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Strategic Planning with ePROs

Nancy Kline Leidy and Makiko Meguro at United BioSource Corporation examine the need for electronic patient-reported outcomes, and ask what strategies will lead to the best outcomes

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As the industry moves toward paperless clinical trials, patient-reported outcome (PRO) measures are also migrating toward electronic options. Although 'paper-and-pencil' modes of administration will continue to prevail in the short-term, the medium- and long-term outlook for electronic methods to capture PROs (ePROs) looks promising, particularly with the advancement of new, user-friendly technology and the development of questionnaires designed with the ePRO platform in mind.

With the burgeoning number of e-options – from web-based and interactive voice response (IVR) systems to handheld devices, such as personal digital assistants (PDAs) – it will become increasingly important for decision-makers within pharmaceutical companies to make the best strategic decisions about whether, when and how to use various technologies. Identifying the best platform for ePROs must take into consideration a variety of factors, including the type and nature of the outcome, the patient population, trial design, regulatory requirements and the drug development programme overall. Frequently, the best solution is not a single platform, but a combination of data collection methods.

WHAT FACTORS SHOULD BE CONSIDERED IN SELECTING AN ePRO PLATFORM?

While multiple platforms may be viable for any given PRO measure, there are times when the particular needs of a trial or drug development programme will mandate one choice over another. Things to consider when selecting one or more modes of administration for a PRO include:

- The PRO concept – complexity, variability, required frequency of assessment
- The PRO measure – number of items, length of items, skip patterns
- Respondent characteristics – age, disease state, physical and cognitive status
- The PRO measure's validation status – tested in the interface of interest
- PRO translation status – availability and any new languages required
- Trial design – sampling method, duration, frequency and timing of clinic visits
- Site logistics – capacity to transfer electronic data, space to train patients or complete ePRO questionnaires
- Timelines to trial launch – sufficient to programme and pre-test
- Timelines to submission – need for rapid turnaround of data
- PRO positioning – primary, secondary or tertiary outcome and intended use

An interesting and perhaps less well-known example of a trial design in which ePROs can be particularly effective is one in which sample enrolment criteria are based on a minimum level of symptom severity during run-in. Gathering these PRO data electronically – through a daily diary administered via PDA or IVR, for example – can mean immediate, centralised score computation, with potentially more accurate screening of trial participants. Continuing this mode of data collection throughout the trial takes advantage of the data quality and rapid and efficient data availability generally associated with this mode of administration. Device-based patient reminders improve patient adherence to the diary completion protocol; time- and date-stamped data entries document this adherence.

ARE THERE SPECIAL CONSIDERATIONS IN TRANSLATING PRO MEASURES ACROSS LANGUAGES AND PLATFORMS?

In today's global trial environment, consideration must be given to the availability and quality of multiple translations in selecting or developing a PRO measure generally and ePRO measures specifically. What may be a simple question suitable for a PDA in one language may be less suited to this technology in another. For example, "How do you rate your pain today? None, mild, moderate, severe, very severe," is relatively short in English, so could fit easily onto a single PDA screen. In other languages, however, this same item may require two screens. What is the solution to this dilemma? One option that may come to mind is to mix modes of administration, with paper-pencil versions in some languages and PDA in others. Is this a viable approach? The answer is no: mixing modes of administration can lead to serious data discrepancies with method effects nested within site or country effects. When choosing an ePRO interface, select one mode for all sites.

Another possible solution to the language-fit dilemma is to ask whether the wording of items can be changed to fit the screen? The answer here is a hearty and resounding, absolutely not. Changes in a PRO measure should never be made in one or two languages for purposes of 'screen fit'. These changes can alter the way respondents interpret the item, adversely affecting the reliability and validity of the measure in these languages and leading to potentially serious problems aggregating and interpreting data.

In this expanding global trial environment, it is important to think ahead during trial design, taking into consideration the target countries, the language and translation implications and the pros and cons of the technology – in short, to trouble-shoot and develop solutions before the trial is launched.

SHOULD THE ePRO MEASURE BE VALIDATED?

In selecting and using ePRO measures, consideration must be given to two types of validation: software and psychometric. It is important to realise that the concept of a 'validated measure' has a completely different definition in the field of information technology than in health outcomes research. *Software or application validation* refers to the accuracy and usability of the system supporting the electronic measure. By contrast, *psychometric or clinimetric validation* refers to the underlying performance properties of the PRO measure – that is, reviewing empirical evidence of its measurement precision or accuracy. Thus, an ePRO measure may be considered technologically 'validated', whilst showing no evidence of reliability and validity and vice versa.

