Missing Endpoints

Rare Disease Advocates' Relevance in Clinical Trial Design and the Consequences of Non-Inclusion

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RARE ADVOCACY MOVEMENT

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Introduction

An estimated 7,000 rare diseases impact nearly 30 million Americans and 350 million people worldwide, according to the National Organization for Rare Disorders (NORD).

A *rare disease* is any disease, disorder, illness or condition affecting fewer than 200,000 people in the United States. Patients are typically diagnosed at a young age and face a clinically progressive and life-limiting prognosis. The National Institutes of Health estimate that half of all rare disease patients are children, and 3-in-10 of these children will not live to see their 5th birthday.

Manufacturers of orphan drugs (Industry) are making headway to increase the number of available treatments for rare disease patients. However, even the FDA acknowledges that there are numerous and difficult hurdles to developing clinical trials for rare disease patients:

- Populations are small, limiting traditional statistical methods to design and measure safety and efficacy outcomes;
- Small populations introduce many regulatory hurdles; and
- Manufacturing costs are often high due to the complexity of disease-modifying agents that target genetic mutations, the root cause for most rare diseases. As a result, the development of the drug for clinical trial use is very expensive.

EvaluatePharma estimates the orphan drug market will increase 11% annually for the next decade, with the potential to reach more than $2.5 billion in sales. To put this in context, the entire pharmaceutical market expects to grow by 6.4% during the same period.

Rare disease communities are generally encouraged by Industry's efforts but are often frustrated by the clinical development process. While seen as critical partners in the drug development process, they, along with their families and advocates, are routinely absent when clinical research programs are designed. In particular, rare disease advocates, many who spent decades researching and advocating on behalf of their community, are either often left out or are brought in too late.

> ***"In many cases, developing a treatment for a rare disease can be especially hard and present unique challenges. Each success is the end of a long uphill climb. It requires the concerted efforts of many stakeholders, including scientists, product developers, regulators, policy makers, and of course, the energy and organization from patient advocacy groups."***
>
> ***—FDA Commissioner Scott Gottlieb, MD***

Clearly, the stakes are extraordinarily high for orphan drug developers. At the same time, the financial and emotional investments patients and caregivers make to participate in clinical trials are extensive. In many cases, a clinical trial represents a patient's best hope for a 'normal' life or even life itself. The results also impact the rare disease community represented in the trial, as treatments are 'rare' for rare disease patients.

Even with stakes this high, trials often fail to measure functional outcomes that reflect patients' *greatest unmet needs*. Failure to identify outcome measures that capture what patients' value most contribute to delays, or worse denials, to disease-specific therapy. The inclusion of patient advocates could mitigate the risk of missing endpoints. Further, advocates communicate the importance of clinical trial participation which, in turn, improves clinical trial enrollment and retention.

The current paradigm of clinical research design begs the question: ***What is a missing endpoint worth?*** More importantly, how can Industry be convinced to include advocates early and often in the clinical design process. The authors of this paper lay the foundation for what Industry has to gain by including rare disease patients and advocates in the clinical trial design.

Clinical Trial Design: Begin with the End in Mind

Anne Pariser, M.D., former Associate Director for Rare Diseases, FDA, wrote in 2014, "Begin with the end in mind." Here, she acknowledges disease natural history is a critical element of any clinical development program; however, diseases with a low prevalence inherently come with significant knowledge gaps. Industry must review available natural history data *and* be prepared to conduct natural history studies to develop a robust scientific foundation upon which to build a clinical research program.

Laying the Foundation

As Pariser suggests, natural history studies give scientists and researchers a better estimate of the prevalence of the disease, help identify potential biomarkers, affect clinical outcome assessments, and determine the feasibility of established assessments for clinical trials. Sufficient natural history studies must identify:

- Incidence and prevalence;
- Phenotypic differences;
- Causes of morbidity and mortality;
- Impact on quality of life; and
- Cultural differences and other difficult-to-measure obstacles that may impact response to therapy

Without sufficient natural history data, Industry cannot move forward with identifying clinically meaningful outcomes for the study patient population and must conduct its own research.

Identifying Sources of Information

Natural history information can come from multiple sources, including literature reviews, meta-analyses, and patient chart audits. However, direct communication with patients and caregivers is often overlooked as an important source of natural history. Industry can easily facilitate this through a Rare Disease Advocate (RDA) partnership. As a trusted entity, professional advocates provide a bridge, bringing together Industry and Community to close the information gaps. An RDA partnership also lets patients and advocates lend their voice to the clinical design process and helps Industry avoid pitfalls when informing hypotheses that drive the selection of clinical trial outcome measures.

