Advisory Panel on Rare Disease Meeting Summary

Overview

On October 30, 2015, the PCORI Advisory Panel on Rare Disease (RDAP) held its fifth meeting in Washington, DC.

RDAP's 14 members 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.

The RDAP reviewed recent revisions to the PCORI Guidance on Research in Rare Diseases and suggested that PCORI consider whether to classify rare subsets of common diseases as rare diseases. The panel learned about the Hydrocephalus Clinical Research Network, which created a successful data infrastructure for the active sharing of data across health systems that fosters clinician learning and supports new research projects, through a presentation of a PCORI-funded clinical trial comparing the effectiveness of two common surgical procedures for hydrocephalus from Dr. William Whitehead of Baylor College of Medicine. Panel members were enthusiastic in their response to the presentation, noting that it offers them insights on successful rare disease research models and stimulates their own thinking about what can be accomplished. RDAP members then separated into breakout groups to discuss the development of guidance in three areas: human subjects issues specific to rare diseases, importance of and best practices for research prioritization, and challenges of producing reliable evidence for rare diseases. The breakout group chairs then summarized their group's discussions for the full RDAP. The RDAP received updates on PCORI's rare disease portfolio and on the progress made by PCORI's clinical data research networks (CDRNs) in establishing rare disease cohorts. The CRDNs are part of the PCORI-funded National Patient-Centered Clinical Research Network, PCORnet.

Related Information

- About this Advisory Panel
- Meeting Details and Materials
- Advisory Panel on Rare Disease May 27, 2015, Meeting
- PCORI Guidance on Research in Rare Diseases
- Rare Disease Landscape Review
- A Randomized Controlled Trial of Anterior Versus Posterior Entry Site for Cerebrospinal Fluid Shunt Insertion

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

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Final PCORI Guidance on Research in Rare Diseases

Dr. Danielle Whicher, Program Officer for the Clinical Effectiveness Research (CER) team at PCORI, summarized the recent revisions to the PCORI Guidance on Research in Rare Diseases. Changes included simplifying the document's language, adding a table comparing the requirements for CER in common and rare diseases, and adding a hyperlink to a list of PCORI-funded rare disease projects. PCORI is disseminating the document through a blog post, FAQs for applicants, and a PDF on PCORI's website.

RDAP members pointed out that in the world of personalized medicine, any variant of a disease can be considered rare. Whether a study of a rare subset of a more common disease should be classified as rare disease research requires a policy decision by PCORI. Phenotypic definitions of diseases might help make this distinction.

A Randomized Controlled Trial of Cerebrospinal Fluid Shunt Insertion for Pediatric Hydrocephalus: Current Progress and Lessons Learned

Dr. William Whitehead of Baylor College of Medicine described the Hydrocephalus Clinical Research Network (HCRN), whose mission is to dramatically improve the lives of children with hydrocephalus, a rare disease, through multicenter clinical research. The network's nine high-volume centers contribute data and biospecimens to a registry, and each center uses these data to develop research projects. Network studies have identified risk factors for the failures of shunts (the most common hydrocephalus treatment), which has led to the development of standardized diagnosis and treatment protocols.

Dr. Whitehead leads a PCORI-funded clinical trial to compare the effects of two common shunt entry sites—anterior and posterior—on shunt failure. If this trial, which opened in April, shows that one shunt insertion site is associated with less shunt failure than the other site, the Hydrocephalus Association will encourage patients to advocate for the superior technique at its annual conference and through its website and social media.

RDAP members commented that the HCRN and Dr. Whitehead's study provide insights into the characteristics of successful rare disease research. These experiences show that PCORI-funded research projects might be more likely to meet their milestones and goals if they are based on an existing network than one created de novo.

