Advisory Panel on Clinical Trials Meeting Summary

Overview

On November 3, 2017, the PCORI Advisory Panel on Clinical Trials (CTAP) held its 10th meeting in Washington, DC.

The 10 participating CTAP members included patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics along with 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.

During this meeting, CTAP received an update on the PCORI internship program and provided feedback on draft methodology standards for studies of complex interventions and for data management plans. Two sessions focused on pragmatic clinical trials: an update on the characteristics of PCORI's pragmatic trials and a report on the Pragmatic Clinical Studies Workshop at the recent PCORI annual meeting. During the last half of the meeting, CTAP responded to questions from PCORI staff about the definition and flexibility of study interventions, ascertainment of variability, and adherence planning and measurement. The panel's recommendations included broader dissemination of lessons learned from PCORI's unique pragmatic trials portfolio and assistance for investigators in developing appropriate research questions and choosing study designs that match their research questions.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Clinical Trials March 20, 2017, Meeting
- PCORI Methodology Report
- Proposed Standards for Studies of Complex Interventions
- Proposed Standards for Data Integrity and Rigorous Analyses
- 2017 PCORI Annual Meeting
- Pragmatic Clinical 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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Update on PCORI Internship Program

Allie Rabinowitz, Program Associate with the Office of the Chief Science Officer for PCORI, reported that PCORI offers internships for undergraduate and graduate students and for recent college graduates. These internships last 10 weeks, and PCORI posts 6 to 10 internship opportunities for each spring, summer, and fall cycle. Examples of past internships activities include developing PCORI funding announcement materials, performing literature reviews and preparing topic briefs to identify evidence gaps, and coding PCORI projects for PCORI's science database.

CTAP suggested that PCORI expand its internship program to include physicians. PCORI will explore the extent to which it might benefit from interns who are medical residents and whether it has a mechanism for such internships.

Draft Methodology Standards for Studies of Complex Interventions

Dr. Laura Esmail, Program Officer, Clinical Effectiveness and Decision Science at PCORI, explained that complex interventions are those with multiple, interacting components with complex and/or multiple causal pathways. These interventions target multiple entities or levels, are adaptable or flexible, and involve specific behaviors and activities carried out by healthcare staff.

To encourage replicability and internal validity of PCORI-funded studies of complex interventions, PCORI's Methodology Committee has proposed four new draft standards for these studies:

- SCI-1: Fully describe the intervention and comparator and define their core functions
- SCI-2: Specify the hypothesized causal pathways and their theoretical basis
- SCI-3: Specify how adaptations to the form of the intervention and comparator will be allowed and recorded
- SCI-4: Describe planned data collection and analysis

PCORI will accept public comments, including from CTAP members, on these standards until December 29, 2017.

CTAP pointed out that the draft standards are also important for studies of simple interventions. Furthermore, establishing separate standards for complex interventions could be a disincentive to proposing studies of these interventions. Dr. Esmail agreed that all applications to PCORI should address the proposed complex intervention standards, but she noted that these standards are particularly critical for studies of complex interventions. Over time, PCORI might suggest that all studies comply with these standards. CTAP also discussed what would happen if an intervention needed to be changed during a study. In circumstances where an intervention has changed over the course of a study, mixed methods exploration may help to determine which factors influence the intervention's effectiveness.

Methodology Standards for Data Management Plans

Dr. Jason Gerson, Senior Program Officer, Clinical Effectiveness and Decision Science at PCORI, explained that the Methodology Committee has developed a proposed standard for data integrity and rigorous analysis:

- IR-7: In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.

PCORI will accept public comments on this standard until December 29, 2017.

Good data management is fundamental to ensuring the scientific integrity of clinical research. A data management plan discusses how the data will be obtained or collected, how the individual data items will be described, who will have access to the dataset, who will have permission to edit or change the data, and the mechanisms used to share the data when the project ends.

A CTAP suggestion was to call for including information in the data management plan on how the investigators will safeguard participant privacy. Dr. Trontell explained that PCORI's human subjects template does address participant privacy and data security.

Pragmatic Clinical Studies

Dr. Trontell reported that PCORI's funded pragmatic trials collect robust, real-world evidence about the comparative effectiveness of known efficacious interventions to inform decisions by various stakeholders when choosing among competing treatment options. The goal is to lessen the gap between implementation of an intervention in a trial and how that intervention is applied in practice. PCORI articulates the features it seeks in pragmatic trials in PCORI funding announcements (PFAs) for pragmatic clinical studies. Many other PCORI-funded studies have pragmatic features.

Unlike the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2), PCORI focuses on comparisons of two or more active interventions rather than evaluations of the effectiveness of a new intervention being considered for introduction into practice. PCORI's approach is strongly aligned with PRECIS-2 with respect to patient populations, real-world settings, less complex protocols, and the need for large samples. However, PCORI's focus differs from that of PRECIS-2 in its more precise determination of how flexible studies must be, requirements for measurement and ascertainment of adherence, and discouragement of usual care comparators.

