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Validation of Electronic Systems to Collect Patient-Reported Outcome (PRO) Data—Recommendations for Clinical Trial Teams: Report of the ISPOR ePRO Systems Validation Good Research Practices Task Force

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ABSTRACT

Outcomes research literature has many examples of high-quality, reliable patient-reported outcome (PRO) data entered directly by electronic means, ePRO, compared to data entered from original results on paper. Clinical trial managers are increasingly using ePRO data collection for PRO-based end points. Regulatory review dictates the rules to follow with ePRO data collection for medical label claims. A critical component for regulatory compliance is evidence of the validation of these electronic data collection systems. Validation of electronic systems is a process versus a focused activity that finishes at a single point in time. Eight steps need to be described and undertaken to qualify the validation of the data collection software in its target environment: requirements definition, design, coding, testing, tracing, user acceptance testing, installation and configuration, and decommissioning. These elements are consistent with recent regulatory guidance for systems validation. This report was written to explain how the validation process works for sponsors, trial teams, and other users of electronic data collection devices responsible for verifying the quality of the data entered into relational databases from such devices. It is a guide on the requirements and documentation needed from a data collection systems provider to demonstrate systems validation. It is a practical source of information for study teams to ensure that ePRO providers are using system validation and implementation processes that will ensure the systems and services: operate reliably when in practical use; produce accurate and complete data and data files; support management control and comply with any existing regulations. Furthermore, this short report will increase user understanding of the requirements for a technology review leading to more informed and balanced recommendations or decisions on electronic data collection methods.

Keywords: electronic data collection, ePRO, PRO, systems validation.

Background to the Task Force

The ISPOR ePRO Systems Validation Good Research Practices Task Force was formed from a previously established working group on the topic and approved by the ISPOR Board of Directors in March 2011. The task force leadership group was composed of experts in the electronic data collection systems field with experience in design and development, quality control, and regulatory affairs as well as clinical trial experience. The leadership group met bimonthly to develop an outline to support the ultimate objective of generating guidelines to inform system users of the quality and content required for validated data collection systems. Authors worked in teams or singly to develop sections of the report, which were then reviewed by the full task force for comment and input.

Once a solid first draft was developed, it was sent for review by the 400+ member ISPOR PRO Review Group and a Food and Drug Administration (FDA) staff person versed on the topic. In addition, the work to date was presented for comment at a forum presentation at the ISPOR 16th Annual International Meeting in Baltimore. ISPOR members contributed to this consensus report by submitting written comments during the review process and oral comments during the forum presentation. The authors revised the report several more times and sent the final draft once again to the ISPOR PRO Review Group, as well as announced an invitation to review to the full ISPOR membership.

All comments, many of which were substantive and constructive, were considered and addressed as appropriate by the task force authorship team. Further adjustments were made per the feedback gained and once consensus was reached by all authors, the final report was submitted to *Value in Health*.

Written comments and a list of reviewers are published at the ISPOR Web site on the task force's Web page: http://www.ispor.org/sigs/ePROsystemvalidationsg.asp. The task force report and Web page may also be accessed via the ISPOR homepage (www.ispor.org) via the purple Research Tools menu, Good Practices for Outcomes Research.

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Introduction

The patient's experience has become increasingly important in evaluations of the effectiveness and safety of medical products, particularly drugs and devices. It complements the use of clinician evaluations, objective statistics, such as survival rates, and other traditional indicators of clinical efficacy and safety. Clinical researchers routinely incorporate patient-reported outcome (PRO) assessments in clinical trials to help measure the effect of a medical product on concepts such as symptom severity and physical or mental function. PRO assessments can be a primary or a secondary end point in determining treatment efficacy. In some cases, such as fatigue or pain assessment, a PRO may be the only feasible end point because there are no markers of disease or treatment activity measurable by a clinician, observer, or laboratory [1].

According to the US FDA, a PRO is "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" [2]. It can be measured in absolute terms (e.g., severity of a sign, symptom, or state of a disease) or as a change from a previous measure [2]. The European Medicines Agency's (EMA's) Reflection Paper on the Regulatory Guidance for the Use of Health Related Quality Of Life (HRQL) Measures in the Evaluation of Medicinal Products defines a PRO similarly as "any outcome directly evaluated by the patient and based on patient's perception of a disease and its treatment(s)" [3]. More simply, PROs are the effects of the disease and/or its treatment reported by the patient [1].