The Path to Optimal Endpoint Selection

Clinically relevant endpoint selection should include differentiating measures that are also meaningful to patients and caregivers. This model leads to the identification of endpoints that offer the best chance of clinical success and community support. The use of patient-reported outcomes (PROs) is not a new concept; however, its adoption by Industry has been slow and fragmented. The main reason is that most manufacturers do not have an internal infrastructure (staff, resources, plans) to support an Industry-Advocacy partnership early in the trial design process.

Industry & Advocate Partnership–Figure 1

Pre-Trial: Identifying Optimal Clinical Trial Endpoints

Step 1 Develop the Partnership: Recognition by Industry of the value of partnering with Advocate(s) and Patient Community by allocating staff and budget to initiate and maintain partnership

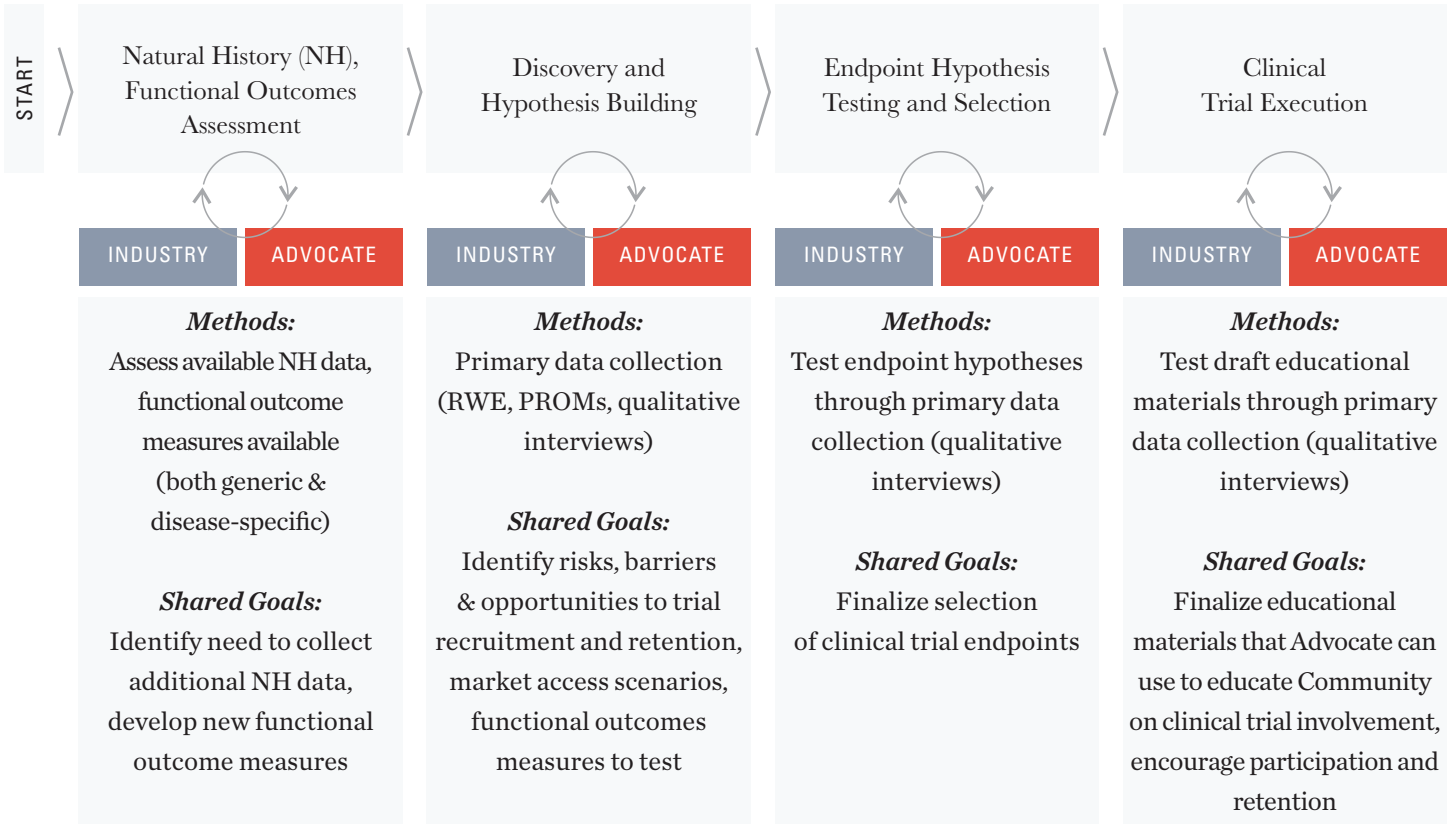

Figure 1. illustrates the elements of a successful partnership during and after natural history review.

