Advisory Panel on Clinical Trials
Meeting Summary

June 2014

Overview

On May 1, 2014, the PCORI Advisory Panel on Clinical Trials convened for the first time in Alexandria, Virginia, to begin discussing the scope of work and priority issues for the newly appointed group.

The Advisory Panel on Clinical Trials is made up of 10 representatives, including patients, clinical trialists, biostatisticians, epidemiologists, and an expert in the ethical dimensions of clinical trials. The panel also includes two ex-officio members from PCORI's Methodology Committee: Dr. Steven Goodman and Dr. Mary Tinetti. The meeting was open to the public via webinar, and meeting materials were posted to the website in advance of the session.

At the meeting, PCORI staff and Methodology Committee members gave several presentations to provide specific information about the existing clinical trials in the PCORI portfolio. The panel discussed and generated a list of topics and issues for consideration as possible priority action items. Finally, the panel went over several organizational issues and made decisions regarding meeting scheduling and frequency.

Related Information

- About This Advisory Panel
- Meeting Details and Materials
- About PCORI's Methodology Committee
- About PCORnet
- About PCORnet's Clinical Trials Task Force
- About PCORI's Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes Funding Announcement
- Register for the June 17 Board of Governors Meeting

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

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Introduction

The Advisory Panel on Clinical Trials generated a list of topics and issues for consideration as priority action items.

Setting the Stage

Prior to their first meeting, each panelist was asked to complete the PCORI New Panelist Training, which provided fundamental information about PCORI and its processes and procedures. To kick off the meeting, Dr. Bryan Luce, PCORI's Chief Science Officer, gave an overview of the panel's charter, which highlighted the panel's purpose, its scope of work, and the role and composition of its future subcommittees.

Then, Dr. Robin Newhouse, the chair of PCORI's Methodology Committee, described the Methodology Committee's roles and key activities. She also referenced the PCORI Methodology Standards, and proposed a few areas of overlap between the Methodology Committee's scope of work and the panel's, such as the oversight of PCORI's clinical trials portfolio, the identification of methodological issues related to clinical trials, and the consultation on methods issues for applicants. Dr. Steve Goodman, co-chair of PCORI's Methodology Committee and panel ex-officio member, also provided further clarity regarding the committee's vision for the panel. PCORI's Methodology Committee foresees this panel examining PCORI's funded clinical trials portfolio to provide a review of the methodology in terms of possible modifications and improvements. Additionally, it was suggested that the panel could also help with generating additional methodology standards currently missing—for example, standards for human subjects, specifically for clinical trials.

Lastly, representatives from each of PCORI's four programmatic research portfolios described the clinical trials that PCORI has already funded, and program staff gave a presentation on PCORI's new funding initiative: the PFA for Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes. Rachael Fleurence presented on PCORnet, a large, highly representative, national network for conducting clinical outcomes research.

Methodological and Policy Issues for Priority Consideration

Throughout the day, the panel discussed the following wide range of topics and issues for consideration as priority action items:

1. **Collaboration with other PCORI entities:** Panel members expressed a strong interest in collaborating and possibly meeting in conjunction with the Advisory Panel on Rare Disease, the PCORnet Task Force, and possibly PCORI's multi-stakeholder advisory panels that help set PCORI's topic research priorities. Specific collaborations could include:

- **a.** Rare Disease Advisory Panel (RDAP): Possibly develop methodological standards specific to rare disease clinical trials.
- **b.** PCORnet Task Force:
  - i. Help to flesh out study design specifications of the trials before the RFP posting
  - ii. Explore opportunities to embed parallel randomized and nonrandomized designs to potentially identify the differences between the patients that participate in randomized trials and those that do not.
  - iii. Manage the input from PCORnet task forces and vet it.

2. **Usual care as the comparator arm:** Advise PCORI on whether and how PCORI should provide clarity on the definition and use of usual care as the comparator arm in clinical trials. To do so, the panel could analyze how PCORI-funded clinical trials have defined usual care.
3. **Innovative study designs:**
   - **a.** Generalize lessons and generate white papers: Engage with the panel's target audience to identify the current issues that require more engagement, and provide guidance to other researchers on how to design such studies with more ambitious designs.
   - **b.** Contribute to the design of merit reviewer training: Encourage PCORI reviewers to accept and value innovative designs, by first identifying gaps in the existing training.
   - **c.** Define the settings in which innovative designs, such as pragmatic or adaptive designs, may be useful.
4. **Clinical trials methodology standards:** The panel was particularly interested in discussing minimum standards for trial design, conduct, and analysis, especially for pragmatic trials. Such standards would ideally result in trials giving more useful and more valid results.
   The panelists suggested that they undertake two tasks in regards to standards:
   - **a.** Compile a list of the standards that are relevant for clinical trials based on the current PCORI Methodology Standards,
   - **b.** Identify standards that are missing for clinical trials, and possibly even identify those that the panel would recommend to the Methodology Committee.
5. **Clinical trials as case studies:** The panel suggested that they could learn from the experience of the current PCORI-funded clinical trials and identify particular case studies with educational value. This could, in turn, allow the panel to:
   - **a.** Advise us on the formulation of PCORI's PCORI Funding Announcements.
   - **b.** Advise us on the methodologic research we commission.
   - **c.** Evaluate our portfolio and identify gaps and areas of improvement to further develop a policy going forward.
6. **The PFA for Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes:**
   - **a.** Advise PCORI on how to provide more details regarding what we are looking for in terms of pragmatic trials, although Dr. Steve Goodman emphasized that focusing on principles and goals that PCORI has set out is sometimes more effective than spending time on definitions. It was mentioned that the PRECIS statement used in the PCORI funding