In a clinical trial, after subject safety, a primary concern of regulators is data quality and integrity [4]. From the clinical trial sponsor's perspective, the integrity and quality of data are critical for trial credibility as well as compliance with FDA, EMA, and other governing bodies. FDA's acceptance of data from clinical trials for regulatory decision-making purposes depends on its ability to verify the quality and integrity of the data during FDA onsite inspections and audits [5].

Clinical trial managers are increasingly using ePRO, electronic collection of PRO data directly from the patient for PRO-based end points. ePRO leads to improved data quality, more complete data, less subject and administrative burden, as well as better implementation of skip patterns [1,6]. Electronic data collection yields more reliable and accurate data, allowing a stronger test of the study objectives and a better picture of the patient's experience [6]. Regulatory review dictates the rules to follow with electronic data collection. Whether a trial manager uses an electronic or paper-based questionnaire to collect data, the fundamental issues affecting data accuracy, (e.g., traceability and change control) are common to both electronic and paper systems.

Evidence may be desired to demonstrate that subjects interpret and respond to the PRO instrument's items/questions the same way regardless of the data collection mode [1,5]. Changing the mode of data collection and the assessment of measurement equivalence between modes are covered in a previous ISPOR PRO task force report, "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" [1].

Regardless of the mode of administration (self- vs. interviewer-administered) or the method of electronic data collection (the tool used for capturing the data, such as interactive voice response systems, Web-based data entry, or ePRO devices), systems validation must meet the standards of the FDA and the EMA. This is done by validating the process used to develop, support, and maintain the device and computerized system [5–7]. In simple terms, there must be proof that the process does what it is supposed to do. For example, if a "5" is entered on the screen through a handheld or desktop data entry device, the subject's response must "map" correctly on the database—registering correctly as a value of 5 in the database.

For ePRO, this is complicated by the fact that existing regulations and guidelines were originally developed for paper questionnaires and diaries. At this time, there is no single development or deployment method prescribed by either regulatory authorities or industry best practices. *Because there is no specific regulation or guidance from these agencies regarding exactly how validation of ePRO systems should be performed*, we infer the appropriate standards from their guidance on similar topics, such as validation of systems used to manufacture medical devices. (See Supplementary Materials for regulations relevant to clinical trials and ePRO systems development & validation, found at http://dx.doi.org/10.1016/j.jval.2013.04.002.)

With ePRO, there are two software delivery choices, each with its own validation process. The first is a traditional, custom software method—developing one software system for each trial. Portions of existing software code may be reused for this. The entire system undergoes a rigorous set of validation activities prior to deployment for trial use [8]. The second choice is a vendor-created platform that is tailored and redeployed for each trial. The platform undergoes a rigorous set of validation activities during the initial development. This method allows simply validating the tailoring effort for each trial. Both delivery methods have value. One retains complete flexibility at a greater development time and cost, while the second features a faster development time with the cost of limited flexibility.

Because the techniques for validating the performance of ePRO systems and the regulations impacting validation may *not* be clear to all sponsoring project managers and trial team members, the primary goal of this report is to assist in understanding the technical nature of ePRO systems and the ePRO system validation process. With an ePRO system, validation is a responsibility split between the provider of the ePRO system and the sponsor that uses it. It is important to understand the nature of these responsibilities and how they should be shared.

The secondary goal of this report is to make recommendations for sponsors and trial project managers on system validation—more specifically on the responsibilities of each participating party. This report addresses the technical nature of ePRO data collection systems and validation process. It will provide the sponsor with insight into the requirements for a technology review and a basis for comparison of different ePRO system providers and their respective service offerings leading to more informed and balanced recommendation(s) or decision(s) on electronic data collection systems.

Furthermore, the report will provide an understanding of the effort required by the sponsor to complement the validation services proposed by the system provider. When an ePRO system provider simply offers the device and data system, but does *not* offer the required validation service, the burden of fulfilling that responsibility falls on the sponsor. Note that throughout the document, "sponsor" is used to refer to the clinical trial team working with an ePRO provider. These recommendations would apply equally to a contract research organization (CRO) or other entity that is engaging an ePRO system provider for the creation of an ePRO system to be used in medical product registration trials. The general principles addressed in this report can be applied to other research settings in which subjects use an electronic means to enter data that represent an answer to a question.

Finally, the report includes relevant regulations due to the critical nature of compliance in these processes and within the clinical trial itself. Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.04.002 includes the international standards for clinical trials and manufacturing and major