Advisory Panel on Rare Disease Meeting Summary

Overview

On October 27, 2016, the PCORI Advisory Panel on Rare Disease (RDAP) held its sixth meeting in Washington, DC.

RDAP's 15 members include patients, caregivers, representatives of patient advocacy organizations and industry, clinicians, payers, and researchers. The meeting was open to the public via webinar, and meeting materials were posted to the PCORI website in advance.

The new RDAP members learned about the mission and vision of PCORI and RDAP as well as RDAP's function and scope of work. Dr. Evelyn Whitlock, PCORI's Chief Scientific Officer, described PCORI's approach to its "one science" vision and opportunities for RDAP to advise PCORI. RDAP members offered recommendations on PCORI's rare disease research portfolio. A presentation on PCORI's Eugene Washington Engagement Awards and Pipeline to Proposal Awards was followed by a presentation of a program funded by a PCORI engagement award designed to train rare-disease patient advocates. A session on PCORnet, The National Patient-Centered Clinical Research Network, focused on its rare disease–related activities. Finally, the panel discussed rare disease activities at the Food and Drug Administration and a draft version of a rare disease methodology paper.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Rare Disease October 30, 2015, Meeting
- PCORI's Guidance on Research In Rare Diseases
- Rare Disease Landscape Review
- PCORnet (National Patient-Centered Clinical Research Network)
- PCORI Methodology Report

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

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Background

Vincent Del Gaizo, Acting Chair, opened the meeting by welcoming the RDAP panelists, going over the housekeeping directions and reviewing the agenda for the day. Dr. Parag Aggarwal, Senior Program Officer for Addressing Disparities, reviewed the mission and vision of PCORI and of RDAP as well as RDAP's function and scope of work. Dr. Danielle Whicher, Program Officer for Clinical Effectiveness Research, explained that RDAP is one of seven PCORI advisory panels, but it is one of only two legislatively mandated panels. Key RDAP activities have included commissioning a review of standards for research on rare diseases, recommending that PCORI create a pool of experts to answer staff questions about monitoring rare disease projects, identifying special considerations for merit review of rare disease comparative effectiveness research (CER) projects, developing guidelines for research on rare diseases, and serving as technical experts to the Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options on genetic testing for rare diseases.

Dr. Evelyn Whitlock, PCORI's Chief Scientific Officer, explained that although PCORI has five national priorities, it has a "one science" vision calling for synergies among PCORI programs, a consistent approach to applicants and awardees, and collaboration across and beyond PCORI departments. Goals for FY2017 are to establish an evidence synthesis program, enhance integration of scientific programs within departments and across PCORI, improve relationships with researchers, and align the mission of PCORI's advisory panels with PCORI's overall direction.

RDAP opportunities are to advise on ways to use the PCORnet infrastructure to study rare diseases, identify rare disease research topics for PCORI to pursue through its existing topic pathway (e.g., targeted funding announcements), and develop a core outcome set for rare disease studies. RDAP could also nominate research methodologies that are important in rare diseases as standards for consideration by the Methodology Committee or develop guidance on these methods. A final suggestion is for RDAP to advise PCORI on ways to strengthen collaborations with existing rare disease programs, such as the National Institutes of Health (NIH) Undiagnosed Diseases Program.

RDAP members recommended that PCORI expand its focus beyond health systems to community systems that deliver many behavioral interventions. An example is the prediabetes education provided by the YMCA. Dr. Whitlock explained that PCORI funds several studies involving community systems under both its Improving Health Systems and Addressing Disparities national priorities.

RDAP members expressed support for developing rare disease core outcomes, which could make evidence syntheses more feasible by ensuring the use of consistent outcome measures in different studies. However, certain types of core outcomes will be difficult to establish in rare disease when their natural history is not understood, and a requirement to use core outcomes could be a barrier to initiating rare disease studies. It might be possible to identify some core outcomes that reflect patient preferences and are common across rare diseases, such as social functioning and quality of life. However, payers and regulators might not be willing to base approvals and claims on such outcomes. A suggestion was for PCORnet to conduct natural history studies of certain rare diseases in its cohorts. The Food and Drug Administration (FDA) would need to agree to accept these core outcomes as meaningful

and integrate them into its review process, and payers would need to agree that these outcomes are important.

PCORI Rare Disease Research Portfolio

Dr. Heather Edwards, Program Officer for Strategic Portfolio Analysis, reported that as of September 2016, PCORI has 22 active or completed CER projects and 3 methods projects on rare diseases with a total budget of $57.3 million. These projects address a broad range of rare diseases and types of interventions and outcomes.

