

# The Difference between the FDA Draft Guidance and Final Guidance:

*How these modifications affect Sponsors and CROs*

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## The FDA Final Guidance<sup>1</sup>: Key Considerations for Sponsors Collecting PRO and ePRO Data

**Clinical researchers who gather data directly from patients** have anticipated the FDA Final PRO Guidance for more than 3 years. The document released in December 2009 provides constructive support for collecting PRO and ePRO (electronic PRO) data with scientific rigor. It establishes that FDA reviewers will evaluate protocols with respect to the targeted labeling claims, an **endpoint model, conceptual framework of PRO instruments** and the **content validity of PRO items**. Each of these key elements is defined and explained in the Final Guidance itself. The collaborative effort extended in developing the Final PRO Guidance should help clinical researchers to rely on patient self-reported information in support of market authorizations and advertising claims.

The purpose of this article is to provide Sponsors and CROs with a point-by-point review of the differences between the Final FDA PRO Guidance and the Draft, highlighting the choices made by FDA during the 3 years following the Draft PRO Guidance. These choices reveal the FDA deliberations and resulting emphasis, and we also suggest in our review what some of the differences might imply. Note that where terms appear highlighted or emphasized in quotes from the Final Guidance, the emphasis has been done in the original FDA document.

The focus of the Final Guidance has been altered from a review of *best practices* for PRO instrument development to FDA review considerations for PRO instruments, establishing guidelines for evaluating existing, modified or newly created [e] PRO instruments. The Final Guidance also provides more precise directives on how to leverage PRO for labeling claims, and greater direction to Sponsors and CROs. The Final Guidance recommends that Sponsors should begin [PRO or ePRO] instrument development and evaluation early in medical product development, and should also engage the FDA in a discussion about a new or unique PRO [or ePRO] instrument before confirmatory clinical trial protocols are finalized.

### 3 Key Takeaways:

1. The Final Guidance emphasizes three aspects of PRO instruments used to support claims in approved medical product labeling: the conceptual framework, endpoint model, and content validity.
2. The Guidance includes an Appendix to help Sponsors prepare a dossier to be submitted to FDA that explains and justifies the PRO instruments planned for an investigation.
3. PRO instrument development and use should be completed before commencing confirmatory trials. PHT suggests that Sponsors discuss planned PRO measures with us during the development phase so that we can help them optimize item and instrument selection to suit the trial objectives and to obtain scientifically compelling data directly from patients as they experience a new medical therapy.

It is critical that the clinical trial protocol define the endpoint measures and the criteria for the statistical analysis and interpretation of results, including a specification of the conditions for a positive clinical trial conclusion, because determination of these criteria and conditions after data are unblinded will not be credible.

<sup>1</sup> <http://www.phtcorp.com/>

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	Key Learnings for Sponsors and CROs	Draft Guidance February 2006	Guidance for Industry (Final) December 2009
PRO instrument review	<i>Sponsors and CROs who plan to rely on PRO and ePRO instruments to support claims in approved medical product labeling will know how FDA will review them.</i>	[Lines 21-24] This guidance describes how the FDA evaluates patient-reported outcome (PRO) instruments used as effectiveness endpoints in clinical trials. It also describes our current thinking on how sponsors can develop and use study results measured by PRO instruments to support claims in approved product labeling.	[Section I] This Guidance describes how the Food and Drug Administration (FDA) reviews and evaluates existing, modified, or newly created <b>patient-reported outcome (PRO) instruments</b> used to support <b>claims</b> in approved medical product labeling.
PRO instrument definition	<i>Sponsors should define how their PRO instruments measure treatment benefit, and should establish suitability of the measures before patient enrollment in confirmatory trials.</i>	[Lines 45-49] In particular, the term <i>instrument</i> refers to the actual questions or items contained in a questionnaire or interview schedule along with all the additional information and documentation that supports the use of these items in producing a PRO measure (e.g., interviewer training and instructions, scoring and interpretation manual.)	[Section I] A PRO instrument (i.e., a <b>questionnaire</b> plus the information and documentation that support its use) is a means to capture PRO data used to measure <b>treatment benefit</b> or risk in medical product clinical trials. [Section III.B. paragraph 5] We suggest that an instrument's measurement properties be well established before enrollment begins for confirmatory clinical trials. Therefore, sponsors should begin instrument development and evaluation early in medical product development, and engage the FDA in a discussion about a new or unique PRO instrument before confirmatory clinical trial protocols are finalized.
PRO instruments measure concepts	A Dossier explains how a concept being measured relates to clinical benefit, endpoints and claims. <i>Sponsors and CROs may elect to utilize Section III as their protocol outline for collecting PRO and ePRO, since it lists key considerations for content:</i> <ul style="list-style-type: none"> <li>• <i>Endpoint Model</i></li> <li>• <i>Choice of PRO Instrument</i></li> <li>• <i>Conceptual Framework of a PRO Instrument</i></li> <li>• <i>Content Validity</i></li> <li>• <i>Reliability, Other Validity, and Ability to Detect Change</i></li> <li>• <i>Instrument Modification</i></li> <li>• <i>PRO Instruments Intended for Specific Populations</i></li> </ul>	[Lines 82-89] Note, however, that PRO instruments that measure a simple concept may not be adequate to substantiate a more complex claim. For example, PRO-based evidence of improved symptoms alone generally is not sufficient to substantiate a claim related to improvement in a patient's ability to function or the patient's psychological state. Rather, to substantiate such a general claim, a sponsor should develop evidence to show not only a change in symptoms, but how that change translates into other specific endpoints such as ability to perform activities of daily living, or improved psychological state. Accordingly, many PRO instruments are specifically designed to assess both symptoms and other possible consequences of treatment.	[Section II, paragraph 1] In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more <b>concepts</b> (i.e., the <i>thing</i> being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition.)

