Advisory Panel on Clinical Trials
Meeting Summary

Overview

On May 7, 2018, the PCORI Advisory Panel on Clinical Trials (CTAP) held its 11th meeting in Washington, DC.

CTAP's 13 members include patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics along with two ex-officio members from PCORI's Methodology Committee. The meeting was open to the public via webinar, and meeting materials were posted to the PCORI website in advance of the session.

During this meeting, CTAP provided feedback on draft PCORI guidance on pragmatic clinical trial design considerations in comparative effectiveness research. The committee also discussed the use of different types of estimands, described as the parameter which is to be estimated in a statistical analysis, in randomized clinical trials as well as the value of intent-to-treat analyses. After recognizing the three retiring CTAP members (Drs. Jason Connor, Elizabeth Stuart, and Merrick Zwarenstein), CTAP provided feedback on factors proposed by PCORI staff that might be used to predict clinical trial challenges or successes. Finally, Dr. Evelyn Whitlock, PCORI's chief science officer, gave updates on plans for PCORI's future, PCORI support for individual participant-level meta-analyses, and collaborative efforts to reduce wasteful practices in research.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials November 3, 2017, Meeting
- PCORI methodology standards
- PCORI funding announcements (PFAs) for pragmatic clinical studies
- PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2)
- Addendum to the International Conference on Harmonization's Statistical Principles for Clinical Trials E9

The Patient-Centered Outcomes Research Institute (PCORI) is an independent organization created to help people make informed healthcare decisions.

1828 L St., NW Suite 900
Washington, DC 20036
Phone: (202) 827-7700
Fax: (202) 355-9558
Email: info@pcori.org
Follow us on Twitter: @PCORI

CTAP Feedback on Draft Pragmatic Clinical Studies Guidance

Anne Trontell, MD, MPH, Associate Director, Clinical Effectiveness and Decision Science at PCORI, explained that Merrick Zwarenstein, a CTAP member, led the CTAP Subcommittee on Communicating Complex Topics. The subcommittee developed a document on pragmatic clinical trials which will be submitted as a manuscript to a peer-reviewed publication.

In parallel, PCORI is developing and vetting a companion document for dissemination on the PCORI website. A draft of this document, "PCORI Guidance on Pragmatic Clinical Trial Design Considerations in Patient-Centered Comparative Effectiveness Research" was shared with CTAP members to solicit their feedback. This document asserts that virtually all PCORI trials are pragmatic in that they include diverse types of patients and reflect the complexities of real-world clinical practice and settings. They are distinctive in comparing two or more healthcare alternatives directly.

Pragmatic clinical trials in comparative effectiveness focusing on patient-centered outcomes research are similar to trials that meet the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) criteria in that they are fit for answering stakeholder-driven questions, have similarly diverse patient populations and study settings, and use minimally burdensome data collection methods.

Distinctions of PCORI-funded pragmatic trials are their requirement to comply with the PCORI methodology standards, use "usual care" comparators only if they are well defined and coherent, and judiciously monitor intervention fidelity and adherence. PCORI-funded trials also carefully balance internal and external validity and the need to control study conduct while ensuring real-world flexibility.

CTAP members approved of the draft guidance, noting that it will help investigators understand the types of trials that PCORI seeks to fund. They offered the following suggestions:

- Add examples of studies that meet the PCORI criteria
- Create templates of a table for PIs to describe the pragmatic design choices and explain the rationale
- Ask investigators to update the table explaining how their study design choices reflect pragmatic or explanatory features once a year, perhaps in their reports to PCORI
- Explain more explicitly the need to consider the real-world settings in which the intervention will ultimately be used
- Emphasize the tradeoff between internal and external validity
- Emphasize recently finalized PCORI Methodology Standards: Standards for Studies of Complex Interventions and the need for a causal model
- Include guidance on how to handle changes that occur over the course of a study's progress from design, to implementation of the trial, to handling of the modifications that occur
- Create short videos to provide training on how to design a pragmatic tria

Estimands in Clinical Trials

Andrea Troxel, ScD, Incoming CTAP Co-Chair, gave the CTAP an overview of estimands and a recent publication on the concept of "treatment strategy" by Miguel A. Hernan, MD, DrPH, and Daniel Scharfstein, ScD. Dr. Troxel defined an estimand as the quantity of interest in an analysis or the thing that is being estimated. Examples include the intent-to-treat (ITT) and per-protocol (PP) effects. Estimands should be meaningful, investigators should be able to estimate them, and the assumptions required for these estimates must be identified.

An addendum to the International Conference on Harmonization's Statistical Principles for Clinical Trials E9 guidance is being prepared to address modern developments in randomized controlled trials and statistical inference in general. The draft addendum identifies four attributes of all estimands: population, endpoint, effect measure, and approach to handling "intercurrent events." The population should be the target population for the treatments being compared. The endpoint is the primary endpoint in a clinical trial that is being measured and used to evaluate differences among treatments. The effect measure is a statistical concept used to assess differences in outcomes. Intercurrent events are those that might interfere with the ability to measure the estimand.

