Advisory Panel on Rare Disease
Meeting Summary

Overview

On January 13, 2015, PCORI's Advisory Panel on Rare Disease held its fourth meeting in Arlington, Virginia.

The 13 members of the Advisory Panel on Rare Disease include patients, caregivers, representatives of patient advocacy organizations, clinicians, payers, researchers, and industry representatives. 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 offered comments and suggestions on the results of a PCORI analysis of rare disease application reviews. A joint session with the Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options addressed the research topic 'effectiveness of genetic testing for rare diseases'. The panel discussed the use of alternative statistical methods for clinical trials with small samples and the formation of ad hoc advisory panels to consult with individual studies focused on rare diseases. PCORI updates focused on collaborations between the Advisory Panel on Rare Disease and the Advisory Panel on Clinical Trials as well as a PCORI landscape review on rare diseases. Finally, panel members offered suggestions on compensation for patient partnership in research and the development of guidance on rare disease clinical trials.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Rare Disease October 7, 2014, Meeting
- About PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options
- About PCORI's Advsory Panel on Clinical Trials
- About PCORI's Advisory Panel on Patient Engagement

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

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Analysis of PCORI Review of Applications on Rare Diseases

Dr. Laura Forsythe, Senior Program Officer for Evaluation and Analysis at PCORI, summarized the results of an analysis to identify and address disparities between review outcomes for applications related to rare diseases and those focused on more common conditions. The conclusions were that PCORI receives a limited number of applications on rare diseases, they score as well or better than other applications, and are more likely to be discussed and funded than other applications.

The advisory panel suggested that PCORI further analyze these data to determine the:

- Sizes of target populations in applications for more common diseases
- Scores from academic investigators and patient reviewers
- Proportion of patient reviewers who have experience with rare diseases
- Proportions of rare and more common diseases applications that are selected for merit review
- Scores of funded rare disease applications
- Focus of these rare diseases applications (really a rare disease or the use a rare disease population to answer a broad question)
- Types of organizations submitting these rare disease applications

Most advisory panel members favored a separate merit review panel for applications on rare diseases. Rare disease applications may have lower scores for statistical merit than applications for other conditions if these applications are compared directly. However, several panel members believed that rare disease applications should have similarly high quality to, and compete directly with, other applications.

Other panel suggestions were as follows:

- Most rare disease applications probably come from academic centers, so future funding announcements should include patient advocacy group components to increase patient involvement.
- Broad funding announcements related to treatment may have limited relevance for rare diseases. Research on such topics as care giving, quality of life, and mental and social disabilities is more likely to lead to improved outcomes for rare diseases.
- PCORI should encourage more rare disease applications.
- PCORI should develop a brief PowerPoint presentation for discussing the goals of the Advisory Panel on Rare Disease and PCORI's interest in rare disease proposals with applicants.
- Dissemination efforts should include the international community.

Genetic Testing for Rare Diseases

A joint session with the Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options (APDTO) led by Dr. Marshall Summar of the Advisory Panel on Rare Disease and Dr. Uday Deshmukh of APDTO focused on the discussion of the following research topic: *"Genetic Testing for Rare Diseases: Compare the effectiveness of genetic testing for select rare diseases in terms of patient care, treatment choices, and relevant clinical and patient-centered outcomes."* A recent PCORI topic brief identified nine top research questions pertaining to genetic testing in children who might have a rare disease. Summar and Deshmukh served as topic experts to inform the discussion of the APDTO panel. They explained no

consensus has been reached about physicians' responsibilities with respect to genetic testing and sharing results with patients. Other concerns expressed included the effectiveness of genetic testing, whether genetic counseling is valuable to patients, how to interpret test results meaningfully, and the lack of standard techniques for conducting genetic tests and reporting their results.

Clinical Trials in Rare Diseases

Dr. Jason Connor, a member of the PCORI Advisory Panel on Clinical Trials (CTAP), described statistical methods to consider for clinical trials with limited numbers of potential participants. Traditional clinical trial design relies on classical statistical methods and are not useful for small clinical trials. When no standard treatment for a condition exists and a condition is rare, alternative trial designs might be useful in determining an intervention's efficacy.

During the discussion, Connor explained that the Food and Drug Administration (FDA) allows statisticians to explain the utility of unique analysis approaches during the application process. However, some grant application review panels lack expertise in alternative statistical models. Studies of diseases with a longer course and a heterogeneous population require tailored statistical approaches.

