

Development of Disease-Specific Patient-Reported Outcomes Shifts Clinical Trials Toward Patient-Focused Data

In 2009, the US Food and Drug Administration (FDA) issued guidance that it would consider validated patient-reported outcome (PRO) instruments to support drug labeling claims.

At the time, Chad Heatwole, MD, MS-CI, a neurologist, was working with myotonic dystrophy (DM) and realized that there were no validated PRO instruments for the disease. So he earned a master's degree focused on psychometric methodology and began developing and rigorously validating regulatory-grade PROs, including the Myotonic Dystrophy Health Index (MDHI).

"Previous to that, the trend was not to prioritize a patient's input when assessing if a therapeutic agent was beneficial. Clinical trials were largely based on survival, biomarkers, or functional measures, and the patient was not asked, 'Are your symptoms better?'" Dr. Heatwole says. "That's important because oftentimes a patient can detect small but meaningful changes before any other outcome measure can. It also allows a pathway to determine whether a therapy is actually meaningful and perceptible to a patient."

Today, Dr. Heatwole is the Director of the Center for Health and Technology (CHeT) at the University of Rochester Medical Center, and his lab maintains more than 250 regulatory-grade PRO instruments covering 40 diseases, which have been translated into 42 languages.

How does it work?

A PRO instrument comprises a questionnaire and the information and documentation that support its use. It is designed to measure disease burden and therapeutic gain during clinical trials.

Dr. Heatwole's team incorporates large-scale patient interviews into the development process, and their input guides the questions for each disease-specific PRO instrument. The instrument is composed of subscales that measure granular aspects of health that are important to patients. For example, the MDHI has subscales measuring fatigue, pain, myotonia, mobility, and other symptoms.

Dr. Heatwole compares it to caring for a patient in a clinic. "As a clinician, I would ask a patient, 'How are you doing?' And they would tell me how they are doing in multiple areas that are related to their disease. But in the clinical setting, you can't really quantify their responses," he says.

Dr. Heatwole's PRO instruments, however, can quantify disease burden in many symptomatic domains. With each use, his PROs score patient responses from 0 to 100 across multiple relevant subscales, yielding quantifiable results that represent the patient's point-in-time disease burden.

"This allows you to track scores over time. In an industry therapeutic trial, you can compare the change in patient perception of disease burden in a treatment group to a placebo group, and you can tell if there's a perceived benefit due to that therapeutic agent," Dr. Heatwole says.

What are the advantages?

Dozens of studies have shown that patients prefer Dr. Heatwole's disease-specific instruments over generic health measures, such as SF-36 or PROMIS, because the content is more relevant to them.

"Patients prefer instruments that are disease-specific due to a higher relevance, even when they're slightly longer than the generic instruments," Dr. Heatwole says.

In addition, head-to-head studies have demonstrated that disease-specific PRO instruments are more responsive than generic ones at detecting small, clinically meaningful changes in response to a therapeutic intervention.

As an example, Dr. Heatwole cites a postmarketing study of nusinersen (Spinraza) in adults with spinal muscular atrophy (SMA). The study used the SMA Health Index (SMA-HI), which demonstrated therapeutic benefit in response to the therapy before it was detected by functional measures.

The use of a disease-specific patient-reported outcome measure, when it's developed the right way, has a tremendous benefit to the community because it allows a patient to give quantifiable input into a treatment's effectiveness," Dr. Heatwole says.



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How are they used?

Disease-specific PRO instruments are primarily designed for phase 3 drug approval studies, but some researchers have found them useful for collecting data during phase 1 and phase 2 clinical trials.

The MDHI, the first PRO instrument Dr. Heatwole developed, is highly recommended by the National Institutes of Health (NIH) as a marker of disease burden, and it is now used in nearly every industry trial for myotonic dystrophy therapies.

Dr. Heatwole's team has developed instruments for types 1 and 2 myotonic dystrophy (DM1 and DM2), Duchenne muscular dystrophy (DMD), facioscapulohumeral muscular dystrophy (FSHD), amyotrophic lateral sclerosis (ALS), inclusion body myositis (IBM), mitochondrial diseases, myasthenia gravis (MG), limb girdle muscular dystrophy (LGMD), and SMA, among many other diseases (HealthIndexes.com). They have instruments for movement diseases, such as Huntington disease, Parkinson's disease, and Friedreich's ataxia, and even diseases outside of neurology, including Crohn's disease and lung cancer.

Dr. Heatwole's team also created an instrument for caregiver-reported outcomes, which is being used in a two-year natural history study called LEOPARD-DMD (MDA is funding this study). Using both patient- and caregiver-reported outcome measures allowed the study to include a wider age range of boys who are ambulatory and nonambulatory.

The role of patient-centered research

Dr. Heatwole emphasizes that researchers have an obligation to ensure that treatments provide meaningful effects to patients. "I am a strong advocate for the use of well-developed and validated patient-reported outcome measures for this purpose," he says. "They give the patient a voice, and they have the ability to detect a therapeutic benefit where maybe other outcome measures can fail."
The 2009 FDA guidance acknowledged the value of patient-centered research. Disease-specific PRO instruments are becoming increasingly important in therapeutic clinical trials because they can produce critical data to support approval and drug labeling claims.

Resources

- US Food and Drug Administration (FDA): Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
- University of Rochester: Center for Health + Technology (CHeT)

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