Help Wanted:
An Emerging Opportunity in Rare Disease Research

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NEW CHALLENGES FOR PATIENTS WITH RARE DISEASES

Patients with rare diseases have played important roles in discovery and translational research programs needed to find cures and treatments. They had to. The causes of their diseases were unknown or too small to attract the attention of researchers and industry. The patients formed advocacy groups, established their missions and set course. They found researchers to search for discoveries, organized research networks for clinical trials and volunteered as human subjects. They established registries and raised funds to support discovery and translational research programs. In the process, they gained knowledge and experience in getting promising treatments from the laboratory into clinical trials and eventually through regulatory review. And, they have been effective; think of ivacaftor (Kalydeco) for cystic fibrosis, alglucosidase alfa (Myozyme) for Pompe disease, and cysteamine ophthalmic solution (Cystaran) for corneal crystals from cystinosis, to name just a few. However, the patients and their patient groups did not do all this alone; they formed partnerships with pharmaceutical manufacturers, medical device makers, academic researchers and commercial research organizations.

These patients are now facing new challenges that research can again help them overcome. Manufacturers and regulators do not always consider outcomes valued by patients, which risks approval denials for products that could have addressed issues important to patients. Clinicians are not always attuned to signs and symptoms of rare diseases, which leaves some people undiagnosed and untreated. Payers are demanding evidence about total cost impacts, patient outcomes, and patient preferences, and not having that information available can lead, in some cases, to decisions against coverage. The types of information needed to address these challenges are not new to the healthcare industry and research community in general, but they are new as now applied to drugs and devices in rare diseases. Rare disease patients can rise to these challenges, but they will need help from organizations with expertise in the research methods needed to design and execute studies to fill in the evidence gaps for manufacturers, regulators, clinicians and payers.

Thus, rare disease patient groups are looking for the right partners — those that understand rare disease patients and their organizations — with the right research programs — those that bring all the support mechanisms needed for patients to fully participate. My objective with this article is to characterize rare disease patients and provide ideas on the elements of programming that would contribute to successful collaborations.

I hasten to add that many rare disease patients wish they had this challenge. The National Institutes of Health (NIH) estimates that there are more than 6,800 rare diseases,[1] and yet there are only about 400 drugs for 450 rare disease indications. While coverage policy problems in particular are actually a sign of success for rare disease research, developing diagnostics and treatments remain the biggest challenge for most of the rare diseases.

THE RIGHT PARTNERS UNDERSTAND RARE DISEASE PATIENTS

I approach any attempt to characterize rare disease patients with trepidation. A dominant characteristic of these patients generally is the variability among them that matches the variability among the general population. I will, however, make a few generalizations that should help researchers understand rare disease patient involvement in research and the frameworks shaping some of their expectations and demands.

Patient advocacy groups are usually the main conduit for patients involved in rare disease research. Hundreds of rare disease patient advocacy groups have formed, and indeed several groups can exist for just one disease. Although research for a cure or treatment is very often their top priority, the people in these groups do not come to them from a primary interest in biomedical research, or even much of an interest in biomedicine at all. They come out of necessity and with urgency because they or someone they know has been stricken with a rare disease. They are people from commerce, government, education, services, trades, homes and the many other sectors of society that do not touch healthcare in any significant way. Their stories of how they became involved in rare disease research are unique until they get to the part of their stories where they all say, "and then." And then, their stories start to merge around efforts to find cures and treatments, which led them into research.

Rare disease patients, therefore, come to research from the bottom up, and they learn about research along the way. In contrast, the researchers they work with generally come to research from the top down through an interest in biomedical sciences and with formal training. Rare disease patients and research scientists have learned to work together and have successfully combined efforts to discover treatments and marshal them through to clinical adoption. However, natural tensions emerge when the bottom up meets the top down in research. Patient urgency meets researcher deliberate methods ("more research is needed"). Patient daring meets researcher risk aversion (tenure requirements, funding preferences). Patient push for novelty meets researcher resistance to change (adherence to existing concepts). Therefore, researchers who accept the invitation from rare disease communities needing help with research studies should be prepared to adapt to expectations driven by urgency, high risk tolerance and impatience with the status quo. Rare disease patients are looking for revolutionaries, not just puzzle solvers tinkering around the edges of established concepts. The right partner will recognize and reconcile these tensions.

RARE DISEASE PATIENTS AND RESEARCH SCIENTISTS HAVE LEARNED TO WORK TOGETHER AND HAVE SUCCESSFULLY COMBINED EFFORTS TO DISCOVER TREATMENTS AND MARSHAL THEM THROUGH TO CLINICAL ADOPTION.

