# Advisory Panel on Clinical Trials Meeting Summary

## Overview

On October 26, 2016, the PCORI Advisory Panel on Clinical Trials (CTAP) held its eighth meeting in Washington, DC.

CTAP's nine members include patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics along with one ex-officio member 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 panel, which includes several new members, learned about the role of CTAP and discussed the idea of using the reports of its two subcommittees to develop PCORI guidance documents, peer-reviewed publications, or both. Dr. Evelyn Whitlock, PCORI's Chief Science Officer, described PCORI's research framework and funding priorities. CTAP discussed ways to contribute to PCORI's scientific goals, including serving on study advisory committees, giving advice on specific issues in specific trials, and answering staff questions about common issues in ongoing trials. CTAP learned about PCORI's new portfolio management information system and the reports it could produce, and they were invited to the upcoming PCORI annual meeting. A discussion focused on the incorporation of draft methodology standards developed by the Recruitment, Accrual, and Retention Subcommittee into PCORI's Methodology Report, and CTAP identified priority topics to address in the coming year.

## Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials April 14, 2016 Meeting
- Subcommittee on Recruitment, Accrual, and Retention
- Subcommittee on the Standardization of Complex Concepts and their Terminology
- PCORI Methodology Report

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

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## Welcome

Dr. Anne Trontell, Associate Director in the Clinical Effectiveness Research Program at PCORI, welcomed the new members to this panel. She explained that CTAP advises PCORI on research questions, designs, or protocols, and it serves as a resource for technical questions that arise during conduct of this research. CTAP has three ad hoc subcommittees:

- Subcommittee on Recruitment, Accrual, and Retention (RAR)
- Subcommittee on the Standardization of Complex Concepts and their Terminology (SCCT)
- Post-Award Expert Subcommittee

CTAP member suggestions included a call for the panel to help increase PCORI's visibility and help researchers understand the difference between randomized controlled, observational, and pragmatic trials.

## CTAP Guidance Documents and Publications

CTAP can potentially develop two types of products describing its advice:

- A PCORI guidance document published on the PCORI website (see PCORI's guidance on research in rare diseases as an example)
- A peer-reviewed publication

PCORI is finalizing its publications policy for PCORI-associated authorship in a peer-reviewed publication. If a publication by PCORI staff or a member of one of its advisory or governance bodies could be construed as expressing a PCORI viewpoint, the draft manuscript must be reviewed and cleared by PCORI's Scientific Publications Committee. The draft document on pragmatic trials developed by the SCCT Subcommittee, which represents input from PCORI staff and CTAP members, might be a good test case for the new policy.

The SCCT Subcommittee would prefer publishing a document that represents agreement between CTAP and PCORI on practical guidance for readers to meet PCORI's expectations for pragmatic trials. Such a paper ideally would enhance the visibility and impact of PCORI's portfolio of pragmatic trials.

## Welcome from PCORI's Chief Science Officer

Dr. Evelyn P. Whitlock, PCORI's Chief Science Officer, described the PCORI research framework. PCORI's Board of Directors established five national priorities for research, but in the next phase, PCORI needs to function as a coherent and integrated scientific program in executing its research strategies. The institute wants to produce applicable evidence to support the move from understanding to implementing what works in the US healthcare system and transferring these approaches into common practice to improve patient-centered outcomes. PCORI is also synthesizing evidence that is not up to date or not well disseminated. In addition to its broad funding for investigator-initiated studies, PCORI has targeted funding for studies on specific topics and funding for pragmatic clinical studies.

CTAP recommendations for PCORI were to issue a funding announcement on research methodologies to achieve PCORI's patient-centered, outcome-improvement goal and to leverage other supplemental funding mechanisms to assess how well PCORI-funded primary research addresses PCORI's broadest

goals. CTAP could assist PCORI by answering PCORI staff questions to the panel and giving annual reports to the Methodology Committee.

## Future Directions and Priority Setting

Dr. Trontell noted the mutual interest of CTAP and PCORI in establishing annual goals for CTAP. CTAP can offer advice as a deliberative advisory group whose input is considered in PCORI decisions and actions, through subcommittees or working groups that articulate a PCORI viewpoint or scientific recommits, and as consultants to specific PCORI research studies. CTAP members may serve on study advisory committees (SACs) for large pragmatic or targeted clinical trials or provide advice to clinical studies on specific issues. Through these two types of activities, CTAP members can identify questions and issues to share with CTAP.

PCORI staff have identified several questions based on issues that are arising in ongoing clinical trials that might benefit from CTAP input. Examples are:

- How can outcomes be ascertained most appropriately?
- Are there times when changes might be warranted to a study's protocol, analysis, plan, outcomes, or other key study features after a study has been initiated?
- Is PCORI using the right milestones to monitor trials so that it can anticipate, detect, and mitigate risks of study delay or compromise?
- What are criteria or principles for making trade-offs between pragmatic versus tightly controlled study designs that can affect internal and external validity?
- How should the variability of standard of care or usual care in trials be handled?
- What are appropriate measures and benchmarks based on aggregate data from all funded clinical trials for PCORI to use in evaluating the performance of its funded clinical trials?