> ***"You need Industry to take these treatments across the finish line, but you need the patient too. You have to work together, especially in rare disease. You need more conversations about the patient experience. If you really study the natural history of the disease, you'll find your endpoints. You'll know what the disease outcomes will be, because natural history will guide trial design."***
>
> ***— Kari Rosbeck, President and CEO, Tuberous Sclerosis Alliance***

Industry would have an easier time utilizing RDA resources and community networks if they incorporated this relationship into their protocol and budgets. For example, putting RDAs into a strategic plan automatically creates KPIs and other measurements that are visible to senior leadership. A budget legitimizes the importance of the Industry-Advocacy partnership internally and extends goodwill throughout the rare disease community.

Rare disease research is challenging, and the community often has specific needs that make it even more difficult. Historically, Industry has relied on casual encounters with little follow-up to capture Advocacy and Community input into clinical trial protocols. This is a missed opportunity because once protocols are approved by the FDA it is too late to course correct.

This too-little-too-late model lacks foresight, and as witnessed in several recent clinical trial failures, it is not enough to overcome the unique challenges inherent in rare disease. With this in mind, Industry must develop a plan to systematically capture input at specific points in time. Advocacy and Community should be brought into the design process early and engaged with often to avoid unnecessary delays, unforeseen costs, and ultimately meet the desired outcomes that benefit all stakeholders.

> *"We proactively asked Rett parents, what do you want to see, what are some of the challenges to trial participation? We used this information to design our clinical program protocols. It didn't stop there. We went back and discussed the protocol design with parents. From there, we knew that we had to reduce the number of visits for the trial because travel is terrible for a child diagnosed with Rett. So we designed a program where some clinic visits were replaced with phone calls and in-home reviews."*
>
> *— Christopher U. Missling, PhD,Anavex Life Sciences Corp.*

Industry & Advocate Partnership–Figure 2

Pre-IND / FDA Approval Process

Step 2 Continue The Partnership:
Preparation for commercialization through key stakeholder engagement

Payers	FDA	Patients and HCPs
INDUSTRY ADVOCATE	INDUSTRY ADVOCATE	INDUSTRY ADVOCATE
Methods: Advocates / Community may opt to share information through written letters, video documentation/ stories, social media tagging, and one-on-one meetings ***Shared Goals:*** Improve understanding of burden of disease and HEOR to reduce denials and improve access / retention	***Methods:*** Advocates / Community may opt to start a social media campaign, share information through written letters, video documentation of PROs, and attend patient-focused (Patient Voice) or PFDD meetings ***Shared Goals:*** Regulatory buy-in and preparedness for IND review	***Methods:*** Primary data collection ***Shared Goals:*** Develop unbranded and branded education materials to improve awareness and adoption among patients and HCPs

Industry & Advocate Partnership–Figure 3

Commercialization

Step 3 Sustain The Partnership:
Long-term success is dependent upon Industry's continuing its relationship with the Community

Reassess Community Needs / Collect RWE		Stay Involved	
INDUSTRY	ADVOCATE	INDUSTRY	ADVOCATE
Methods: Primary data research, social media surveillance, video documentation		***Methods:*** In-person meetings, event attendance, share success stories	
Shared Goals: Track patient outcomes on commercial drug, understand resources and support gaps, continued surveillance of unmet needs		***Shared Goals:*** Lasting partnership with Community	

The Industry-Advocacy partnership in Figure 1 is very similar to the FDA's Roadmap to patient-focused outcome measurement in clinical trials, which is a simple three-step process:

- Understanding the disease through natural history;
- Conceptualizing the expected treatment benefit; and
- Developing and selecting outcome measures to test in clinical research.

A strong case can be made to add a final step to the process: *Testing Industry's hypotheses with the patient community*. For example, qualitative interviews with the rare disease community provide the platform to test hypotheses prior to regulatory review. Access to the community is easy with an Industry-Advocacy partnership already in place.

Continue and Sustain the Partnership to Achieve Long-Term Success

It is important to note that the relationship does not have to end once the trial begins. Figure 2 demonstrates how Industry-Advocate partnerships continue throughout the FDA approval process. While Industry cannot dictate what the Advocate/Community does during this phase, the goals and objectives of each party typically remain the same: *obtain buy-in from all stakeholders*.

Industry-Advocacy partnerships continue during commercialization, as shown in Figure 3. In fact, Advocates and Community *want* Industry to stay involved so patients and caregivers remain invested and continue to be heard. Surprisingly, many Advocates state that Industry neglects the patient/caregiver once the trial concludes. Patients and caregivers echo this belief, and feel abandoned by Industry's lack of post-trial follow-up. Industry does have valid concerns with ongoing patient/caregiver communication, such as adverse event reporting. However, the benefit of Industry's continued involvement and frequent touchpoints on patients and caregivers outweighs the concerns.

