Emmes

Designing Fit-for-Purpose Endpoints in Rare Disease Trials:

Five Areas of Meaningful, Patient-Centered Assessment

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<5%
Marketed treatments exist

10,000+
Recognized Rare Diseases

400
Million
People affected worldwide[1]

34.6%
Approval success rate of orphan drugs was shown in an analysis[2]

1. https://globalgenes.org/rare-disease-facts/

2. Berdud, M., Drummond, M. & Towse, A. Establishing a reasonable price for an orphan drug. Cost Eff Resour Alloc 18, 31 (2020). https://doi.org/10.1186/s12962-020-00223-x

Today, marketed treatments exist for less than 5% of recognized rare diseases.

This begs the question: What can be done to improve the odds?

The answer may lie in bolstering the efficacy endpoints used to evaluate rare drug candidates. Too often, drug sponsors must resort to using primary endpoints that, while validated and approved by regulators, are not particularly appropriate for the rare disease under study because *they do not measure the outcomes that matter most to patients and their caregivers.* It is no wonder, then, when pivotal trials fail to demonstrate statistically significant positive results.

Through our work in rare disease clinical development, we've created and validated assessments – and can modify or develop others – to produce robust and sensitive outcome measures based on factors relevant to patients' daily lives. With the right preparation and design, these assessments can be accepted by regulators and payers as meaningful considerations in their decision-making processes.

As medical treatment becomes ever more personalized, we believe that clinical endpoints for rare disease therapies can and should move in that direction as well.

Read on to learn how assessments measuring patients':

- **Functional capabilities (including range of motion)**
- **Independence**
- **Endurance**
- **Socialization**
- **Communication**

can be used to complement the outcomes dictated by regulators in rare disease studies.

Specialized Assessments: The Heart of Patient-Focused Drug Development

Endpoint selection is, of course, critical to not only the success of a clinical trial, but also to a product's commercial success. Choosing the wrong endpoint can lead to a failed study, to a product label that is narrower than it might otherwise have been, or to a marketed product that does not meet patient/caregiver expectations.

For more than a decade, the US Food and Drug Administration (FDA) has emphasized the need for Patient-Focused Drug Development (PFDD), recognizing that

> "People living with a condition are uniquely positioned to inform an understanding of the therapeutic context for drug development and evaluation."[3]

The agency urges drug developers to understand the

> "...specific experiences that matter most to patients [and] patient perspectives on meaningful treatment benefits..."[4]

The logical antecedent to this concept is that the measures upon which investigational treatments are evaluated should address the outcomes that matter most to patients and caregivers. Especially in rare disease areas, the assessments available to drug sponsors often measure results that are at best irrelevant to patients/caregivers and at worst lead reviewers to draw the wrong conclusions about a potential product's value.

What If?

What if you weren't constrained in this way?

What if you could also assess what matters most to patients and caregivers?

What if you could capture data on subtle improvements that differ from one patient to the next?

3. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings

4. https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings

4

Measures of Functional Capabilities

For various neurological and neuromuscular diseases, such as Duchenne Muscular Dystrophy (DMD), clinical trials have relied on timed testing to measure functional capabilities and assess disease progression.

The Six-minute Walk test has been adopted as a standard measure of functional status in neuromuscular diseases, although it was originally developed to be used to assess functioning in patients with cardiac and pulmonary diseases. The Four-stair Climb test is another assessment routinely used to assess motor function.

Such tests fall short, however, of measuring the type of functioning in everyday life that is important to many patients and their caregivers.

> "Unless there's a fire, it's not important to me how fast he can walk. Even he is not interested in being a fast walker. He's more concerned about his gait – the *way* in which he gets from Point A to Point B."
>
> **Mother of a son with DMD**

In neurological and neuromuscular diseases, measures that are more relevant encompass one's ability to perform such tasks as:

- Feed oneself (take 10 bites)
- Raise one's hand in class
- Don and remove a t-shirt
- Reach across a table to grab a cell phone

This list is very abbreviated, but is enough to illustrate the point that ease of movement matters to these patients and caregivers – just not as measured by certain standard timed tests.

The Duchenne Video Assessment

Emmes developed and validated the Duchenne Video Assessment (DVM) as a way for caregivers to capture functional benefit on video using a mobile app. Caregivers are asked to record a video of the patient performing a compensatory pattern of movement. The measures are taken during a two-week window that is best for the participants, and the videos are automatically uploaded to cloud storage.

