



Making the clinical trial connection

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Guidance For Industry
Patient Reported Outcome Measures: Use in Medical Product Development to Support
Labeling Claims

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Docket Number: 2006D-0044

ClinPhone respectfully submits comments on the draft Guidance For Industry Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. ClinPhone is recognized as one of the leading Clinical Technology Organizations (CTO). ClinPhone have developed applications for the majority of the world's Pharmaceutical and Biotechnology organizations using a unique combination of internet-powered and telecommunication based technology for clinical trials. We applaud the agencies efforts to move forward with industry in identifying appropriate strategies for managing Patient Reported Outcome (PRO) measures used in clinical trials to support labeling claims. The new draft guidance is a valuable step in that direction and the increased emphasis on PRO measures is especially welcome.

The draft guidance for industry was reviewed by our organization and we have outlined several comments and questions in the following document.

Thank you for providing the opportunity to submit these comments and look forward to continuing our work with the agency and industry on the development of appropriate strategies for PRO measures.

Respectfully Submitted by

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General comment on the draft guidance 1: The guidance does not adequately cover the use of ePRO as source data for NDA submissions to support labeling claims? Is ePRO data acceptable as a stand alone instrument to evaluate the data in support of an NDA submission. We recommend outlining general guidelines to the document covering the acceptance of data collected via an electronic instrument in support of a labeling claim as part of the NDA submission.

General comment on the draft guidance 2: By explicitly addressing the review issues identified in this guidance, sponsors can increase the efficiency of their endpoint discussions with the FDA during the product development process, streamline the FDA's review of PRO endpoint adequacy, and provide optimal information about the patient's perspective of treatment benefit at the time of product approval. We understand that sponsors can increase the efficiency of their endpoint discussions with the FDA at any time during the product development phase, but we suggest additional guidance be added on the optimal period the FDA would recommend sponsors have discussions with the FDA development process based on the areas outlined throughout the document.

Lines 45-49: In particular, the term *instrument* 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).

Comment: The definition of instrument based on the examples appears to be directed towards paper based instruments. We suggest the instrument examples be expanded to include alternate means (e.g. electronic) of capturing PRO measures.

Lines 127-137: Self-completed questionnaires that are given directly to patients without the intervention of clinicians are often preferable to the clinician-administered interview and rating. Self-completed questionnaires capture directly the patient's perceived response to treatment, without a third party's interpretation, and may be more reliable than observer-reported measures because they are not affected by interobserver variability. On the other hand, PRO measures may be affected by interpatient variability if the instrument is not easily understood and completed by the patient. Despite these concerns, well-developed and adequately validated PRO instruments have been shown to give answers that match the results obtained by the most expert assessors (indeed, that is the usual way their validity is assessed), and they appear to be particularly suitable in studies involving many investigators.

Comment: We agree with the concept of interpatient variability, but the section should be clarified to demonstrate the examples of PRO equivalent to expert ratings. For example, depression ratings such as IDS or computerized HAM-D compared to investigator assessed HAM-D.

Line 191 Figure 1: The PRO Instrument Development and Modification Process diagram.

Comment: We suggest clarification in item iv. Modify instrument to include mode of administration. We do not think method of administration adequately covers and appears not to be consistent throughout document when referring to electronic instruments.

Line 223-225: Evidence from a patient cognitive debriefing studies (i.e. the interview schedule, transcript, and listing of all concepts elicited by a single item) can be used to determine when a concept is adequately captured by a single item.

Comment: Please elaborate on the FDA's expectations for cognitive debriefing. In particular, it would be helpful to provide an example of a readability test and an indication of the number of patients expected in a debriefing study.

Line 307-308: Of course, it would be critical to know that each item refers to something that a patient actually does.

Comment: A patient may not do certain normal activities even though the condition is not preventing them. In such cases, a negative response (or indication of little to no activity) would be misleading. We suggest the guidance clarify how would one achieve this in practical terms.

Line 321: ..including data quality control procedures and lines 740-751: 2. *Clinical Trial Quality Control* Study quality can be optimized at the design stage by specifying procedures to minimize inconsistencies in trial conduct. Examples of standardized instructions and processes that may appear in the protocol include:

- Standardized training and instructions to patients for self-administered PRO instruments
- Standardized interviewer training and interview format for PRO instruments administered in an interview format
- Standardized instructions for the clinical investigators regarding patient supervision, timing and order of questionnaire administration during or outside the office visit, processes and rules for questionnaire review for completeness, and documentation of how and when data are filed, stored, and transmitted to or from the study site.

