

## PATIENT REPORTED OUTCOMES

Companies should consider implementation, concepts, and instruments when planning a clinical trial.

# Measurement is Strategic

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**W**hat happens when we are very confident that our new product is going to be a break-through treatment, but we cannot measure its effects? The answer is simple—the product is dead. If we can't measure it, we don't have a product. Measurement is strategic.

On the surface, this analysis seems trite. Of course, if we cannot measure the efficacy of a product, then there is no way to proceed. Yet, in the context of planning clinical trials to demonstrate our product's efficacy, we seem to regularly forget this simple, fundamental component of clinical research.

How is this manifested? One of the clearest examples is in the development of our clinical trial protocols. We struggle for months (years, at times) to define the patient population, to elucidate in excruciating detail the inclusion/exclusion criteria for our trial. We pour over the PK/PD data to determine the optimal dose(s) for the trial. We seek consultation from experts in the field on the ideal treatment period, and the frequency of assessments to evaluate the effect of the product. Then, at the 11th hour, we turn to our last protocol, or to a published clinical trial in the area, and we “grab” the instruments (i.e., questionnaires, assessments, measures) to measure the product's effects. We vigorously search these sources to ensure the term “validated” is associated with the instruments. We then proceed with simply dropping these instruments into the protocol.

While this example is an exaggeration and intended to be provocative, it does raise a question for those of us planning a biopharmaceutical development program: When do we think about how to best measure our product's efficacy?

Patrick et al.,<sup>1</sup> responded to this question in their article on a specific type of instrument used in clinical trials, the patient reported outcome (PRO): “Begin with the end in mind.” These authors consider their target PRO-based labeling claims at the beginning of their program planning. Specifically, they suggest we consider the following questions: What are the concepts (e.g., signs and/or symptoms) that we believe are central to establish-

ing the drug's efficacy? Then, what are the instruments that can validly and reliably measure those concepts? That is, what instruments are fit for the purpose of measuring our concepts? Finally, how will instruments be implemented in our trials so that we can construct the optimal endpoints to support our label claims?

It is noteworthy that Patrick et al.'s proposed considerations for PRO instruments are readily applicable to all instruments that will be used to evaluate a product's efficacy and support its registration and labeling. Whether the instrument measures the patient's perspective directly (no interpretation by a clinician), the instrument is utilized by a trained health professional, the instrument is used by a third party (like a parent), or the instrument is a biomarker of some type, it is essential to consider if the instrument is fit for purpose. More specifically, in order to defend the data underlying our registration claims, we must be able to provide evidence that any and all of the instruments used to measure those claims were actually right for the task.

Let's take each of these questions and consider their implications for our product development planning.

**What are the concepts (e.g., signs and/or symptoms) that we believe are central to establishing the drug's efficacy?**

Quite often in our development planning, especially when we are rushed to finalize protocols for our trial, we quickly jump to selecting the instruments for our studies. Patrick et al., reflecting on FDA's proposed path for optimally supporting labeling claims, suggest that we start with considering what it is that we want to measure, before we consider how to measure it. The first step is to identify the concepts that we believe are important and relevant in establishing the product's effectiveness (and safety). These concepts may be the core signs and symptoms that the product should modify or treat. Additionally, these concepts might include the follow-on effects that we expect the product to generate, for example, positive impacts on the patient's life—also known as health-related quality of life (HRQoL). Together, the identified signs and symptoms and the HRQoL effects can convincingly demonstrate that the product works, and is meaningful and valu-

able to patients. It all begins with the concepts or what we want to measure.

**What are the instruments that can validly and reliably measure those concepts? That is, what instruments are fit for the purpose of measuring our concepts?** Once we have identified the relevant and important concepts, we can then move to selection of the instruments. This is where the traditional terminology “validated instrument” comes into play. However, FDA has suggested the terminology of “fit for purpose” rather than “validated.” Why? An instrument may perform differently with different patient populations, and may not optimally evaluate the key concepts identified as central for the product. We need to show that the instrument validly and reliably measures what we believe is important for our specific product with our specific patient population. Our instruments have to be “fit for purpose.”

**How will instruments be implemented in our trials so that we can construct the optimal endpoints to support our label claims?** Finally, after we have decided what concepts we want to measure, and how to measure them, we are prepared to consider how the instruments will be implemented in the clinical trial to generate the optimal endpoints. It is important that the clinical trial study design deploy the instrument on a schedule that best evaluates the product. For example, asking patients about their

symptoms, such as pain, once per week, or once per month may not yield sufficiently robust data to understand the product’s treatment effects on pain. It may be necessary to ask about pain every day, or at specific times of the day. The construction and interpretation of the endpoints is typically considered very late in the planning of trials. In contrast, the FDA specifically suggests developing an endpoint model—showing the connection between the proposed labeling claims, the concepts being measured, and the endpoints to be constructed from the instruments—at the beginning of the product development planning. Indeed, in our experience, the FDA would like to review such an endpoint model at the time of the IND submission.

For our products to live, and thrive, through the clinical trial process, it is essential that we have fit for purpose instruments. Measurement is strategic.

#### References

1. D.L. Patrick, L.B. Burke, J.H. Powers, et al., “Patient reported outcomes to support medical product labeling claims: FDA perspective” *Value Health*, (10) Supp. (2007).

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