

Advisory Panel on Clinical Trials Meeting Summary

Overview

On May 28, 2015, the PCORI Advisory Panel on Clinical Trials (CTAP) held its fifth meeting in Washington, DC.

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.

First, the panel was given a report from its three subcommittees: Subcommittee on Recruitment, Accrual, and Retention and its finalized list of tasks for the next 12–18 months; Subcommittee on the Standardization of Complex Concepts and their Terminology and its draft document characterizing pragmatic clinical trials; and Subcommittee on Post-Award Projects, which functions as a pool of experts available to PCORI program staff to consult on individual funded projects on an ad-hoc basis. The panel then discussed methodology standards for clinical trials and several areas that they would like to consider as standards for eventual recommendation to the Methodology Committee. To get started, the committee discussed study blinding and data management plans. The panel also commented on and proposed revisions to PCORI's draft DSMP policy. Finally, the panel was given presentations on PCORI's pre-award methods consultation and trial simulation and response-adaptive trials.

Related Information

- [About this Advisory Panel](#)
- [Meeting Details and Materials](#)
- [Advisory Panel on Clinical Trials January 14, 2015 Meeting](#)
- [CTAP Subcommittees: Scope of Work](#)
- [PCORI Methodology Report](#)
- [PCORI Funding Announcement: Large Pragmatic Studies to Evaluate Patient-Centered Outcomes](#)

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

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Reports from Subcommittees

Subcommittee on Recruitment, Accrual, and Retention (RAR)

Margo Michaels explained that a top priority for the subcommittee is to add definitions of, and practices related to, patient-centered RAR in the PCORI methodology report for clinical effectiveness research (CER; available in the *PCORI Methodology Report*). Over the next 12–18 months, the subcommittee will also advise on the development of a toolkit for PCORI staff who monitor funded awards. Finally, subcommittee members will be invited to serve on the Post-Award Subcommittee to assist Program Officers in ensuring appropriate RAR practices in PCORI-funded research projects.

Michaels recommended a new principle to have clinical trial recruitment by healthcare providers incorporated into their standard care delivery processes. The aspirin trial being done in PCORnet will serve as a test case of online recruitment systems built upon standard care processes and record keeping, and will inform PCORI's ability to conduct efficient trials using such an infrastructure.

Post-Award Subcommittee

Anne Trontell, MD, MPH, reported that the Post-Award Subcommittee addresses methodological designs of applications that have undergone PCORI's merit review process and provides technical advice to PCORI program staff.

Advisory Panel on Clinical Trials (CTAP) members offered the following recommendations regarding ways for the subcommittee to report back to the full panel:

- Provide details on the issues with PCORI-funded trials for which they have been consulted
- Share information with CTAP on methods issues that arise in funded projects and require assistance from the subcommittee
- Report how frequently the subcommittee meets regarding a certain research study and how to balance the subcommittee's roles and the role of PCORI's Merit Review

Standardization of Complex Concepts and their Terminology

Dr. Merrick Zwarenstein reported that this subcommittee's first task was to reach consensus on key terms (such as "pragmatic") used in PCORI materials based on reviews of relevant funding announcements and scientific papers. Dr. Zwarenstein asked for CTAP's feedback on the subcommittee's first product, a draft review on the definition of pragmatic randomized controlled trials.

CTAP members responded with the following comments and suggestions regarding the document and its future dissemination:

- Encourage applicants to minimize exclusion criteria and maximize study generalizability
- Recommend that applicants consult the new [PRECIS-2 tool](#) to design pragmatic trials that are fit for purpose (but make clear that PCORI will not expect all pragmatic trials to have high scores in all nine PRECIS-2 domains)
- Ask applicants to demonstrate that their trial design is the most appropriate for answering a research question that is relevant to patients, practitioners, and policy makers

- Address the tradeoffs that might be required in pragmatic trials, such as conducting studies efficiently and cost-effectively in real-world settings but without some of the advantages (such as minimization of biased results) of randomized clinical trials
- Instruct investigators planning to use a “usual care” comparator group to define “usual care” carefully and precisely
- Discuss how to interpret the results of comparison studies showing that neither of two treatments is superior to the other
- Develop a shorter version of the document for posting on the PCORI website
- Make the document available to all potential PCORI applicants

The document will be further circulated to the CTAP for one last chance to provide written comments before the subcommittee works on incorporating them into a new version.

Methodology Standards for Study Designs Using Clusters

Dr. David Hickam, Program Director for Clinical Effectiveness Research at PCORI, described the process that PCORI staff and the [Methodology Committee](#) used to develop 11 draft methodology standards for studies that use a cluster design.

Recommendations from CTAP included the following:

- Instruct applicants to justify the level of clustering (e.g., individual, physician, or health system) they plan to use
- Work with the RAR subcommittee to address informed consent and ethical issues
- Avoid recommending specific approaches (such as stratified randomization in Standard 8) to a particular challenge in study designs that use clusters
- Address gaps in general methodology standards that apply to all trials, not just clustered designs (for example, ethics, informed consent, recruitment/accrual/retention, adherence, blinding, and others).
- Clarify which standards apply to cluster designs and which apply to all research studies.

