Advisory Panel on Clinical Trials
Meeting Summary

Overview

On March 30, 2017, the PCORI Advisory Panel on Clinical Trials (CTAP) held its ninth meeting in Washington, DC.

CTAP's 10 members include patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics along with 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 first half of the meeting focused on recruitment, accrual, and retention (RAR) in PCORI-funded clinical trials. CTAP responded to presentations on recruitment progress in PCORI trials and sessions of the 2016 PCORI annual meeting on planning for successful RAR and related challenges. A CTAP discussion of best practices for RAR included a recommendation to embed studies comparing different RAR approaches into PCORI-funded trials. After recognizing three departing CTAP members, CTAP learned about PCORI's funded research in 2016 and plans for 2017. The panel responded to updates on PCORI's cluster-designed trials, to potential implications for PCORI related to changes to the Common Rule on human subjects protection, and PCORI's developing initiatives on publishing study findings and data sharing. The panel advised PCORI to recommend a research protocol template in response to a presentation on existing guidelines and requirements for protocols.

Related Information

- About this Advisory Panel

- Meeting Details and Materials

- Advisory Panel on Clinical Trials October 26, 2016 Meeting

- Subcommittee on Recruitment, Accrual, and Retention

- PCORI Methodology Report

- 2016 PCORI Annual Meeting

- Common Rule

- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement

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

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2016 CTAP Accomplishments and Plans for 2017

Dr. Anne Trontell, Associate Director in the Clinical Effectiveness Research Program at PCORI, reported that in 2016, PCORI successfully recruited new members to CTAP, and the committee had a fruitful discussion at its October 2016 meetings of its short- and long-term goals and activities. CTAP's RAR Subcommittee has shared patient-centered RAR principles with PCORI's Methodology Committee, which is incorporating these principles into the methodology standards associated with patient-centeredness. CTAP's Subcommittee on Standardization of Complex Concepts and Terminology (SCCT) prepared a draft document on pragmatic clinical studies.

In 2017, PCORI plans to develop guidance on pragmatic clinical studies based on the SCCT Subcommittee's report, and Dr. Merrick Zwarenstein, a CTAP member and the subcommittee's chair, will draft a companion journal commentary. The RAR Subcommittee will help PCORI develop guidance on best practices in RAR and offer advice on PCORI monitoring practices for RAR.

Recruitment Progress in PCORI Trials

Dr. Michele Orza, Senior Advisor to PCORI's Executive Director, explained that PCORI actively monitors the projects it funds. PCORI has established standardized next steps for projects facing recruitment difficulties, including asking the principal investigator for a project remediation plan when recruitment is behind schedule. PCORI would like assistance identifying benchmarks it can use to track study progress.

As of July 2016, PCORI had funded 211 projects that had initiated or should have initiated recruitment. Based on the recruitment milestones established by the investigators, recruitment was late in 43 percent of projects, on time in 28 percent, and early in 24 percent. Another 5 percent of projects were late pending initiation. The vast majority of projects with late recruitment were no more than six months behind, with PCORI aiming to have 90 percent of its studies delayed no more than six months.

CTAP suggested that PCORI:
- Publish its recruitment experience because its studies are different from those funded by industry
- Seek potential collaborations with the Recruitment Innovation Centers of the Clinical and Translational Science Awards for useful best practices to share.

RAR Issues Raised at the 2016 PCORI Annual Meeting

Know Before You Go: Planning Upstream for Successful Recruitment in PCOR and Clinical Trials

Dr. Cynthia Girman, a Methodology Committee representative on CTAP, summarized the discussion at this panel session, which she moderated during the November 2016 PCORI annual meeting. The main topics addressed were recruitment barriers and facilitators, strategies for recruitment and retention and for assessing trial feasibility and site selection, effective partnerships, and communication planning. Speakers recommended spending time at recruitment sites; including community/patient partners in the budget; using multiple communication methods; and valuing patient contributions to recruitment,

planning, and monitoring. However, they advised against sending junior staff to do on-site work, relying on flyers to recruit patients, and neglecting community partners.

CTAP suggestions to improve recruitment based on this presentation were to:
- Engage patients in RAR planning
- Track patient engagement and RAR planning
- Reach out to community physicians to address misgivings they and the public may have about participating in clinical trials

Challenges and Best Practices for Communication, Patient Recruitment, and Site Management

Allison Ambrosio, a Program Associate in PCORI's Clinical Effectiveness and Decision Science Program, explained that this session at the 2016 PCORI annual meeting was for program managers, and it focused on systems or processes used to begin and manage PCORI-funded clinical trials. The session covered when to begin a study, how much site and investigator communication is too much, what to include in communications, and how to maintain confidentiality and Health Insurance Portability and Accountability Act (HIPAA) compliance.

CTAP suggested that PCORI offer more sessions like this one to study coordinators, who need opportunities to discuss common issues with their peers. These discussions could take place at annual meetings or through blogs or teleconferences. The National Institutes of Health (NIH) research networks have communication systems for study coordinators that could serve as a model for PCORI.

Best Practice Development for RAR

During this CTAP discussion, moderated by Dr. Girman, CTAP noted that the evidence on best ways to approach potential participants in different types of studies is weak, and no formal studies have compared different RAR methods. RAR is particularly well suited to engagement from CTAP, and CTAP members are eager to contribute to PCORI activities in this area.