Panel members offered the following recommendations:

- Adaptive designs allow sponsors to determine whether an intervention is effective in a subgroup at an early stage and then test the intervention in that subgroup in a Phase III trial. These designs should be initiated prior to a Phase III trial.
- The principles of decisions rule should be communicated to the rare disease community.
- The panel should share its ideas with the Advisory Panel on Clinical Trials, Methodology Committee, and PCORI leadership so that PCORI can consider incorporating these ideas into funding announcements

Luce asked for feedback on the development of guidance and methods and the role of adaptive statistical methods for clinical trials in rare diseases. Panel member suggestions were as follows:

- PCORI should determine whether investigators submitting rare disease trial applications are aware of PCORI's guidance on adaptive clinical trials or whether PCORI needs to develop a new document for these applicants.
- Although PCORI has guidance on methodology standards for adaptive randomized clinical trials, no one-size-fits-all solution is available for rare disease clinical trials, and guidelines for such trials might have limited value.
- PCORI should encourage use of innovative methodology as long as applicants meet certain reporting requirements.
- The panel should invite a representative of Grading of Recommendations Assessment, Development and Evaluation at McMaster University to give a presentation on its adaptation of National Institutes of Health guidelines to issues on which evidence is insufficient to support evidence-based guidelines.

Expert Advisory Panels for Rare Disease Studies

Dr. Bryan Luce, Chief Science Officer at PCORI, asked for feedback on a proposal to form RDAP ad hoc advisory panels to consult on individual research studies. Emma Djabali, Research and Project Assistant in PCORI's Office of the Chief Science Officer, reported that based on a pre-meeting survey, most Advisory Panel on Rare Disease members agreed that the expert advisory panels should provide advice pre- and post-award.

Panel members offered the following recommendations:

- PCORI should inform Program Officers when ad hoc advisory panels are formed so they know they have access to expertise on the studies they are monitoring.
- Instead of creating several ad hoc advisory panels, PCORI staff should form a pool of specialists with expertise in different rare diseases and issues related to rare disease research. PCORI staff could then consult these experts as needed. PCORI will develop a skills matrix for the ad hoc advisory panels.

PCORI asked for the following from the panel:

- Names of panel members who would like to join this expert panel
- Names of colleagues who have the appropriate expertise to serve this expert panel

Updates

Luce gave an overview of existing collaboration between CTAP and RDAP and went over potential future collaboration.

During the panel's first meeting in April 2014, panel members suggested PCORI commission a rare disease research landscape review, which would provide a solid starting point for the panel. This review could provide a gap analysis to shed light on what the panel should focus on. Luce explained that PCORI is in the process of issuing a contract to conduct a landscape review on rare diseases. The contractor will develop rare disease registry standards/guidance, minimal datasets, data standards, guidance on evidence and standards needed for new treatments related to rare disease, and evidence-grading systems for rare disease research. PCORI staff have recommended that the contractor create an advisory work group that includes members of the Advisory Panel on Rare Disease and Luce called for panelists to volunteer during the meeting.

Summar clarified that PCORI is seeking landscape advisory work group members with methodological expertise, experience across a multitude of rare diseases, and experience creating guidance for the FDA or large-scale registry projects.

Compensating Patient Partners in Research

Suzanne Schrandt, Deputy Director of Patient Engagement at PCORI, explained that PCORI's Advisory Panel on Patient Engagement is articulating a PCORI framework on compensation (including for time, expertise, and expenses) for patient partners in research. PCORI requires investigators to demonstrate that they value patient time and expertise. The panel has developed a patient engagement rubric with

six engagement principles and a new engagement officer position. The engagement officers are creating a repository of solutions used in projects to date.

Panel members offered the following suggestions:

- Compensation for patients and physicians should be equitable.
- A standard rate for patient compensation could provide guidance for patients who also serve as scientists on research teams.
- A patient member of the Advisory Panel on Rare Disease should review the draft compensation framework.
- To facilitate the distribution of compensation by universities, PCORI might provide compensation directly to patients.
- The Advisory Panel on Patient Engagement should consider the impact of union policies on patient compensation.

The panel also noted that patient compensation could result in bidding wars for patient engagement, especially for rare diseases. Schrandt clarified that a panel is addressing the issues that arise when a patient participates in a study that the patient also helped design.

Next Steps

PCORI staff will work on a follow up analysis of the review of rare disease applications. They will also create the ad hoc expert advisory panel, which will serve as a pool of experts available to Program Officers, and will invite RDAP members to join and/or suggest other appropriate experts. During their next meeting on May 27, 2015 the panel will discuss the completed landscape review and the gaps in rare disease research standards that they are interested in helping develop, among other agenda items.