Follow-Up Guidance to the Rare Disease Landscape Review: Breakout Groups

Dr. Parag Aggarwal, Senior Program Officer, reported that since the last RDAP meeting, when the panel discussed topics missing from the Rare Disease Landscape Review, PCORI staff and RDAP leaders have proposed reframing the priority topics into the following three:

- Human subjects issues specific to rare diseases
- Importance of and best practices for research prioritization
- Challenges of producing reliable evidence for rare diseases

RDAP participants separated into breakout groups, each chaired by an RDAP member, to discuss each priority topic for the Rare Disease Landscape Review (see appendix for discussion summaries). After the breakout discussions, each group gave a report to the full RDAP, summarized below.

Human Subjects

Patricia Furlong, chair of the Human Subjects breakout group, reported that this group focused on privacy and informed consent in the context of registries. Types of expertise that the breakout group needs are ethics, government regulations, informed consent research, and patient/family members' experiences with informed consent. To inform future discussions, the breakout group proposed reviewing the literature on informed consent for children (as they doubted much literature would be found on informed consent for children with rare diseases). The breakout group requested a survey of patients with three distinct kinds of experiences: those who have agreed to participate in a registry, those who have been asked to join a registry but refused, and those who have never been asked to join a registry. The purpose would be to identify issues that patients and family members should consider when invited to participate in a registry and issues that investigators should address in their registry design and pre-consent[1] and consent forms. The group plans to produce separate reports for professionals and patients.

RDAP members suggested that the Human Subjects breakout group address the advantages and disadvantages of consent from multiple Institutional Review Boards (IRBs) versus a central IRB for registries within networks. Other suggestions for the group were to review the publications of the American Academy of Pediatrics on assent and consent for pediatric populations, consider ways to ensure that informed consent is broad enough to make patient data available for research questions that have not yet been identified, and address protection of patient biospecimens.

Please see Appendix A for a full summary of the breakout discussion.

Research Prioritization

Dr. Marilyn Bull, chair of the Research Prioritization breakout group, reported that this group identified the HCRN and the Cystic Fibrosis Therapeutics Development Network as examples of cohesive rare disease research communities that came to consensus on research priorities for a given rare condition. Best practices to engage patients and stakeholders in setting a research agenda include: strategic planning, modifying study designs based on outcomes chosen by patients, obtaining input from advocacy organizations and scientific agenda meetings on patient-reported outcomes, educating patients on the value of their input, and sharing information gained at scientific agenda meetings by patients with their communities. Best practices for forming strong partnerships between rare disease patient and caregiver communities and research communities include: assigning a research leader and a patient leader to research efforts, using grassroots outreach methods to ensure inclusion of diverse

[1] Panel members noted that most consent forms are not subject to change by an individual investigator, and that therefore, for the most part, there are documents called "pre-consent" forms that accompany the consent forms and are actually the documents that can be modified to explain the study/registry to the patient. Thus, pre-consent and consent are not the same.

populations, and identifying funding channels to support initial rare disease research. The group plans to develop a roadmap for interested parties that will include tools for strategic prioritization.

RDAP members encouraged the group to address data sharing and development of standards that make it possible to share data and collaborate with other groups. Dr. Bull clarified that these issues will be part of the roadmap the group plans to develop. She added that a literature search will help the group identify existing standards and other relevant resources to include in the toolkit.

Please see Appendix B for a full summary of the breakout discussion.

Challenges with Producing Reliable Evidence for Rare Diseases

Dr. Naomi Aronson, chair of the Challenges with Producing Reliable Evidence for Rare Diseases breakout group, reported that this group identified many characteristics of rare diseases that present barriers and opportunities for creating an evidence base for rare diseases, including differences in prevalence, lethality, non-disease characteristics, and temporality, among others. The group highlighted that cross-cutting rare disease research that includes conditions with similar characteristics may be a good opportunity to increase eligible research participants. The group also identified infrastructure-related challenges, such as the sustainability and utility of existing networks or registries, ethical and legal issues, variations in regulations, and the availability of specialists and/or centers of excellence in medicine and methodology. The group's next steps include soliciting additional advice from experts in clinical trials and other areas, conducting a literature and web search for typologies and definitions of disease characteristics and for research techniques related to the degree of relatedness of rare diseases and the ability to use unrelated evidence.

