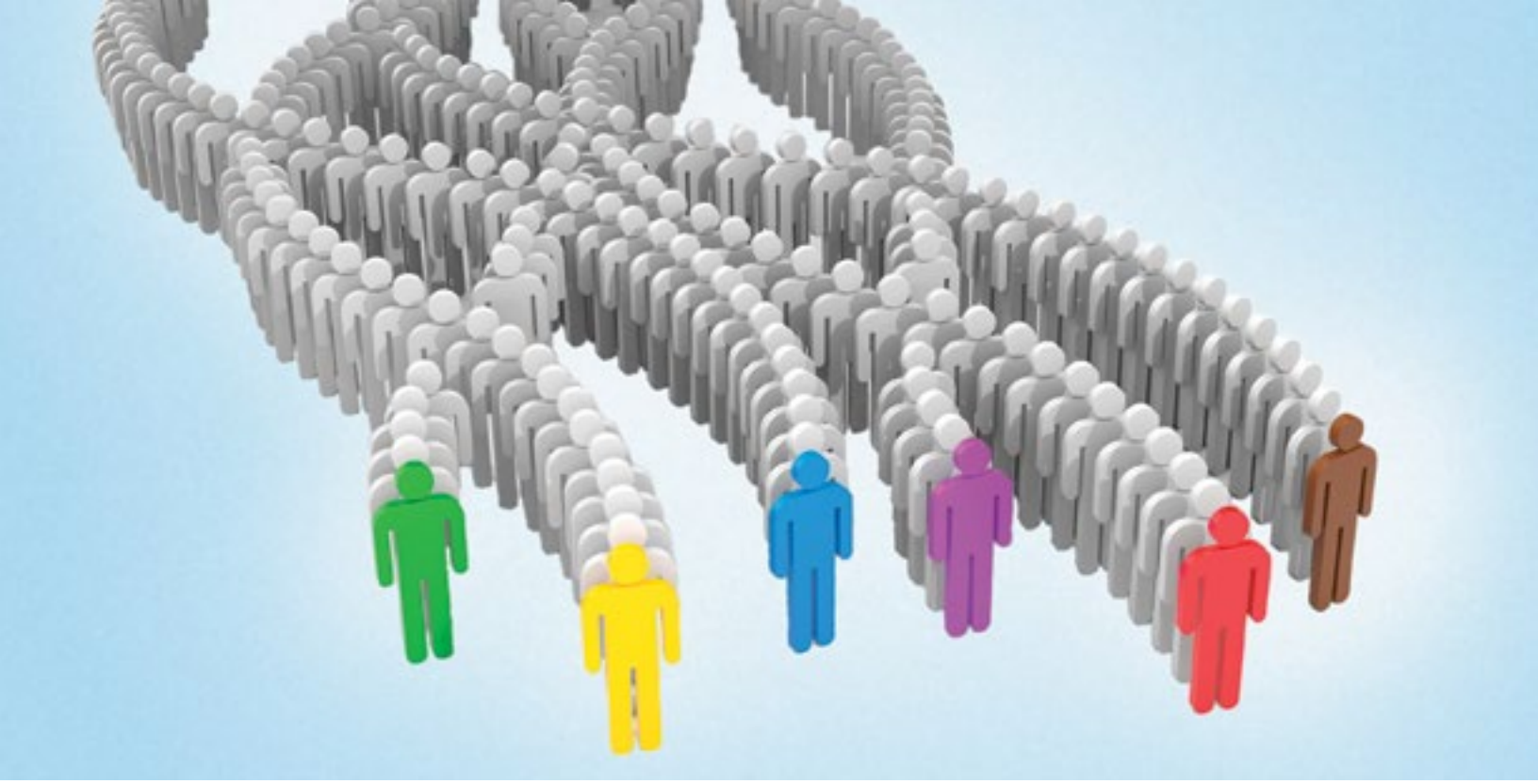

Clinical Outcome Assessment Selection for Rare Disease Trial Programs

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While there are a number of regulatory and industry guidance documents about the need for, and selection of, clinical outcome assessments (COAs), navigating through all of the information can be overwhelming. When you consider the nuances of a rare disease trial program, the overwhelming challenge can seem insurmountable. The aim of this article is to provide some baseline knowledge about the "why, who, what, and how" when it comes to clinical outcome assessments for rare disease trials.

Why include the patient perspective?

Patients are the recipients of the intervention being developed, but beyond that obvious reason, there is a legislative benefit for including patient perspectives. Under the 21st Century Cures Act (Title III, Subtitle A), there is a call to include patient experience data throughout the drug development process.[1] Sponsors have the opportunity to showcase the patient experience data, and there is a mandate for those data to be made public.

