumptions are required to estimate it

Background Continued

- International Conference on Harmomization (ICH) E9 Guidance Addendum
- Four attributes of an estimand
  - Population
  - Endpoint
  - Effect measure
  - Approach to handling “intercurrent events”

Background Continued

ICH E9 guidance Addendum Recommendations:

- Consider other treatment effect estimate
  - Treatment policy strategy (i.e., ITT)
  - Composite strategy
  - Hypothetical strategy
  - Principal stratum strategy
  - While on treatment strategy
- Clarify missing data issues
- Clarify the analysis set
- Conduct extensive sensitivity analyses

Discussion

- Concept of “treatment strategy” a la Scharfstein and Hernan
- Best use of ITT?
  - Added assumptions required if moving away from ITT
- Dangers of principal stratification?
- Application of these principals to behavioral rather than drug trials?

Discussion

- What are the most relevant estimands for PCORI?
- How should PCORI think about the trade-offs between the relevance and the assumptions required?
- Could PCORI use strategies such as those in Scharfstein & Hernan?

Lunch

12:15 – 12:45 p.m.

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Recognition of Departing Panelists & Chair

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

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What Factors Predict Clinical Trial Challenges or Success?

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

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Underlying Hypotheses to Explore

- Are design and operational characteristics of clinical trials associated with poor performance in timeliness, cost, efficiency, or data quality? If yes…
  - Can they help predict if a trial is at high risk?
  - Does knowing these risks allow their mitigation?
- Conversely, what characteristics are associated with timely, efficient, high quality trials?
  - Are they predictive?
  - Will adherence increase the chance of trial success?

Purpose of Today's Discussion

- Support PCORI funding & management decisions about clinical trials
- Operational definition of "successful" trial performance
  - Ability to produce meaningful, scientifically and statistically sound evidence to inform health care choices
  - Timely completion with adequate enrollment, retention, and data quality
- Help PCORI anticipate the risk of clinical trials
  - To inform decisions with risk information
  - To mitigate/control identified risks to enable successful trials
  - To recommend/guide best practices in trial conduct

Potential Uses of Risk Information

- Decision-making
  - In developing and recommending funding slates
  - Overall portfolio risk/reward balancing
  - Individual study management
- Remediation, management, or oversight
  - More stringent contract terms, milestones, or deliverables
  - Increased reporting/monitoring
  - Risk containment with pilots, contingent funding, or other contractual mechanisms

Today's Discussion

- Suggested factors nominated by PCORI staff and from the literature
- Focus today on factors other than recruitment in study success
- Seeking expert opinion, advice on factors as well as other data sources to inform assessment

Proposed Approach to Discussion

- **For each factor**
  - Is it associated positively or negatively with trial success?
  - Can its degree of association be categorized?
    - Weak, moderate, strong
  - Can the factor's contribution to risk be categorized in terms of its potential impact? Are there criteria that can be applied?
- **Overall**
  - Which factors are most important or weighty?
  - What are *de minimus* core factors to use?

Potential Factors

- Characteristics for discussion today if time permits
  - Primary site
  - Participating Sites
  - Study intervention and design
- Future discussion by CTAP
  - Factors associated with good recruitment, accrual & retention of study participants

Panel-Led Ordering of Discussion of Factors

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

Potential Factors: Primary Site Characteristics

Principal Investigator

- PI experience with studies of similar size or scope

  What is key? # sites, total enrollment, budget, complexity?
- 'Adequate' time commitment
- Academic career stage or other commitments (clinical or otherwise)
- Overall strength of investigative team leadership

Potential Factors: Primary Site Characteristics

Support Staff

- TBN project manager need to be recruited or hired vs. an experienced project manager is already available

Budget

- Resource allocation between the prime institution and contracted study sites

Potential Factors: Site Characteristics

- Number of sites: What is too many? How can the optimal number be best determined?
- Availability and number of “back-up” study sites

- Prior experience or institutional collaboration with the primary institution/investigator
- Using or built upon an established research network of prior collaborators

Potential Factors: Site Characteristics

- Resource structure for sites
  - Personnel support vs. per patient fee vs. hybrid/other

- Regular, real time reviews of study progress and milestones with sites' leadership

Potential Factors: Study Design Characteristics

- Complexity of study interventions or procedures
  - Ease/complexity/efficiency of screening process
  - Duration of run-in period needed to establish eligibility
  - Available time window to “capture” eligible participants
- Competition for study population with other trials
- Cost coverage for interventions and comparators
- Clinician burden(s) to participate

Potential Factors: Study Design Characteristics

Regulatory

- IND or other regulatory requirements
- Human subjects concerns
  - Vulnerable populations (children, prisoners, pregnancy)

Potential Factors: Study Design Characteristics

Pre-Work

- Draft protocol in place at study onset
- Sites, investigators aided in trial design and/or protocol development
- Patient input and engagement
  - Study communications
  - Acceptability of randomization
  - Time or other study burdens

Next Steps

- PCORI consideration of how it might operationalize CTAP recommendations
- Future consideration by CTAP of risk factors that are critical to trial performance
  - Recruitment and enrollment
  - Retention
  - Missing data
  - Others

Break

2:30 – 2:45 p.m.

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Updates from PCORI's Chief Science Officer

Evelyn Whitlock, MD, MPH

Chief Science Officer, PCORI

May 7th, 2018

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Celebrating CTAP

- To date, CTAP has offered meaningful scientific advice and input that PCORI has incorporated into the following areas:
  - Pragmatic clinical studies
  - PCORI Methodology Standards on Patient-Centeredness (from RAR Subcommittee)
  - Cluster randomized clinical trials
  - Data Safety and Monitoring
  - Specific study design and analysis questions (via Subcommittee)

- Going forward, additional CTAP advisory opportunities
  - PCORI monitoring and management of our large portfolio of clinical trials (to date, 310 clinical trials totaling $1.281 billion, 80 total PCS and Targeted trials, 51 of these 80 trials have sample sizes above 1000)
  - Initiatives in preparation for PCORI 2.0

Preparing for PCORI 2.0: Potential opportunities for CTAP participation

- Continuing to expand evidence synthesis activities to produce valid, actionable evidence in an efficient manner
  - Assist in identifying and encouraging IPD meta-analysis opportunities
- Expanding heterogeneity of treatment effect analyses for large trials using baseline risk
  - Assist Methodology Committee in reviewing recommended approaches for identifying and funding trial re-analyses (firewall considerations)
- Reducing Waste Funders Forum—international efforts to encourage best practices in ensuring value in research investments
  - US efforts: NIH Collaboratory, VA, DOD, others—mega-trial consortium
  - Other ideas to improve research community preparedness and uptake of best practices in proposing, funding, conducting clinical trials to influence practice and policy.

Transition of Chief Science Officer

Dr. Diane Bild will be serving as Acting Chief Science Officer starting June 8th, 2018.

She will be joining you at a future meeting in-person (she is currently on a pre-planned family vacation)

Questions?

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

Kaleab Abebe (Incoming Chair)

Associate Professor, University of Pittsburgh School of Medicine

Andrea Troxel, ScD (Incoming Co-Chair)

Professor and Director, New York University School of Medicine

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science, PCORI

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Thank You!

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