Advisory Panel on Rare Disease Meeting Summary

Overview

On September 27, 2017, the PCORI Advisory Panel on Rare Disease (RDAP) held its eighth meeting in Washington, DC.

The RDAP's 13 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 RDAP learned about the activities of the International Rare Diseases Research Consortium (IRDiRC), its task force on patient-centered outcome measures for rare diseases, and a Canadian effort to develop a core outcome set (COS) for comparative effectiveness trials in pediatric inherited metabolic disorders. The RDAP offered feedback on PCORI's plans to develop a COS for pediatric rare diseases, including suggestions to identify outcomes measured by Rare Diseases Clinical Research Network (RDCRN) studies, validated instruments used to measure the potential core outcomes, and previous experience with a COS in comparative effectiveness research. The panel also provided recommendations for PCORI's web-based rare disease resources and a slide set that RDAP members can use for presentations on PCORI's rare disease research activities. Dr. Nicholas Ah Mew described successes and potential outcomes of a PCORI-funded study comparing the effectiveness of liver transplantation and medical management of urea cycle disorders. The RDAP's final discussion focused on nominations for potential discussion topics for future RDAP meetings.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Rare Disease April 26, 2017, Meeting
- International Rare Diseases Research Consortium
- PCORnet, the National Patient-Centered Clinical Research Network
- PCORI-Funded Rare Disease Projects and Related Resources
- Research Spotlight on Rare Diseases

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

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International Rare Diseases Research Consortium and Patient-Centered Outcome Measures

Thomas Morel, a research fellow at KU Leuven, explained that the goals of the International Rare Diseases Research Consortium (IRDiRC) are to stimulate, better coordinate, and maximize the output of rare disease research efforts around the world. Through this public-private partnership, more than 200 new drugs for 170 rare diseases have now reached the market.

The IRDiRC Task Force on Patient-Centered Outcome Measures issued a report, *Patient-Centered Outcome Measures Initiatives in the Field of Rare Diseases,* in 2016. Mr. Morel and Dr. Stefan Cano, another task force member, subsequently wrote a scientific article, to be published in *Orphanet Journal of Rare Diseases,* explaining that patient-centered outcome measures reflect patients' daily experiences of disease, preferences, concerns, hopes, and values. The manuscript offers several recommendations, including for use of patient-centered outcome measures in value frameworks, registries, and outcome-based agreements and dissemination of patient-centered outcome measure best practices.

During the discussion, Mr. Morel stated that several research drug development initiatives in Europe involve patients, although some of these efforts do not focus on rare diseases. For example, patients select drug development research topics for the European Medicines Initiative, a partnership between the European Union and industry. The IRDiRC is forming a new task force on patient engagement to increase patient participation in all aspects of research. The RDAP expressed concerns regarding how specific the patient-centered outcome measures are, and how researchers can balance the utility of existing measures with the time and resources required to develop new ones. Mr. Morel recommended focusing on measures of concepts that are common to many rare diseases, such as fatigue.

Catalyzing Registry-Based Randomized Comparative Effectiveness Trials for Inherited Metabolic Diseases in Children: Establishing a Core Outcome Set and Data Collection Tools

Maureen Smith, an RDAP member, reviewed a new project funded by the Canadian Institutes of Health Research in which she is a co-investigator. This project will establish a core outcome set (COS) for future comparative effectiveness trials in pediatric inherited metabolic disorders. Ms. Smith explained that inherited metabolic disorders are caused by many different defects in genes, and no standardized patient-centered outcome measures are available for these disorders. The initial focus of this project will be on two rare inherited metabolic disorders. The hope is that the outcome measures developed for these two diseases can be generalized to other inherited metabolic disorders.

Core Outcome Set for Pediatric Rare Diseases

Dr. Gyasi Moscou-Jackson, Program Officer, Healthcare Delivery and Disparities Research at PCORI, reminded the RDAP that the panel had agreed on the need to develop a COS—a minimum set of outcomes or outcome measures for use in all trials in a specific area—for pediatric rare diseases. During the Spring 2017 in-person meeting, the RDAP chose to focus on pediatric rare diseases because about 50% of rare diseases affect children.

Since the spring RDAP meeting, PCORI staff have reviewed the published literature and identified seven published COS focused on pediatric diseases, but there have been none on rare disease at-large. PCORI staff then developed a list of 191 potential outcomes based on the literature; the PCORnet Common Data Model, the National Patient-Centered Clinical Research Network Common Data Model; and the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) pediatric and adult health measures. Staff then narrowed the list down to 25 unique outcomes and asked the RDAP to prioritize these 25 outcomes. A review of PCORI's portfolio identified 15 rare disease studies involving children that measure 113 health status and well-being outcomes, which included some of the prioritized outcomes.

