



White Paper

Electronic Patient Reported Outcomes (ePRO): Focus on Site-Based Assessments

by:
Brian Tiplady, Ph.D.
Senior Scientific Consultant
PRO Consulting, a division of invivodata, inc.

date:
October 2010

Executive Summary

Electronic patient reported outcomes (ePRO) are collected on a frequent basis in the context of the patient's daily life, or when the patient visits a clinic for a healthcare or clinical trial appointment. This paper discusses the second type of ePRO, *site-based assessments*, and the considerations for successfully collecting patient data at the site.

The use of ePRO reduces or eliminates missing and inconsistent data, thus improving data quality and integrity. Data management is simplified, as editing and manual data entry are eliminated. Data security and privacy issues are readily managed with modern network and data encryption methods. In many cases the cost of implementing ePRO is less than the cost of paper. In other cases, it represents only a modest increase in study costs given the gains in efficiency and data quality.

A variety of platforms have been used for ePRO, including conventional computers, computers with touchscreens, tablet PCs and personal digital assistants (PDAs), with screen sizes ranging from 3.5 to 12 inches or more.

Patients generally find ePRO easy to use, and often prefer it to paper. This is equally true of the elderly, those unfamiliar with computers, and those with special use needs, such as Parkinson's patients. Thoughtful evaluation of applications and the flexibility of design makes ePRO possible for anyone.

A large body of data supports the validity of ePRO and the equivalence of ePRO versions of questionnaires to paper originals. In particular the use of small screens, requiring presentation of single items per screen, does not have any significant impact on data provided that all important information is available on a single screen. This may put a lower bound on screen size in some cases, though many questionnaires have been successfully implemented on a 3.5" screen. This validity data influences the design and implementation choices for both everyday life and site-based assessments.

Summary and Conclusions

Site-based ePRO has a number of benefits, including

- Only valid, in-range entries can be made
- Missing data can be reduced or eliminated
- Elimination of manual data editing and entry

With a minimum of training, ePRO systems are easy for patients to use, including the elderly, those unfamiliar with computers, and special needs patients.

Modern ePRO systems are compliant with requirements on data security, privacy, and investigator responsibility for data.

Extensive data supports the equivalence of ePRO systems with their paper counterparts.

A variety of device sizes ensures that questionnaire layouts convey sufficient information with good readability.

Introduction

Patient Reported Outcomes (PRO) may be defined as "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" (FDA 2009). PROs are increasingly being collected using electronic methods (ePRO) including computers of various kinds and sizes, and telephones, both using landline and mobile (cell) technologies.

There are two main approaches to collecting PRO data. The first uses assessments at a clinic, doctor's surgery/office or other location visited by the patient when obtaining healthcare or taking part in clinical research. I refer to this as *site-based* assessment. This generally uses relatively infrequent assessments, typically once a month or less. The second approach uses frequent assessments, for example using daily symptom reporting. Patients may make entries at home, or wherever they happen to be at the time the assessment is due. I refer to this as *home-based* or *everyday life* assessment.

This paper will deal specifically with site-based ePRO. A wide variety of assessment instruments for site-based ePRO data collection are available in electronic form, including generic measures of quality of life, measures of health status and disability, and disease specific measures of symptoms and impact on the patient's life. I shall review some of the extensive literature on this form of data collection, present examples of experience in this area, and offer recommendations to obtain the best value from the method. I shall only deal with dedicated computer systems used for site-based ePRO. Other technologies have been used to collect patient data, such as telephone and web-based systems, but are more geared to home-based assessments, and will not be considered here.

Historical Background

Site-based ePRO is not a recent innovation. The first reported use of a computer for collecting data directly from patients was reported in 1966, using a "small" minicomputer, the LINC-2 (Slack et al., 1966). One thing that *was* small about this machine was the size of the display, as may be seen from Figure 1. A single question was presented on the screen at a time, and patients made their responses on the keyboard.

The use of computers in the 1960s and early 1970s was confined to specialised research facilities. More general use would become practical when personal computers became available in the 1980s. Screens became much larger, and the touch-screen was introduced. Like the mouse, it made it possible to point directly at the preferred choice, but it did not require any particular skill to use (French and Beaumont, 1987; Yarnold et al., 1996). Desktop PCs, however, are bulky and require a "workstation" of some kind, limiting their flexibility in the clinical environment.