It is important to know that transforming an existing measure – developed, tested and subsequently used in paper-pencil form – to an electronic form can affect its performance characteristics, improving or intruding on its reliability and/or validity, and potentially changing normative values. Users should be attuned to the impact of this alteration and be prepared to provide evidence of reliability and validity of the new e-version when submitting the PRO trial outcomes to regulatory authorities.

Both the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) stipulate that PRO measures must demonstrate evidence of reliability and validity. This requirement holds true across modes of administration. The EMEA reflection paper on health-related quality of life evaluation – an important PRO – was released in 2005 (1). The FDA's draft guidance on PROs was released in 2006 (2), with release of the final document forthcoming. It has been suggested that the EMEA will follow the FDA guidance as an international industry standard for PROs, with additional consideration given to country-specific data requirements related to the protection of data privacy.

User-acceptance testing (UAT) in software/system development generally refers to an assessment of the functionality of the system. With ePROs, the UAT should address the ease with which patients can use the device. Patient acceptance testing should be considered and assessed prior to using an ePRO in a study or trial. This evaluation can be performed during cognitive debriefing interviews with a sample of patients with characteristics similar to those to be enrolled in the trial(s). Cognitive debriefing interviews are used to evaluate patient comprehension of items comprising a new or adapted PRO measure in order to make certain patient interpretations are consistent with the item's and measure's intent. While these data on content validity are being gathered, the patient's ability to use the electronic device can be evaluated, training needs can be identified and plans for addressing these needs can be included in the trial protocol and investigator training programme.

ARE SPECIALISED SITES REQUIRED FOR TRIALS GATHERING PROs ELECTRONICALLY?

Evaluating and qualifying sites for a trial in which ePROs will be used is both similar to and different from evaluating sites for

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trials involving other forms of electronic data capture (EDC). Experienced sites with the appropriate technical resources and expertise are, of course, preferred. In the case of ePROs, additional factors to consider include patient familiarity or comfort with technology generally or the selected platform specifically, the availability of technological resources at the site and whether staff training will be required to ensure full compliance with the protocol, and the complete, accurate collection of data. For example, while clinicians at a certain site might be well equipped to enter clinical data via a web-based system, the patients in that location might require both additional training and an internet connection to complete their outcome measures electronically. Consider asking the following questions during both mode and site selection:

- Will the patients be comfortable with the technology?
- Are the site investigators and/or coordinators comfortable with the technology?
- How much training will be required? Of site investigators? Site coordinators? Patients? Caregivers? Will this training need to be repeated or refreshed during the course of the trial?
- For devices taken home, such as PDA diaries, will the patients be able to upload the data from their homes? If so, wirelessly or via telephone lines?
- Are there any other mitigating circumstances that would influence site selection, or alter the decision to use one platform over another?

ARE THERE ANY SIMPLE GUIDELINES FOR SELECTING ePROs?

Just as there are no simple rules for clinical trial design, there are no simple rules for selecting a PRO measure to assess the target concept, and no simple rules for selecting the best platform or mode of administration. Making the right choice requires a combination of strategic thinking and purpose-platform matching. Here are some examples of study designs where ePROs have the greatest potential for return – that is, for improving precision and efficiency.

- Large cross-sectional or longitudinal population-based studies conducted to understand epidemiology and burden of disease during the early phases of drug development can use web-based surveys administered via tablet, laptop or desktop computers in clinic offices.
- Clinical trials involving outcomes that require short recall periods and frequent entries, such as rapidly changing or highly variable symptoms, are excellent candidates for PDAs and IVR. In these cases, the quality of data is increased through multiple administrations and greater compliance.
- Clinical trials involving patient experience with periodic events that should be captured as soon as possible after the event occurs are also appropriate for ePROs. PDA and IVR-based systems have the benefit of easy access and are therefore suitable for evaluating the effect of treatment on frequency or severity of such conditions as migraine, epilepsy or asthma exacerbations.
- Clinical trials involving multi-item surveys completed by patients during clinic visits can be administered through desktop, laptop or tablet PC. Monthly assessments of health-related quality of life or well-being could be done by patients electronically at the clinic.
- Studies involving a large number of patients with infrequent assessments and few questions are often ideal candidates for an IVR system. Monitoring healthcare utilisation patterns of a new product over a two-year period, for example, can be performed via monthly IVR calls to collect information about visits to doctors, emergency rooms and hospitals. Automated phone reminders can be used to ensure compliance.