RDAP members noted that some interventions need to focus on a single rare disease, such as surgery for hydrocephalus. Other interventions could help individuals with different diseases, such as interventions designed to address psychosocial issues of infants with life-threatening conditions.

Please see Appendix C for a full summary of the breakout discussion.

Breakout Group Next Steps

An RDAP suggestion was to create a single brief document that includes the guidance generated from each breakout group and an overview section that identifies some common themes. Panel members also called for updating the document over time to reflect new developments in rare disease research.

The timeline for breakout group participants to develop guidance around the three main topics is as follows:

- November 2015 – January 2016: Refine the workgroup objectives and deliverables and develop an outline for the workgroup document. At the January 2016 RDAP meeting, time will be reserved for workgroups to meet and review their document outlines.
- January 2016 – April 2016: Draft a document that provides guidance to the rare disease community based on the outline discussed at the January 2016 RDAP meeting. At the April 2016

RDAP meeting, time will be reserved for the workgroups to discuss the complete draft documents.

- April 2016 – July 2016: Revise and finalize the draft document. Time will be reserved at the July 2016 RDAP meeting for presentations of the final guidance documents. The goal is to publish the documents produced by each group on the PCORI website and in a special issue of a peer-reviewed medical journal.

Update on PCORI's Rare Disease Portfolio

Mary Kay Margolis and Vadim Gershteyn of PCORI's Evaluation and Analysis program reported that as of October 2015, PCORI has 52 rare disease projects that represent 6 percent of PCORI's research portfolio. Among the 20 rare disease projects funded under broad funding announcements and the one rare disease pragmatic clinical trial, the most common disease category is congenital, hereditary, and neonatal diseases and abnormalities. Ten of the 21 projects (47 percent) focus on children, and three general population studies (14 percent) include children. The proportions of racial and ethnic minorities (33 percent), low-income populations (10 percent), and women (14 percent) in these studies are lower than in the overall portfolio. Of the 21 rare disease projects, 4 focus on rare cancers and 3 on sickle cell disease.

RDAP members agreed that this report was useful. They suggested that in addition to the types of information provided in the current report, future reports should specify types of interventions in rare disease research, levels of engagement of various stakeholders (e.g., whether researchers are part of an existing research network), number of applications submitted versus number funded, and overarching reasons why some applications were not funded.

PCORnet Update

Dr. Maryan Zirkle, Program Officer for the CER Methods and Infrastructure program, provided an update on the 13 Clinical Data Research Networks (CDRNs) of PCORnet, the National Patient-Centered Clinical Research Network. In Phase I of PCORnet, which is now coming to an end, the CDRNs began recruiting a rare disease cohort using available electronic data. In Phase II, CDRNs will conduct preliminary analyses and continue to develop their rare disease cohort. The CDRNs are establishing advisory groups that include patients, caregivers, clinicians, and researchers. Some CDRNs are trying to develop novel recruitment approaches in which patients can opt out of a study at the time of recruitment and are spending most of their time working on this with respect to their cohorts. Dr. Zirkle is creating a template to collect data on rare disease cohorts from the CDRNs.

Recap and Next Steps

Prior to the next RDAP meeting in winter 2016, workgroup members will refine their objectives and deliverables and develop an outline for the workgroup document. At the January 2016 RDAP meeting, time will be reserved for workgroups to meet and review their document outlines.