The next major development was the introduction of portable touchscreen devices which used a stylus for tapping or drawing on the screen. These proved highly suitable for clinic use. They are compact, and could easily be stored out of the way when not in use. Their personal nature makes it practicable to use them in casual settings such as a clinic waiting room. Several patients could be using such devices at a time without causing disturbance to others.

There are two main types of portable touchscreen device suitable for site-based ePRO. The smaller of the two is the PDA, or handheld, which, from the start was aimed at the consumer market as a personal organiser (Drummond et al; 1995; Le, et al., 1995). Larger devices are known as tablet computers (Main et al., 2004). The concept of a tablet computer was first developed in the early 1990's when Operating Systems with pen support, such as Windows for Pen Computing® and PenPoint®, became available. Pen computing was not a success in the consumer market, but tablet PCs became established in a number of "vertical" markets, being used primarily for surveys, questionnaires, and other professional data gathering activities (Blickenstorfer, 2005). The Apple iPad® is the first tablet to make a major impact in the consumer market. Three widely used sizes of tablets are shown in Figure 2.



Figure 1: Site-based ePRO, 1966 style. The computer is the LINC-2, a "small high speed computer". From Slack, W. V., Hicks, G. P., Reed, C. E., & Van Cura, L. J. (1966) A computer-based medical-history system, *New England Journal of Medicine*, 274: 194-198



Figure 2. Examples of pen devices for site-based ePRO in 1997. Clockwise from top-left: the Palm Pilot 1000, with a 3.3" monochrome screen; the Apple MessagePad MP 2100, with a 5.9" monochrome screen; and the Fujitsu 510 Point, with a 10.4" colour screen. The Fujitsu tablet had wireless LAN capability. Modern devices tend to be more compact for a given screen size. Screen sizes between about 3.5" and 12" are in use for current tablet computer ePRO applications

Reading the older research papers, it is striking that the benefits recorded for the systems and the concerns voiced about their use are very much the same as the issues being raised today. Benefits include the simplification of data handling processes, improved accuracy, elimination of missing and inconsistent responses, and ease of use for patients (particularly with questionnaires involving branching logic). Concerns are raised about whether some patients may be unwilling or unable to use computer systems, cost, reliability, privacy/security issues, and whether ePRO can be used interchangeably with paper questionnaires. In the remainder of this paper I will address each of these issues, and also discuss matters around selecting and specifying a system for site-based ePRO, including the preferred size for a device and questionnaire layout and formatting.

Data Quality and Integrity

Site-based ePRO is used in a supervised setting where issues of attribution (ensuring that the patient and visit time/date are correctly recorded) are straightforward and similar to those with the use of paper records. The two key benefits of ePRO in a site-based context are (i) the elimination of ambiguous or inappropriate responses; and (ii) the elimination or reduction of questions to which no response is given.

Response Consistency. In a paper questionnaire, patients may find that none of the responses exactly corresponds to how they feel. In this case, they may innovate, and make a mark between two choices, or cross out the options and write in their own description. This is understandable, but usually cannot be scored, and such data must be excluded from the analysis. ePRO does not allow anything other than valid, in-range responses.

No Response. Patients sometimes leave a question blank. This may be because they do not wish to reveal sensitive information, they may feel that none of the response options are appropriate, or it may be a simple error. In some situations, it may be appropriate to have an explicit "not applicable" or "I do not wish to answer" option, for example for questions asking about specific activities, financial status or sexual matters.

(Though in a study explicitly targeting sexual issues, patients unwilling to answer such questions would presumably be considered unsuitable for inclusion.) In other cases, we generally wish patients to answer all questions. On paper, there may be an instruction at the beginning of the questionnaire along the lines of "If you are not sure how to answer a question, please give the answer that is closest to how you feel." In ePRO, such encouragement can be strengthened by having this text appear whenever a patient attempts to move on to the next question without answering the current question. The software may allow a blank response or not in this situation. If a blank response is allowed, this verification question prevents accidental missed questions and reduces overall missing data (Hanscom et al., 2002). White et al. (1985) have reported that patients do *not* respond unfavourably to not being allowed to leave a question blank, and we have also found this acceptable to patients (cited in Tiplady, 2010). However some ethics committees may take a different view.