announcement does not provide enough criteria to apply to the types of proposals that PCORI is seeking. Panelists also informed PCORI that a second PRECIS statement would be published in the next few months, which was bookmarked as a future subject of discussion for the panel.

   b. Critique the PFA and provide comments on how to improve it.
   c. Analyze these proposals as case studies, as this might shed light on the best characteristics of a possible methodological consultation, and may even be a way to predict usability in decision making.
   d. Work through the complex issues faced when designing a pragmatic study to be genuinely applicable and easily disseminated.
   e. Provide guidance on the best way to connect two or more applications that were essentially proposing to answer the same questions—a potential "matchmaking policy."

7. **DSMBs:** Review and advise on PCORI's policy regarding DSMBs.
8. **Ethics:** Perform some ethical analysis of low-risk trials, and think about what the philosophical, ethical implications are for these, especially in regards to those that are part of PCORnet.

PCORI's Methodological Consultation Proposal

Dr. Steve Goodman presented the Methodology Committee's proposal for the methodologic review of proposed trials. The idea is that this methodologic review or consultation would follow the merit review panel meetings and would involve the proposals being evaluated by one or more methodologists. For each selected proposal, one or more methodologists would provide a set of recommendations to the investigators for improving the methodology and for them to have the opportunity to respond to these. In some rare cases, the team could also recommend that a certain proposal be dismissed. This methodologic consultation would not only improve applicant trial methods, but would encourage the use of innovative methods and prevent the personal beliefs of one single methodologic reviewer to dismiss certain types of methods. It would also allow for an internal team of PCORI methodologists that would encourage consistency, as well as a high level of engagement of the methods community.

The panel's involvement in the consultation is still up for discussion, and it was suggested that a subset of voluntary panelists could participate in it. Some panelists expressed some concern about their involvement shifting the panel's purpose from advisory to decision making in the line of review. As a solution, it was proposed that the panel only discuss proposals as case studies. Furthermore, the panel agreed that a subset of panel members ready to commit more time to PCORI's work could still be engaged with the consultation to be able to report back to the panel and make sure the panel is engaged with the reviewers. This subset would be one of the subcommittees outlined in the panel's charter. The panel also suggested that a bright line should be drawn between the panel's inputs and decision making about a given proposal, and that its outputs should be learning materials and white papers to be widely shared that would incorporate the reviewers' feedback. Panel members suggested that one of their roles could be to provide guidance on how to enhance the methods review process to actively improve the protocols and avoid having proposals with innovative methods get rejected.

Finally, the "post-LOI-submission stage" was discussed as potentially a good time for individual panel members to provide consultation to applicants, as this would waste less of the investigators' time and would give them the opportunity to build a stronger proposal. It was even suggested that preliminary funding could be offered to those willing to spend the time creating a strong study design with rigorous methodology, to remedy the disincentive created by the amount of time necessary to build such a proposal.

Key Priority Items for the Panel

- Provide guidance on the trial design of the usual care arm
- Collaborate with PCORnet's clinical trials task force
- Provide guidance for applicants and others on innovative and/or rigorous trial designs
- Review methodology standards related to clinical trials and advise on new needed ones
- Analyze PCORI-funded trials as case studies to generate white papers and other training materials
- Advise PCORI on developing policies for DSMB oversight and other human subject issues for clinical trials
- Perform an ethical analysis of low-risk trials

Organizational Issues

Dr. Bryan Luce invited each panel member to submit nominations, including self-nominations, for the panel's chair and co-chair. The panel also discussed meeting frequency and agreed that two to four in-person meetings a year would be appropriate, with additional webinars in between the in-person meetings. It was also suggested that such meetings be scheduled around PCORI's funding cycles to give the panel the opportunity to discuss case studies as a group.