RDAP offered the following recommendations:

- Support a change in investigator mindset to ensure that patient-centered outcomes are truly embedded in grant applications and are not afterthoughts
- Train investigators before they submit applications on the need to involve patients from the very beginning
- Include rare disease experts in merit review panels that review rare disease proposals
- Target outreach to the rare disease community to ensure timely awareness of PCORI's rare disease research opportunities, including targeted funding announcements, Eugene Washington PCORI Engagement Awards, and Pipeline to Proposal (P2P) Awards
    - Discuss this issue with PCORI's engagement and communication staff at a future RDAP meeting
    - Identify organizations that might be particularly interested in specific targeted funding announcements
    - Provide PCORI outreach at major meetings attended by rare disease researchers and clinicians
- Develop standards for cross-cutting research on multiple rare diseases
- Encourage communities to include health services researchers in their research teams
- Use innovative approaches, such as crowdsourcing, to generate research priorities from the community
- Encourage investigators conducting studies in large numbers of patients to analyze data on rare diseases
- Make PCORI's interest in rare diseases more visible in broad funding announcements

Eugene Washington PCORI Engagement Awards and P2P Awards Focused on Rare Diseases

Lia Hotchkiss, Director of the Eugene Washington PCORI Engagement Award Program, explained that this funding opportunity supports projects that build a community better able to participate in patient-centered outcomes research (PCOR) and CER and to serve as channels to disseminate study results. The program has awarded $29.6 million to 91 engagement award projects and 61 conference support projects in 35 states. Approximately 15–20% of engagement awards go to rare disease organizations. Examples of two engagement award projects focused on rare diseases are:

- Novel Stakeholder Engagement for Nemaline Myopathy, Patient Centered Research: Ongoing collaboration with stakeholder groups to encourage patient-centered research, foster better patient-physician communication, and develop a path to treatment for this rare disease
- Developing and Testing "Best Practices" in Training for Academic/Community Research Partnerships: Development of online training with usability and value to research partners, focusing on unique needs of rare and/or genetic condition patient-partner trainees

The P2P program offers three tiers of funding to build a national community of patients, stakeholders, and researchers who have the expertise and passion to participate in PCOR and to create partnerships within that community that lead to high-quality research proposals. The three funding tiers are:

- Tier I: Up to $15,000 for up to 9 months to build partnerships and expand the skills needed to develop a patient-centered CER project
- Tier II: Up to $25,000 for up to 12 months to develop research capacity, create new partnerships, and build the infrastructure needed to conduct research
- Tier III: Up to $50,000 for up to 12 months to develop high-quality research proposals that can be submitted for PCORI funding

PCORI has funded 123 tier I, 71 tier II, and 22 tier III projects to date, including rare disease projects in all three tiers.

Ms. Hotchkiss noted that RDAP had offered several engagement-related recommendations in this meeting that she plans to share with staff in the Engagement Program: to make clear PCORI's interest in applications focused on rare diseases in funding announcements, pull together all funding announcements related to rare diseases into a single place on PCORI's website, conduct a webinar on how the rare disease community can become more engaged in PCORI, and share tips on how to write more effective proposals for PCORI (including the need to consult a health service researcher).

PCOR Training: A Program for Rare-Disease Patient Advocates

Dr. Eleanor Perfetto of the University of Maryland, Baltimore, summarized a program she led to train rare-disease patient advocates that was funded by a PCORI engagement award. The program consisted of a half-day introductory session and a full-day advanced session at the National Organization for Rare Disorders 2015 summit, resources (acronym list, glossary, successful partnerships checklist, and resource list), and three post-training research club teleconferences. Lessons learned included that patient groups may benefit from more support than other investigators, team efforts are important to overcome barriers to engaging patients in research, and an active and engaged advisory group and champions at all partner organizations are needed. Two projects, the Cholangiocarcinoma Foundation and the Platelet Disorder Support Association are led by individuals who completed the training have now received PCORI funding.

RDAP members commented that the use of real-life examples, as in the curriculum that Dr. Perfetto described, is very important. They recommended including testimonies from others who have completed the training and providing training to researchers and clinicians on how to work with patients

as research colleagues. Dr. Perfetto's program could help patient communities learn how to use other federally funded resources, including other grant programs.

PCORnet Rare Disease Patient Powered Research Networks (PPRNs)

Sharon Terry, President and CEO of Genetic Alliance and co-principal investigator of the PCORnet (the National Patient-Centered Clinical Research Network) Coordinating Center, explained that PCORnet—a large, highly representative, national patient-centered clinical research network—supports large-scale clinical research that helps people make informed health decisions.

PCORnet has 20 Patient-Powered Research Networks (PPRNs) made up of patients and/or caregivers who conduct patient-centered CER. The PPRNs are studying a broad range of conditions from common to rare. Through the PPRNs, 250,000 people with more than 100 diseases, many of which are very rare, are ready to participate in research. Ms. Terry provided examples of several PPRNs that are addressing rare diseases, including the MoodNetwork and the Community Engaged Network for All. The 13 PCORnet Clinical Data Research Networks (CDRNs) are health system networks that conduct randomized trials and observational research using data from their practices and populations. Each CDRN has chosen a common disease cohort and a rare disease cohort. With data on 145 million people, the PPRNs and CDRNs are developing a national evidence system with unparalleled research readiness.

