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Key ePRO Implications of the New Guidance for Biopharmaceutical Companies

Implications of the FDA's
Final Guidance for Industry
on Patient-Reported Outcome
Measures: Use in Medical
Product Development to
Support Labeling Claims
(December 2009)



Electronic Patient-Reported Outcomes (ePRO) solutions support worldwide clinical trials of all sizes and complexities in every major therapeutic area. These systems have been used to capture patient self-reported data ranging from simple diaries to validated instruments such as health-related quality of life (HRQL) questionnaires to complex clinical assessments. Regulatory agencies have broadly acknowledged the many advantages of ePRO, including the importance of consistent, systematic assessment, instant validation checks and date/time stamping of patient responses. It is important to note that both PRO (Wilke et al. 2004*) and ePRO data has been accepted by the U.S. Food and Drug Administration (FDA) as a primary endpoint in new drug applications (NDAs). By issuing the final guidance on patient-reported outcomes (PROs), the FDA is explicitly reminding study sponsors of the importance of PROs. This guidance, which follows the issuance of the draft guidance in 2006, means that sponsors can move forward with their use of PROs and ePRO with a more clear understanding of the FDA's expectations.

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Key ePRO Implications of the New Guidance for Biopharmaceutical Companies

1. Electronic PRO Collection is Acceptable

Both phone-based (IVR) and computer-based ePRO systems are specifically mentioned in the guidance. Electronic modalities are an acceptable method to collect patient-reported outcomes in clinical drug trials. Sponsors are under increasing pressure to defend PRO data integrity, which adds incentive for the use of electronic solutions. Sponsors can benefit through electronic modalities that are capable of performing real-time logic checks along with sophisticated questionnaire branching to eliminate ambiguous data.

2. ePRO Directly Addresses FDA Concerns

ePRO directly addresses one of the FDA's concerns of knowing exactly when study participants have completed their diaries and self-report instruments. ePRO solutions should therefore have an automatic date and time stamp that helps sponsors demonstrate the integrity of their PRO data. If a paper diary is used, the FDA plans to review what steps are taken to ensure entries are made at the appropriate time as opposed to retrospectively.

*Ref: Wilke, Burke, Erickson. Measuring treatment impact: A review of patient reported outcomes and other efficacy endpoints in approved product labels. *Controlled Clinical Trials*, 2004; 25:535-552.

3. Areas that Apply to ePRO

It is important to note that this guidance is relevant when the sponsor intends to use PRO data to make a labeling claim. Thus, it does not apply to ePRO for exploratory data, medication dosing and/or protocol compliance. Today, ePRO is commonly used to collect primary and secondary efficacy data; inclusion/exclusion data; and safety, medication and HRQL data.

4. Additional Considerations When ePRO is Used

The FDA has made specific statements with respect to use of electronic patient-reported outcomes which include: 1) The sponsor should provide details of the electronic collection of PRO in study protocols and investigator brochures e.g. which instruments, which modalities, procedures to be followed, etc.; 2) the regulatory agency plans to review data quality control procedures including ePRO screen shots and IVR scripts; 3) the FDA recommends that sponsors establish appropriate system and security controls, as well as cyber security and

system maintenance plans that address data integrity during network attacks and software updates; and 4) the regulatory agency requires an electronic audit trail documenting all changes to data after it is recorded.

5. Implications for Simultaneous Use of Multiple Modalities

It appears the FDA acknowledges that multiple modalities, e.g., both Interactive Voice and Web Response (IVR/IWR) systems, might be used within a single trial, but the FDA will look to ensure that the results within administration mode are consistent. As a result, sponsors should plan to demonstrate that the two modalities are equivalent. However, the guidance seems to have a preference for responder analyses, which are often based on the change from the baseline PRO response. Thus, if responder analyses are important, then mixing modes within a trial, even if they are shown to be broadly equivalent, would seem to carry some risk as the determination of whether a patient is a responder or not may be affected by intra-mode variations.



FDA Guidance

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

Additional Information

Patient self-reported data are increasingly playing a key part in efficacy and HRQL assessment, patient recruitment, safety data assessment and medication compliance monitoring. In some therapeutic areas, PROs are the only means available to accurately assess the effects of treatments.

The new FDA guidance provides a benchmark for research practices which will help ensure that outcomes reported from the patient perspective are robust and meaningful. The emphasis on formulating a clear strategy for the inclusion of PROs in clinical trial programs, on content validity when evaluating the suitability of an instrument and on specifying the role of the PRO instrument amongst other study endpoints will provide more weight to the evidence being generated for different interventions.

Although several years old, the EMEA has issued a reflection paper that details its perspective with respect to health-related quality of life assessment (Ref: EMEA/CHMP/EWP/139391/2004). In addition, EMEA feedback elicited by the FDA prior to final publication indicates that the principles outlined in the guidance match many of EMEA principles with respect to development, validation and use of PROs.

The EMEA has specifically mentioned “electronic patient diaries” in published guidance (Ref: CPMP/EWP/519/98 and CPMP/EWP/ 519/98). The FDA’s PRO guidance states, “Data collection methods can include paper-based, computer-assisted, and telephone-based [IVR] assessments.” It is clear that regulatory agencies acknowledge that ePRO is an acceptable method to collect data directly from study subjects. Regulatory agencies will expect documentation that supports not only the use of the instrument, but also the method of data collection. If PRO data is likely to be used as part of a regulatory submission, the study’s sponsor should compile a PRO dossier. The appendix to the FDA’s PRO guidance entitled, “INFORMATION ON A PRO INSTRUMENT REVIEWED BY THE FDA” is a useful reference document. Additional peer reviewed publications on these subjects may be obtained by writing to info@perceptive.com.



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