

White Paper | PRO Consulting

Documentation of PRO Instruments to Meet Contemporary FDA Standards

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Introduction

The U.S. Food and Drug Administration (FDA) published for comment its “Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims” (hereafter referred to as the PRO Guidance) to describe how it will evaluate PRO instruments. This FDA document implicitly gives credibility to PROs as the basis for evaluating drugs and biologics and provides structure for a more efficient, effective and appropriate use of these tools. Challenges exist, however, in interpreting the PRO Guidance. For example, the breadth of information covered and the technical writing style in the PRO Guidance may make it difficult for researchers to discern the FDA’s recommendations on how to justify and appropriately document the intended use of their PRO instruments.

- The goal of this paper is to describe what information clinical researchers should provide to the FDA to support the use of a given PRO instrument in a clinical trial or program.

Documentation and PRO Instruments

The PRO Guidance discusses a variety of factors that, if appropriately documented, can support use of a given PRO instrument. We summarize these factors under four categories of information: the conceptual framework, the administration characteristics, the performance characteristics and the study design characteristics that describe the instrument as used in the trial (see Box 1).

Box 1: Assessment Information the FDA Recommends Accompany Clinical Trial Applications using PRO Data

Conceptual Framework	Administration Characteristics	Performance Characteristics	Study Design Characteristics
<ul style="list-style-type: none"> Concepts and domains (what) Applications (how) Labeling claim (why) Intended populations (who) 	<ul style="list-style-type: none"> Format, instructions, training Items Recall period Response options Data collection method Scoring procedures Patient understanding Respondent burden Administrator burden 	<ul style="list-style-type: none"> Reliability <ul style="list-style-type: none"> • Internal consistency • Test-retest • Interrater Validity <ul style="list-style-type: none"> • Content-related • Construct-related • Predictive Sensitivity to change <ul style="list-style-type: none"> • Minimally important difference • Definition of responders 	<ul style="list-style-type: none"> General protocol considerations <ul style="list-style-type: none"> • Blinding & randomization • Clinical trial quality control • Missing data Frequency of measurements Duration of study Multiple endpoints Study interpretation ePRO Data analysis Data interpretation

Conceptual Framework

The conceptual framework is the basis for all the other PRO instrument evaluations and for assessing the instrument's relevance to product labeling. When specified correctly, the conceptual framework ensures that a researcher identifies and defines the following:

1. What he or she intends to measure (i.e., the PRO concept)
2. How he or she will measure it (i.e., the PRO instrument)
3. Why he or she is measuring it (i.e., the label claim supported by the PRO data)
4. Whom he or she will be assessing (i.e., the study population)

PRO assessments evaluate both signs and symptoms of a condition or Health-related Quality of Life (HRQOL) domains. Researchers should be aware that measures of signs and symptoms, whose relationship to the underlying disease is well-known and which are measured unidimensionally, will tend to generate a very simple and straightforward conceptual framework model. On the other hand, the conceptual framework is more complex and elaborate when researchers propose to measure HRQOL domains, which are measured multidimensionally and whose relationship with disease processes are indirect and mediated, for example, by symptom improvements. We discuss this further in another PRO Consulting paper.¹

Administration Characteristics

The FDA wants researchers to demonstrate what the selected PRO instrument will look like when administered. Thus, administration characteristics of a PRO instrument reflect, for example, test format, patient instructions, test items and response options, data collection method, and scoring procedures. When using an existing and unmodified PRO instrument, this information can be gleaned from the instrument. However, when creating a new instrument, or using a modified tool, it is the researcher's responsibility to provide a sound logical and empirical rationale for why an instrument looks as it does (e.g., how did you generate a pool of items? How did you select the final test items?) or why a particular modification was made (e.g., why did you add or omit items from the original version?).

Furthermore, researchers should be prepared to document their expectations that the instrument can be read, understood and tolerated by the intended population. Parameters such as reading level and tool length are relevant here, but cognitive debriefing (having a small number of subjects complete the instrument and then interview them about the experience) is useful in ensuring the respondents understand the items and are not over burdened by them.

Performance Characteristics

Reliability, validity, and sensitivity to change are the principal performance characteristics that the FDA will evaluate.

- 🔵 *Reliability* is the extent to which measurements are stable and repeatable (i.e., free from measurement error or random “noise”).
- 🔵 *Validity* is the extent to which a test is measuring what it says it will measure.
- 🔵 *Sensitivity to change* is demonstrated when scores on an instrument change in the theoretically proposed direction following the introduction of a known effective treatment (i.e., scores reflect clinically meaningful improvement).

When using existing PRO instruments, this information can often be obtained from previous reports (e.g., published studies, test manuals). However, it is not enough to say that PRO Instrument X is a reliable and valid tool because it has been previously administered. Clinical researchers need to first identify the appropriate reliability, validity and sensitivity estimate and then show that the previously reported estimates apply to the intended use, meaning that they were obtained under conditions of administration resembling those planned for the new trial (e.g., similar patient population, same instruction set, items, recall interval).

Study Design Characteristics

Study design features can systematically alter how patients respond to PRO questions and can systematically alter conclusions drawn from PRO data. Examples include these:

- 🔵 Unblinded or inadequately blinded studies²
- 🔵 Studies relying on global assessments or retrospective recall³
- 🔵 Studies relying on paper-and-pencil diaries⁴

Clinical researchers already discuss study designs with the FDA. However, the PRO Guidance suggests that researchers discuss specifically how the study design might interact with the PRO assessments and endpoints proposed for the study.

Conclusion

Justifying the use of a PRO instrument to meet contemporary FDA standards can be challenging. These challenges can be managed, however, by thoroughly documenting a variety of factors related to the developmental history and current or intended use of the PRO instrument. These factors can be summarized under four categories of information including the PRO instrument’s conceptual framework and the administration, performance and study design characteristics that describe the instrument as used in the trial.

References

¹ PRO Consulting (2006). Distinguishing among symptom vs. health-related quality of life PRO concepts: Developing a conceptual framework.

² Schulz, K.F., Chalmers, I., & Hayes, R.J. (1995). Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*, 273, 508–512.

³ Norman, G., Stratford, P., & Regehr, G. (1997). Methodological problems in retrospective computation of responsiveness to change: The lessons of Cronbach. *Journal of Clinical Epidemiology*, 50, 869–879.

⁴ Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., & Hufford, M. R. (2002). Patient non-compliance with paper diaries. *British Medical Journal*, 324, 1193–1194.