Appendix A: Meeting Summary of Human Subjects Breakout Group

Attendees: *Patricia Furlong (chair), Sindy Escobar-Alvarez, Kate Lorig, Philip Ruff*

Staff: *Beth Kosiak, Meheret Shumet*

Key Considerations

The group agreed to focus initially on informed consent for registries in the United States but planned to address broader privacy issues and informed consent for clinical trials in its final document. The most important characteristics of consent forms for registries of people with rare diseases include:

- A literacy level that is appropriate for the target audience
- A disclosure, or pre-consent, form that patients read before signing a consent form
    - Many consent forms cannot be changed because their content is mandated by state or federal legislation.
    - A pre-consent form explains what is in the consent form.
- Broad stipulations that allow academic institutions to share registry data with other investigators without obtaining informed consent again and to avoid the need to change the consent form in the future
- An explanation that the patient's data will remain in the registry in perpetuity
- An explanation that as new information becomes available, the data might be used in different ways
- Opt-out clauses stating that volunteers can remove their consent at any time without giving a reason and request removal of all data
- Information on how researchers and/or patients can access registry data

Sharing Registry Data

There are divergent interests that must be addressed for this to be the case. For example, a common business model in the pharmaceutical industry is for a company that is the sole manufacturer of a drug for a disease to create a valuable registry that is the only one in the world. But when other companies start to develop drugs for that same disease, each creates their own registries and the data is not aligned or shared among the companies.

Rare disease data from registries should be shared with investigators. By definition, very few patients have these diseases, and the more data that are available to be analyzed, the better the outcomes for patients will be. However, pharmaceutical companies do not usually have this perspective.

Questions that are important to address about access to and use of registry data are:

- Who owns the data in a registry?
- Who has access to registry data?
- How will those with access use these data?

- Will patients find out how their data are used?
- Will the data be shared?
- If the registry closes, what is the process for transferring the data to other registries?

In research on highly prevalent diseases, patients have a range of concerns, one of which is that they are often concerned about privacy issues and may not want their data to be shared because of fears that these data might be used inappropriately.

Informed Consent for Children

The breakout group wondered about the age at which children take on responsibility for their own data in a registry and whether children have the right to decide whether to remain in or drop out of a registry. Taking on responsibility for one's own registry data should depend on the child's cognitive ability and emotional maturity. Sometimes, parents continue to manage the care of their adult children with rare progressive diseases because these adult children do not have the emotional maturity to obtain the care they need. However, that is not always the case, and such issues need to be assessed.

Parents of children with a rare disease often regard an informed consent form as their "ticket" to obtain a new treatment for their child and do not necessarily think about the long-term consequences of such consent. Parents are often so focused on the opportunity to engage their child in something that may help them that they are not particularly concerned with what the form says; they are willing to sign it regardless.

Participant Knowledge of Their Registry Records

People who have consented to be part of a registry might not remember that they have done so or know how to contact that registry. This situation could arise, for example, when a child becomes an adult and the parent who consented to include the child in the registry has died or the custodian of a registry has changed. Similarly, if a patient is part of a registry managed by a company that manufactures a drug and the patient starts using a different drug instead, the patient is unlikely to find out what happened to his or her data in the first company's registry. In addition, a company may go out of business, be involved in a merger, or the key personnel in the company or an academic institution responsible for a database may leave and the database may not be easily traceable under such circumstances.

If a patient does not recall the name of the principal investigator, the patient might remember the name of the company that owns the registry. But a patient might not know whom to contact if the original owner is now part of a different company. It was suggested that perhaps the best person for a patient to ask about the status of a registry is his or her healthcare provider, who should be able to find out which company manufactures the drug and where the data may reside.

Patients should have access to their own registry data. This is especially important for young adults who may not have other records to take to new physicians.

Ownership of Registry Data

Pharmaceutical companies want exclusive ownership of registry data, which gives their drug a competitive advantage and this is clearly antithetical to the open sharing of data that patients need and want. Several suggestions were made to address this impasse. One option might be to have companies agree to combine all registry data a year after a Phase II trial starts, but this would require new legislation. Another option is that patients could refuse to join any pharmaceutical company registry unless the owner agrees to share their data.

Companies primarily own drug registries, not disease registries. Although these registries collect a variety of disease-specific data, they focus on measuring the impact of their drug on the disease. Simply collecting data on a disease and not how to modify it rarely serves a company's interests.