Conclusion

The stakes are extraordinarily high for both orphan drug developers and rare disease communities. Trials often fail to measure functional outcomes that reflect patients' greatest unmet needs. Failure to identify outcome measures that capture what patients value most contribute to delays, or worse denials, to therapy. Industry-Advocacy partnerships are key to mitigating the risk of missing endpoints. Moving forward it is critical for Industry to adopt internal strategies to fill the empty chair at the table and allow RDAs to influence and support clinical trial design.

Glossary

(Rare Disease) Community: Patients, caregivers, advocates whose lives are affected by a rare disease.

(Orphan Drug) Industry: Manufacturer or academic center that is in the process of developing an orphan drug.

Rare Disease Advocate (RDA): Individual or groups of individuals who advocate on behalf of patients, survivors, and caregivers within one or more specific diseases or disorders.

Rare Disease Organizations

National Organization of Rare Disorders (NORD)

NORD is a nonprofit patient advocacy organization founded in 1983 by leaders of several rare disease patient organizations. NORD focuses its attention on issues specific to rare disease patients, their families, and the organizations that serve them.

NORD, along with its more than 280 patient organization members, is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services. More information can be found on NORD's website: https://www.rarediseases.org

Global Genes

Global Genes is a nonprofit patient organization founded in 2008 by Nicole Boice, founder and CEO. Originally called 'The Children's Rare Disease Network', Global Genes' mission is to eliminate the challenges of rare disease. As of 2014, Global Genes offers 12 programs to the Rare Disease Community, including educational webinars, collaborative partnerships, annual events, and awareness platforms. More information is available at https://www.globalgenes.org

EveryLife Foundation

The EveryLife Foundation for Rare Diseases is a nonprofit organization dedicated to accelerating biotech innovation for rare disease treatments through science-driven public policy. EveryLife Foundation focuses on educating and activating the patient community to ensure they are heard by policy makers and Industry developing treatments for rare diseases. More information can be found at https://everylifefoundation.org

Rare Advocacy Movement (RAM)

The Rare Advocacy Movement (RAM) is a patient advocacy initiative focused on documenting the structure and dynamics of the rare disease patient advocacy landscape. RAM was founded by seasoned advocacy leaders dedicated to the Rare Disease Community. RAM supports transparency and clarifies misunderstandings about rare disease to ensure the Community is not overlooked, ignored or misrepresented. More information can be found at https://www.rareadvocacymovement.com

About the Authors

Nadia Bodkin

Born with three rare conditions herself, Nadia Bodkin is a seasoned rare disease patient advocate. After earning her Pharm.D. and M.S. from Rutgers University, Nadia went straight into patient advocacy work through EDSers United, a foundation she founded for Ehlers-Danlos Syndrome. She also facilitated and coordinated the development of the Rare Advocacy Movement (RAM), a patient advocacy Center of Insights initiative focused on documenting the ever-evolving complex structure and unique dynamics of the rare disease patient advocacy landscape. Nadia functions on the premise that she is to make the most of the time that she has left on this earth. She is determined to make a difference in the lives of those affected by rare conditions through advocacy and facilitating collaboration among all rare disease stakeholders that aim to improve the lives of those affected by rare conditions.

Terri Ellsworth

Terri Ellsworth advocates for Duchenne Muscular Dystrophy, a genetic condition that affects her son, who was diagnosed at the age of four and is now thriving at 18. Terri's son represents a small subset of rare disease people who have experienced success after being enrolled into a clinical trial for a drug that has significantly improved his quality of life and ability to function. She speaks to the mother care partner perspective, providing insight into the experience of gaining access to an efficacious therapeutic product for her son. Regardless of her son's good fortune, he still experiences difficult obstacles and challenges that are important to note and understand.

Heather Flaherty

Heather Flaherty has 15 years of experience executing primary market research studies for pharmaceutical and biotechnology companies. She currently works for ThinkGen, a healthcare market research firm located in Philadelphia, PA. While her therapeutic experience extends across multiple categories and audiences, Heather is passionate about rare diseases and helping Industry connect with patient communities. She recently had the opportunity to present a workshop at the Intellus Institute on how to include empathy in product and program design for rare diseases.

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About ThinkGen

ThinkGen is a healthcare market research consultancy that routinely conducts primary research (e.g., natural history interviews, ad board moderation) on behalf of Industry. ThinkGen has a history in rare disease research, has published rare disease papers and articles, and is a NORD corporate sponsor.

More information can be found on ThinkGen's website: ***https://think-gen.com***

Resources and Links

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