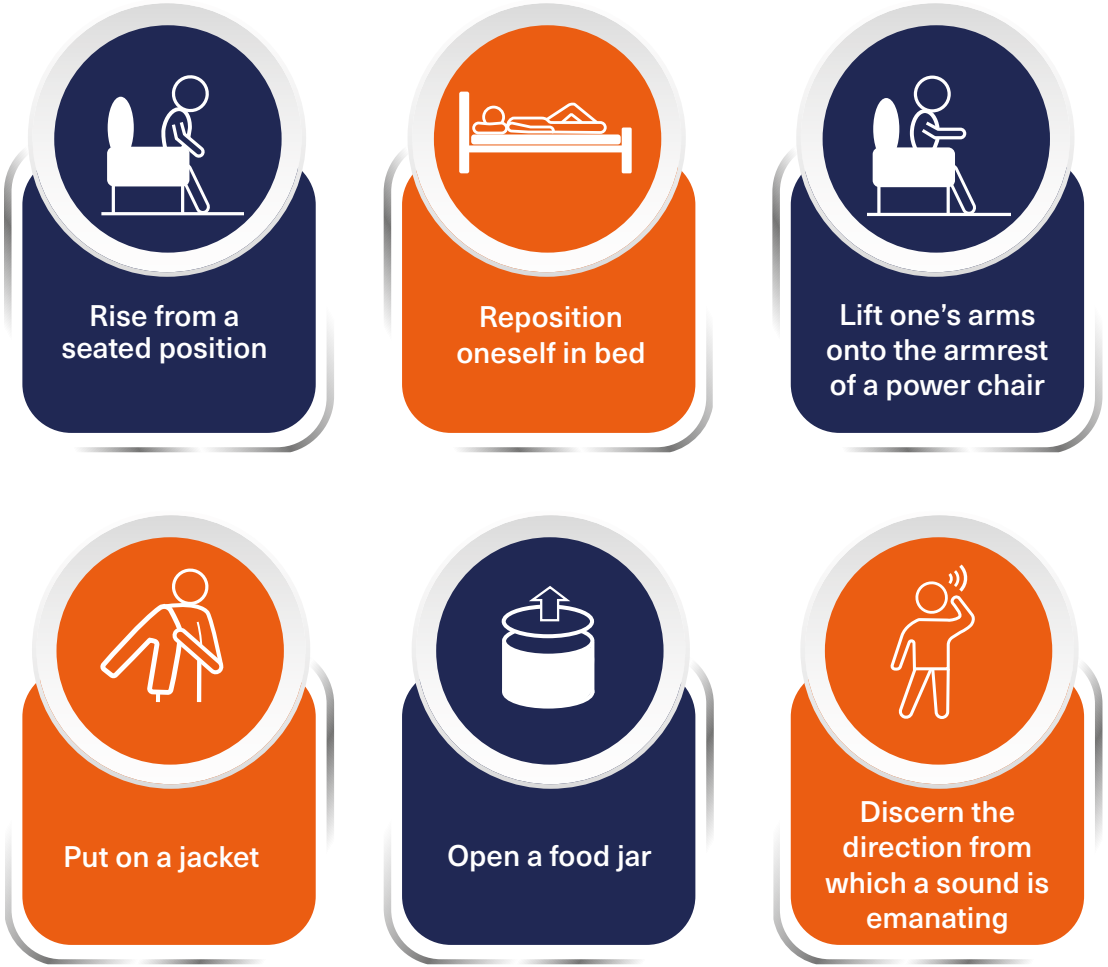
They are then checked for their quality, HIPAA compliance, and scored by certified, central raters (trained physical therapists). The assessment has the benefit of being conducted in the patient's home, rather than in a clinic, and has the potential to detect incremental, yet clinically meaningful, functional changes over short time periods. The data captured is rigorous enough to be submitted to regulators.

2

Measures of Independence

Again, off-the-shelf assessments used in many rare disease areas are not always meaningful measures of a patient's independence, which is one of the most important concepts of interest to patients and caregivers alike. There are many activities that are directly related to a patient's safety and ability to be untended that are not measured by existing standard tests.

These include, for instance, the ability to:



While the need for people to perform some of these activities may be obvious, the significance that people place on them may not be. For example, in our conversations with hearing impaired college students, we found that they stressed the need to be able to tell from which direction a sound was coming.

Why? Not just because it was helpful in crossing a street in traffic, but for fear of not knowing which direction to run in the event of there being an active shooter on campus.

Nor are existing assessments always performed objectively and consistently. For instance, a test that measures the time required to rise from the floor is meaningful for some disease states (in that if a patient cannot rise from the floor, he or she cannot be left alone).

However, it relies on a caregiver to time the activity and the manual aspects of timing can lead to inconsistencies in the data collected.

Objective measures of independence can be developed and assessed either quantitatively (via video) or qualitatively (through semi-structured interviews).

3

Measures of Endurance

While there are standardized tests to measure a patient's endurance – such as the Six-minute Walk test – they don't necessarily relate to the tasks that are most difficult for, and important to, patients with certain diseases. And often patient interests are very individualized.