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The endpoint model	<i>Sponsors and CROs should define the role of a PRO or ePRO endpoint within the protocol, and plan the endpoint model.</i>	[Lines 791-798] A PRO instrument could be the primary endpoint measure of the study, a co-primary endpoint measure in conjunction with other objective or physician-related measurements, or a secondary endpoint measure whose analysis would be considered according to a hierarchical sequence.	[Section II.A.] Sponsors should define the role a PRO <b>endpoint</b> is intended to play in the clinical trial (i.e., a primary, key secondary or exploratory endpoint) so that the instrument development and performance can be reviewed in the context of the intended role, and appropriate statistical methods can be planned and applied. It is critical to plan these approaches in what can be called an endpoint model.
Safety outcomes and endpoints	<i>Sponsors and CRO trial designers should be wary of combining efficacy measures and measures of adverse consequences to measure a general concept. Instead, it is recommended that they separate measures of treatment effectiveness from measures of that treatment's adverse consequences into separate domains that can be clearly related to proposed claims.</i>	[Lines 164-165, Table 1] The intended use of the measure is <ul style="list-style-type: none"> <li>• To define entry criteria for study populations</li> <li>• To evaluate efficacy</li> <li>• To evaluate adverse events</li> </ul> [Lines 269 – 271] The PRO instrument can be developed for a variety of roles, including defining trial entry criteria, including excessive severity, evaluating treatment benefit, or monitoring adverse events.	[Section III.B.] Claims representing general concepts often are not supported, even though the PRO instrument was developed to measure the general concepts, because the instrument may not distinguish adverse side effects of treatment that affect the general concept that may not be known at the time the clinical trials are designed. If adverse effects are captured, PRO instruments should aim to measure the adverse consequences of treatment separately from the effectiveness of treatment. As with any clinical trial evaluating FDA-regulated medical products, all adverse events detected with a PRO instrument should be included in the clinical trial report.
PRO instrument validation	<i>Sponsors and CROs should include all validation transcripts, as detailed in Appendix Section V and Appendix C – Transcripts.</i>	[Lines 501-504] The FDA recognizes that the validation of an instrument is an ongoing process and that validity relates to both the instrument itself and how it is used. Sponsors should consider a PRO [or ePRO] endpoint for evidence of content-related validity, the instrument's ability to measure the stated concepts, and the instrument's ability to predict future outcomes, as illustrated in Table 4.	[Appendix Section V. Content Validity Documentation.] Evidence that instrument captures all of the most clinically important concepts and items, and that items are complete, relevant (appropriate), and understandable to the patient. This evidence applies to both existing and newly created instruments and is specific to the planned clinical trial population and indication.

