Partnersing with Patients to Develop Meaningful Endpoints – Practical Considerations

Author

Juliane K. Mills
Director, PRA Center for Rare Diseases
PRA Health Sciences
“You can’t change what you don’t measure.”

Widely-regarded management guru Peter Drucker is often credited with some version of this quote. It means that the only way to know if something is improving, worsening, or staying the same is to measure it. Within medicine, there are many ways to measure change in a patient’s health status, such as temperature, blood pressure, or white blood cell count. Within clinical research, these measures are called endpoints.

The selection of appropriate endpoints for a clinical trial design, and in particular the design of clinical trials in rare diseases, requires special considerations.

Challenges in Rare Disease Research Design

When designing clinical studies in the rare disease space, many challenges can arise. These challenges are due to the small sample size and heterogeneity in disease presentation, severity, and progression and treatment. This heterogeneity is compounded by delays in diagnosis. Differences in treatment and outcomes can result due to a lack of access to clinical care, information, emotional, and/or financial support. Cultural and geographical variance can also have an effect on how patients receive care or support.

To understand whether treatments and interventions for rare disease have clinical benefit in how a patient feels, functions or survives, these changes must be measured. One challenge in measuring these changes in rare disease research is to identify an endpoint or clinical outcome assessment (COA) that is validated specifically in a rare indication and can meet regulatory approval requirements for efficacy.

Selecting Appropriate Clinical Research Endpoints

Selection of appropriate endpoints is critical to the success of clinical trials in assessing the efficacy of new medicines. All of the people who review clinical study data, such as regulatory authorities, payers and physicians, and patients, have different needs and perspectives. For this reason, a single endpoint may not serve all groups. Multiple endpoints may be chosen as primary, secondary or exploratory. The primary endpoint(s) typically measure outcomes that answer questions about a medical product’s efficacy. Secondary endpoint(s) are usually not sufficient to address efficacy, but can answer questions about other effects, disease pathways, or product mechanism of action. Exploratory endpoint(s) are typically hypothesis-generating.

An endpoint must be validated before it can be used to prove efficacy. There are several types of validity, but the most important for proving efficacy from a regulatory perspective are construct and content validity.

An endpoint must be shown to measure what it is supposed to measure to have construct validity. To have content validity, a clinical outcomes assessment must be comprehensive enough to capture change in a specific patient population. Partnering with patients, caregivers, and advocacy groups to develop existing COAs in a specific indication is an effective means to ensure content validity.

Developing tools to assess endpoints is a costly and time-consuming endeavor. This development is made more difficult in rare disease research by the lack of resources, funding, and available patients for participation. Endpoint development can be the objective of a research study: the “Defining Clinical Endpoints in Limb Girdle Muscular Dystrophy (LGMD) (GRASP)” study was launched in June 2019 to define a standard COA for LGMD that can be used in future gene therapy drug development.
In its 2019 draft guidance on Common Issues in Drug Development Guidance for Industry (rev Feb 2019), FDA acknowledged the time and expense involved in developing novel COAs and advises the consideration of modifying existing validated COAs to be disease specific. Two such strategies are the use of surrogate and/or composite endpoints.

According to FDA (2019), a surrogate endpoint “is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.” Surrogate endpoints that are “considered reasonably likely to predict clinical benefit” may be acceptable for product approval via an accelerated approval pathway (US FDA 2019). Composite endpoints combine two or more individual outcome assessments into an overall score. This is done when there is no one single endpoint that is sufficient to capture the change in disease expected in the clinical trial. Composite endpoints are also used to account for the possible heterogeneity in diseases and outcomes: a change in only one of the endpoints can still have an impact on the final analysis if there is an increased number of events (McMenamin, 2018).

What Do Patients Value?

Collaboration with patient communities via patient advocacy groups can help with content validation of new and/or existing COAs. But whether clinical trials include new, surrogate, and/or composite endpoints, regulatory authorities encourage the selection of an endpoint to be driven by what is important to patients. Thus, another goal of engagement with rare disease patient communities is to ensure that a rare disease treatments address clinical endpoints meaningful to clinicians (i.e. can be used to assess patient status), as well as quality of life attributes most important to patients, caregivers, and their families. For example, patient-reported outcomes (PROs) are frequently developed to capture the patient experience with their disease and their quality of life.

As explained by L.P. Forsythe et al (2014) “Engagement of patients and other stakeholders in clinical research may help to ensure that research efforts in rare diseases address relevant clinical questions and patient-centered health outcomes.”

After all, what is important to a patient may not be the most important disease attribute to other stakeholders, such as payers or clinicians.

There is some evidence to suggest that inclusion of a PRO supports patient engagement and retention in a clinical trial. In the pivotal phase III trial for ruxolotinib in patients with myelofibrosis, patients were asked to self-report their symptoms via a smartphone. 95% of the 300 enrolled patients were compliant in their reporting. This endpoint of symptom improvement was included in the final product approved label and was estimated to cost less than 3% of the overall budget (Basch, E., Bennett, AV. 2014).

