Advisory Panel on Clinical Trials Meeting Summary

Overview

On October 26, 2015, the PCORI Advisory Panel on Clinical Trials (CTAP) held its sixth meeting in Washington, DC.

CTAP's nine members include patients, clinical trialists, biostatisticians, epidemiologists, and an expert in the ethical dimensions of clinical trials. 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 agreed on a PCORI definition of "clinical trial" by revising the National Institutes of Health definition. The Subcommittee on Recruitment, Accrual, and Retention (RAR) received CTAP feedback on five proposed RAR standards. The CTAP offered suggestions on the draft definition and characterization of "pragmatic clinical trials" by the Subcommittee on the Standardization of Complex Concepts and their Terminology. The Post-Award Subcommittee reported results from a survey evaluation of program officers' experiences with utilizing the subcommittee's expertise. CTAP discussed new methodology standards for clinical trials and how to contextualize the existing PCORI methodology standards for clinical trials. The panel also heard a summary of the Pragmatic and Large Clinical Studies Summit. CTAP provided feedback on PCORI efforts to monitor large pragmatic clinical trials, plans to increase the use of adaptive designs in pragmatic trials, as well as PCORI's data safety and monitoring plan policy.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials May 28, 2015, Meeting
- CTAP Subcommittees: Scope of Work
- PCORI Methodology Report
- National Institutes of Health Definition of "Clinical Trial"
- 2015 PCORI Annual Meeting

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

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"Clinical Trial" Definition

Dr. Jason Gerson, Associate Director for Comparative Effectiveness Research Methods and Infrastructure at PCORI, explained that PCORI lacks a standard definition of "clinical trial." The National Institutes of Health (NIH) has the following definition: "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

CTAP members recommended revisions to the NIH definition, as follows:

- The term "participants" is more precise and less objectionable than "human subjects." This is a patient-centered term that underscores the importance of partnership with the research team.
- PCORI-funded studies can be randomized at the individual or cluster level.
- PCORI encourages but does not require the use of randomized trial designs
- The interventions in PCORI studies are broader than those defined by NIH.

The following definition was proposed as PCORI's definition: "A research study in which one or more participants or groups are assigned by randomization or other predefined strategies to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related outcomes."

Reports from Subcommittees

Subcommittee on Recruitment, Accrual, and Retention (RAR)

Margo Michaels, the subcommittee chair, proposed the following five RAR methodology standards:

1. Ensure integration of research into delivery of care, programs, or services
2. Ensure that the proposed study meets an unmet need of those with the disease or condition
3. Address participants' knowledge and behavior needs throughout accrual and recruitment
4. Provide adequate support to encourage ongoing participation and retention
5. Form partnerships to increase referrals and inquiry

CTAP members offered some feedback, including pointing out the need for a higher degree of specificity and clearer indications of each of their goals, and suggesting that one RAR standard incorporating the goals of each of the standards may be a more efficient approach, as they noted some of the standards have overlapping intent.

Standardization of Complex Concepts and their Terminology

Dr. Merrick Zwarenstein, the subcommittee chair, asked for the panel's input regarding some unresolved issues pertaining to the subcommittee's definition and characterization of "pragmatic clinical trials" (pRCTs). The issues raised included the mention of the term "usual care," the size of pRCTs due to "noise" (i.e., heterogeneous patients, practice patterns, etc.), the appropriateness of blinding, and a variety of study designs, including equivalence and noninferiority designs.

CTAP members provided some suggestions, including replacing "usual care" with "community care" or "delivered as part of the flow of care," asking pRCT investigators to address treatment heterogeneity,

focusing on issues that are specific to pRCTs (as opposed to all clinical trials), expanding the focus to clinical interventions and measurement of individual patient outcomes.

Post-Award Expert Subcommittee

Dr. Jason Gerson provided an update on the work of the subcommittee by presenting results from a survey asking program officers to provide information on the nature and logistics of their utilization of the pool of experts, and asking them to evaluate the process. This subcommittee is made up of experts available on an ad hoc basis to address program staff questions related to monitoring funded projects. The results showed that the need for the consultation was to finalize, refine, or amend a proposed protocol or to assist with a project that was not meeting its timeline. The experts were asked to address concerns regarding the validity of endpoints, feasibility of recruitment, and generalizability, among other issues. Program officers noted the following benefits of the CTAP subcommittee: the usefulness of concrete, actionable recommendations, the opportunity for investigators to obtain technical expertise from leading methodologists, and the promotion of thoughtful discussions between program officers and awardees. Survey results also listed some proposed process improvements, including the need to clarify roles of experts and the need to define more clearly the expected time commitment of each consultation.

CTAP members found the report useful and made a few suggestions regarding future reports on the work of the subcommittee, including providing a forum for the experts to discuss the studies they were consulted on with one another, inviting program officers and investigators to discuss their experiences at a future CTAP meeting, surveying the investigators about their experience of the process, and letting the investigators know that this is an available resource if they lack a particular type of expertise on their research team. CTAP members also suggested that PCORI staff use feedback from the consultations to identify broad issues that PCORI needs to address.