Perhaps consent forms should let patients know of other registries of patients with their disease or inform them that other registries might be created in the future. This could be part of the pre-consent form.

Patients should have access to their own registry data. This is especially important for young adults who may not have other records to take to new physicians.

Opting In and Out of Registries

A key element of a consent form could be agreement to undergo periodic assessments of whether the patient still has the ability to understand what he or she has consented to do. To avoid diminishing the number of people in registries unnecessarily, registry owners should have permission to periodically ask (up to, for example, three times) those who have opted out whether they are willing to opt back in. If a patient is upset with a pharmaceutical company and drops out of a registry, the patient might be willing to reconsider this decision after some time has passed.

Another suggestion was to ask patients periodically whether they still want to be part of a registry. This would keep patients informed of the status of the registry, such as whether its ownership has changed and whether it is still active. Registry owners could simply remind patients of what they have consented to and ask these patients whether they want to continue being part of the registry.

Objectives

A main objective of this work group is to get input from patients with rare diseases on what should be clarified in a consent form. This can be done using the following methods:

- Ask patients to read a sample consent form and describe what information they obtained from the form and what needs to be explained more clearly. Perhaps these questions could be asked as part of a dinner meeting sponsored by a pharmaceutical company. They could also be

discussed in online patient forums and at patient conferences on rare diseases. The questions could be sent to PCORI's network of patients, perhaps through PCORnet.

- PCORI could ask patient advocacy organizations (especially organizations that address multiple rare diseases, such as Genetic Alliance or the National Organization for Rare Disorders) to send a survey to three distinct groups of adult patients and parents of pediatric patients:
- Those who have signed a consent form to participate in a registry
- Those who have been asked to sign a consent form for a registry but refused
- Those who have never been asked to sign a consent form for a registry

Questions to ask might include:

- What information should be included in a pre-consent form?
- If you declined an offer to participate in a registry, why did you do that?
- If you have a child with a rare disease, how do you discuss informed consent with your child?

Next Steps

As a next step, we will be identifying informed consent experts who could conduct this research. The study following up on the research would require funding. It might be possible to obtain accelerated institutional review board approval for the study. With the appropriate expertise, the design of this research could be streamlined for prompt completion of the project.

Experts to Include

Experts that the group suggested to contact are:

- Donald Patrick, University of Washington, an expert in patient-reported outcomes who has a child with a rare disease
- Arthur Caplan, a bioethics expert at New York University
- An expert in government regulations pertaining to informed consent
- A parent of a child with a rare disease (such as Vincent Del Gaizo, the RDAP co-chair) who has discussed informed consent with that child
- An expert in informed consent (such as Dr. Yaffa Rubinstein, an RDAP member)
- Patients who have thought about informed consent for rare disease registries
- Society for Clinical Trials
- PCORI's Advisory Panel on Clinical Trials
- The Clinical Trials Transformation Initiative (CITTI), which has an informed consent project
    - Pamela Tenaerts, Executive Director, is also on the Advisory Panel on Clinical Trials Expert Post-Award Subcommittee

These experts could help the group identify the questions to ask the three groups of patients.

Literature Review

Before the group conducts the proposed study, it needs to review the literature to assess the state of the literature and determine if others have already studied these issues. There is probably no literature on informed consent for rare diseases per se. However, the literature on informed consent in general might have some relevance. It might also be worthwhile to review the literature on informed consent in children and adults to determine whether there are any differences and identify the issues that arise in longitudinal studies in children. The group should also review relevant publications by CITTI.

