

## FDA PRO Guidance Documents Impact on Data Collection A White Paper By CRF Health Staff

### Introduction

Patient reported outcome measurement has evolved from the capture of a generic measure of well being to more disease-specific symptom and functional change outcome measures. These changes have occurred over the course of 15 years and most recently the United States Food and Drug Administration (FDA) began the rather lengthy process of defining the aspects of change in the patient's condition that could potentially be used for purposes of labeling in a new drug application. The proposed measurement concepts in the FDA Draft Guidance for PROs released in 2006 received a large number of comments following publication in the Federal Register. The public comments influenced the resulting final version of the Guidance released in 2009, [Patient Reported Outcome Measures: Use in Medical Product Development to Supporting Labeling Claims](#). The purpose of the Guidance is to offer information regarding the topics that are relevant to the review of Patient Reported Outcome (PRO) data which may be used to substantiate claims and product approval. The guidance requirements are informative and specific especially regarding the development and modification of PRO instruments, and the submission of dossier materials.

### Historical Perspective

At the time the draft Guidance was released, a conference was convened in Chantilly, Virginia to discuss a series of papers written by five expert panels. The papers were intended to reflect current science and provide the foundation for discussion on topics anticipated as elements of the Guidance document. The draft papers covered topics germane to measurement of patient reported data in clinical trials. The draft Guidance provided substantive information reinforcing topics under discussion. Several members of the FDA staff participated in the discussion and responded to the content of each paper. The final papers, including one from the FDA panelists, were disseminated in a supplementary issue of *Value in Health* (2007). These papers addressed the following topics and were ultimately accompanied by the FDA paper:

- Conceptual Issues
- Designing a Measurement Strategy
- Instrument Selection Issues
- Sufficient Evidence for the Reliability and Validity of PRO
- Analysis, Interpretation, and Reporting Results of ePRO

The papers provided a scientific background for conference participants to understand the past practice and published scientific reports. All papers were revised post-conference to reflect the discussion and new perspectives derived from the meeting.

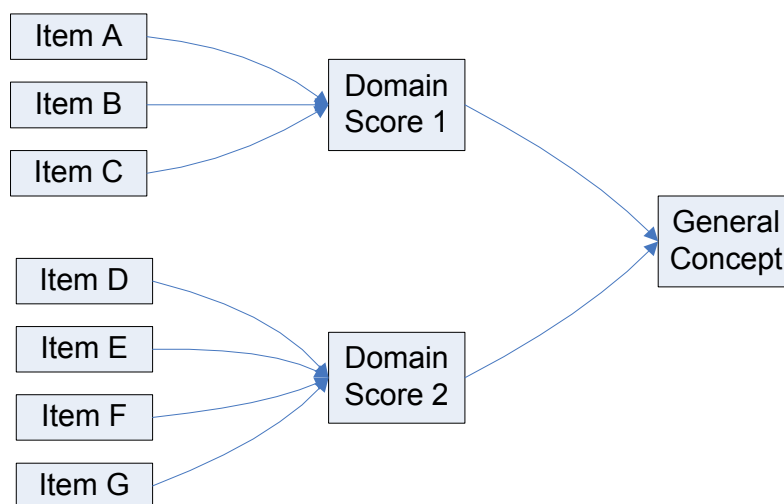
The release of the final PRO Guidance in 2009 demonstrated the commitment of the FDA to guide the use of patient reported outcomes in all forms. The final guidance offers details surrounding the issue of instrument development and modification, and provides information of specific interest to the pharmaceutical industry as well as organizations that assist in the implementation of trials. Further, the guidance has articulated specific definitions for

terminology used in clinical trials: Patient Reported Outcome (PRO) – Any report coming directly from patients (i.e. study subjects) about a health condition and its treatment.

Definitions in this version of the guidance indicate that the agency views Quality of Life (QoL) and Health Related Quality of Life (HRQL) as different entities. Quality of Life is a multidimensional measure of an individual’s life situation including concepts unrelated to health and Health Related Quality of Life (HRQL) is a multidimensional measure of the health and treatment experience reported by the patient. Quality of Life is no longer considered appropriate for labeling because it includes not only health issues but issues unrelated to the patient’s health status. HRQL may be a relevant endpoint for clinical trials but needs to be carefully considered as an endpoint, since it is difficult to adequately measure in all populations. Further, most treatments are unlikely to result in a change across the multiple dimensions of the HRQL measure, as is required for a global HRQL label claim to be successful. In the future the FDA will look for more contemporaneous information about how the subject feels and functions. Instruments that capture change in the subject’s status in real time may have more relevance for purposes of a claim.

