Advisory Panel on Clinical Trials
Meeting Summary

Overview

On April 14, 2016, the PCORI Advisory Panel on Clinical Trials (CTAP) held its seventh meeting in Arlington, Virginia.

CTAP's nine members include patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics. The panel also includes 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 learned about PCORI's plans for its Publications Committee and suggested ways to assess PCORI's contributions to research. CTAP also heard an overview of PCORI's plans to improve the quality of its research applications and make the application process easier for investigators. Panel members discussed plans to define different types of PCORI work products and their approval processes. CTAP provided input on PCORI's clinical trials portfolio, the ongoing revision of PCORI's draft open-science policy, and the appropriate uses of N-of-1 study designs. Another discussion topic was the potential uses of the reports of CTAP subcommittees on recruitment, accrual, and retention and on complex concepts to inform new methodology standards. The panel also weighed in on how it might best contribute to methodology standards development in the future.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials October 26, 2015 Meeting
- CTAP Subcommittees: Scope of Work
- PCORI Methodology Report
- The Consort Group
- PCORnet

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

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Recap and Reexamination of Opportunities for Impact

Dr. Evelyn Whitlock, Chief Science Officer at PCORI, discussed PCORI's plans through 2019, when PCORI's current funding period ends. PCORI will accelerate its opportunities for funding with a focus on large pragmatic clinical studies on high-priority topics. At the same time, PCORI will seek to improve the quality of the applications it receives while making it easier to submit applications to PCORI. PCORI is also upgrading the instructions for merit reviewers and enhancing its post-award interactions with applicants. PCORI's Publications Committee will establish procedures for the peer-review process to approve the publication of funded research findings as well as PCORI documents addressing different types of PCORI policies, advice, or recommendations.

CTAP members suggested that PCORI encourage investigators to use study designs that are likely to affect health service delivery. To assess its contributions to research, PCORI could determine whether the typical trials funded by the National Institutes of Health (NIH) have the characteristics (e.g., high level of applicability to health service delivery) of PCORI-funded studies.

CTAP Activities and Work Products—Past, Present, and Future

Dr. Anne Trontell, Senior Program Officer in the Clinical Effectiveness Research Program at PCORI, listed examples of CTAP's invaluable input into PCORI's work. CTAP has provided advice on PCORI policies under development and recommendations to the Methodology Committee about methodology standards that are relevant to clinical trials. CTAP Subcommittees on Recruitment, Accrual, and Retention (RAR) and on Standardization of Complex Concepts and Their Terminology (SCCT) have developed draft reports, and next steps for those documents need to be determined.

The Publications Committee will define different types of PCORI publications and create a process for approving these products. Documents can articulate PCORI policies and practices through the following types of products (whose definitions are being finalized):

- Policies: rationale or framework of PCORI's work
- Guidance documents: interpret policies or governance in a given context or document committee advice or decisions
- Guidelines: non-mandatory suggestions of best practices or clarifications of a policy or process

PCORI now requires large pragmatic and targeted clinical studies to establish study advisory committees (SACs) after they receive an award. SACs will be made up of patients and families, clinicians, payers, and representatives of health plans. These groups may also include scientific and methodological experts, such as CTAP members or subcommittee members. SACs will help investigators refine study questions, outcomes, and protocols.

Only the Methodology Committee may approve methodology standards, and CTAP may recommend new methodology standards to this committee. CTAP members recommended that the Methodology Committee clarify its requirements for establishing a methodology standard in consultation with the Publications Committee.

PCORI's Clinical Trials Portfolio

Dr. Dave Hickam, Program Director for Comparative Effectiveness Research (CER) Methods at PCORI, provided an overview of the 149 clinical trials that PCORI has funded to date, which represent slightly more than half of all PCORI-funded studies (not including studies on improved CER methods). Most of these trials had a budget of less than $2 million, although a few had budgets of $5 million or higher. These trials address a broad range of clinical conditions, the most common of which are mental/behavioral health, cancer, and respiratory diseases. The studies also use many different comparators, especially usual care or, for behavioral studies, another behavioral intervention. The most common outcomes in PCORI's randomized controlled trials (RCTs) are health status and quality of life, health behaviors, and treatment outcomes. Approximately one-quarter of the RCTs use a cluster design, and some use a pragmatic design.

CTAP recommended that future overviews of PCORI's RCT portfolio indicate whether the studies are randomized to individuals or are clustered, their settings, and whether they have more than two treatment groups. Pharmaceutical companies rarely fund studies of more than two interventions, and such studies produce robust information. Scores on the problem areas in portfolio reviews would also be useful. Another suggestion was to use Pragmatic Explanatory Continuum Indicator Summary (PRECIS) and PRECIS-2 to assess the generalizability of RCT findings and the maturity of the interventions studied. PCORI might consider funding studies that randomize nonresponders to the treatment they did not respond to or to a new treatment—only four of these trials have ever been done.

Application Enhancement

Dr. Whitlock described changes that PCORI will roll out in its application process over the next two funding cycles. Some of the recurrent issues that PCORI hopes to address with these changes are the need for well-justified sample-size calculations along with appropriate assurance that the study will be able to recruit the target sample and that its design can be implemented. PCORI will send CTAP more specific guidance on how it can best provide input on these proposed changes.

The RAR Subcommittee is addressing recruitment assurance, and it proposes to create language for PCORI's funding announcements. CTAP members pointed out that one way to ensure "honest" sample-size calculations is to ask investigators to identify which of the data used for these calculations come from solid evidence and which components are based on educated guesses. The expected event rates that investigators calculate for cardiovascular outcomes trials might be a good model for sample-size calculations, and the substantial amount of data on risk might also be useful. Instead of asking investigators to provide a single sample-size estimate, PCORI could ask for a range of sample sizes and the probabilities of each. PCORI could facilitate consultation of clinical reviewers with statistician reviewers prior to review meetings to synergize their respective areas of expertise.