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Enhanced Wheel & Spokes diagram	<i>Sponsors and CROs should follow the Wheel &amp; Spokes objectives and specific action steps.</i>	[Figure 1] The PRO Instrument Development and Modification Process provides general action steps did not include specific details about the development process.	[Section III.C., Figure 3] Development of a PRO Instrument: An Iterative Process includes 5 objectives with specific action steps: (i.) Hypothesize Conceptual Framework, (ii.) Adjust Conceptual Framework and Draft Instrument, (iii.) Confirm Conceptual Framework and Assess Other Measurement Properties, (iv.) Collect, Analyze, and Interpret Data, (v.) Modify Instrument.
Reasons for <a href="#">changing</a> a PRO instrument	Sponsors and CROs are encouraged to utilize ePRO for subsequent trial phases, since the reasons for moving to electronic data capture can be easily demonstrated within these new table of reasons.	[Lines 590 – 670] 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 when one or more of the following modifications occur. <ol style="list-style-type: none"> <li>1. Revised Measurement Content...</li> <li>2. Application to a New Population or Condition...</li> <li>3. Changed Item Content or Instrument Format...</li> <li>4. Changed Mode of Administration...</li> <li>5. Changed Culture or Language of Application...</li> <li>6. Other Changes...</li> </ol>	[Section III.C.] Table 1. Common Reasons for Changing Items during PRO Instrument Development <ul style="list-style-type: none"> <li>• Clarity or relevance...</li> <li>• Response range...</li> <li>• Variability...</li> <li>• Reproducibility...</li> <li>• Inter-item correlation...</li> <li>• Ability to detect change...</li> <li>• Item discrimination...</li> <li>• Redundancy...</li> <li>• Recall period...</li> </ul>

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5 criteria used to demonstrate content validity	<p><i>Sponsors and CROs can provide evidence of content validity from these sources, as outlined in the Appendix:</i></p> <ul style="list-style-type: none"> <li>A. <i>Literature review and documentation of expert input</i></li> <li>B. <i>Qualitative study protocols, interview guides, and summary of results for focus group testing, open-ended patient interviews, and cognitive interviews</i></li> <li>C. <i>Origin and derivation of items with chronology of events for item generation, modification, and finalization</i></li> <li>D. <i>Qualitative study summary that supports content validity for item content, response options, recall period and scoring</i></li> <li>E. <i>Summary of qualitative studies demonstrating how item pool was generated, reduced, and finalized.</i></li> </ul>	<p>[Lines 1101-1109] Validation – The process of assessing a PRO instrument’s ability to measure a specific concept or collection of concepts. This ability is described in terms of the instrument’s measurement properties that are derived during the validation process. At the conclusion of the process, a set of measurement properties is produced that are specific to the specific population and the specific form and format of the PRO instrument tested. The validity process involves:</p> <ul style="list-style-type: none"> <li>• Identifying the concept to be measured</li> <li>• Assessing the content validity (i.e., being sure the items in the questionnaire cover the important aspects of the concept from the patient perspective)</li> <li>• ...</li> </ul>	<p>[Section III.D.] Content validity is the extent to which the instrument measures the concept of interest. Content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use..</p> <p>[Glossary] <b>Content validity</b> - Evidence from qualitative research demonstrating that the instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity.</p>
Proof of data entry times required	<p><i>Sponsors and CROs should choose an ePRO System that can prove data entry times, prove what steps are taken to ensure that patient entries are authentic and accurate; and include this proof in the archive for reconstruction.</i></p>	<p>[Lines 334 - 337] ... If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what measures are taken to ensure that patients make entries according to the study design and not, for example, just before a clinic visit when their reports will be collected.</p>	<p>[Section III.D.] ... If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what <b>steps</b> are taken to ensure that patients make entries according to the <b>clinical trial</b> design and not, for example, just before a clinic visit when their reports will be collected.</p>
Evaluating a <u>modified</u> PRO instrument	<p><i>Sponsors and CROs are required to prove a modified instrument’s adequacy.</i></p>	<p>[Lines 176 -181] A new PRO instrument can be developed or an existing instrument can be modified is sponsors determine that none is available, adequate, or applicable to their product development program. When considering an instrument that has been modified from the original, the FDA generally plans to evaluate the modified instrument just as it would a new one.</p>	<p>[Section III.F.] ... When a PRO instrument is modified, sponsors generally should provide evidence to confirm the new instrument’s adequacy. That is <b>not</b> 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>

