Advisory Panel on Clinical Trials Meeting Summary

Overview

On January 14, 2015, the PCORI Advisory Panel on Clinical Trials (CTAP) held its fourth meeting in Arlington, Virginia.

CTAP's 10 members include patients, clinical trialists, biostatisticians, epidemiologists, and an expert in the ethical dimensions of clinical trials. The panel also includes 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.

The key agenda items covered during the CTAP meeting were methodology standards for clinical trials and trial-specific subcommittees. The PCORI Advisory Panel on Rare Disease chair, Marshall Summar, attended the meeting to discuss guidelines and methods to use for clinical trials in small populations. The Advisory Panel on Clinical Trials then received updates on clinical trial-related activities at PCORI. After learning about the development process of the PCORI methodology standards, panel members provided recommendations for new standards that address clinical trials. Then, the CTAP received reports from the subcommittee chairs. Dr. Robert Califf, Co-Principal Investigator of the PCORI National Patient-Centered Clinical Research Network (PCORnet) Coordinating Center, discussed recent PCORnet activities. Finally, CTAP members provided input to a proposal to form trial-specific subcommittees.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials Fall 2014 Meeting
- About PCORI's Methodology Committee
- *The PCORI Methodology Report*
- CTAP Subcommittees: Scope of Work
- Subcommittee on Recruitment, Accrual, and Retention
- Subcommittee on the Standardization of Complex Concepts and their Terminology
- PCORnet

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

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Advisory Panel on Rare Disease Collaboration Updates

Dr. Marshall Summar, the chair of the PCORI Advisory Panel on Rare Disease, discussed recent thinking and work by the Rare Disease Panel. He explained that the Rare Disease Panel had recently concluded that instead of trying to study each of the approximately 7,000 rare diseases, PCORI should use innovative statistical and evidentiary methods to study groups of rare diseases. Dr. Summar encouraged CTAP to develop guidelines for methods for different types of clinical trials in small populations.

CTAP members identified challenges for clinical trials of rare diseases:

- obtaining consent for first-in-humans studies in children
- distinguishing between rare diseases and underserved populations
- obtaining favorable results from review panels for innovative study designs

Potential solutions to some barriers to rare disease clinical trials are:

- use approaches that increase the likelihood of enrolling patients in a study's active arm
- fund rare disease studies that use innovative methodologies
- build the information base on the prevalence and patterns of care of rare diseases
- use patient-driven data registries, including for non-experimental studies of interventions

PCORI Updates

Dr. Bryan Luce, Chief Science Officer at PCORI, reported the following PCORI news related to clinical trials:

- PCORI is cosponsoring the 8th Annual Conference on Statistical Issues in Pragmatic Clinical Trials at the University of Pennsylvania on April 15, 2015. The event will feature several PCORI-affiliated panel members and speakers, including the keynote speaker, Dr. Robert Califf, Co-Principal Investigator of the PCORI National Patient-Centered Clinical Research Network (PCORnet) Coordinating Center. Dr. Luce encouraged CTAP members to attend.
- About 60 percent of the 215 clinical trials that PCORI funds are now registered on ClinicalTrials.gov, and another 31 percent are not required to be registered until they recruit their first patient.
- The FY2015 CTAP budget includes funding for three in-person meetings per year, two landscape reviews, subcommittee work, and CTAP member presentations at national conferences.

Methodology Standards for Clinical Trials

The Development Process of PCORI's Methodology Standards

Dr. Steve Goodman, Methodology Committee Vice-Chair, described the approach that the Methodology Committee used to develop the PCORI methodology standards and its process for revising them. The

goal of the presentation was to give an idea to the panel about how they could propose new standards for clinical trials for the Methodology Committee to endorse.

Dr. David Hickam, Program Director for Clinical Effectiveness Research at PCORI, explained that the Methodology Committee and PCORI staff have developed draft standards for cluster designs for the methodology standards for clinical effectiveness research. Methodologists will review the draft standards at a meeting later this spring. Dr. Hickam encouraged one or two interested CTAP members to attend this meeting.

New PCORI Methodology Standards for Clinical Trials

The panel expressed interest in developing new standards that address clinical trials methodology.

CTAP members offered to add the following tasks to the upcoming agenda in relation to proposing new methodology standards:

- create a consistent process for identifying gaps in the methodology standards and finding ways to fill those gaps
- consider adding standards on maximization of generalizability; recruitment, accrual, and retention; dissemination and implementation of research findings; and which patients to recruit based on whose care could be informed by the study results
- articulate the differences between guidelines and standards

Other comments included that the standards might not be implemented in ancillary studies funded by other sources and that standards and their impact on health should be explained to lay audiences. CTAP members also requested a copy of the revisions that the Methodology Committee had made to the standards after receiving public comments on the first draft of the report. The CTAP and its subcommittees will begin to identify gaps in the methodology standards that are related to clinical trials prior to the May 2015 in-person CTAP meeting.

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

Dr. Robert Califf, PCORnet Co-Principal Investigator, attended to discuss potential areas of collaboration between the panel and PCORnet, a large national network that supports comparative effectiveness research using clinical data gathered in real time and in real-world settings. The PCORnet Clinical Trials Task Force provides methods, standards, and principles for clinical trials using PCORnet. The first PCORnet trial will study the optimal aspirin dose for patients with coronary artery disease.