### Conceptual Frameworks

The guidance recommends use of a Conceptual Framework when the trial results are intended for labeling. The conceptual framework is an explicit description or pictorial representation of the relationships between the items in a PRO questionnaire and the concepts measured. Figure 1 below reflects a generic example of conceptual framework for a PRO instrument where individual items are aggregated into domain score 1 and domain score 2; the two domain scores and general concept each represent related but separate concepts.



**Figure 1: Conceptual Framework**

The important issue to note regarding the Conceptual Framework (Figure 1) is that it is not necessary to contain multiple items. It is possible for a single item and/or domain to be used as a specific PRO measure. Any review would also require evidence of the concept derivation and transcripts from concept elicitation interviews.

The details of how an instrument is developed and how the concepts are derived and documented are important concerns. The documentation of concept development history could be displayed in several ways although the guidance calls for an item tracking matrix and evidence of saturation within the data gathering interviews. The transcript of interviews along with the item tracking matrix and saturation tables are the elements considered as evidence of content validity in the development of a PRO instrument.

### The Iterative Process of Instrument Development

The guidance document also provides a circular diagram (Figure 2), referred to as a wheel and spokes, to represent the PRO Instrument Development and Modification Process. The diagram suggests an iterative process is to be used for the development of an instrument or the modification of an existing instrument. The steps in the process indicate that modification may also require validation efforts to ensure that the instrument maintains its content validity and intended purpose for the target population.

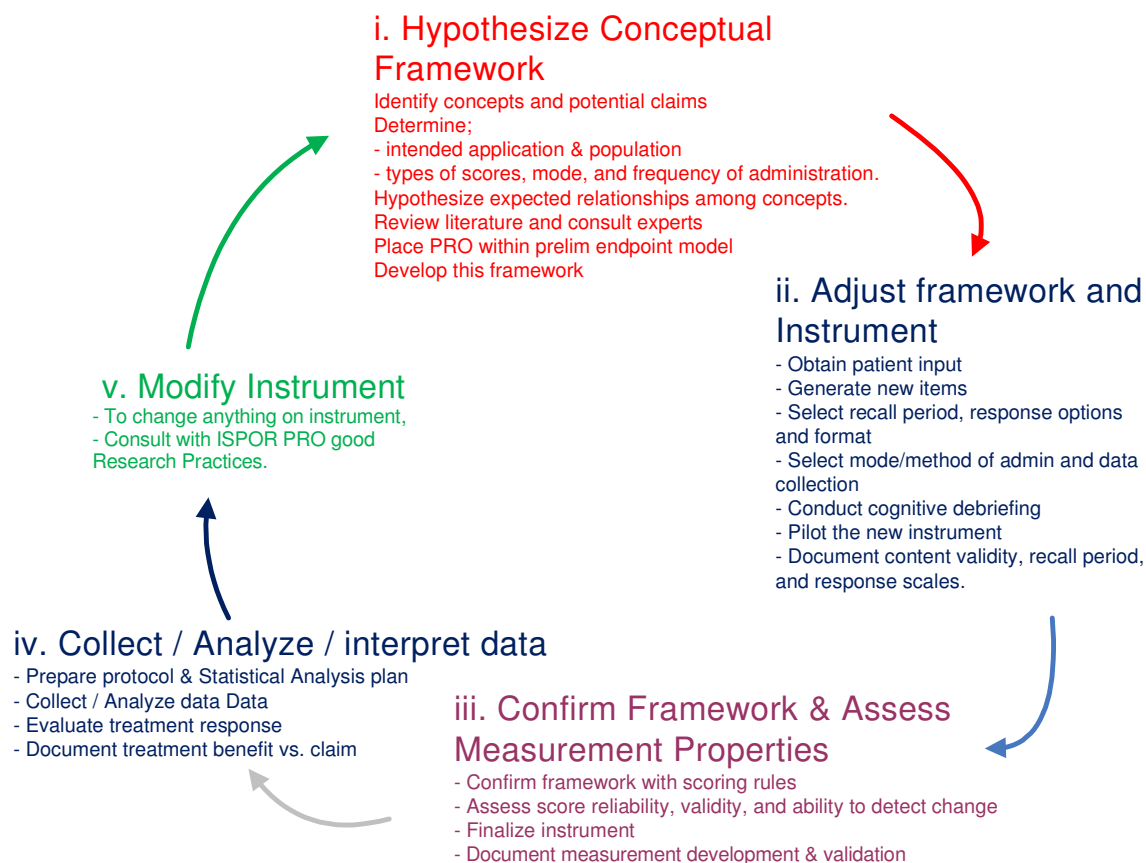


Figure 2

To assess the level of effort required for a given modification, consideration must be given to issues of wording change, altered response options, or changes in the method of data collection. The type of change would dictate the procedure required to establish evidence that a modified instrument could be used as part of a claim. Evidence may be needed to ensure that modifications did not alter the measurement properties of the instrument. Small cognitive debriefing studies may be adequate for minor changes, while full crossover studies might be necessary for larger changes. Full documentation is required for all modifications. The decision to include this data with the submission depends on the criticality of the PRO based claims. At a minimum, the information should be available upon request.

