



FDA Final Guidance on Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims

Summary of Changes from the Draft to the Final Version

Since the 2006 release of the FDA Draft Guidance for Industry on Patient-Reported Outcomes (PROs), the field has been looking forward to the release of the final version. On December 8, 2009, the FDA released the Final Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. This guidance represents the FDA's current thinking on use of PROs to support labeling claims.

Key highlights of the Final Guidance Document are:

- Inclusion of endpoint model definition and examples
- Heavy emphasis on content validity with recommendations on required documentation and item tracking matrix
- Removal of reference to minimal importance difference (MID)
- Inclusion of cumulative distribution function for score interpretation
- Inclusion of Appendix to outline requirements for FDA PRO review

UBC health outcomes researchers have reviewed and compared this final guidance with the draft version and have compiled a summary of the differences. We hope you find this comparison useful.

Part 1: Main Content

Topic	Draft Guidance Section & Page	Final Guidance Section & Page	Changes
INTRODUCTION	Section I, page 1	Section I, page 1	<p>The focus of the guidance has shifted from describing how the FDA evaluates patient-reported outcome (PRO) instruments used as effectiveness endpoints in clinical trials to how it reviews and evaluates existing, modified, or newly created patient-reported outcome (PRO) instruments used to support claims in approved medical product labeling.</p> <p>A PRO instrument is a means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials. <i>Risk not previously mentioned.</i></p> <p>FDA acknowledges that PRO instrument development is an iterative process and there is no single correct way to develop a PRO.</p>
BACKGROUND	Section II, page 2	Section II, page 2	<p>"The use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective."</p> <p>A PRO instrument, like physician-based instruments, should be shown to measure the concept it is intended to measure, and the FDA will review the evidence that a particular PRO instrument measures the concept claimed. Claims can appear in any section of the labeling and PRO instrument evaluation principles apply regardless of location.</p>

Topic	Draft Guidance Section & Page	Final Guidance Section & Page	Changes
Definition	Page 2	Page 2	A more streamlined definition of PRO instrument is presented: "a means to capture data plus all the information and documentation that supports its use" including the concepts being measured, number of items, conceptual framework of the instrument, medical condition, patient population, data collection method, administration mode, etc.
PATIENT-REPORTED OUTCOMES – REGULATORY PERSPECTIVE	Section III, page 3	REMOVED	Information incorporated into Introduction and Background.
Why Use Patient-Reported Outcomes Instruments in Medical Product Development?	Section III.A, page 3	REMOVED	Information incorporated into Introduction and Background.
A Taxonomy of PRO Instruments	Section III.B, page 4	REMOVED	
EVALUATION OF A PRO INSTRUMENT	Section IV, page 3	Section III, page 3	This section details the information (Trial Population, Clinical Trial Design, Conceptual Framework, Measurement Properties) that will be evaluated for a PRO instrument to support a labeling claim. This section contains no major changes from prior guidance, but further clarification is provided.
Endpoint Model	Not Discussed	Section III.A, page 3	<p>Sponsors should include endpoint models to define the role of the PRO endpoint (primary, key secondary, exploratory) in the clinical trial. The adequacy of the PRO instrument will be evaluated in the context of its role and its relationships to other endpoints in the clinical trial. Two example endpoint models are presented on page 4 - one with a PRO as a secondary endpoint and one with a PRO as the primary endpoint.</p> <p>Target product profile can be used to facilitate communication with the FDA about potential labeling claims and clinical trial designs.</p>
Choice of PRO Instrument	Section IV, page 6	Section III.B, page 5	The final guidance discusses the use of PRO instruments to measure safety endpoints. Additionally, the final guidance advises that evidence of content validity is needed for existing instruments without an available development history.
Conceptual Framework of a PRO Instrument	Section IV.A, page 7	Section III.C, page 7	This section has been streamlined in the final guidance. A definition of conceptual framework has been added with more details regarding how the FDA will determine the adequacy of the final conceptual framework including the item generation process, rationale for item deletion/modification and the intended population. Final guidance emphasizes that the terms used to represent the concepts measured should be derived from patient input.
Creation of the PRO Instrument	Section IV.B, page 9	Renamed Content Validity	
Content Validity	Not Discussed	Section III.D, page 12	The final guidance includes a definition of content validity and emphasizes the importance of establishing content validity before other measurement properties are assessed.