Appendix B: Meeting Summary of Research Prioritization Breakout Group

Attendees: *Marilyn Bull (chair), Lisa Heral, Mardi Gomberg-Maitland, Vincent Del Gaizo, William Whitehead, Jacqueline Alikhaani*

Staff: *Parag Aggarwal, Mychal Weinert, Randa Abu-Rahmeh*

Key Considerations

Rare Disease Research Communities

Members of the breakout group cited exemplar rare disease research communities that have come to consensus on research priorities for a condition. Strong partnerships between rare disease patient/caregiver communities and research communities are key to having a cohesive research agenda. The following are examples of communities that have established this:

- Hydrocephalus
- Cystic fibrosis
- Down syndrome
- Spinal muscular atrophy
- Sickle cell disease
- Pediatric rheumatology
- Trisomy 13
- Trisomy

Best Practices for Establishing Priorities

To set a unified rare disease research agenda, researchers must strategically engage stakeholders. Forming partnerships with community advocacy organizations, for example, allows researchers access to rare disease patient contacts and networks. These networks can be leveraged to collect data on patients' concerns and desired outcomes when seeking treatment, which can be collated and used to build comparative effectiveness research (CER) questions. This engagement strategy can also be used to identify and unify disparate research efforts that are already under way, as opposed to one in its initial phases, by integrating current patient-reported data and redesigning the study, if needed.

Best Practices for Engagement and Implementation

Having a cohesive community, as well as ensuring the successful dissemination and implementation of the research priorities, is of the utmost importance for rare disease populations. Below are specific implementation strategies brought forth in this breakout group:

- Hold regular scientific agenda meetings to share and discuss information among diverse stakeholders, which include rare disease patients
- Educate patient attendees on the value and impact of their input and encourage them to share the information they gain at these meetings with their communities
- Allocate grassroots outreach methods to ensure inclusion of diverse and disparate populations
- Identify funding channels that might better support research efforts, especially research efforts that are in their infancy

- Develop effective processes for data collection and data ownership
- Invest in improving data warehouse infrastructures to support high-quality data collection and management

Objectives

The purpose of this workgroup was to consider and identify best practices to unify communities, stakeholders, and patients when soliciting research priority questions to set a rare disease research agenda. The following set of objectives, which may be helpful in achieving the overall purpose, was developed:

- Identify diverse outreach and collaboration strategies/methods to determine what is in the field in terms of literature and expertise.
    - When scanning the landscape, data should be gathered from efforts at different stages in their research (e.g., in their infancy, intermediate, well-defined). The narrative of this process can be used to develop a ***roadmap*** for other researchers in similar phases in their research. The roadmap would include the different stages:
        - Infancy: Initial topics and ideas have been identified and groups of individuals are starting to work on attempting to address outstanding questions and evidence gaps;
        - Intermediate: Different groups (researchers and other stakeholders alike) are actively involved in researching identified priority topics, but may not be aware of the other research currently ongoing, creating research silos;
        - Well-defined: Various stakeholders have come together to jointly address priority topics and are actively working together with each other (researchers, patients, other stakeholders alike), sharing results and disseminating and implementing meaningful findings.
- Encourage researchers to break down research efforts into small attainable goals. This can help identify the most suitable funding resources to support each respective phase of the research.
- Support efforts to develop, refine, and utilize data collection toolkits (e.g., EPIC, SurveyMonkey), which will help build a strong data set and can also be used to define specific variables for registries.
    - Conduct grassroots, granular quantitative data collection (e.g., one-on-one interviews with researchers/health advocacy groups at different stages in their research and with individuals in the community).

Consider experts from unique areas of expertise. For example, include and engage clinical epidemiologists; individuals from data coordination centers (i.e., statisticians); and information technologists.

Next Steps

PCORI staff and panel members will collaborate to refine the objectives of this workgroup and develop an outline for a formal document delineating best practices. The next RDAP meeting will convene January 2016 where the workgroup will meet again and review their work to date.