During the discussion, Ms. Terry explained that outside groups will be able to collaborate with PCORnet starting in early 2017. One question that the network needs to address is how to involve groups that were not selected to form a PPRN or CDRN and that would like to participate. To start to address that question, PCORnet is developing a process for outside investigators to submit data queries and research proposals for studies that leverage PCORnet data. Other options will also need to be considered.

Ms. Terry reported that PCORnet's leaders would like to bring questions to RDAP for discussion and RDAP could help get the word out that the network is ready to start many activities and this research is a high priority. At the same time, PCORnet would be receptive to priorities identified by RDAP and advice on whether the PPRN model is effective and which research methods the PPRNs should use.

FDA Rare Disease Activities

Dr. Gayatri Rao, Director of the FDA's Office of Orphan Products Development, listed just a few of the many FDA centers and offices with activities related to rare diseases. Among the most relevant is the Rare Diseases Program within the Center for Drug Evaluation and Research, which coordinates development of the center's policies, procedures, and training for the review of rare disease treatments. The Center for Biologics Evaluation and Research has a Rare Disease Coordinating Committee, and the FDA's Rare Disease Council, which includes representatives from all FDA centers and offices that work on rare disease issues, meets monthly.

The FDA is also focusing on patient engagement, especially within the Office of Health and Constituent Affairs, which administers the FDA's Patient Representative Program. Through this program, more than 200 patients (including patients with rare diseases) and caregivers play an active role on FDA advisory committees and consult with agency components. The Center for Devices and Radiological Health has a Patient Preference Initiative that will include the Patient Engagement Advisory Committee and guidance development on ways to elicit, measure, and incorporate patient preferences into the medical device total product life cycle. The FDA's patient focused drug development activities include meetings with patients on specific disease areas, several of which are rare.

RDAP recommendations were to:

- Define such terms as "patient," "patient advocacy," and "patient advocacy group"
    - RDAP agreed to discuss this topic at a future meeting with representatives of PCORI's engagement staff.
- Solicit feedback from patients directly (not only through advocacy groups), when patients can speak for themselves
- Encourage a culture shift toward increased patient engagement within industry
- Train companies in engaging patients throughout the drug development process and overcoming legal barriers to engagement by showing that patient engagement speeds up implementation of research results in clinical practice
- Find ways to collect data from patients who cannot speak for themselves

Rare Disease Methodology Paper

Dr. Whicher explained that RDAP commissioned a landscape review, finalized in May 2015, on current literature about registry and research methods for rare diseases. RDAP members identified several areas in which additional information and guidance was needed, and Dr. Naomi Aronson, ex-officio RDAP member from PCORI's Methodology Committee, led a small group that explored how rare disease features affect decisions about appropriate study designs.

The group has now completed a draft report summarizing its findings from the literature and from a review of the PCORI portfolio. The draft has been circulated to RDAP members of their review and their comments have been incorporated. The report describes promising methodological approaches for rare disease research, which methods are most frequently used in the PCORI rare disease portfolio, and areas for further development. This report can help promote the use of a broader range of research

methods in rare disease projects and inform investigators of the rare disease cohorts that are part of PCORnet. It also identifies areas where additional methods research and guidance is needed.

RDAP members offered the following suggestions:

- Use the report to inform PCORI merit reviewers that various experimental designs are available and are often optimal for rare disease studies
- Promote use of the report by anyone doing any kind of clinical trial assessment
- Communicate that rare disease research does not use different methodologic principles, but the barriers to implementing these principles can be greater in rare disease studies
- Publish the report in a peer-reviewed journal to disseminate it more broadly
- Consider drafting additional papers on related topics, such as:
    - how to develop strong recommendations based on low-level or indirect evidence
    - how to measure outcomes without knowing the natural history of the disease to address heterogeneity

An important message of the report is that rare disease research can be of high quality, even when the number of patients included is small. However, this type of study requires thoughtful approaches and leadership that is committed to supporting the research.

Closing

Vincent Del Gaizo, recognized the following retiring RDAP members and thanked them for their service on the panel and their unique contributions:

- Jacqueline Alikhaani
- Mardi Gomberg-Maitland
- Philip W. Ruff

Mr. Del Gaizo presented each departing RDAP member with a plaque.

Dr. Whicher summarized next steps:

- Continue the discussion related to developing core outcome sets for rare diseases
- Continue to develop rare disease guidance for merit reviewers
- Develop a feedback loop between RDAP and PCORnet
- Continue to refine the RDAP methods paper, ask the Methodology Committee for feedback, and develop a version for submission to a peer-reviewed journal
- Hold RDAP meetings in person twice a year with an optional third yearly meeting in person or by teleconference
    - Schedule these meetings as far in advance as possible

An action item for RDAP members is to send Dr. Whicher agenda items for future RDAP meetings.