In rare disease product development, the patient perspective is particularly important because, often, not much is known about the disease experience. How the patient experiences the condition and the impacts of the condition are frequently heterogenous and not well understood. The US Food and Drug Administration (FDA) draft guidance, *Rare Diseases: Common Issues in Drug Development*,[2] concedes that, "medical and scientific knowledge, natural history data, and drug development experience" are often limited. The FDA is particularly interested in the patient experience and, as evidence of their interest, held a Public Workshop to outline their desire for such data.[3] The workshop illustrated avenues for

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engaging the FDA through patient advocacy and included case studies of how the patient's perspective can be introduced, and included, in the FDA's understanding of the patient populations.

The FDA has also produced guidance documents to assist Sponsors in rare disease drug development. The Pre-Investigational New Drug (IND) draft guidance specifically states Sponsors should be prepared to discuss the plan for including patient perspectives in their drug development program during the pre-IND meeting (line 281).[4] Furthermore, during the pre-IND meeting, Sponsors should also report about novel endpoints such as COAs (line 285).[4] COAs can be in the form of patient-reported, observer-reported, clinician-reported, or performance outcome measures.

Who should report the data?

The patient's perspective about their own experience should be reported directly by the patient. This may not be possible in rare disease as about 80% of the diseases hold a genetic component and nearly 75% of those affect children.[5] Other stakeholders such as a caregiver or patient advocate may be appropriate for reporting observations related to the patient.[6] Caregivers, such as a parent, can report observable signs, events, or behaviors. It should be noted that performance outcome assessments such as physical functioning assessments or cognitive testing may require specialty training and should be conducted by a healthcare professional.

What concepts from the patient perspective do we measure in a trial program?

When considering what concepts to measure in a trial program, begin by considering what is important, or meaningful, to the patient. The FDA advises, "signs and symptoms that are most important to patients" (line 151).[2] With a heterogeneous, rare population it can be a challenge to identify the most meaningful concepts.

Information about the concepts that may be measured can come from a literature review, desk research (e.g., Google), clinicians, and market research that may have been conducted by the Sponsor; there may also be an opportunity to partner with a patient advocacy group to gather qualitative data from the stakeholders themselves. These types of reports begin with concept elicitation about signs, symptoms, and impact. The report can also summarize risks and benefits of current treatment, adherence to medication regimen, economic burden, etc.

The disease experience information can be visually represented in a conceptual disease model (CDM), a tool that can be used to evaluate which aspects of the disease experience can be targeted for the trial program. Clinicians can be very helpful in giving insight into concepts that are clinically important. Consider focusing on common symptoms that can be directly reported by the patient, or observed by the patient caregiver, as well as concepts that will have time to change within the trial context. In rare diseases, it is often important to consider damage to the body that may be permanent and irreversible. Irreversible damage should not be captured as there would be no opportunity for improvement, even with successful intervention. The goal is to measure concepts that are important to patients, clinically relevant, and have the ability to react to a positive intervention.

How do we measure the patient perspective in the trial program?

The selection, or development, of a COA for a trial program should consider several factors.

- Who is reporting the data?
- How often are data being reported?
- What challenges with mobility or ability to report does the population have?
- What operational considerations exist (need for translations, mode of administration, and time to trial kick-off)?

In rare diseases, it is unlikely there will be a COA that will directly match the need for the trial program population. The Sponsor may wish to target very specific concepts and select individual COA measures. For example, an itch or sleep measure that can be reported by the patient or a physical function or cognitive performance assessment that would be evaluated by a clinician. The Sponsor can use the CDM to target areas to measure and then perform a review of existing COAs to identify measurement options. The goal is to see where the content you wish to measure overlaps with the content in existing COAs.

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It is possible that an existing COA measure has been developed and can be adapted to the rare disease. There is an example presented in this issue of *The Evidence Forum* by Drs. Murray and Bacci about the Evaluating Respiratory Symptoms (E-RS®) for idiopathic pulmonary fibrosis (IPF) (E-RS: IPF). The Sponsor may need to develop a new COA measure specific to their patient population. Considerations for rare disease can be made but the FDA guidance on PRO measures to support labeling claims should still be followed as closely as possible.[7]

While there can be challenges in the selection and inclusion of COAs in a rare disease trial program, hopefully the

information presented here has helped reiterate the value of including such measures. The patient's unique perspective is a critical aspect of evaluating efficacy. Often laboratory or imaging endpoints are used to evaluate efficacy of an intervention, but the patient is at the heart of the research and the question remains – how do we know if a change in those endpoints gives the patient a meaningful benefit? Supportive endpoints that rely on the patient or caregiver are vital. Sponsors should consider how the patient perspective is represented in the trial endpoints. If there is a question about what to include, the answer may be as easy as asking the expert – the patient! ■

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