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Concerns about unintentional and intentional unblinding	<i>Sponsors and CROs should design questions that minimize the effects of possible unblinding, such as using response items that ask for current status, not giving patients access to previous responses, and using instruments that include many items about the same concept.</i>	<p>[Lines 725 – 726] The importance of blinding can be determined, in part, by the characteristics of the PRO instrument used.</p> <p>[Lines 729-731] Questions that ask for current status, or PRO instruments that ask many questions, are harder to answer in a biased way when previous answers are not available.</p> <p>[Lines 735-738] There are certain situations, particularly in the development of medical devices, where blinding is not feasible and other situations where there is no reasonable control group (and therefore no randomization). When a PRO instrument appears useful in assessing patient benefit in those situations, the FDA encourages sponsors to confer with the appropriate review division.</p>	<p>[Section IV.A.1.] Open-label clinical trials, where patients and investigators are aware of assigned therapy, are rarely adequate to support labeling claims based on PRO instruments.</p> <p>To prevent influencing patient perspectives, PRO instruments administered during a clinic visit should be administered before other clinical assessments or procedures.</p> <p>If the treatment has obvious effects, such as adverse events, the clinical trial may be at risk for unintentional unblinding.</p> <p>Suspicion of inadvertent unblinding can be a problematic review consideration for the FDA when assessing PRO endpoints. Therefore, when PRO instruments are included in a clinical trial, we encourage sponsors to include a single item during or at the end of the trial to ask patients to identify the clinical trial arm in which they believe they participated.</p>
Missing data from patient withdrawal	<i>Sponsors and CROs should use PRO instrument administration techniques to minimize unblinding.</i>	[Lines 765- 768] We recommend the study protocol describe how missing data will be handled in the analysis. It could also establish a process by which PRO measurement is ascertained before or shortly after patient withdrawal from treatment exposure due to lack of efficacy or toxicity.	<p>[Section IV.A.2] The clinical trial protocol should describe how missing data will be handled in the analysis.</p> <p>Patients should remain in the clinical trial, even if they have discontinued treatment, and should continue to provide PRO data. The protocol should also establish a process by which PRO measurement is obtained before or shortly after patient withdrawal from treatment should early withdrawal be unpreventable.</p>

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Design requirements for multiple endpoints	<i>Sponsors and CROs should design protocols with the end in mind, a standard practice for PHT and the PHT PROvision Science Team.</i>	[Lines 796- 798] The FDA recommends that the study protocol define the study endpoint measures and the criteria for the statistical analysis and interpretation of results, including a clear specification of the conditions for a positive study conclusion.	[Section IV.D] It is critical that the clinical trial protocol define the endpoint measures and the criteria for the statistical analysis and interpretation of results, including a specification of the conditions for a positive study conclusion, because determination of these criteria and conditions after data are unblinded will not be credible. Sponsors should avoid separate consideration of PRO endpoints from the clinical trial's primary objectives in terms of clinical trial design or data analysis. Sponsors also should avoid <i>cherry picking</i> or post hoc selective picking of PRO endpoint results for inclusion in proposed labeling.
Interpreting data beyond statistical significance	<i>Sponsors and CROs should define and develop the responder definition early in trial preparation, rather than describing the minimally important difference.</i>	[Lines 474-475] The FDA generally intends to review a PRO instrument for: reliability, validity, ability to detect change, and interpretability (e.g., minimum important difference).  [Lines 802-807] The FDA recommends that sponsors discuss with the appropriate review division how best to plan for the interpretation of study findings. In some cases, the FDA may request an <i>a priori</i> definition of the minimum observed difference between treatment group means (i.e., MID) that will serve as a benchmark to interpret whether study findings are conclusive. In other cases, the FDA may request an <i>a priori</i> definition of a treatment responder that can be applied to individual patient changes over time.	[Section IV.E.] Planning for Clinical Trial Interpretation Using a Responder Definition. Regardless of whether the primary endpoint for the clinical trial is based on individual responses to treatment or the group response, it is usually useful to display individual responses, often using an <i>a priori responder definition</i> (i.e. the individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit.) The responder definition is determined empirically and may vary by target population or other clinical trial design characteristics. Therefore, we will evaluate an instrument's responder definition in the context of each specific clinical trial.