Through its Patient Focused Drug Development (PFDD) initiatives, the FDA strongly encourages drug developers to engage with the target patient community in the drug development process, inclusive of selection and validation of existing or, as needed, development novel of endpoints to be used in clinical research. The International Rare Diseases Research Consortium (IRDiRC) published recommendations from a 2015 task force. This task force specifically convened to define a pathway and best practices for developing patient-centered outcome measures (PCOMs), including patient-reported outcomes (PROs). In further acknowledgement of the time and expense in developing these endpoints, the PFDD program purposefully includes a grant program to encourage patient-centered clinical outcome assessment development.

From what we’ve seen regarding engagement and collaborative design of rare disease clinical trials, evidence to date suggests applications of these recommendations are limited. Recent analysis of published literature unfortunately suggests that this is not frequently done (Lanar, S., Acquadro, C., Seaton, J, et al. 2020; Slade, A., Isa, F., Kyte, D., et al. 2018).

Previous systematic literature review of rare-disease patient advocacy organization (POA) engagement (Forsythe, LP, Szudyowski, V., Murad, MH., Ip, S. et al. 2014) found 6 out of an identified 35 papers referenced selection of study outcomes important to patients as the rationale for engagement. These examples include engagement with members of the fibromyalgia, cerebral palsy, vitiligo, neuromuscular diseases, degenerative ataxias, and hemophilia disease communities. A recent review of package inserts from FDA approved products...
for orphan indications found only 13 of the 156 approvals between 2002 and 2017 included a PRO-based claim in the labeling. 6 of those 13 approvals included PROs as part or all of the primary endpoint (Hong, YD., Villalonga-Olives, E., Perfetto, EM. 2019).

Engaging with Patient Advocacy Organizations

In addition to PFDD guidelines and published literature, many PAOs provide guidance on how to collaborate with their communities to support medical product development. Collaborative engagement to support product development, including clinical trial design, is different from more transactional engagement like event sponsorship that may also form part of a company’s engagement plan. It involves systematically collecting input from patient communities throughout the clinical trial development process.

One method of engagement is by conducting surveys and focus groups with the PAO leadership and scientific advisory board, who are typically Key Opinion Leaders within the research and clinical space for the specific rare disease. Other traditional methods include quantitative and qualitative research with patients, caregivers, and family members. Additionally, this research should also be conducted with representatives from the diverse therapeutic and practical care specialists who treat rare diseases, such as gastroenterologists and neurologists as well as nutritionists and radiologists. For example, websites such as The Duchenne Xchange (duchennexchange.org/) gather feedback from patients, caregivers, and family members on clinical trial protocols, barriers to trial participation and changes in healthcare through polls and questionnaires.

A good example of employing these methods as part of a partnership in endpoint development is the Toileting Abilities Survey as a surrogate endpoint in patients with mucopolysaccharidosis II (MPSII) (Hogan, M. J., Stephens, K., Smith, E., Jalazo, E. R., Hendriksz, C. J, et al. 2020). This research was conducted in collaboration with academicians, advocates, and caregivers of patients affected by rare diseases, clinicians, and industry partners.

Toileting abilities are an important activity for independent daily living. They can have a profound impact on a patient and caregiver’s quality of life. There is evidence to show that cognitive processing can be a predictor of functional ability, such as independent toileting; and vice versa: toileting has an association with cognitive ability in the elderly and patients with Alzheimer’s and dementia.

To develop this tool, interviews were conducted with caregivers of patients with MPSII. Researchers also reviewed social media outlets to understand the scope of concerns around toileting. Based on this initial research, a draft Toileting Abilities Survey (TAS) was created to measure independent toileting skills. To establish construct validity, researchers conducted focus groups with caregivers of patients with MPS II to evaluate the draft questions and refine the survey. To determine content validity, the TAS was administered among caregivers of patients with neuronopathic form of MPS II enrolled in a trial receiving an experimental treatment. The outcome showed that the TAS was a reliable endpoint for toileting ability and a potential tool as a surrogate endpoint for cognitive function.

Summary and Recommendations

Engaging with patient communities in the design of a clinical trial, such as collecting input on relevant endpoints, is a well-established milestone in the drug development process – both by patient advocacy organizations and regulatory authorities. It can build a sense of ownership and engagement in the clinical trial itself among patient communities who feel that they have been heard and involved, which can help to de-risk recruitment and retention for clinical research trials.

By incorporating patients, caregivers, and practitioners in the process for endpoint development, product labels for approved products will have meaningfulness to the clinicians who prescribe as well as the patients who are treated with new therapeutic products. Clinicians will know how to assess for change and improvement in disease status or progression. Patients and families will have practical expectations for product effects and be able to contextualize the risks and benefits of approved products and other treatment options for their condition.

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Citations


Contact Information

Do your clinical endpoints reflect what is important to patients with rare diseases? If not, it may be time to look for a trusted partner with experience and expertise in designing rare disease clinical trials.

For further information about PRA’s service offerings or to schedule a complimentary consult with our rare disease expert, please contact Juliane Mills, Director, Center for Rare Diseases.

Juliane K. Mills  
Director, PRA Center for Rare Diseases  
PRA Health Sciences  
731 Arbor Way  
Blue Bell, PA 19422 USA  
Phone: +1 (215) 591 1158  
MillsJuliane@prahs.com

World Headquarters  
4130 ParkLake Avenue, Suite 400  
Raleigh, North Carolina 27612 USA  
Phone: +1 (919) 786 8200  
Fax: +1 (919) 786 8201  
www.prahs.com