CTAP offered the following recommendations:

- PCORI staff should identify and prioritize issues that would benefit from the panel's advice.
- A CTAP subcommittee might be able to answer the questions in Dr. Trontell's list, and it could develop a publication or guidance document.
- CTAP might share its responses to questions about trials with both PCORI and the public.
- CTAP could identify a methodological question and assemble possible solutions based on existing evidence for a guidance document or for submission to the Methodology Committee for consideration as a potential PCORI methodology standard.
- CTAP's input should go beyond studies that have already been funded and include guidance to support future studies.
- CTAP might have some opportunities to weigh in during the review process, but its major focus should be on funded trials.
- PCORI staff might provide a "quick pulse" of what is happening in general in PCORI's clinical trials portfolio at every CTAP meeting.

## Post-Award Management of Targeted and Pragmatic Clinical Trials

PCORI has developed a new research portfolio management information system that will support research management at all stages. This system integrates pre-award, post-award, peer review, dissemination, contractual, and financial activities. The new system, which applicants will begin using in January 2017, provides dashboards and reports, including reports on monthly recruitment overall and by site, individual activity status, and screening and cumulative accrual by site.

CTAP suggested that the reports include comparisons of target enrollment with actual enrollment and data on dropouts and numbers of individuals screened who were deemed eligible for the study. The RAR Subcommittee would like data on numbers of trials that are having recruitment, accrual, or retention difficulties. Other suggestions were to collect perspectives on studies from their principal investigators (PIs) to identify the top barriers to implementation of pragmatic trials, and help decide what to do when the reports show that a study is falling behind.

## PCORI Annual Meeting Update

Dr. Trontell encouraged CTAP members to attend the upcoming PCORI annual meeting on November 17–19, 2016, in National Harbor, Maryland. The meeting will feature several plenary sessions of potential interest to CTAP as well as concurrent sessions led by CTAP members. CTAP recommended that PCORI use this venue to capture information from PIs on their needs.

## Update on the Work of the RAR Subcommittee

Dr. Jason Gerson, Senior Program Officer in the CER Methods Program at PCORI, explained that to address gaps in the PCORI Methodology Report, the RAR Subcommittee came up with four draft standards that it proposed for incorporation into the next version of the PCORI Methodology Report. The Methodology Committee decided that three of these draft standards align well with existing standards, and it will fold the language from the RAR Subcommittee into these standards. The committee did not think that the informed consent issues at the core of proposed standard RAR-2 were suitable for a methodology standard because of existing guidance from regulatory bodies.

The RAR Subcommittee is pleased that the next version of the Methodology Report will incorporate some of its proposed language, but it had hoped that its suggested standards would become new standards. Although a great deal has been written about the informed consent document, little information is available on how to ensure that the informed consent process is conducted appropriately or about the human capital required. A CTAP guidance document might be an appropriate way to address the issues raised in RAR-2.

## Future Directions: Prioritized Activities

### Most Important Issues for CTAP to Address

CTAP members reviewed the results of an electronic survey they had taken earlier in the day to prioritize potential CTAP activities for FY 2017. In the survey, CTAP members ranked the following candidate activities from most to least valuable (with the most valuable listed first):

1. Assuring that study adjustments (to the protocol, analysis plan, etc.) that arise during study conduct do not compromise the validity of study findings
2. Actionable criteria or principles for use in merit review and scientific oversight on striking the right balance between trade-offs in pragmatic implementation designs and tightly controlled study conduct as they affect internal and external validity
3. Outcomes ascertainment issues, including when to consider the need for adjudication or for blinding of participants

### Impact of CTAP's Activities

A CTAP member asked how PCORI could implement recommendations coming from CTAP. Dr. Trontell said that in addition to weighing CTAP advisory opinions in its actions, PCORI may work with CTAP to develop guidance documents for widespread dissemination. Such guidance documents would serve as useful advisory references that would be distinct from the required standards promulgated by the Methodology Committee. CTAP members may also express or publish their recommendations independently without attribution to CTAP or PCORI.

PCORI will develop a list of issues of interest to CTAP that are high priorities for PCORI. CTAP has the opportunity to change the science of how PCORI clinical trials are conducted and to make a huge contribution to the field.

### Most Engaging/Interesting Topics to Address

Dr. Trontell asked each CTAP member to identify the most exciting or engaging topics for the panel to work on to help PCORI. Suggestions were as follows:

- Balancing internal and external validity in pragmatic trials based on case studies of actual funded pragmatic trials and the complexities encountered
- Patient-centered informed consent based on what patients want from the consent process and how to involve them in developing consent materials that are sensitive to their needs
- PCORI's criteria for patient-centered trials, including informed consent requirements, and for pragmatic trials, making clear that studies that meet these criteria have a better chance of being funded
- Difference between pragmatic and explanatory trials
- Issues pertaining to the entire spectrum of clinical trials, from beginning to end
- What makes PCORI's funded patient-centered research different from the research funded by the National Institutes of Health, corporations, and others
- Lessons learned from PCORI-funded clinical trials
- Best practices for sharing clinical trial results (both interim and final) with participants