Advisory Panel on Clinical Trials
Meeting Summary

Overview

On November 16, 2018, the PCORI Advisory Panel on Clinical Trials (CTAP) held its 12th meeting in Washington, DC.

CTAP's 15 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.

During this meeting, CTAP continued its previous discussion of the factors that predict clinical trial challenges or successes. Their recommendations focused on characteristics of the primary site, other study sites, communications, study design, and engagement. CTAP learned about the concept of studies within a trial (SWATs) and identified issues for PCORI to consider in determining whether to fund SWATs. The final session featured a presentation on PCORI's policy on data sharing and data management.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials May 7, 2018, Meeting
- PCORI Methodology Standards
- Trial Forge Guidance 1: What Is a Study Within a Trial (SWAT)?
- Data Management and Data Sharing Policy
- Data Management and Data Sharing Policy FAQs

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

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Factors That Predict Clinical Trial Challenges or Successes

Anne Trontell, MD, MPH, Associate Director, Clinical Effectiveness and Decision Science at PCORI, asked CTAP to help PCORI identify and refine aspects of clinical trials associated with a high or low risk of success (defined as efficient, timely, complete, and high-quality evidence generation).

Study Leadership Team

CTAP members commented that a principal investigator (PI) who has not yet led a clinical trial could be a red flag, but including an investigator who has led a trial, even in a different scientific area, could overcome this weakness. Other comments on the leadership team were:

- A team whose members have already worked together on other studies is valuable.
- The business literature might have evidence on the components of strong leadership teams that PCORI could use in its objective review criteria.
- Several different types of teams could lead successful studies.

CTAP emphasized the importance of including an appropriately qualified project manager in the study team and recommended that PCORI require applicants to submit biographical sketches for project managers and list project managers as key personnel. Project managers do not have a standardized career development pathway and may be known under different job descriptions and titles. CTAP recommended that PCORI include sessions for project managers at its annual meetings and list resources for project managers (e.g., best practices, email lists, conferences) on its website.

Study Sites

CTAP members discussed the need to nurture study sites, including those that do not conduct research but want to develop research capacity. Study teams need to articulate plans for ensuring that the less experienced sites do well to increase the chance that the study will succeed and help these sites gain research experience.

Communications

CTAP noted that site coordinators need informal opportunities for candid discussion of recruitment and retention best practices as well as problems. In addition, study sites need clear lines of decision-making authority, roles, and responsibilities.

Design Considerations

Trontell explained that PCORI's pragmatic trials are in between explanatory clinical trials and fully pragmatic trials that operate in existing healthcare systems. Many PCORI trials include very broad populations and a high level of flexibility, and they have many pragmatic design features. David Hickam, MD, MPH, Program Director of the Clinical Effectiveness and Decision Science program at PCORI, added that the PCORI Methodology Standards address study design issues, noting that the study outcomes should be important to patients and give preference to patient-reported outcomes.

Engagement

CTAP identified several effective engagement mechanisms:

- Giving patients aggregate study results and their own results
- Involving patient advocates in designing the trial and reviewing all study materials
- Sharing study results for their patients with participating clinicians and health systems
- Maintaining frequent communication that begins during the recruitment and consent period
- Distributing branded items (e.g., pens, postcards) to participants and study personnel
- Telling patients how long it might take for the all study data to be collected and analyzed and for the final report to be available

Engagement can be challenging, especially if study teams lack funding and personnel to send results to participants. Ensuring that studies communicate results with patients is particularly important for PCORI, given its emphasis on patient-centeredness. Additional sources of information on engagement include the NIH *All of Us* Research Program, the National Academy of Medicine's *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*, and the NIH Collaboratory.

How best to relay information and create the infrastructure to support communications is not clear. Collating data and sending them to participants is time consuming, and returning results to participants can even be harmful. Studies rarely provide good summary information to participants, even though doing so is neither difficult nor controversial. A one-page, lay-language summary of the primary findings article would be sufficient in most cases.

Other Beneficial Study Characteristics or Processes

CTAP recommendations were as follows:

- Establish a minimum level of effort for the primary site PI and other key study leaders
- Evaluate the level of effort of key personnel in PCORI's most successful studies to aid in establishing a benchmark
- Describe in advance the responsibilities of the study coordinator, the types of training that must be provided, and the data quality measures to use

Potential Next Steps

Next steps include:

- A discussion of recruitment and enrollment, retention, and missing data
- Analyses of the PCORI portfolio to suggest or illuminate factors associated with study performance
- Case studies of performance outliers from PCORI portfolio analyses
- "Deep dives" into 10 trials that have been clear successes or 10 that have failed in order to determine whether the variables discussed are associated with success or failure

Studies Within a Trial (SWATs)

The concept of SWATs comes from Trial Forge, which aims to increase the evidence base for making randomized trial decisions and improving trial efficiency. SWATs are self-contained research studies embedded in a host trial that are designed to resolve important uncertainties about the processes used

in the trial. SWATs can be performed in one or more host trials. PCORI does not currently fund SWATs, and it is just beginning to consider their potential value.