THE RIGHT PROGRAMS ARE MORE THAN JUST DATA COLLECTION

Rare disease groups are experienced in research to some degree, but probably not extensively in the research regulators, clinicians and payers now require. Neither are they experienced working with scientists doing this kind of research. The right research program will, therefore, incorporate educational, structural and operational components.

Educational

Because the call for research to support rare disease treatment coverage policy decisions is relatively recent, many rare disease groups will need to be informed of these new requirements. I have witnessed shock, dismay and incredulousness on many occasions when patients first hear that payers require more justification beyond regulatory approval for coverage of orphan drugs. In addition, while many of the groups are extremely well versed on methods for discovery and translational research, they need background on research methods used for health economics and outcomes research. Therefore, for patients and groups not yet acclimated to these requirements, education and training on the need for this research and basic methods used are vital to their participation.

The educational component of the right research program, however, is bidirectional. Rare disease patients have important perspectives on their illness experiences. They can contribute to translating clinical endpoints used in trials to aspects of their lives that regulators can incorporate into their reviews and payers can more easily assess against the aims of their health plans. Patients can rank the importance of various features and benefits a particular product offers them, and thereby help bring more precision to research programs designed to assess patient value. By seeking patient input, researchers will likely garner valuable information that will strengthen and enrich their studies.

Structural

While mostly all rare disease groups are tightly connected to their constituents, variability exists in the degree to which they are able to collect the necessary research data. Even those groups with established registries may not be collecting the right information to meet the specific need, or they are unable to make necessary adaptations. Therefore, industry sponsors and research organizations engaging rare disease groups should be prepared to provide guidance in enhancing existing structures or creating new ones to gather the required data. These contributions could include supporting a registry *de novo* or enhancing an existing registry, collaborating with the group in designing the research plans and support materials for potential participants, and providing funding to support rare disease group personnel participation, among other activities.

Generally speaking, collaborations between industry sponsors or research organizations and rare disease groups have heretofore been narrowly focused on only what is needed for a clinical trial program, regulatory approval or post-marketing surveillance requirements. Patient groups, however, are often interested in a broader set of data spanning a longer period of time than the sponsor. Alas, they have to take what they can get. I thus feel compelled to make a plea to organizations working with rare disease patients to consider supporting the broader data needs and interests of the groups. Whatever form these collaborations eventually take, they obviously must comply with legal requirements and meet ethical standards, as well as outline agreed upon stipulations about who controls the data and how the data can be used.

Operational

A lot of the information useful to health economics and outcomes research can come from patients directly. Rare disease patients are highly engaged and often very willing to participate in studies and surveys. If anything, they may participate too much given the cries for mercy I hear from them every so often. This is all the more reason, then, to structure their participation so that individual patients or their caregivers can provide input in the easiest manner possible. The wide range of rare diseases yields a wide range of limitations; researchers need to understand that this will affect patient capabilities and preferences for a given research program.

Rare disease patients are becoming accustomed to being able to interact with data collection mechanisms such as registries. In particular, many of them expect that they can extract data of interest, and they often expect, or at least request, the ability to submit queries and run some analyses themselves to compare their situations with others in their cohort. At the very least, the groups will expect to see outcomes from the studies. My experience working with these patient groups indicates that allowing patients some access to data analysis and reporting activities strengthens overall trust and goes a long way in building stronger relationships.

THE OPPORTUNITY AWAITS

Requirements for data outside that normally gathered during clinical trials are presenting new challenges for rare disease patients in getting access to treatments. Like they did before when they had to stimulate and support discovery and translational research, rare disease patient groups are prepared to support the research necessary to address these new access challenges. But, also like before, these groups will need to form partnerships with industry sponsors and research organizations to generate the necessary evidence. Therein lies the opportunity for research organizations with capabilities in health economics, outcomes research, health services research, market access and like methods. The rare disease groups that are fortunate to have treatments — or the prospect for new treatments — will eagerly engage in these partnerships. The National Organization for Rare Disorders (NORD) is prepared to help facilitate these relationships and contribute to the methods and analyses that will ultimately improve patient access and innovation to rare disease treatments.

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References

[1] National Institutes of Health. National Center for Advancing Translational Sciences. FAQ About Rare Diseases. Available at: http://www.ncats.nih.gov/about/faq/rare/rare-faq.html. Accessed on Sept. 18, 2014.