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Item Generation	Section IV.B.1, page 9	Section III.D.1, page 12	The final guidance provides more details regarding what information (e.g., evidence of saturation, item tracking matrix, item relevancy) the FDA will review to determine the adequacy of the item generation process. The final guidance emphasizes the need to obtain input from a wide range of patients with the condition of interest to represent variations in disease severity, age, gender, ethnicity and language groups, but makes no recommendations regarding the number of patient interviews/focus groups needed to establish content validity. The final guidance cautions against complicated response options (e.g. not applicable, skip patterns) that create scoring problems.
Data Collection Method and Instrument Administration Mode	Section IV.B.2, page 10	Section III.D.2, page 13	<p>The final guidance differentiates between data collection <u>method</u> and administration mode, where previously these were synonymous: "Administration modes can include self-administration, interview, or a combination of both. Data collection methods can include paper-based, computer-assisted, and telephone-based assessments."</p> <p>Discussion of using multiple data collection methods or administration modes now emphasizes comparison of data "within a single clinical trial to determine whether the treatment effect varies by method or mode" rather than pooling of data.</p>
Recall Period	Section IV.B.3, page 10	Section III.D.3, page 14	<p>Both the draft and final guidance state that "choice of recall period that is most suitable depends on the instrument's purpose and intended use", however the final guidance expresses concern that recall over a long period of time and comparison to previous state and averaging responses over a period of time may undermine content validity.</p> <p>Guidance emphasizes preferability of short recall period, current state, and worst or best experience over the recall period for longer durations.</p>
Response Options	Section IV.B.4, page 11	Section III.D.4, page 14	<p>Minor changes, now focusing on consistency of response options with purpose and intended use of each item rather than with the PRO instrument overall.</p> <p>Under considerations for appropriateness, number of response options justified <u>empirically</u>, options represent <u>similar</u> (previously equal) intervals, and concrete example of potential bias due to response options.</p>
Instrument Format, Instructions and Training	Section IV.B.6, page 12	Section III.D.5, page 16	The final guidance emphasizes that the <i>format</i> of the PRO instrument used for data collection in a clinical trial be consistent with that used in the instrument <u>development</u> process with format referring to the exact questionnaire, diary, or interview script appearance. Format is specific to the administration mode and data collection method.

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Patient Understanding	Section IV.B.5, page 12	Section III.D.6, page 16	<p>While the draft guidance focused on readability and patient understanding of items included in the PRO instrument, the final guidance significantly expands the scope to include confirmation of content validity: "This examination should include documentation that the concepts represented in the PRO instrument's conceptual framework are confirmed, that the response options and recall period are appropriately comprehended, and that the instrument's readability is adequate for the intended population."</p> <p>The final guidance includes the addition of "usability testing process description (if applicable)" to the procedures to include in a cognitive interviewing report and emphasizes the use of evidence from patient cognitive interview studies to determine when a concept is adequately captured.</p>
Scoring of Items and Domains	Section IV.B.7, page 13	Section III.D.7, page 16	Sponsors are encouraged to provide justification of the method chosen to combine items/domains to create scores. The final guidance discourages claims expressed in terms of domain or instrument titles as such claims often do not represent the measured concept.
Respondent and Administrator Burden	Section IV.B.8, page 13	Section III.D.8, page 17	No significant changes.
Confirmation of the Conceptual Framework and Finalization of the Instrument	Section IV.B.9, page 14	REMOVED	Incorporated into Section III.C, page 7.
Reliability, Other Validity and Ability to Detect Change	Section IV.C, page 15 Assessment of Measurement Properties	Section III.E, page 18	<p>The final guidance provides enhanced clarity as to measurement properties and their definitions. The final guidance acknowledges challenges in establishing some measurement properties (e.g. test-retest reliability in remitting/relapsing diseases) and the effect of poor measurement properties on study conclusions (e.g. instruments with poor reliability are unlikely to give a false positive result).</p> <p>The final guidance emphasizes the need to demonstrate the instrument's ability to detect change. Interpretability and the minimum important difference are not included in the final guidance.</p>