CTAP noted that SWATs can address the most common challenges for trials, which are recruitment and retention. To conduct SWATs, PCORI would need to determine how to do the following:

- Offer incentives for the PIs of host trials to accommodate SWATs
- Handle delays in host studies that result from SWATs
- Determine whether applications that include SWATs should receive higher review scores
- Distinguish between SWATs and analyses that can be done within the host trial's original design
- Ensure that SWATs do not affect the host trial's intervention or post-baseline procedures

Questions about PCORI-funded SWATS include:

- Who can develop research questions for SWATs—the host study team? PCORI staff who have operational questions? Members of the public?
- Who can initiate a SWAT?
- Will SWATs be covered by the host study's informed consent process, or will each SWAT require its own informed consent?

CTAP members encouraged PCORI to investigate the possibility of supporting SWATs.

PCORI's Policy on Data Sharing and Data Management

Allie Rabinowitz, MPH, Program Associate in PCORI's Office of the Chief Science Officer, explained that PCORI's Board of Governors approved the data management and data sharing policy on September 7, 2018. The policy articulates expectations for awardees regarding data management and data sharing, including which data and documents must be shared. The policy also provides funding for the time and effort required to prepare data for sharing, specifies when awardees must make data available in response to third-party requests, and describes the process for reviewing these requests.

According to the policy, awardees must share de-identified data only. The full data package that awardees with targeted and pragmatic clinical studies must deposit in a PCORI-designated repository consists of the analyzable dataset, full protocol, metadata, data dictionary, full statistical analysis plan, and analytic code. The full data package is to be made available for third-party requests when the final research report is available on PCORI's website or one of the research project's primary results papers is published in a peer-reviewed journal, whichever comes first. For PCORnet, the National Patient-Centered Clinical Research Network, awardees must deposit applicable data elements (e.g., full protocol, analytic code used to query PCORnet data, and aggregate-level datasets). Broad funding announcements require awardees to maintain the full data package for seven years.

An independent review committee will determine whether third-party data requests have scientific merit. This committee will be made up of a representative of the PCORI-designated repository, a data scientist, a clinical researcher with relevant expertise, a PCORI staff member, and a patient representative. A member of the awardee research team that generated the requested data will be invited to attend the review discussion as a nonvoting participant. Approved requestors will sign a data

use agreement with a PCORI-designated repository that will specify the terms and conditions for using the data as well as the responsibilities of data requestors.

PCORI plans to implement the requirements of this new policy in stages, and it will work with awardees individually to facilitate compliance. PCORI has published FAQs about the policy on its website, and questions about the policy can be submitted to OpenScience@pcori.org.

Several CTAP members pointed out that depositing data as soon as the final report is submitted, or the main results paper is published, could be challenging. Hickam said that PCORI has received this type of feedback, and the institute is aware of the potential for unintended consequences, such as slower submission of the final PCORI report or primary results manuscript. However, PCORI's board has approved this policy, which is part of a long-term trend toward more rapid public sharing of data.

The reason for the policy is that the public that provided the resources for PCORI's studies in the form of taxes has a right to have the data be made available. Because PCORI funds large, well-conducted studies with rich datasets, these data are suitable for certain types of reuse. Only the largest and most expensive studies are likely to be required to upload their data into a repository. For smaller studies that represent smaller public investments, PCORI can correctly say that it is not cost-effective to spend resources preparing the data for the repository if these data will not be reused.

The reason to retain study data for seven years is the data might be needed in response to an unexpected situation, such as an outbreak of an unrecognized disease. PCORI expects such requests to be unusual.

Wrap-Up and Next Steps

Suggestions for the next CTAP meeting agenda include an update on the policy on data sharing and data management from Jason Gerson, PhD, Senior Program Officer for PCORI's Clinical Effectiveness and Decision Science program, and a discussion of the characteristics of retention that predict clinical trial success. Another suggestion is to schedule the next CTAP meeting in conjunction with a Methodology Committee meeting so that the CTAP can invite Methodology Committee members to participate in a joint session.

Trontell asked CTAP members to consider replacements for the researchers and patient representatives who were rotating off CTAP.