The PCORnet Ethics and Regulatory Task Force is developing a set of manuscripts for publication in *Clinical Trials* on conducting pragmatic clinical trials in an ethical way that complies with federal and state regulations. NIH and PCORI are jointly supporting four empirical ethics supplements to journals in the field to explore the beliefs of various stakeholders about the acceptability of research in usual-care settings.

During the discussion with the CTAP panel, Dr. Califf called for a "national utility" to provide clinical trial investigators with access to common data elements that are already collected in large networks. Researchers could then focus their resources on collecting the unique data that their trial requires. CTAP recommended that NIH and PCORI develop common definitions of concepts (such as "patient-centered recruitment and retention") for PCORI and NIH Collaboratory clinical trials. The CTAP and PCORnet task forces will continue to communicate and work together to ensure complementary efforts.

Trial-Specific Subcommittee Proposal

Dr. Kara Odom Walker, Deputy Chief Science Officer at PCORI, asked for feedback on a proposal to form CTAP trial-specific subcommittees for large PCORI-funded trials, such as the obesity trials and the PCORnet aspirin trial.

CTAP members offered the following feedback:

- The project-specific subcommittees could provide guidance on changes that, if made early to a given trial, could increase the ability to disseminate and implement its results.
- Many of the proposed subcommittees' responsibilities overlap with those of DSMBs and the PCORI Methodology Consultation Service.
- Because the subcommittees would have limited interaction with investigators, these groups might have trouble providing meaningful input.
- Subcommittee members are likely to have much less knowledge of study details than merit reviewers and investigators who have spent much more time on these applications.
- Investigators might be dismissive of subcommittee recommendations unless the subcommittees take time to build relationships with investigators and earn their trust.
- Once the merit review process has determined that a trial is worthy of funding, which implies that it has a strong design, the need for another group to review that design is questionable.
- Creating yet more CTAP subcommittees will spread the small number of panel members too thinly. To avoid overburdening CTAP members, only one CTAP member could be assigned to each trial-specific subcommittee.
- The subcommittees could impose yet another barrier on investigators and delay study start dates.

CTAP recommended that instead of creating several trial-specific subcommittees, PCORI staff could form a pool of specialists with expertise in different methods-related issues. PCORI staff could then consult these experts as needed. This approach would avoid slowing down the trial approval process and overburdening CTAP members.

Subcommittee Reports

Subcommittee on Monitoring of Funded Clinical Trials (MFCT)

Dr. Craig Nichols described the original draft of the scope of work of this subcommittee. Dr. Nichols questioned the need for this subcommittee because PCORI now plans to create a group that will advise

staff on clinical trials methods-related issues. Although pragmatic trials are different from other trials in many ways, these differences do not warrant a separate set of guidelines. CTAP members agreed to place the MFCT Subcommittee on hold.

Subcommittee on Recruitment, Accrual, and Retention (RAR)

Margo Michaels reported that the RAR Subcommittee will advise PCORI on best practices relating to recruitment, accrual, and retention of stakeholders. She gave a brief overview of the subcommittee's scope of work and reported back from several meetings with PCORI staff during which potential different areas of improvement were discussed, such as post-award project monitoring.

CTAP members suggested that the subcommittee add a representative from the PCORI Advisory Panel on Patient Engagement. PCORI staff will also advise the subcommittee on the assistance they need in improving the recruitment, accrual, and retention in PCORI-funded research projects.

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

Dr. Merrick Zwarenstein explained that the SCCT Subcommittee will provide guidance on the standardization of complex concepts and terminology used in funding announcements, the *Methodology Report*, and other PCORI documents. The plan was that the first concepts the group would review are "pragmatic," "usual care," "mixed methods," and the level of depth that investigators should use to describe their interventions and comparison conditions. The subcommittee's output might be a definitions section in the *Methodology Report*.

During the discussion, SCCT Subcommittee members requested staffing assistance from PCORI to identify the uses of the target terms in documents from PCORI, other relevant programs, and the published literature. The subcommittee should be prepared to send its draft definitions to all CTAP members prior to the next in-person panel meeting, scheduled for May 28, 2015.

The PCORI Board of Governors has discussed the need for a standardized definition of "usual care" because this term is used so inconsistently. In response to the board's concern, PCORI staff members are reviewing the use of "usual care" comparator conditions in funded PCORI clinical trials and developing requirements for such conditions for PCORI applications. PCORI hopes to complete these activities by the end of March 2015. The SCCT Subcommittee should communicate with the staff members involved in this effort. Because PCORI staff are already doing empiric research on the uses of "usual care," the requested landscape review for the SCCT Subcommittee need not include this concept, at least for now.

Next Steps

At the May meeting, the subcommittee chairs will provide updates on their activities, summarize gaps in the methodology standards that are related to clinical trials, and offer recommendations on potential areas of collaboration with the Methodology Committee. PCORI staff will decide how to address the need for trial-specific guidance from CTAP members and other experts. To encourage collaboration with PCORnet's task forces, PCORI staff will circulate meeting agendas and notes with CTAP leadership as appropriate and flag potential areas of collaboration.