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Instrument Modification	Section IV.D, page 20	Section III.F, page 20	<p>This section has been reduced significantly and its scope has changed to focus on the adequacy of the instrument's development and testing as specific to the intended application in terms of population, condition and measurement context, rather than "validity". Evidence to support the new instrument's adequacy when modified is recommended.</p> <p>The guidance <u>no longer</u> states the following: "The FDA intends to consider a modified instrument as a different instrument from the original and will consider measurement properties to be version-specific. The FDA recommends additional validation to support the development of a modified PRO instrument." It now states: "That is not to say that every small change in application or format necessitates extensive studies to document the final version's measurement properties. Additional qualitative work may be adequate depending on the type of modification made."</p> <p>Examples of instrument modifications are mainly format changes that were previously found in the Instrument Format section of the document.</p> <p>Examples no longer discussed in this section include "Revised Measurement Concept," "Changed Culture or Language of Application," and "Other Changes."</p> <p>Recommendation for using the PRO instrument in a <u>significantly different (rather than entirely new)</u> patient population now includes qualitative studies to confirm content validity in the new population in addition to the previously recommended small randomized study to assess measurement properties to minimize risk of inadequate performance.</p>
PRO Instruments Intended for Specific Populations	Section IV.E, page 22	Section III.G, page 21	<p>Major changes include the addition of Culture or Language subgroups to the previous subgroups: Children and Adolescents and Patients Cognitively Impaired or Unable to Communicate.</p> <p>Proxy-reported outcome measures are now strongly discouraged for pediatric and cognitively or communicatively impaired populations when previously they were considered an option. Instead, the guidance encourages "observer reports that include only those events or behaviors that can be observed."</p> <p>For new language versions, the FDA recommends "that sponsors provide evidence that the content validity and other measurement properties are adequately similar between all versions used in the clinical trial. [They] will review the process used to translate and culturally adapt the instrument for populations that will use them in the trial."</p> <p>The guidance no longer discusses the validity of data from a translated/adapted PRO instrument, does not specify methodology used, background of translators, or harmonization. It now refers to the population that will use the translations in the trial, consistent with its emphasis on patient input and confirmation of content validity throughout the guidance.</p>
CLINICAL TRIAL DESIGN	Section V, page 23 STUDY DESIGN	Section IV, page 22	Focuses on Clinical trial design specifically rather than study design in general.

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General Protocol Considerations	Section V.A, page 23	Section IV.A, page 22	<p>New guidance provides additional suggestions for addressing unintentional unblinding in clinical trials including recommendation that the PRO instrument be administered before other clinical assessments and procedures and inclusion of a single item that asks patients to identify which arm they think they participated in to aid interpretation of potential bias.</p> <p>Clinical Trial Quality Control is substantially the same, with the recommendation of a standardized order of administration of PRO and other assessments and the addition of plans for confirmation of the instrument's measurement properties using clinical trial data as a standardized process.</p> <p>New guidance further specifies that the clinical trial protocol should describe how missing data will be handled in the analysis and recommends that patients remain in the clinical trial, even if they have discontinued treatment, and should continue to provide PRO data.</p>
Frequency of Assessments	Section V.B, page 24, Frequency of Measurements	Section IV.B, page 24	<p>The frequency of PRO assessment should correspond with the <u>specific research questions being addressed, length of recall asked by the instrument's response options</u>, demonstrated instrument measurement properties, the disease or condition's natural history, the treatment's nature, and planned data analysis.</p>
Clinical Trial Duration	Section V.C, page 24 Duration of Study	Section IV.C, page 24	<p>The duration of PRO assessment depends on the PRO research questions being posed as well as adequate length to support the claim and assess the disease or condition.</p>
Design Considerations for Multiple Endpoints	Section V.D, page 25	Section IV.D, page 24	<p>The final guidance describes a single hierarchy of endpoints as diagrammed in an endpoint model and considers any endpoints that are not part of the prespecified hierarchy of primary and key secondary endpoints or included for economic evaluation or not intended for labeling claims to be exploratory.</p> <p>Also emphasizes avoiding separate consideration of PRO endpoints from the trial's primary objectives in design and analysis, and avoiding cherry picking or <i>post hoc</i> selective picking of PRO endpoints results for inclusion in proposed labeling.</p>
Planning for Study Interpretation	Section V.E, page 25	Renamed Planning for Clinical Trial Interpretation Using a Responder Definition	
Planning for Clinical Trial Interpretation Using a Responder Definition	Section IV.C, page 19-20	Section IV.E, page 24	<p>The final guidance no longer mentions MID as an option, and recommends an <i>a priori</i> responder definition (i.e., the individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit). A responder definition should be derived using anchor-based methods, while distribution-based methods can support the derived threshold. Alternatively a cumulative distribution function can be performed to avoid the need to select a responder criterion.</p>

