Challenges with Producing Reliable Evidence for Rare Disease Breakout

Advisory Panel on Rare Disease Winter 2016 Breakout Webinars

January 27, 2016

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Welcome and Agenda

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Housekeeping

- Today's webinar is open to the public and is being recorded.
- Members of the public are invited to listen to this teleconference and view the webinar.
- Anyone may submit a comment through the webinar chat function or by emailing advisorypanels@pcori.org.
- Visit www.pcori.org/events for more information.
- Chair Statement on COI and Confidentiality

Today's Agenda

Start Time	Item	Speaker
10:00 a.m.	Welcome and Agenda	N. Aronson D. Whicher
10:15 a.m.	Literature Review Summary and Discussion	D. Whicher
10:45 a.m.	Outline Review	
11:45 a.m.	Recap and Next Steps	N. Aronson D. Whicher
12:00 p.m.	Break	

Background

- During RDAP Spring meeting topics missing in the landscape review were identified to be addressed in a follow up document
- PCORI staff called for volunteers for each topic; 4 topics were covered by volunteers:
  - Human Subjects
  - Incorporating PROs into Registries
  - Registry Purposes
  - Evidence Grading
- PCORI staff/RDAP leadership proposed a reframing of the priority topics

Proposed Reframing of Priority Topics for Further Guidance

- Human subject issues specific to rare diseases
- The importance of and best practices for research prioritization
- Considerations related to the challenges with producing reliable evidence for rare diseases

Breakouts and Participants

- **Human Subjects**
  - Patricia Furlong (chair)
  - Kate Lorig
  - Sindy Escobar-Alvarez
  - Philip Ruff
- **Research Prioritization**
  - Marilyn Bull (chair)
  - Vincent Del Gaizo
  - Mardi Gomberg-Maitland
  - Lisa Heral
  - Jacqueline Alikhaani
  - William Whitehead
- **Challenges with Producing Reliable Evidence for Rare Diseases**
  - Naomi Aronson (chair)
  - Yaffa Rubinstein
  - James Wu
  - Marshall Summar
  - Mark Skinner

Breakout 3: Challenges with Producing Reliable Evidence for Rare Diseases – Key Questions

- What features of a rare disease impact the ability to generate reliable evidence about treatment options for that condition?
- How do each of those features impact evidence generation? How do those features impact which study designs are feasible to implement?
- 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?
- How can we capture considerations of both strength of evidence and the degree of uncertainty and risk that is acceptable in various contexts?

Goals for Discussion

- Review preliminary literature review results and use it to refine the outline
- Decide how best to extract and summarize literature results
- Clarify the goals and scope of the paper
- Discuss the needs for an expert or a technical writer

Project Timeline

- **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 directed at 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 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.

Literature Review Summary and Discussion

Danielle Whicher, PhD, MHS
Program Officer, Clinical Effectiveness Research, PCORI

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Literature Search Strategy

- "Rare Diseases"[Mesh] AND ("clinical trials as topic"[Mesh] OR "research design"[Mesh]) AND (("2003/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])
  - Results returned: 191
  - Danielle and Emma reviewed the abstracts for each reference and obtained the full text articles for all relevant references (n= 32)
- (“Rare diseases "[MeSH Terms] OR "orphan drug production "[MeSH Terms] OR "orphan drug* "[All Fields]) AND ("comparative effectiveness research "[MeSH Terms] OR "comparative effectiveness "[All Fields] OR "evidence - based medicine "[MeSH Terms] OR "methods "[MeSH Terms] OR "outcome assessment (health care) "[MeSH Terms] OR "patient advocacy "[MeSH Terms] OR "patient - centered care "[MeSH Terms] OR "health technology assessment* "[All Fields] OR "registries "[MeSH Terms] OR "patient participation "[MeSH Terms] OR "epidemiology "[MeSH Terms] OR "patient preference "[MeSH Terms]) AND English[lang] AND "humans "[MeSH Terms]
  - Results returned: 1,829
  - This was the same search that was performed by Gagne et al. (2014)
  - Due to time constraints, Danielle and Emma did not have time to review all of these references

DRAFT Data Extraction Template

- **Article reference**
- **Statement of purpose**: In one or two sentences, summarize the purpose of the article.
- **Article focus**: Does the article provide a general discussion of issues related to evidence generation for rare diseases or does the article focus on a specific study design or specific rare disease?
- **Relationship to workgroup discussions**: Which topic in the working outline does this paper relate to? Does this article provide information that would be useful for our working document?
- **Summary or findings**: In one or two sentences, summarize the main conclusions of the article.
- **Other references:** Are there articles referenced in this paper that do not currently appear on our reference list but which you think may be important to review?

Discussion Questions

- Is there anything missing from our search strategy?
- Are there any important articles missing?
- What are your overall thoughts on the literature search and the results?
- What are your thoughts on the proposed extraction template to summarize the literature search?

Outline Review

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Developing a Typology

- So far, the group has developed a list of features that can impact what kind of evidence it is feasible to generate a given rare disease.
- Now: How can we organize these features into an organized typology that will be useful for researchers and other stakeholders?

- Several approaches to consider:
  - Begin by looking at the extremes of the features we identified.
    - For example, one extreme would be rare diseases that have a very low prevalence and which are very heterogeneous while the other would be rare diseases that have a prevalence of around 200,000 in the US and which are very homogeneous.
    - From there, describe how a typology could be created.
  - Discuss whether there are “common” combinations of the features we identified and whether we can identify what evidence can be generated for rare diseases with those combinations of features.

Other Discussion Questions

- How do we categorize the types of evidence that can be generated?
  - RCT, observational studies, …etc.
  - Other ways?
- How do you suggest we categorize the different features?
  - For example, who do we categorize prevalence? Where do we make the cuts?
    - Ranges (in the U.S. or global)?
    - High/medium/low?
- Do we want to solely focus on CER?
- Do we want to solely focus on evidence generation for rare disease treatments?
- Are there members of the group that would like to take responsibility for drafting different parts of this document?

Experts to Engage

- 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

Some potential sources to identify these experts:

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

Requirements for a Writer

- **Are we looking for an expert writer or a technical writer? What do you envision the role of the writer to be?**
  - Formatting and consolidating sections drafted by this group?
    - How much time would you be able to dedicate to the drafting?
  - Drafting the whole document (need for specific expertise)?

Recap and Next Steps

Naomi Aronson, PhD
Methodology Committee, PCORI
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Next Steps

- Identification of any key articles to focus on (from the literature review or otherwise)
- Extract information from articles into the template
  - Volunteers from this group?
- Revision of outline based on today's discussion
- Identification and hiring of expert or technical writer
- Meetings/interviews with experts
  - Involvement of the Methodology Committee
- Drafting of draft concept paper

Thank You!

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