CTAP recommendations during this session were for PCORI to:
- Embed studies comparing the effectiveness of RAR approaches into funded PCORI trials
- Engage CTAP in all PCORI efforts to develop RAR best practices or guidance
- Ask study managers how best to support them
- Create an RAR structure that is similar to PCORI's patient-engagement rubric
- Request trial simulations with all inclusion and exclusion criteria before starting a study
- Assess criteria for site selection to ensure that all study sites have appropriate RAR capability
- Explore ways to share study results (even ones that are negative) with participants
- Thank study participants at the conclusion of the study and consider providing their individualized results along with the journal publication
- Encourage investigators to conduct "prospective post-mortems" to predict, at the design phase, all the reasons why recruitment might fail and then refine the design to try to avoid these issues

The discussion concluded with the decision to create a forum for further conversation in the reconstituted RAR Subcommittee, with the ultimate goal of the creation of a PCORI background document on best practices.

Recognition of Departing Panelists

Dr. Trontell thanked departing panel members Dr. John Lantos, Margo Michaels, and Dr. Frank Rockhold for their service on CTAP. She also thanked Jessica McCreary for her work on behalf of CTAP.

Board of Governors Recommendations on Priorities of Clinical Trial Monitoring

Dr. Evelyn Whitlock, PCORI's Chief Science Officer, reported that in 2016, PCORI funded 74 studies for a total of $293 million. To date, PCORI has invested approximately $500 million in 23 large pragmatic studies and 29 targeted studies, and has been moving toward more targeted funding opportunities since 2013. In 2016, PCORI pilot-tested several innovations that it plans to continue this year, including reposting targeted funding opportunities that did not lead to enough meritorious applications and issuing pragmatic clinical studies announcements focused on certain areas of special emphasis. Other 2016 accomplishments were the launch of PCORI's peer review and research synthesis programs and publication of three PCORI-funded studies in the *Journal of the American Medical Association.*

Recommendations were for PCORI to:
- Issue press releases when PCORI studies are published in major peer-reviewed journals
- Determine whether projects that require mitigation plans have features that would have predicted problems at the proposal stage
- Identify systemic issues encountered in the past that could be addressed systematically

PCORI's Cluster-Designed Trials

Dr. David Hickam, Director of PCORI's Clinical Effectiveness and Decision Science Program, reported that as of March 2017, PCORI has funded 47 projects that use a cluster design (i.e., a study design that assigns and compares treatment interventions at the level of patient groups rather than by individual patients). The largest proportion of cluster-design trials (43 percent) address healthcare systems interventions. Among the 18 cluster randomized controlled trials launched since 2014, 11 (61 percent) had reached their recruitment and retention goals by mid-2016, 4 (22 percent) had not, and 3 (17 percent) had retention problems.

CTAP suggestions were to:
- Share data on numbers of clusters per study with CTAP
- Schedule more time at a future CTAP meeting or webinar to discuss cluster-designed trials
- Instead of requiring a minimum number of clusters per arm, establish a standard for power analyses to ensure that if the number of clusters per arm is small, it is appropriate
- Publish intracluster correlation coefficients (ICCs) from completed cluster-designed trials for use in planning future studies
- Consider re-estimating the sample size during the trial based on the observed ICC

Implications of Changes to the Common Rule

Dr. Lantos summarized the recent revisions to the Common Rule (the federal policy on human subjects protection in biomedical research) to make informed consent forms clearer and more focused. Consent forms often do not achieve their purpose, which is to help potential participants make decisions about whether to enroll in a given study, because they are typically long and difficult to understand.

As a study funder rather than a sponsor, PCORI cedes informed consent oversight to the institution's IRB. The CTAP encouraged PCORI to consider how it could promote informed consent documents that not only meet the new requirements but make the process more patient-friendly. If PCORI considers any changes, it will seek CTAP's input.

Protocol Guidance for Awardees

Dr. Harold Sox, Director of PCORI's Peer Review Program, explained that a trial protocol describes how the clinical trial will be conducted and states how procedures will ensure participant safety and data integrity. PCORI does not have a template for protocol submissions. A systematic review of the literature published in 2006 found many protocols do not adequately describe the primary outcome, treatment allocation methods, or adverse event reporting plans. PCORI requested advice from the CTAP on whether PCORI should offer one or more guidelines for applicants to follow in developing and submitting protocols. If so, PCORI suggested potentially recommending the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement as a minimum set of elements that clinical trial protocols should address.

CTAP recommendations for PCORI were to:
- Assure all PCORI clinical trials have an adequate trial protocol
- Consult the different 2010 Consolidated Standards of Reporting Trials (CONSORT) statement versions for different types of trials when developing PCORI's protocol requirements
- Advise awardees, absent any formal PCORI policy or template, to consult the SPIRIT and CONSORT statements and the joint NIH/FDA Draft Clinical Trial Protocol Template

Open Science Update

Dr. Jason Gerson, Senior Program Officer for Clinical Effectiveness and Decision Science at PCORI, explained that PCORI now requires all funded trials and observational studies to be registered on ClinicalTrials.gov, and it plans to require a comprehensive final research report as well as technical and lay abstracts for posting on the PCORI website. PCORI now has a policy on public access to journal articles that present findings from PCORI-funded studies.

CTAP recommended that PCORI:
- Help sites mitigate the costs of maintaining study data in a repository over the long term
- Encourage investigators to document their data-sharing decisions so that the process will be clear to other researchers
- Establish a partnership with the NIH All of Us Research Program, which is developing a large data repository

- Encourage investigators to add their studies to ResearchMatch

Wrap-Up and Next Steps

Next steps for PCORI are to:

- Include a longer discussion of cluster-designed trials in a future CTAP meeting
- Report back to CTAP on any actions taken related to recommendations regarding informed consent and protocol templates
- Reactivate the CTAP RAR Subcommittee
- Solicit resources from CTAP and others that PCORI could use as benchmarks for monitoring its studies
- Schedule a teleconference in approximately three months for CTAP's next meeting