At the same time that the FDA was drafting the PRO Guidance an ISPOR Task Force was working on papers pertaining to good research practice (Rothman et al, 2009). The Task Force report identified threats to content validity and concept identification within the context of labeling efforts.

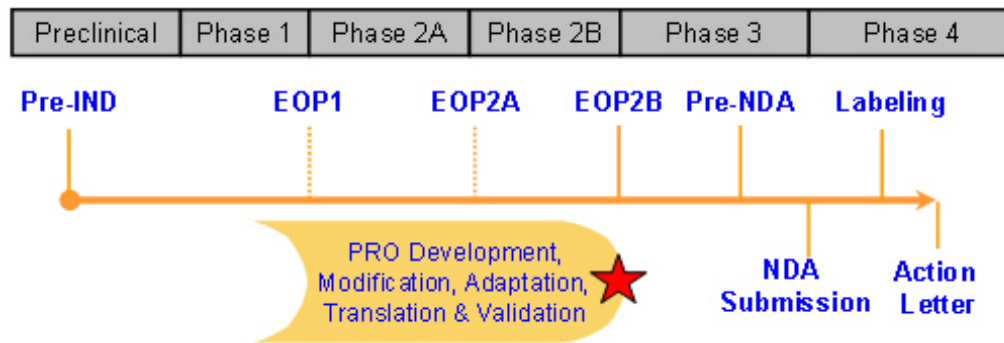
An explanation of instrument modification was described in a recent paper that focused on the evidence required to support measurement equivalence when moving a measure from a paper to an electronic format (Coons, 2009). When minor changes are required cognitive debriefing is essential but moderate changes may require more extensive studies to affirm the psychometric properties. These documents provide an excellent companion guide with detailed information about instrument development. The Guidance states that ‘when a PRO instrument is modified, sponsors generally should provide evidence to confirm the new instrument’s adequacy’. One example of a change is the move from paper to an electronic version.

The European Medicine Agency has also considered the same issues. Although Guidance documents have not been released in the EU, it appears that a more pragmatic approach might be considered to identify changes where full PRO re-validation is required. The basis for labeling may or may not correspond with the FDA position.

The FDA requires that information pertaining to instrument use, modification and analysis be included in the Statistical Analysis Plan (SAP) and made available by the end of phase 2b. The EMEA regulators recognize that in order to achieve this there needs to be practical, rather than an idealistic approach. This is due to the timelines needed for linguistic validations in the many cultures and languages involved in the EU. The key topic of concern to regulators is an early agreement on the use of any PRO based claims.

### **Critical Path**

The FDA has noted that there are intervals in the Critical Path for drug development (Figure 3) during which the agency may review new PRO instruments. The early FDA review of a proposed instrument developed for a specific indication and acceptance of the PRO endpoint may expedite use of the instrument for a claim in phase 3. The current efforts of the FDA to review instruments under development and certify them could enhance the prospect of labeling.



**Figure 3**

In October of 2010 the FDA released a draft Guidance on the Qualification of Drug Development Tools. This guidance provides detailed information on the planned qualification processes and the intervals for communication with the agency. The agency encourages collaborative efforts in PRO instrument development and outlines the process to be used. The intent appears to be to minimize the variation of instruments being developed for the same indication.

### Electronic Patient Reported Data

The PRO Guidance document comments on the electronic collection of patient reported outcome measures and calls out the requirement for potential review of screen shots of the data collection mode at the time of a review. Specific segments generally follow the standard industry practice for clinical data collection tools and reiterate some of the 21CFR§11 clauses for electronic records.

In summary, the bar has been raised for data collection using patient reported outcomes. The rules for labeling are now clearer for sponsors and their colleagues, and all parties have a much better idea of how to prepare for submissions. The Guidance recommendations may continue to evolve and further clarity may be offered as pharmaceutical companies use this version of the PRO Guidance for their NDA and draft language for labeling using a patient reported outcome measurement tool.

### References:

Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. December 2009.

Special Issue: The FDA Guidance for Patient-Reported Outcomes. Value in Health, November/December 2007.10: Supplement s2; s59-s147.

Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification: The ISPOR Good Research

Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value in Health* 2009; 12(8):1075-1083.

Coons SJ, Revicki DA, Lenderking WR, Cella D, Basch E. Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practices Task Force Report. *Value in Health* 2009; 12(4):419-429.

Guidance for Industry: Qualification Process for Drug Development Tools. Draft Guidance. U.S. Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. October 2010.