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Specific concerns about ePRO Instruments	<p><i>Sponsors and CROs should choose an ePRO System that</i></p> <ul style="list-style-type: none"> <li>• <i>Archives eSource data;</i></li> <li>• <i>Documents all data changes with an electronic audit trail;</i></li> <li>• <i>Provides database backup;</i></li> <li>• <i>Prevents eSource modifications except by Investigator or designated site staff (not the Sponsor, not the ePRO provider.)</i></li> <li>• <i>Ensures retention of any adverse event data captured by the system;</i></li> <li>• <i>Prevents premature access to unblinded data;</i></li> <li>• <i>Ensures timely transmission of important PRO safety data to the clinical investigator responsible for the patient; and</i></li> <li>• <i>Enables full trial reconstruction from archival records by an FDA investigator at each clinical site.</i></li> </ul>	<p>[Lines 847-857] Sponsors should also plan to avoid the following:<sup>9</sup></p> <ul style="list-style-type: none"> <li>• Direct PRO data transmission from the PRO data collection device to the sponsor (i.e., the sponsor should not have exclusive control of the source document)</li> <li>• The existence of only one database without backup (i.e., risk of data corruption or loss during the trial with no way to reconstitute or verify the data)</li> <li>• Removal of investigator accountability for confirming the accuracy of the data</li> <li>• Loss of adverse event data</li> <li>• Access to unblinded data</li> <li>• Inability of an FDA inspector to inspect, verify, and copy the data at the clinical site during an inspection</li> <li>• An insecure system that allows for easily alterable records.</li> </ul> <p><sup>9</sup>The FDA specifically welcomes comment and additional information that will inform these policies as new electronic PRO technology is developed and used in the medical product development setting.</p>	<p>[Section IV.F]... Sponsors also should avoid the following:</p> <ul style="list-style-type: none"> <li>• Direct PRO data transmission from the PRO data collection device to the sponsor, clinical investigator, or other third party without an electronic audit trail that documents all changes to the data after it leaves the PRO data collection device.</li> <li>• Source document control by the sponsor exclusively.</li> <li>• Clinical investigator inability to maintain and confirm electronic PRO data accuracy. 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.</li> <li>• The existence of only one database without backup (i.e., risk of data corruption or loss during the trial with no way to reconstitute or verify the data).</li> <li>• Ability of any entity other than the investigator (and/or site staff designated by the investigator) to modify the source data.</li> <li>• Loss of adverse event data.</li> <li>• Premature or unplanned access to unblinded data.</li> <li>• Inability of an FDA investigator to inspect, verify, and copy the data at the clinical site during an inspection.</li> <li>• An insecure system where records are easily altered.</li> <li>• 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.</li> </ul>

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How to demonstrate treatment benefit	<i>Sponsors and CROs should elicit PRO data to characterize the treatment effect, and be prepared to explain the mean improvements within different patient subsets.</i>	[Lines 109-119] Patients Provide a Unique Perspective on Treatment Effectiveness. PRO instruments can be developed to measure what patients want and expect from their treatment and what is most important to them. When used to measure study endpoints, PRO instruments can augment what is known about the product based on the clinician perspective or physiologic measures. This is important because improvements in clinical measures of a condition may not necessarily correspond to improvements in how the patient functions or feels...	[Section V.E.] Because statistical significance can sometimes be achieved for small changes in PRO measures that may not be clinically meaningful (i.e., do not indicate treatment benefit), we encourage sponsors to avoid proposing labeling claims based on statistical significance alone.  To demonstrate treatment benefit, we find it informative to examine the cumulative distribution function (CDF) of responses between treatment groups to characterize the treatment effect and examine the possibility that the mean improvement reflects different responses in patient subsets...
Proving that the concept is measurable, and the instrument is the measure of the concept.	<i>Protocol designers should use PRO instruments to measure treatment benefit, and should examine the results in ways that reveal whether medical therapies work best only for certain individuals or subsets in the treatment population.</i>	[Lines 49-52] The term <i>conceptual framework</i> refers to how items are grouped according to subconcepts or domains (e.g., the item <i>walking without help</i> may be grouped with another item, <i>walking with difficulty</i> , within the domain of <i>ambulation</i> , and <i>ambulation</i> may be further grouped into the concept of <i>physical activity</i> .	<i>[Glossary] Conceptual framework of a PRO instrument</i> - an explicit description or diagram of the relationships between the questionnaire or items in a PRO instrument and the concepts measured. The conceptual framework of a PRO instrument evolves over the course of instrument development as empiric evidence is gathered to support item grouping and scores. We [FDA] review the alignment of the final conceptual framework with the clinical trial's objectives, design, and analysis plan.
Appendix as PRO and ePRO dossier	<i>Sponsors and CROs should include all relevant Appendix components within their PRO dossier.</i>	No dossier outline was provided.	[Appendix] Information on a PRO Instrument Reviewed by the FDA. The following topics represent areas that should be addressed in PRO documents provided to the FDA for review.

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A proxy-reported outcome is not a PRO	<i>Sponsors and CROs should elect observer-reported outcomes for patients who are not able respond for themselves.</i>	[Lines 694 - 699 ] Over the course of some clinical trials, it can be anticipated that patients may become too ill to complete a questionnaire or to respond to an interviewer. In such cases, proxy reporting may help to prevent missing data. When this situation is anticipated, the FDA encourages the inclusion of proxy reports in parallel with patient self-report from the beginning of the study (i.e., even before the patient is no longer able to answer independently) so that the relationship between the patient reports and the proxy reports can be assessed.	[Section III.G.] ... We discourage <b>proxy-reported outcome</b> measures for this population (i.e., reports by someone who is not the patient responding as if that person were the patient). For patients who cannot respond for themselves (e.g. infant patients), we encourage observer reports that include only those events or behavior that can be observed. For example, observers cannot validly report an infant's pain intensity but can report infant behavior thought to be caused by pain.