RDAP members offered the following recommendations for proposing a COS:

- Ask patients with rare diseases, their families, and researchers whether the outcomes identified by PCORI are the most important
- Recommend, but not require, that all PCORI studies of pediatric rare diseases measure the outcomes in the COS when appropriate
- Determine:
  - The overlap among the outcomes in the published COS for common pediatric diseases
  - Whether a COS developed for one disease has been used in studies of other diseases
  - Outcomes measures developed or refined by the NIH Rare Diseases Clinical Research Network
  - Which validated instruments can be used across multiple pediatric rare diseases with the goal of recommending that common outcomes and measures of each outcomes are collected and used in studies
  - How the outcomes information will be used once it is collected
- PCORI to share recommendions with a few PCORI-funded investigators who have conducted pediatriatric rare diseases to discuss the feasiblity of collecting the recommended outcomes.

Developing PCORI Informational Resources to Better Serve the Rare Disease Community

William Silberg, Director of Communications at PCORI, showed RDAP several new resources on PCORI's website that are relevant to rare diseases:

- PCORI-Funded Rare Disease Projects and Related Resources: Landing page with applicant resources, links to webinars, blogs, feature stories, videos, and information on PCORI-funded research
- Research Spotlight on Rare Diseases: An easy-to-understand, two-page overview of PCORI's rare disease research
- Research Topics: Links to pages with detailed information on specific topics (e.g., cardiovascular disease, pain care and opioids, and transitional care)

The RDAP recommended adding information to the website on advocacy groups focused on rare diseases and links to resources for rare disease research. They suggested that the rare disease landing page be targeted primarily to patients.

Presentation Materials for PCORI's Rare Disease Portfolio

Dr. Parag Aggarwal, Senior Program Officer, Healthcare Delivery and Disparities Research at PCORI, reviewed the slides that PCORI developed for RDAP members to use for presentations about PCORI and its rare disease initiatives and activities. The slide set includes information on PCORI's mission and rare disease focus, types of PCORI awards for rare disease research, and PCORI resources that are specific to rare diseases. RDAP members can choose from among these approximately 40 slides to tailor each presentation to the audience.

RDAP members offered the following recommendations:

- In the map showing the states with PCORI-funded projects, indicate more clearly that the dark-colored states are those in which PCORI contracts are based and include PCORI's research network sites
- Select a core set of the slides that should be included in all presentations
- Add the following information to the slides:
    - Differences between PCORI and other funding agencies, such as NIH
    - Patient and advocacy organization engagement with PCORI
    - Research approaches for rare diseases compared with those for common diseases
    - Examples of research questions asked in PCORI rare disease studies
    - How rare diseases can be studied in a comparative effectiveness research paradigm
    - Talking points, including what to say to different audiences

Case Study: PCORI-Funded Rare Disease Study on Urea Cycle Disorders

Dr. Nicholas Ah Mew, Medical Geneticist at Children's National Health System, described the PCORI-funded study that he leads: Comparative Effectiveness of Therapy in Rare Diseases: Liver Transplantation vs. Conservative Management of Urea Cycle Disorders. Conversion by the urea cycle of ammonia, a waste product, into urea requires coordination of six enzymes and two transporters. A person with a defect in any of these enzymes or transporters has a urea cycle disorder. Treatment of these rare disorders can consist of special diets, medications, and dietary supplements. Despite these treatments, patients can develop cognitive problems or liver disease, and some die. A liver transplant can eliminate the need for special diets and medications, but this procedure can cause complications. This PCORI study is comparing survival rates, cognitive function, and patient-reported quality of life in patients treated medically and those who have a liver transplant. The study will continue enrolling patients until March 1, 2018, and the formal analysis will begin after that.

Dr. Ah Mew reported that writing the PCORI application was harder than writing an NIH proposal because PCORI requires many more details. However, the information that must be included in a PCORI application helped Dr. Ah Mew consider some issues he might not otherwise have thought about, and the PCORI requirement to include recruitment milestones help keep the project on track.

An RDAP member suggested that the researchers use the results of this study to develop a decision rubric that could help families choose the best treatment option for their child. Such a rubric could be

helpful in many other diseases for which liver transplant is an option. The RDAP also suggested that some of the measures used in this study be added to the COS for pediatric rare diseases.

Closing and Next Steps

Dr. Aggarwal reported that PCORI recently funded two studies on transitions from pediatric to adult care for patients with sickle cell disease, and this program could be a model for future PCORI rare disease research. Although transitions of care are not unique to sickle cell disease, children with a rare disease tend to have worse outcomes during the transition from pediatric to adult care. This could be a discussion topic for a future RDAP meeting.

The RDAP identified the following potential future meeting topics:

- Linkages between clinical outcomes and patient-reported outcomes using PCORnet
- Success rates for rare disease applications at PCORI and sharing lessons from this experience to applicants
- More frequent presentations on the challenges and successes of PCORI-funded projects
- Dissemination plans and innovative dissemination approaches used in PCORI-funded projects

Sarah Philbin, Program Associate, Clinical Effectiveness and Decision Science, reported that the manuscript, *An Overview of the Impact of Rare Disease Characteristics on Research Methodology,* which was prepared by PCORI staff under Dr. Naomi Aronson's leadership. The manuscript was then circulated to RDAP members for review, and presented at the Spring 2017 RDAP meeting for discussion, and has now been submitted to *Orphanet Journal of Rare Diseases*.