The addendum recommends that investigators consider at least five treatment effect estimates: treatment policy (ITT; what actually happens), composite, hypothetical, principal stratum, and while-on-treatment strategies. Other recommendations are to clarify missing data issues and the analysis set and to conduct extensive sensitivity analyses.

During the discussion, CTAP noted that many of the estimands that are easiest to interpret, such as the while-on-treatment estimand, are difficult to estimate well because participants drop out of different study arms at different rates, which essentially nullifies the randomization. The question is how to retain the benefits of randomization and estimate something meaningful that is related to real-world practice. They also noted that ITT is easy to understand, and the mathematics are easy to do. However, more sophisticated analysis methods are available now that can provide answers that are important for patients, payers, and other stakeholders. Furthermore, doing both ITT and PP analyses can be useful. Finally, CTAP suggested continuing this discussion with PCORI's Methodology Committee.

Recognition of Retiring Panelists

Dr. Trontell thanked the panel members whose terms were ending for sharing their rich trove of knowledge and PCORI-specific expertise: Jason Connor, PhD; Elizabeth Stuart, PhD; and Merrick Zwarenstein, MBBCh, MSc, PhD.

What Factors Predict Clinical Trial Challenges or Success?

An operational definition of a successful trial is one that can produce meaningful, scientifically, and statistically sound evidence to inform healthcare choices. In addition, a successful trial is completed in a timely way and has adequate enrollment, retention, and data quality. Dr. Trontell explained that PCORI is interested in developing criteria to identify trials at an early stage that are more or less likely to be successful. PCORI could use these criteria to predict the level of risk of clinical trials to inform decisions

on study monitoring and budget needs, mitigate or control identified risks to help trials succeed, and develop best practices in trial conduct.

PCORI staff identified potential factors in trial success related to characteristics of the primary site, participating sites, and the study design.

CTAP discussed several general factors that could predict success:

- Good organization
- Readiness to start the trial
- Involvement of stakeholders who can implement the study findings
- Feasible implementation
- Patient advocate involvement in planning and managing the study
- Complexity of the informed consent process
- Questionnaire complexity

CTAP also identified more specific factors for PCORI to consider:

- Study Team:
    - Experienced and competent Project Director is assigned (not "TBN" or "support staff")
    - Qualified Study Data Lead
    - Extent of prior experience or leadership of the PI in collaborations with the proposed study sites
    - PI's success in solving problems in other studies
    - Attentiveness to project administration
- Study sites:
    - Inclusion of study sites with experience conducting trials
    - Inclusion of sites that can recruit underserved populations
    - Beware of sites contributing small amounts of patients
    - Have contingency sites available
    - Opportunities for site coordinators to come together
    - Continuous communication between the primary site and other sites
    - Treatment of all sites as true collaborators in protocol development and design
    - Up-front funding for sites beyond that provided per recruited participant
    - Site champions who can help address logistical issues

The CTAP will continue discussion of potentially predictive factors in trial success during future meetings. CTAP also suggested that PCORI investigate how well PCORI trials meet the PRECIS 2 criteria and whether the individual PRECIS factors predict success.

Update from PCORI's Chief Science Officer

Evelyn P. Whitlock, MD, MPH, Chief Science Officer at PCORI, reported that PCORI has invested a total of $1.28 billion in its 310 clinical trials. Of these, 80 are pragmatic or targeted trials.

PCORI is preparing for "PCORI 2.0," which will begin when PCORI's current funding ends in September 2019. PCORI is developing the justification for its reauthorization using the lessons learned from PCORI's initial experiences.

The results will be available soon of PCORI's first individual participants meta-analysis using data from more than 40 clinical trials on the role of progesterone in prevention of preterm birth. The Methodology Committee developed draft standards for individual participant meta-analysis for review by PCORI's board of governors. A PFA has been issued to plan individual participant-level meta-analysis.

The PCORI Predictive Analysis Resource Center is evaluating methods to assess baseline risk of a major outcome in a trial or set of trials and to identify quartiles or quintiles of risk within which to examine stratified results. The center will meet with the National Academy of Medicine and international experts on May 31 to discuss the inherent limitations of using group data to guide treatment decisions for individuals.

PCORI is part of an international research funders working group to reduce waste because, for example, research results are not published, duplicative research is funded, results are only partially reported, and studies are poorly done. PCORI and other large U.S. funders are increasingly coordinating their research.

Wrap Up and Next Steps

Dr. Elizabeth A. Stuart, CTAP chair, and CTAP members requested information at a future meeting about PCORI's dissemination and implementation activities. She also identified several issues for CTAP to discuss in the future:

- How to use the breadth of experience from the 310 PCORI-funded clinical trials to inform the field
- The estimand issues raised during this meeting (potentially to be discussed with the Methodology Committee)
- A review of PCORI's portfolio of clinical trials
- Continued discussion of factors that predict clinical trial challenges or success
- Development of a data dictionary to help investigators develop better research questions