Experts to Include

Experts that the group suggested to contact are:

- Experts at National Organization for Rare Disorders (NORD)
- Experts at The Cystic Fibrosis Foundation
- Dr. Sharon Terry, PCORnet awardee
- Experts at the Biostatistics Center at George Washington University
- Paul Gross, founding partner of the Hydrocephalus Clinical Research Network (HCRN)
- Dr. Melissa Parisi, Eunice Kennedy Shriver National Institute of Child Health and Human Development, funded and developed the Down Syndrome registry.
    - NIH launches tool to advance Down Syndrome research
- Experts at Cornelia De Lange Syndrome Foundation
- Fanconi Anemia patient/advocacy group
    - American Society of Hematology
- Experts at Adult Congenital Heart Association
- Muscle Atrophy patient/advocacy group
    - NORD Spinal Muscular Atrophy; Dr. Barry Russman
- Experts involved with PSCANNER in San Diego
- Trisomy 13 and 15, Salt Lake Group.
- Experts at American Heart Association

Appendix C: Meeting Summary of Challenges with Producing Reliable Evidence for Rare Diseases Breakout Group

Attendees: *Naomi Aronson (chair), Lisa Heral, Mark Skinner, Yaffa Rubinstein, Jim Wu*

Staff: *Danielle Whicher, Harold Sox, Kim Bailey, Emma Djabali*

Key Considerations

The following questions were considered by the participants.

1. *What features of a rare disease impact the ability to generate reliable evidence about treatment options for that condition?*
2. *How do each of those features impact evidence generation? How do those features impact which study designs are feasible to implement?*
3. *Is it possible and would it be useful to organize those features into a framework or typology to help decision makers and researchers understand what type of study designs can be implemented and what level of evidence can be produced in different situations?*
4. *How can we capture considerations of both strength of evidence and the degree of uncertainty and risk that is acceptable in various contexts?*

Members agreed that creating a typology of rare diseases (question #3) would be useful to answer questions #1 and #2. During the breakout session, they generated a list of features of rare diseases (in terms of disease and infrastructure characteristics) that would impact evidence generation. The list is included below and will serve as the starting point for the typology.

Disease Characteristics

- **Prevalence**
  Members agreed on the need to generate appropriate ranges of prevalence for diseases that are considered rare (both nationally and globally), since the prevalence impacts the number of individuals eligible for a study of a given rare disease. In the United States, a disease or condition that affects less than 200,000 cases is considered rare disease. There is a wide range in the size of the populations affected by various rare diseases, so the ability to recruit adequate numbers of patients varies considerably, and limits that apply to the smallest populations do not apply to the largest populations. Additionally, some diseases or conditions may be rare in the United States but common in other countries. Finally, the number of untreated and "treatment experienced" patients may also impact the ability to generate reliable evidence, as these features may drastically narrow the eligible population for participation in research.
- **Mortality/Morbidity**
- **Homogeneous/heterogeneity**

- Within one rare disease (e.g., disease severity)
    - Molecular and genetic diagnostics have made the definition of patient subgroups much easier (e.g., Philadelphia positive and negative subtypes of leukemia)
- Heterogeneity among patient willingness to participate in rare disease research

- **Disease course and progression**
    - Progressive
    - Relapsing/remitting
    - A combination of the above-mentioned types

  The timing of the onset or progression of clinical manifestation and the resulting morbidity or mortality vary widely among rare diseases. Early onset in a pediatric population or slow progression through adulthood may limit the ability to collect robust cohorts of patients for comparison of an intervention.
- **Age of patient population**
    - Pediatric (neonate, infancy, juvenile)
    - Adolescent/young adult
    - Adult (mid-life, late life)
- **Non-disease characteristics of the population:**
    - Demographic (race, ethnicity, socioeconomic status, health literacy)
    - Patterns of care and referral
    - Psychosocial
    - Comorbidities
- **Etiology**
    - Genetic
    - Infectious
    - Environmental
    - Interaction of genetic and environmental
- **Temporality (Duration)**
- **Cross-cutting targets and pathways/relatedness of different diseases:**
    - Emerging research techniques on related conditions and the use of indirect evidence may support aggregation across diseases.
    - Certain endpoints and analyses (analyses looking at supportive care; conditions that manifest similarly/share disease processes; diseases that affect same organs, share common interventions/pathways of care) may allow aggregation across disease types, to allow for widening of rare disease population for research.
    - We may want to articulate a technique of applying evidence from one disease to another, and what is required to evaluate the strength of that evidence; for example, a research technique related to the degree of relatedness of rare diseases and the possibility of indirect use of related evidence.
        - Collaboration across disciplines of science (e.g., animal models) may also be included under this topic
        - Similarities in the pathway of care delivery for rare disease with common symptoms or outcomes

- In a registry, you could define performance measures to help include a sub-population that appears to be pretty similar.