Dr. Trontell clarified that the reason why PCORI discourages use of usual care comparators is that usual care varies a great deal, and a usual care comparator arm might compromise the ability to find differences. However, CTAP pointed out that capturing what usual care involves is important, perhaps through observational studies. CTAP also recommended that PCORI explain the gradations in the different domains required for a trial to be pragmatic.

Pragmatic Clinical Studies Workshop: Debrief and Take-Aways

Dr. Cynthia Girman, a CTAP member, reported on a well-received session on pragmatic trials that she moderated and also served as a discussant at the recent 2017 PCORI Annual Meeting. Dr. Trontell provided an overview of PCORI's pragmatic clinical trials at this session, and Dr. Susan Ellenberg described PRECIS-2. Three investigators. Drs. Elliot Israel, Michael Kappelman, and Mark Neuman, discussed the challenges they faced in their PCORI-funded pragmatic trials and solutions they had used.

A theme throughout the session was the need to design studies to answer the research question without sacrificing internal validity to make the study pragmatic. The discussion also addressed use of intention-to-treat (ITT) versus per-protocol analyses.

CTAP commented that investigators often start pragmatic trials that have an active comparison group with a superiority hypothesis, even though they really want to show that the two interventions are not different from one another. These investigators should be encouraged to use a non-inferiority design. Whether ITT or per-protocol is the right analysis population depends on the research question. CTAP also offered the following recommendations:

- Develop a methodology standard on the best alternatives to ITT
- Disseminate lessons learned from investigators who have conducted PCORI trials
- Articulate PCORI's pragmatic trials guidance more clearly
- Develop continuing medical education on pragmatic trials

Definition and Measurement of Study Interventions

Dr. Trontell asked CTAP to respond to the following questions about definition and flexibility of study interventions:

- How can PCORI best guide the appropriate definition and allowable flexibility of how practitioners apply study interventions?
- How might the complex intervention standards help define what is allowable and what is inviolate in an intervention?
- How can PCORI distinguish "allowable" variations from significant departures?
- Does the PCORI description of usual care offer a model for guidance?

Questions about ascertainment of variability are:

- How can PCORI best guide appropriate measurement of variability in how practitioners apply study interventions?
- How can assessment be done without undue burden or distortion of intervention delivery?

CTAP commented that the goal is not to make PCORI comparative effectiveness research (CER) trials as pragmatic as possible based on the PRECIS-2 standards. Rather, it is to find the best way to conduct PCORI trials to meet the CER needs of PCORI and stakeholders.

Dr. Joe Selby, PCORI's executive director, said that PCORI needs to be explicit about the importance of clearly defining the research question because this affects many aspects of the research. He characterized the term "pragmatic" as unfortunate because the studies in PCORI's Pragmatic Clinical Studies Initiative address a wide range of questions, and not all of these questions lend themselves well to a fully pragmatic approach.

CTAP suggested that PCORI publicize three examples of the range of pragmatic trials along with a simple qualitative analysis of PCORI-funded studies that will help investigators determine whether their study designs are fit for answering their research questions. Another recommendation was to ask investigators to use the PICOTS (patient, intervention, comparison, outcomes, time, and setting)) format to frame

their research questions. CTAP members agreed that allowable variations are those that do not prevent the study from addressing the research question.

Issues in Adherence Planning and Measurement

Dr. Trontell asked CTAP to answer the following questions:

- Are there best practices, considerations, or criteria to assist in determining the most appropriate monitoring of participants' (often patients') adherence to an intervention?
- What methods of adherence measurement are least burdensome or intrusive upon patient behaviors being measured?

CTAP wondered about the extent to which investigators need to monitor participant compliance with interventions, given that in the real world, clinicians do not typically check whether their patients are taking their medications as directed. CTAP members agreed that if adherence is important enough to measure, it is important enough to target with an intervention as part of a complex intervention.

Suggestions for monitoring adherence were to:

- Embed a smaller study in a subset of participants in a large study to answer questions about adherence
- Instruct investigators to treat adherence monitoring as part of a complex intervention
- Use data that is routinely collected through quality assurance or other health care system oversight efforts
- Use electronic health record data
- Develop a minimal set of validated questions that clinicians in different health-care systems and regions use to monitor adherence. This may be feasible for simple interventions, but probably not for complex ones)
- Call for methodology applications to PCORI for research on ways to monitor adherence fidelity

Wrap Up and Next Steps

Suggestions for PCORI action identified during this meeting were:

- In PFAs, encourage investigators proposing a pragmatic trial to use PRECIS-2 as a discussion prompt for examining their study design carefully (but not necessarily for scoring how pragmatic their study is)
- Consider having investigators briefly describe their study design choices for each of the PRECIS domains, perhaps in tabular format
- Help investigators develop appropriate research questions and design studies that can answer the research question by publishing examples of different types of study designs that do and do not answer the research question
- Share lessons learned from PCORI's large portfolio of pragmatic trials with investigators, including those around the world who do not have PCORI funding
- Establish a learning network of current and potential PCORI principal investigators

- Continue to emphasize the importance of involving patients and stakeholders in designing studies from the beginning, including participation of patients and stakeholders in PCORI merit review panels