For a young Boy Scout, the Six-minute Walk test may not relate to his aspiration of being able to join his troop on a five-mile hike. And it certainly won't address the full array of concerns of patients with mitochondrial disease, which causes extreme, chronic fatigue. One such patient discussed how important it was to her that she style her hair with a hairdryer every morning. She was unable, though, to do so without bracing her elbow on the grille of a nearby window. That is precisely the kind of detailed understanding needed to effectively develop assessments that are relevant to a given disease state.

We've addressed the individualistic nature of endurance concerns by developing patient-reported outcome (PRO) assessments through which patients are able to select the activity of importance to them. Study staff help them standardize the activity for consistency across timepoints. Patients then report periodically, per the protocol, on any changes they notice in how they perform that chosen activity.

4

Measures of Socialization

Socialization is the other factor, along with independence, that in our experience is of greatest concern to, and interest for, patients and caregivers.

Human beings, by their very nature, want to “fit in,” and many rare diseases have the unfortunate effect of making that difficult for patients. Their special needs are often observable to others, making some patients uncomfortable in certain social situations.

Picture a woman with ALS who no longer goes out to eat for fear of spilling food on her clothing.

Or the man with Huntington’s disease who no longer walks around the neighborhood after being accused of being intoxicated.

Or the student who elects not to go to the prom because of speech issues impairing his ability to communicate.

Each is distancing himself from others and losing out on human connections.

We can develop qualitative interview questions that can be administered to patients in a clinical trial to identify how their comfort level with regard to social activities has changed, including what made the change noticeable and when it was first observed. The feedback can provide important context to other study data.

5

Measures of Communication

There is great heterogeneity in the way that patients with many rare diseases communicate – including, for example, those with Angelman Syndrome.

Unfortunately, the existing assessments of communication abilities do not reflect such differences, which can be quite nuanced.

For example, some participants are non-verbal, but they communicate in complex ways, whereas others might have verbal ability, but their communications are simplistic. Some use eye gaze as meaningful communication tool while others avoid eye contact with a caregiver and rely heavily on gestures.

Many assessments are not sensitive enough to pick up on subtle differences in outcomes seen in one patient versus another.

It is possible, however, to assess changes in communicative abilities for an “N of one” using video to capture a patient’s reaction to a stimulus.

We’ve developed a communications module that assesses the complexity and nuance of both nonverbal and verbal modes of communication (expressive communication) as well as comprehension (receptive communication) within the context of functional abilities.

Caregivers are of course trained on how to capture the patient’s reaction on video, and central raters – speech language pathologists – are trained to evaluate what is presented.

How to Move beyond Standard Endpoints in Rare Disease Studies

To ensure that new assessments are developed with the rigor that regulators require and capture the outcomes that are of greatest concern to disease patients and their caregivers, we recommend that sponsors follow a thoughtful process for endpoint selection or development.

The resulting assessment should reflect input from all stakeholder groups, be easy to administer, reduce confounding related to testing outside of the home environment, and allow for consistency in the data collection.

Whether the assessment will be used as a secondary endpoint or to furnish contextual data that supplements primary endpoint findings, it is important to:

STEP 1

Be open to the possibilities. Consider the benefits of developing an assessment tool that is flexible enough to reveal the different ways that patients experience improvements in their functioning, independence, endurance, socialization, and communication.

STEP 2

Gather input from patient communities on their views of relevant endpoints. An industry partner such as Emmes can facilitate such Patient Advisory Board Meetings.

STEP 3

Learn what assessments exist, how they might be modified, and what new ones might be developed. Emmes Endpoint Solutions is available to consult with you on the approach and tools they recommend to address the findings from Step 2, taking into consideration regulatory guidance on patient-focused drug development.

STEP 4

Request an early meeting with regulators to discuss the recommended endpoints and assessment tools. It is critical to get feedback from the agency before committing to a direction.

Emmes Endpoint Solutions' areas of expertise

- Conducting literature searches to understand the current state of assessment in the disease area
- Interviewing patients and caregivers to learn what outcomes they deem relevant
- Consulting with clinician experts to ensure clinically relevant assessments
- Developing strong relationships with advocacy groups
- Supporting clients with regulatory conversations
- Developing assessment tools including questionnaires, interview guides, and remotely administered clinician reported outcome assessments
- Creating training materials for patients/ caregivers and raters
- Validating the assessment if needed
- Delivering the assessment within a trial
- Analyzing and interpreting the captured results to support regulatory submissions

At Emmes Endpoint Solutions, we're prepared to help you through all stages of developing an endpoint suitable for the rare disease you're studying. Our dedicated Rare Disease team has experience across a wide range of rare diseases and are equipped to develop assessments, collect patient data, and analyze the results.

For additional information on how we can support your rare disease project, please email **info@emmes.com**