Comment: The Clinical Trial Quality Control guidance appears to focus on paper based PRO measures. We suggest the guidance outline general data quality control procedures that could be implemented when the mode of administration may be by electronic means.



Lines 373-378: Sponsors are encouraged to examine the procedures used with patients to determine readability and understanding of the items included in the PRO instrument. The FDA's evaluation of these procedures is likely to include a review of a cognitive debriefing report containing the readability test used, the script used in patient cognitive debriefing interviews, the transcript of the interviews, the analysis of the interview results, and the actions taken to delete or modify an item in response to the cognitive debriefing interview or pilot test results.

Comment: When evaluating the patient's understanding it appears the guidance is based on the readability of paper based instruments. We suggest including guidance to evaluate the patient understanding when electronic instruments are utilized, which may have a different set of criteria during the evaluation process.

Line 391-392: Changing the timing of or procedures for PRO instrument administration within the clinic visit.

Comment: It should further be pointed out how the use of a PRO instrument in the home setting (rather than during clinic visit) could be affected to assess the speed of onset.

Lines 434-458: Undue physical, emotional, or cognitive strain on patients are burdens that will generally decrease the quality and quantity of PRO data. Factors that can contribute to respondent burden include the following:

- Length of questionnaire or interview
- Formatting
- Font size too small to read easily
- New instructions for each item
- Words or sentence structures that require a technical knowledge or developmental level beyond that of the patients in the trials
- Requirement that patients consult records to complete responses
- Privacy of the setting in which the PRO is completed (e.g., not providing a private space for patients to complete questionnaires containing sensitive information about their sexual performance or substance abuse history)
- Inadequate time to complete questionnaires or interviews
- Literacy level too high for population
- Questions that patients are unwilling to answer
- Perception by patients that the interviewer wants or expects a particular response

The degree of respondent burden that is acceptable for instruments in clinical trials depends on the frequency and timing of PRO assessments in a protocol and on the severity of the illness or toxicity of the treatment studied. For example, if the questionnaire contains instructions to skip one or more questions based on responses to a previous question, respondents may fail to understand what is required and make errors in responding or find the assessment too complicated to complete. Sponsors should consider missing data and the refusal rate as possible indications of unacceptable patient burden or inappropriate items or response options.



Comment: We suggest adding factors when considering a respondents burden via electronic means. What types of factors could potentially add to the respondent's burden when utilizing a PDA, telephone or computer?

Line 470 Table 3: Common Reasons for changing PRO Instruments during Initial Development.

Comment: We suggest adding priority items for the length, mode of administration and translations including reasons for change or deletion.

Line 481: Table 4: Measurement Properties Reviewed for PRO Instruments Used in Clinical Trials under Test-retest. What is Assessed; Stability of scores over time when no change has occurred in the concept of interest"

Comment: The accepted best statistic for assessing this (the intraclass correlation coefficient) should be mentioned to discourage poor practice of using the Pearson correlation coefficient. This would then be consistent with the entry for internal consistency which mentions coefficient alpha

Line 481: Table 4: Measurement Properties Reviewed for PRO Instruments Used in Clinical Trials under Reliability. What was the quality of evidence of reliability?

Comment: How is the quality of evident of reliability rated? We suggest adding guidance on a rating scale to the measurement table 4.

Line 496-497: When PRO instruments are interview-administered, intern-interview reproducibility is critical.

Comment: We suggest additional clarification be added to discuss how much inter-rater variability is acceptable.

Line 543-545: For many widely used measures (pain, treadmill distance, HamD), the ability to show *any* difference between treatment groups has been considered evidence of a relevant treatment effect.

Comment: We disagree with the statement where most disease areas use the concept of the minimum effect which has clinical relevance in the management of patients. However, we suggest that it may be true to say that establishing a minimum important difference (MID) is more difficult for PRO instruments.

Lines 550: The FDA has reviewed MIDs derived in many ways. Examples include:

Comment: We agree with the examples, but the examples be expanded to include the method of surveying knowledgeable clinicians who have experience with the population and instrument as a method that can be used for re-evaluation of the MID.



