

White Paper | PRO Consulting

Distinguishing Among Symptom vs. Health Related Quality of Life PRO Concepts: Developing a Conceptual Framework

Written by:
Alan Shields, Ph.D.
Chad Gwaltney, Ph.D.
Jean Paty, Ph.D.
Saul Shiffman, Ph.D.

Date:
August 22, 2006

© 2006 PRO Consulting. All rights reserved.



Introduction

The Food and Drug Administration (FDA) Draft Guidance on Patient Reported Outcomes (PRO) measures outlines several areas that will be considered when evaluating PRO instruments.¹ One of the principal areas is the development of the conceptual framework that underlies the use of the PRO measure. This is important because it allows the FDA to evaluate the instrument's relevance to product labeling. If it is unclear what a PRO instrument is actually measuring or how the measured construct is related to the underlying disease, claims based on this measure may not be approved for labeling. PROs commonly evaluate either the signs and symptoms of a condition or Health-related Quality of Life (HRQOL) domains.

- ❶ The goal of this paper is to evaluate differences between symptom and health-related quality of life PRO assessments and evaluate the implications of these differences in terms of developing a conceptual framework.

Differences Between Symptoms vs. HRQOL

Symptom and HRQOL measures have conceptual and practical differences that distinguish one from the other, as shown here in Box 1:

Box 1: Typical Characteristics of PROs Assessing Symptoms and HRQOL

PRO Instrument Characteristic	Symptoms	HRQOL
PRO concept as a behavioral "objective" measure	Often	Seldom
Complexity of concepts	Simple	Complex
Dimensionality	Uni-dimensional	Multidimensional
Relation to disease	Direct	Indirect
Relation to treatment effects	Direct	Indirect
Primary target of treatment	Often	Seldom
Mirrors clinician and patient discourse	Often	Seldom
Dynamic time course	Often	Seldom

Definitions

Signs and symptoms often reflect actual, primarily objective manifestations of disease, while HRQOL domains (e.g., physical, psychological and social functioning) reflect the perceived, subjective impact of illness and treatment on a patient's ability to pursue activities of daily living.

The PRO Concept as a Behavioral "Objective" Measure

Symptom measures are typically observable events, such as frequency of bowel movements. HRQOL measures tend to be subjective and unobservable, such as perceived improvements in physical function.

Complexity of Concepts and Dimensionality

By definition, symptoms reflect specific PRO concepts while HRQOL domains are more conceptually complex and general. This is the primary reason why the concepts underlying symptomatic assessment can often be assessed by a single item or uni-dimensionally (i.e., assessed via a single scale), whereas HRQOL assessments are often abstract (i.e., assessed with arbitrary metrics) and multidimensional (i.e., assessed across several scales or domains).

Relation of PRO Endpoints to the Disease and Treatment

Symptoms are often directly related to the underlying disease or condition being treated and, in many cases, define the actual disease or condition. In this way, symptoms are frequent targets of treatment and may be the basis of regulatory review and approval. Alternatively, HRQOL is indirectly related to both the underlying disease or condition and the treatment. It is important to note that the indirect relationships between HRQOL and both disease and treatment are often mediated through symptoms (i.e., HRQOL may improve because symptoms are relieved, but not vice versa). In fact, HRQOL has been related to disease and treatment indirectly through symptoms in several ways, including the following:

- ① Symptom count (fewer symptoms = improved HRQOL)
- ① Symptom severity (less severe symptoms = improved HRQOL)
- ① Symptom duration (less persistent symptoms = improved HRQOL)
- ① Symptom remission (less frequently recurring symptoms = improved HRQOL and/or fewer recurring symptoms = improved HRQOL)

Mirroring Clinician and Patient Discourse

PRO assessment items that closely mirror real-world patient/provider interactions are desirable in clinical trials for a variety of reasons. Chief among them is that study results become more generalizable and can be easily interpreted by both patients and providers. In many, if not most, clinical or real-world circumstances, patients will present specific symptoms (e.g., “I have stomach pain and defecate more often than usual”) and providers often have the responsibility of evaluating and learning about these symptoms but not necessarily their HRQOL implications. Thus, clinic discussions between patients and providers tend to be symptom-focused and may or may not involve HRQOL discussion.

Dynamic Time Course and Mode of Assessment

Symptoms and HRQOL may call for different approaches to assessment because symptoms may vary more dynamically over time than HRQOL. For example, as a more general and stable PRO, HRQOL is expected to change slowly and may be adequately captured by a single pre- and post-treatment assessment schedule. Symptoms, however, often have a more variable time course. For example:

- ❶ Symptoms often follow a particular natural history and may vary meaningfully even within a single day (e.g., patients with gastroesophageal reflux disease tend to experience more symptoms in the evening hours).
- ❷ Symptoms can vary quickly over time, often in response to treatment.

Conclusions

Both symptom and HRQOL measures can address important aspects of the patient experience. However, because symptoms are a direct manifestation of the underlying disease or condition and are often the direct and explicit target of treatment, symptom measures may more easily be used to support labeling claims. If HRQOL measures are used to support claims, it will be imperative to consider the complex relationships between the measure, the patient and the targeted disease condition to meet the recommendations of the FDA draft Guidance.

Reference

¹ Federal Register, Vol. 71, No. 23; Feb. 3, 2006.