CTAP also raised the following questions:

- Do study designs that use clusters need standards for issues that are not addressed in standards for non-clustered studies?
- Blinding might not be appropriate in cluster trials conducted in usual clinical care settings, so should the standards address blinding?
- Should the draft standards be distributed for public comment, given the tight timeline for completing the document?

Suggestions for new standard topics to be proposed by the CTAP included:

- Recruitment, accrual, retention (including consent issues and electronic recruitment)
- Adherence/non-compliance
- Blinding
- Equivalence designs

- Data management plans (including the use of electronic medical records)
- Limitations of commonly used statistical analysis methods, justification of inclusion/exclusion criteria used in trials, and benefit-to-risk modeling

Some topics might be the focus of studies funded under the [Improving Methods for Conducting Patient-Centered Outcomes Research](#). Additionally, CTAP members commented that the current informed consent process has many weaknesses, including the use of forms that are not understandable, and would be an appropriate topic for standards development by the PCORI [Advisory Panel on Patient Engagement](#).

Methods Consultation Panel for Pragmatic Clinical Studies: Evaluation and Recommendations

Dr. Laura Forsythe, Senior Program Officer at PCORI, and Lauren Fayish, Program Associate, compared the outcomes of application reviews through PCORI's Merit Review to those of the reviews through the Methods Consultation for pragmatic clinical studies in PCORI's 2014 Spring and Fall funding cycles. The evaluation showed that the Methods Consultation identified methodological weaknesses beyond those found by PCORI staff, Merit Review, or the initial peer review; the scope and purpose of the MCP's reviews and consultations need to be clarified; and modifications to the merit review process could enhance reviews of methods in applications.

CTAP members offered these suggestions:

- Ask the Methods Consultation Panel (MCP) to assess RAR plans
- Consider ways to streamline or combine the MCP review, MCP consultation, and Post-Award subcommittee review processes
- Use common weaknesses identified in merit and methods reviews to inform guidance for applicants
- Determine whether different layers of review have consistent findings

Trial Simulation

Dr. Jason Connor, a CTAP member, explained that trial simulation allows investigators to test many aspects of clinical trial design when planning a trial. Trial simulations can be performed by any statistician who works on clinical trials. These simulations can help assess the implications of various accrual rates and recruitment patterns, assess stratification options, conduct sensitivity analyses, and compare the effects of different retention rates.

Panel members supported the merits of trial simulation, which could prevent trials with weak designs from being funded. If investigators lack access to the statistical expertise required for trial simulations, the sophisticated simulation tools are available free online. CTAP members recommended that PCORI require applications to describe any simulations conducted and that PCORI distribute examples of simulations that might be appropriate for different types of trials. PCORI can consider supporting such resources in the future.



PCORI's Draft Data Safety and Monitoring Plan (DSMP) Policy

Dr. Jason Gerson, Associate Director for CER Methods and Infrastructure at PCORI, presented PCORI's draft DSMP policy. The policy indicates that as a funder, PCORI wants to ensure that awardees keep PCORI informed of research progress in a timely way, including recommendations and decisions stemming from DSMP activities.

CTAP suggestions included:

- Indicate that PCORI will not have access to raw study data or attend closed data safety and monitoring board (DSMB) meetings
- State that, unless an institutional review board (IRB) requires more stringent monitoring,
 - If the intervention being studied has Food and Drug Administration (FDA) approval, investigators need to send data to the DSMB only on adverse events that lead to treatment discontinuation, dose changes, or death.
- Require awardees to provide training to nonscientists (e.g., patients and family members) who are members of a DSMB.

Several panel members supported permitting DSMB members to view unblinded data from the trials they monitor. They noted that investigators do not participate in DSMB meetings and therefore would not have access to unblinded data while the study is ongoing. Others suggested that PCORI allow DSMBs to determine whether they should have access to unblinded data. CTAP also discussed the need to encourage awardees to report adverse events to the DSMB, IRB, or FDA, with PCORI notified of any significant reports.

FY16 Budget

Dr. Kara Odom Walker, Deputy Chief Science Officer at PCORI, explained that the draft CTAP budget for fiscal year 2016 includes funds for three CTAP meetings (in Fall 2015, Winter 2016, and Spring 2016) and four landscape reviews. The budget will be finalized in the next few weeks.

Recap and Next Steps

Next steps to accomplish before the next CTAP meeting are:

- The Subcommittee on the Standardization of Complex Concepts and their Terminology will produce and refine the document describing pragmatic randomized controlled trials.
- The Subcommittee on Recruitment, Accrual, and Retention will start developing new methodology standards and review PCORI's template interim progress report and draft SOP on Project Remediation and provide comments.
- CTAP and PCORI will develop a statement of work for contractors to conduct landscape reviews on methodology standards on blinding and data management plans.
- PCORI staff will finalize the DSMP policy and circulate the final version to CTAP.
- PCORI staff will explore trial simulations and platform trial methods and their potential applications to PCORI's trial-focused research.