Line 590-641: The FDA intends to consider a modified instrument as a different instrument from the original...

Comment: When PRO Instruments are modified it isn't clear how trivial changes to the instrument will be assessed. We suggest clearer guidance as to what kind of modification to item content or format would lead to the need for additional validation.

Line 636-638: Paper to Pencil self administered PRO is modified to be administered by computer or other electronic device (e.g. computer adaptive testing, interactive voice response systems, Web-based questionnaire administration, computer).

Comment: In discussion of requirements moving instrument from paper to pencil to electronic it would be helpful to cite PDAs amongst the solutions listed for the avoidance of doubt.

Lines 631, Section 4. Changed Mode of Administration

Comment: We agree with the examples, but could the examples be expanded or additional clarification under each example on what is required in the way of validation when the mode of administration of a validated instrument is changed.

Line 654-656: Sponsors should consider whether generally accepted standards for translations and cultural adaptation have been used to support the validity of data from a translated/adapted PRO instrument...

Comment: We agree with the statement and would like the statement to define or the guidance to reference what the 'generally accepted standards' that are currently in place.

Line 717-718: Because responses to PRO measures are subjective, representing a patient's impression, open-label studies, where patients and investigators are aware of assigned therapy, are rarely credible.

Comment: The tone of this sentence and following paragraph is overly negative and does not cover the situation of trials without a control but where all the treatments are "active". Many studies can not be blinded and should not be barred from use of PRO instruments. For instance a trial of mastectomy versus lumpectomy in breast cancer can not be blinded but one would expect that PRO assessments are important in assessing outcome. It should be pointed out that there may be instances where a PRO instrument is utilized and the study is not blinded, to include a statement of the credibility of responses for certain PRO measures.

Line 828-830: ...because the subject usually returns the diary to the investigator who either retains the original or a certified copy as part of the case history.

Comment: We agree with the statement and would like the statement to define or the guidance to reference the meaning of what is a certified copy.



Lines 830-836: The use of electronic PRO instruments, however, may pose a problem if direct control over source data is maintained by the sponsor or the contract research organization and not by the clinical investigator. The FDA considers the investigator to have met his or her responsibility when the investigator retains the ability to control and provide access to the records that serve as the electronic source documentation for the purpose of an FDA inspection. The FDA recommends that the study protocol, or a separate document, clearly specify how the electronic PRO source data will be maintained.

Comment 1: We suggest the guidance be expanded on when the investigator can maintain control and provide access to the records when using electronic modes of administration.

Comment 2: We suggest the guidance also consider unblinding considerations when an investigator can have access to the data (e.g. during the conduct of the study) when using electronic means.

Line 852: Removal of investigator accountability for confirming the accuracy of the data.

Comment 1: We suggest the guidance expand on this section to include when it is appropriate for the investigator to confirm the accuracy of the data, provide access to the data and retain the data when using electronic modes of administration. If the PRO instrument is administered by electronic means, when should the investigator have access to the records (e.g. do they need it immediately in real-time, during the course of the study within 48 hours, at the end of enrolment?).

Comment 2: We suggest the guidance be expanded to address how the investigator would confirm the accuracy of the data. For example, does this imply some sort of investigator signature?

Line 866: The statistical analysis considerations for PRO endpoints are not unlike statistical considerations for any other endpoint used in drug development.

Comment: It should be pointed out that the considerations regarding stratification are, however, slightly different. As patients serve as their own control, there is less motivation to stratify by centre if standardised training is provided to centres and patients. Conversely there may be more motivation to stratify by country so that there is treatment balance within culture and language of application. If the PRO instrument is being used in conjunction with a central randomisation system such as an interactive voice response system, then the additional value of stratification by baseline PRO score could also be considered; it may be valuable in order to promote balanced allocation given that the extra effort involved will generally be minimal.



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Line 1055-1065: Domain – A Domain is a discrete concept within the multidomain concept. All the items in a single domain contribute to the measurement of the domain concept.

Comment: It should be pointed out that the definition uses the terms "domain" and "multidomain" to define the term itself. We suggest the definition be amended to include that a domain is a logical grouping of PRO items to form a discrete concept to be analyzed.

End of comments.