Missing Data. Unscoreable and blank questions add up to missing data in the analysis set. Missing data is a major problem in the analysis of questionnaire data (Brick and Kalton, 1996; Bernhard et al., 1998; Troxel et al., 1998). While there are methods available for dealing with missing data statistically, these depend on *a priori* assumptions that are not fully testable, and which become increasingly suspect as the amount of missing data increases. Some algorithms specify a maximum amount of data that can be missing if a scale score is to be calculated (Fayers et al., 1998). All the authors cited here agree that the most important priority is to take steps to reduce the amount of missing questionnaire data.

Thus site-based ePRO has the potential to improve one of the key data quality problems with paper PRO data.

Data Management

It was mentioned above that patients may not always complete paper questionnaires according to instructions. Sometimes such responses cannot be interpreted, but even when the patient's meaning is clear, someone has to actually read the paper form, allocate the appropriate response option, and edit the form for data entry. Patients may also write in additional text on the paper form, which someone must read in case it contains important information, such as an adverse event that has not been reported elsewhere.

These editing functions are time-consuming and costly. So is the next step - data entry, which requires further checking, either by double entry or proof-reading, as otherwise data entry errors will occur. With site-based ePRO, data are captured on the device and transferred electronically to the study database at pre-defined or ad-hoc times. Thus there are savings of time and cost, and potential benefits to data quality.

Technical Questions

Issues of data security and integrity arise with the use of electronic data handling methods. Some of these are common to paper and ePRO, as once paper data are entered into a computer they are in electronic form, and issues of ensuring data integrity and preventing unauthorised access are the same for either modality. Specific issues arise with data transfer, and device security. While paper records can be lost or stolen, they are bulky and of little value. A tablet computer is more attractive to a thief, and may contain large volumes of personal data. Modern ePRO applications encrypt data that is stored on the device, as well as when it is being transferred over public networks, and the data is stored on the server when data is transferred after each patient visit or each day.

Another point for clinical trials is that data systems must be set up so that they meet local and global regulatory expectations. For example, the FDA and EMA both require that the investigator maintain responsibility for source data such as that produced by ePRO.

Reliability of the devices used for ePRO has increased over the years due to advances in battery and hardware technology. For example older pen tablets could lose data and applications if the battery went flat. Today's ePRO devices use non-volatile data storage, eliminating this issue. A variety of devices are also available to address specific application needs. More rugged devices, for example, may be a good fit for site-based use due to how often they are carried around the site and passed from patient to patient.

Cost Considerations

Cost and the impact on study processes must be considered. While the up-front costs for software development and purchase of devices may be higher than the "face value" of paper, the real cost of implementing ePRO is often less than or modestly higher than the overall cost of running a paper-based study, (site paper management burden, site patient enrollment and management challenges without real-time data insight, data loss due to incomplete or inaccurate entries, increased monitor visits, DCF resolution) given the gains in efficiency and the quality of the data. The need for setup, testing and staff training before systems are used for live data imposes a "front-end load" on the study process, even if it may not increase total workload. This must be taken into account in study planning.

Ease of Use for Patients

The pioneers of ePRO were concerned with whether patients would be happy using computers to enter their data. Slack et al. (1966) in the first ePRO publication, reported that 12 of their patients preferred paper while

18 preferred the computer. Many more recent studies have reported similar preferences for site-based ePRO, for example with PCs using touchscreens (Crawley et al., 2000) and with pen tablets (Drummond et al., 1995; Richter et al., 2008).

What about elderly patients, or those who are unfamiliar with computers? Again there are consistent findings that elderly and computer-naïve patients are comfortable with site-based ePRO and successful in using it (Yarnold et al., 1996; Allenby et al., 2002; Tiplady et al., 2010).

Specific patient groups may have special problems that may need to be addressed if they are to successfully use site-based ePRO. Patients with Parkinson's disease may have problems tapping on a small target screen area due to tremor and dyskinesia, so the design of the ePRO application must address issues of button size. When this is done, such patients can successfully use ePRO (Nyholm et al. 2004). Incidentally, given the frequency of tremor and poor eyesight in the general population, it is a good idea to make screen elements as clear and as large as possible in all applications.

One case where ePRO has important benefits for ease of use is where the questionnaire has branching logic, for example "If YES, continue with the next question, if NO go to question 34". These questions often confuse patients in paper questionnaires, and this is a common source of patient error (Ganser et al., 2010). Electronic methods allow such navigation to be completely automatic, to the extent that the patient may not even realise that there is any branching – all she sees is a sequence of questions one after the other. This makes the questionnaire simpler to use, and may also improve data quality by reducing errors.