In addition to trial design, the physical location where the PRO is to be administered can influence choice of the ePRO platform. For example, questionnaire data collected at the clinical site can be gathered via tablet, touchscreen computers, or laptops or desktops, with patients themselves using the technology or site coordinators or clinicians conducting patient interviews. Wireless tablets are particularly useful when the office or private location for data collection varies from day-to-day within a site. Web-based systems can be excellent for online questionnaires or diaries completed at home, with patients accessing a secure website via their personal computer at home. The limitation, of course, is the requirement that the respondent has easy access to the web and familiarity with the technology – this may restrict the number or type of respondents in the study.

Most elements of the research process have the potential for complications or error, and technology is no exception. Technical errors can include device malfunction, dead batteries, busy telephone lines, respondent confusion regarding device function and so forth. Complications can be minimised through careful planning and execution. Useful proactive measures to ensure success include careful and on-going site coordinator training with certification on more complex technologies or

PRO administration methods, standardised patient training on devices, ready availability of back-up devices at the site, delivery to the site of additional devices within 24-hours of a request and an easy access helpdesk in the local language for international studies, to name a few.

WHAT TECHNICAL CAPABILITIES SHOULD BE CONSIDERED IN SELECTING OR EVALUATING ePRO PLATFORMS?

It would be difficult to provide a comprehensive list of the various features that characterise ePROs in the space of this article. The following is a condensed list of features to consider in the selection of a device for a drug development programme or trial. (Note: the term 'user' here refers to patients, study monitors and coordinators.)

Set-up

- Flexibility to accept and output all types of data: numeric, binary, ordinal, scales and multiple choice
- Customised layout, formatting and prompt controls from validated questionnaires
- Easy-to-configure branching logic
- Outbound call transfers and reminders

Training

- User-friendly phone and web navigation facilitated by availability of a comprehensive manual and training

Execution

- Logistics of delivering, maintaining and collecting the data entry terminals (PDAs and tablet PCs, for example)
- Language support for the application and helpdesk
- Secure user login
- User-friendly graphical user interface (GUI) for the data entry terminal
- Customised notifications, scheduling and alert management (such as device-based reminder signals)

Reporting

- Customised, real-time web reporting, outcomes and trending analysis
- Subject and study milestone tracking and customised compliance reporting

Audit

- Audit trail

WHAT TECHNICAL QUESTIONS SHOULD BE ASKED OF POTENTIAL OUTSOURCING PARTNERS?

The following is a representative sampling of questions that can be used to determine whether an outsourcing partner can support the modalities under consideration for ePRO data collection:

- Which ePRO modalities do you support? Web-based, IVR, tablet PCs, PDAs?
- Do your systems allow for integration with clinical trial management systems, such as clinical EDC systems, IVR randomisation and others?
- How do you support combination modalities?
- For data collection in the US, is the system 21 CFR Part 11 compliant?
- What kind of help network is available? What materials, online training, investigator meeting training and ongoing support or refresher training are available?
- Is there a 24/7 help desk available for technical problems? Is there a help desk for each country and/or language represented in the trial?

CONCLUSION: IT'S ALL ABOUT STRATEGY

With advances in information technology come opportunities to gather PRO data using a variety of electronic platforms. Selecting the right platform is an important strategic decision that requires careful assessment of a variety of factors.

The key to selecting the best device for a trial or programme is the strategic alignment of purpose, measure, population, design and technology, with attention given to standards of best practice in the evaluation of outcomes in clinical trials. Assuring suitability of the data collection method across all trial sites, using sound scientific principles of instrument design and validation (both technical and psychometric), and considering regulatory issues carefully are all critical.

Given this complexity, why pursue ePRO? When the tool and the technology are selected appropriately and integrated into the planning and execution of the clinical trial, ePROs can be effective and efficient. Consistent with EDC generally, data quality and quantity can improve significantly through a combination of: improved compliance, enabled by reminder systems and date/time verification of entry; less missing data, via programmed prompts to alert/remind respondents to complete their entries; streamlined data collection, eliminating the burden of paper to be faxed, mailed or entered; and real-time information access to facilitate subject recruitment and study monitoring. There is no doubt that paperless trials are coming. Developing a sound strategy to include PROs in this 'e-future' only makes sense. ◆

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