Recognition of Panelists

Dr. Hickam thanked three members whose terms on CTAP were ending: Sanford Jeames, Dr. Anne McTiernan, and Dr. Robert Temple. All have contributed their unique insights to the work of the panel. PCORI has solicited applications for new CTAP members.

Open Science Update

Jason Gerson, Senior Program Officer for CER Methods at PCORI, provided an update on the activities of the PCORI Open Science Working Group, which is revising PCORI's draft open-science policy and developing recommendations for operationalizing this policy. The group has consulted leading national experts about the challenges of implementing an open-science policy. PCORI has also formed an expert advisory group, and it would welcome CTAP members who would like to join. The policy will articulate PCORI's commitment to open science and its expectations for applicants, awardees, and other stakeholders. PCORI plans to issue this draft policy for public comment in the near future. PCORI will also pilot-test the policy using different data repositories to identify the critical repository features for depositing and sharing data, the resources required to prepare data for sharing, and how to address the challenges of complying with the policy. PCORI will revise its application guidelines and research plan template to incorporate its open-science policy and will require applicants to submit a data-management and data-sharing plan.

Recommendations from CTAP were for PCORI to collaborate with existing open-science efforts, provide clear time frames for sharing study data with the public (possibly after publication of the primary journal article), issue a pilot data request, and develop a process for reviewing the scientific merit of data published from PCORI studies. Another suggestion was for the PCORI Publications Committee to establish a process for ensuring that proposed uses of PCORI-generated data are appropriate. Alternatively, PCORI could encourage journals to require authors to acknowledge their use of PCORI data for analyses not specified in the original application.

Methodology Standards for Clinical Trials

Dr. Hickam reviewed the results of a survey of CTAP on the relevance to clinical trials of each PCORI methodology standard. At least one CTAP member deemed the standards for studies of diagnostic tests, data registries, and causal inference methods to be not relevant to clinical trials. The standards in most of the other 12 categories, including most of the cross-cutting methodology standards, were determined to be somewhat, very, or highly relevant to clinical trials. Gaps in the methodology standards include reporting of results, recruitment and retention, and fidelity of interventions. Dr. Hickam noted that the two CTAP subcommittee reports address the latter two issues.

A potential use of the survey data is to inform applicants of the most relevant standards for clinical trials, although some CTAP members believe that all applicants should pay close attention to all of the methodology standards. The survey results show that many of the methodology standards are relevant to clinical trials but that some gaps exist. CTAP members suggested considering whether the new standards for complex interventions should be expanded to all intervention studies. A potential standard for studies of interventions, regardless of whether they are complex, is that the intervention

must be well defined. CTAP members argued against developing methodology standards on reporting of results because the CONSORT group has already developed well-known standards. The next CTAP meeting should include time to discuss in greater depth the gaps related to clinical trials (including the common reasons why funded clinical trials or applications for trials are unsuccessful) in the methodology standards and how to fill these gaps. Another agenda item is overlap between clinical trials guidance from PCORnet, PCORI's National Patient-Centered Clinical Research Network, and CTAP.

Dr. Steven Goodman, Vice-Chair of the Methodology Committee, said that the committee will review and comment on the draft CTAP subcommittee reports, and it recognizes the need to address the issues in these reports. A suggestion was to schedule a joint teleconference or in-person meeting for CTAP and the Methodology Committee to discuss CTAP's potential contribution to new methodology standards on fidelity of interventions, use of the two CTAP subcommittee reports for methodology standards or other purposes, and a process for CTAP to contribute to methodology standards in the future.

N-of-1 Designs

Dr. Whitlock reported that the PCORI Board of Governors has asked for methodological input on n-of-1 designs because PCORI receives a growing number of applications for studies that use this type of design. PCORI would like input from CTAP on this issue, including the types of studies that are best suited to such designs. CTAP members commented that n-of-1 designs are appropriate for studies of rare diseases and cluster randomized studies of a health service or training program, and their use is in line with PCORI's interest in individualized medicine. Because these studies resemble crossover studies, n-of-1 designs are inappropriate in the contexts in which crossover studies are inappropriate. Although blinding is desirable, it is not essential for studies of low-cost interventions that have no adverse effects. Standards on n-of-1 studies include those of the CONSORT group, Standard Protocol Items: Recommendations for Interventional Trials, and Agency for Healthcare Research and Quality.

Advisory Panel on Clinical Trials Charter Update

Dr. Hickam reported that PCORI is reviewing the charters of all of its advisory panels and will ask CTAP for input on proposed changes in the near future.

Panel Discussion

Dr. Elizabeth Stuart, CTAP Chair, and Dr. John Lantos, CTAP Co-Chair, asked panel members to propose activities for the next year, discuss whether subcommittees are the best way to generate work products, and identify agenda items for the next CTAP meeting. A PCORI suggestion was to ask the panel to weigh in on processes or policies for resolving common difficulties in funded trials. CTAP member ideas were to include time at each meeting for updates on the issues discussed at the previous meeting, distribute presentations in advance of each meeting, and establish goals for the year based on PCORI's needs.

Potential agenda items for the next in-person CTAP meeting are:

- Engagement in development of new methodology standards
- Clinical trials issues requiring new standards
- Feedback on the SACs
- Contributions to PCORI funding announcements
- Next steps for the two CTAP subcommittee reports