New Methodology Standards for Clinical Trials

Dr. Elizabeth A. Stuart, the CTAP chair, led this session during which three main tasks were discussed. The first was the identification of topics for new methodology standards for clinical trials development. CTAP members concluded their discussion from their Spring 2015 meeting on the subject of blinding, and discussed additional topics for methodology standards development, including statistical methods for monitoring adherence, heterogeneity, adherence, intensity of follow-up efforts, sustainability of interventions, and inclusion/exclusion criteria. Members suggested evaluating PCORI-funded trials to assess the impact of blinding and other issues raised during this discussion, by collecting and analyzing data on how investigators are justifying addressing these aspects of their trial in different contexts.

The second was the contextualization of existing PCORI methodology standards for clinical trials. A survey of CTAP members showed broad agreement on which existing standards are most relevant to clinical trials. Because the PCORI Methodology Committee is currently in the process of revising the standards, CTAP members and PCORI staff agreed that a second survey will be sent out to the panel with the revised standards and an open text question for additional language that would expand or clarify

what already exists in the standards for the applicability to clinical trials. CTAP members proposed the development of a document that would briefly explain the contexts in which the existing methodology standards are relevant to clinical trials.

The third topic of discussion was the possible endorsement of other existing methodology standards, such as the CONSORT statement.[1]

The three tasks will be laid out to the Methodology Committee by Dr. Liz Stuart at their November 23 meeting for input.

Pragmatic and Large Clinical Studies

Dr. Anne Trontell, Senior Program Officer for Clinical Effectiveness Research at PCORI, provided some updates regarding the Pragmatic and Large Clinical studies portfolio. She provided an overview of the Pragmatic and Large Clinical Studies summit, which was part of PCORI's annual meeting, and which brought together the principal investigators, team members, and stakeholders of 19 PCORI-funded clinical studies. A public session focused on clinical study conduct and operations, including common reasons for trial failure. A closed session for investigative teams was designed to foster a collaborative community of practice. Most participants indicated that they would like to continue meeting regularly face to face or by webinar, and PCORI will establish a virtual discussion group for these investigators.

CTAP suggestions included to: establish an advisory committee for the pragmatic studies community of interest, collaborate with the NIH Collaboratory, and receive updates at CTAP meetings on overarching issues that arise in large and pragmatic clinical studies

Dr. Trontell explained that efforts to monitor large pragmatic clinical trials are evolving. Science and engagement staff meet bimonthly to develop data-monitoring systems and procedures for funded projects. Staff are also exploring the use of an external clinical trials system and identifying core milestones for studies. Plans include providing a dashboard and other study progress and status reports to CTAP and PCORI governing bodies, asking CTAP for advice on challenging questions, and nominating topics for development of guidance or standards by CTAP. CTAP members supported these plans.

Clinical Trial Designs at PCORI

Dr. Bryan Luce, consultant at PCORI, reported that although PCORI encourages submissions of pragmatic trials with adaptive designs, PCORI has received few, if any, such submissions. Few trialists or statisticians have relevant expertise, and investigators might be concerned that PCORI merit reviewers would not appreciate such approaches. To encourage the use of these novel designs, PCORI is more explicitly encouraging these designs in its funding announcements, integrating a cadre of trial design experts, the PCORI Adaptive Trial Expert Research Network (PATERN), with the PCORI methods consultation service, and funding consultation and redesign efforts for selected principal investigators who have submitted applications with high scores.

[1] 1. K. F. Schulz, D. G. Altman, D. Moher, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.

CTAP members suggested including representatives of advocacy organizations and of underrepresented patient groups in PATERN. They also encouraged PCORI to consider adaptive designs at the letter-of-intent stage to prevent the need to revise proposals that investigators have invested a lot of effort in developing.

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

Dr. Gerson summarized recent revisions to PCORI's draft DSMP policy (some of them based on previous comments from CTAP members), including the requirement for every data safety and monitoring board (DSMB) member to be independent, the presumption that PCORI staff will not attend closed and executive sessions of any DSMB, and the need for DSMBs to have access to unmasked data as the DSMB deems appropriate.

Recap and Next Steps

Dr. Stuart identified the following next steps for PCORI staff:

- Revise the NIH definition of "clinical trials" for PCORI's purposes and circulate it to the panel for final review
- Prepare an updated report on the Post-Award Expert Subcommittee for the next CTAP meeting
- Facilitate the presentation of the CTAP's proposed plans for developing new methodology standards for clinical trials to the Methodology Committee

Next steps for CTAP members are as follows:

- The RAR Subcommittee will revise the RAR standards based on CTAP feedback.
- The SCCT subcommittee will revise its definition and characterization of pRCTs.
- CTAP will provide input to PCORI staff on ways to contextualize the existing methodology standards for clinical trials.