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Specific Concerns When Using Electronic PRO Instruments	Section V.F, page 25	Section IV.F, page 26	<p>Sponsors must ensure that FDA regulatory requirements (21 CFR part 11) are met and adds that the clinical trial protocol, or a separate document, should specify how the electronic PRO source data will be maintained <u>and how the investigator will meet the regulatory requirements.</u></p> <p>Additional warnings to sponsors in final guidance are the following:</p> <ul style="list-style-type: none"> - The data maintained by the clinical investigator should include an audit trail to capture any changes made to the electronic PRO data at any point in time after it leaves the patient's electronic device. <p>Avoid</p> <ul style="list-style-type: none"> - Ability of any entity other than the investigator (and/or site staff designated by the investigator) to modify the source data. - <u>Premature or unplanned</u> access to unblinded data. - Direct PRO data transmission of important safety information to sponsors, clinical research organizations, and/or third parties, without ensuring the timely transmission of the data to the clinical investigator responsible for the patients.
DATA ANALYSIS	Section VI, page 27	Section V, page 27	No significant changes.
General Statistical Considerations	Section VI.A, page 27	Section V.A, page 27	No significant changes.
Statistical Considerations for Using Multiple Endpoints	Section VI.B, page 27	Section V.B, page 28	No significant changes. The final guidance provides a clearer discussion of multiple endpoints in clinical trials, determining effectiveness and methods to control for Type 1 error rate (e.g. sequential analysis).
Statistical Considerations for Composite Endpoints	Section VI.C, page 28	Section V.C, page 29	No significant changes. The final guidance provides a clearer discussion of composite endpoints and labeling claims.
Statistical Considerations for Patient-Level Missing Data	Section VI.D, page 29	Section V.D, page 29	The final guidance provides a more general discussion of how to handle missing data. The final guidance recommends that two or more sensitivity analyses be conducted with different methods for missing data imputation.
Interpretation of Clinical Trial Results	Section VI.E, page 30	Section V.E, page 30	The discussion of minimum important difference in the draft guidance has been replaced by a recommendation to use the cumulative distribution function of responses to characterize the treatment effect. A responder definition can be applied to the cumulative distribution function. The final guidance states that the interpretation of PRO endpoints follows similar considerations as for other endpoint types.

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GLOSSARY	Page 31	Page 31	Expanded from 16 to 31 definitions of key terms in the PRO field. Terms added: Ability to detect change, Construct, Content, and Criterion validity, Endpoint and Endpoint model, Item tracking matrix, Measurement properties, Proxy-reported outcome, Recall period, Reliability, Responder definition, Saturation, Sign, Symptom, Target Product Profile (TPP), Usability testing Terms modified: Cognitive debriefing interviews is now Cognitive interviewing, Patient-Reported Outcome, Treatment benefit. Terms removed: Minimum Important Difference (MID), Validation
APPENDIX: INFORMATION ON A PRO INSTRUMENT REVIEWED BY THE FDA		Page 35	Outline of topics that should be addressed in PRO documents provided to the FDA for review.

Part II: Figures

Topic	Draft Guidance Section & Page	Final Guidance Section & Page	Changes
Endpoint Model: Treatment of Disease X	Not included	Figure 1, page 4	Example of PROs as secondary endpoints.
Endpoint Model: Treat- ment of Symptoms As- sociated with Disease X	Not Included	Figure 2, page 4	Example of PRO as a primary endpoint and supportive secondary endpoints.
Development of a PRO Instrument: An Iterative Process	Figure 1, page 7	Figure 3, page 7	Modified Wheel-and-Spokes Diagram describes the process of developing and refining the conceptual framework in relation to the claim rather than the PRO instrument itself. Expanded from 4 to 5 steps as follows: <ul style="list-style-type: none"> i. Hypothesize Conceptual Framework ii. Adjust Conceptual Framework & Draft Instrument iii. Confirm Conceptual Framework & Assess Other Measurement Properties iv. Collect, Analyze, & Interpret Data v. Modify Instrument
Diagram of the Conceptual Framework of a PRO Instrument	Figure 2, page 9	Figure 4, page 8	Overall Score changed to "General Concept".

Part III: Tables

Topic	Draft Guidance Section & Page	Final Guidance Section & Page	Changes
Common Reasons for Changing Items during PRO Instrument Development	Table 3, page 15	Table 1, page 9	Recall period added as an item property and examples for inter-item correlation, item discrimination, and ability to detect change have been revised.
Measurement Properties Considered in the Review of PRO Instruments Used in Clinical Trials	Table 4, pages 16-17	Table 2, page 11	FDA review considerations have been changed from questions to actual statistics/data that will be reviewed (e.g. intraclass correlation coefficient, Cronbach's alpha, cognitive interview transcripts, effect size statistic).
Response Option Types	Table 2, page 11	Table 3, page 15	Minor textual changes.
Taxonomy of PROs Used in Clinical Trials	Table 1, page 5	REMOVED	Attributes now appear as a list of instrument characteristics in Section III.B, Choice of PRO Instrument.

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