Infrastructure Characteristics

- **Existing networks, registries, or repositories**
  - Governance/ownership
- **Linkages/potential for data sharing are critically important, especially for rare diseases**
  - Allows aggregation of data from various sources and across various countries
  - Allows monitoring of disease progression and response to treatment
  - Allows clinicians to see what other approaches may be useful within a given patient
- **Ethical/legal issues**
- **Variations in regulations**
  A lack of harmonization/standardization across registries (e.g., using different terminology) and regulatory bodies (e.g., trials for drug approval versus for off-label use of drugs), especially where global trials are needed due to prevalence of a condition, can be a barrier to rare disease research, which often requires international recruitment due to an insufficient number of patients. This is particularly true when seeking to examine a specific manifestation/outcome for a sub-population of a rare disease.
- **Availability of specialists and/or centers of excellence:**
  - Level of knowledge about the pathogenesis and genetic/molecular underling of the disease, including natural history of the disease
  - Clinical expertise (e.g., number of physicians who are experts in a certain rare disease)
  - Methodological expertise
- **Patient support network**
  - Level of funding (capacity)/sources of funding support (potential for financial conflict)
  - Focus on research agenda
  - Ability to identify and articulate key outcomes of relevance defined from a patient perspective, which may differ from those identified by clinicians or endpoints used in clinical trials.
  - Level of organization, scope, and representativeness of the organization
- **Patterns of care**
  Heterogeneity or homogeneity of standards of care/treatment guidelines and practice pattern changes over time, or from one geographical area to another, can make evidence generation challenging.

Other considerations

- **Potential impact of different types of research on evidence generation**
  - In some cases, observational data may be the only option.
    - Heterogeneity of standards of care and practice pattern changes over time make observational research challenging.

- The type of intervention (e.g., drug, device, health system) may also impact the generation of reliable evidence.
    - When the intervention is a device, it is difficult to have true randomization and a placebo trial is not possible. This is not an issue specific to rare disease, but may potentially lead to an amplified impact in the rare disease research space.
    - Pathways of care may not be well organized or defined for a rare disease. The total direct and indirect burden of the rare disease on a health system or family may not be well understood.
- Adaptive designs can be appropriate for rare disease research
- Instrumental variable analysis could be used in cases where physician preference drives treatment choice (e.g., surgical approach/technique).

Objectives

Participants identified the following three objectives:

1. Delineate characteristics that present barriers and opportunities for creating an evidence base for rare diseases: ceiling and floor of the evidence that can be produced
2. Create a visual matrix typology relating the characteristics to study considerations and design
3. Outline implications of the typology for practice/implementation/regulation

Next Steps

- **Identify individuals with the following expertise**

    - 2 or more trialists
    - individual(s) with expertise in observational study design and analysis
    - individual(s) with expertise in creating data networks
    - individual(s) with expertise in transforming individual groups (working in a silo) into collaborative communities
    - Expert medical writer

    Some potential sources to identify these experts:

        - IOM/PCORI 2013 symposium attendee list
        - Methodology Committee
        - CTAP
        - ISPOR
        - FDA
        - AHRQ
        - NORD

- **Conduct literature/web searches, regarding:**

    - Other typologies and definitions of disease characteristics (for both rare diseases and more common diseases) (e.g., NORD, OrphaNet, EURORDIS, GARD?)

- Research techniques related to the degree of relatedness of rare diseases and the ability to use unrelated evidence (e.g., GRADE)

- **PCORI staff to draft outline and work plan for the workgroup, to include an engagement plan for the identified experts.**