While site-based ePRO is easy for patients to use, it is necessary to ensure that patients are trained in the use of the system, and that the training process is properly documented.

Validity and Equivalence

The issues around validity of ePRO measures are in principal no different from that for other modalities, e.g. paper. In the ideal situation, a new PRO instrument will be validated for all intended modalities from the initial conception of the instrument. For example in the PROMIS initiative, validation is being carried out on paper and electronic administration in parallel (Fries et al., 2009). For many established instruments this is not the case, and we must address the question of paper/electronic equivalence for instruments where all the validation work has been carried out on paper. Can the paper-based validation data be used to support the validity of the electronic version of the instrument? Can data from electronic and paper versions be used interchangeably?

We have suggested a hierarchical approach to issues of establishing equivalence between modes (Shields et al., 2006). A slightly modified form of this approach has been used in the ISPOR guidelines on migration that were published last year (Coons et al., 2009). Three levels are suggested. At the lowest level, where least change has been made, cognitive interviewing of patients as a check that they construe ePRO and paper in the same way is sufficient. This level includes both trivial changes (touch rather than circle a response choice) as well as changes that are supported by empirical findings in the literature. At the second level, equivalence studies comparing the scores obtained from the two modes should be carried out. At the third level, where most change has occurred, the ePRO instrument must be treated as a new instrument, and complete psychometric validation carried out.

There is a great deal of evidence supporting the general equivalence of paper and ePRO methods. Gwaltney et al. (2008) have reported a meta-analysis in which they included 46 studies evaluating 278 scales. They concluded that there was good agreement between paper and ePRO, and no evidence of systematic bias. These results are important, and offer support for specific features, such as for devices of different sizes, and for the changes that are most frequently made in migration, such as changing multiple to single questions per page. However they do not provide proof for any particular case, and the changes made in each specific migration need to be evaluated in the light of the hierarchy. McEntegart (2010) has recently discussed the issues around migration and equivalence in more detail.

There is one area where ePRO and paper may not be equivalent, and that is in the reporting of socially undesirable behaviours. There have been a number of reports that people are more willing to report such behaviours on a computer questionnaire than on paper. If this was the case, it would represent more accurate reporting, and therefore be a desirable feature of ePRO. Later reports have been more equivocal, but meta-analyses suggest a real, though small, effect with ePRO (Dwight and Feigelson, 2000; Richman et al., 1999).

Device Size and Questionnaire Layout

Tablets used for ePRO range in size from a screen size of about 3.5" (e.g. Palm TX) to about 12" (Tablet PC). A number of factors influence the choice of device size, which in turn influences the approach taken to questionnaire migration.

The most basic issue is cost. All else being equal, small devices are less expensive than larger ones, so it makes sense to use the smallest device that will display the material adequately. (What is adequate will be discussed below). All else is not equal, of course – a 7" Android tablet may be considerably less expensive than a much smaller smartphone, the cost of the latter being due to many extra features, which may or may not be relevant to the ePRO application.

An issue which is not generally relevant for site-based assessment is portability. However in some studies both diary and site-based data may be collected for the same patient. In this situation it may be desirable to use the same device for both purposes, and this will probably mean a handheld device.

A larger device has obvious advantages where portability is not required. Larger text may be used, and more material may be presented on the screen. In particular several questions may be shown on each screen. This makes it possible for the screen display to resemble a paper original more closely, and may also reduce the number of keystrokes required for navigation. How important is this?

Most implementations of questionnaires on small screens, and some on larger screens, use presentation of a single item per screen. Paper questionnaires often present items in groups. Sometimes these groups are logical, for example when items all refer to a particular domain. Sometimes the grouping is arbitrary, as when a set of questions is grouped because they all have the same response options.

Responses to questions in a group tend to be higher than when the same questions are presented singly. If the grouping is arbitrary, then this correlation is spurious. Making each question self-contained should, if anything improve the veracity of the data. This effect was studied by Couper et al. (2001) in a web study. They found trends towards a grouping correlation, but this was small and not statistically significant.

Another line of evidence that such effects are small, if they occur at all, comes from the meta-analysis by Gwaltney et al. (2008), referred to above. They compared the equivalence data for PDAs and for larger screen devices separately. While many research papers do not specify whether single or multiple items per screen were used, it may be safely assumed that PDA implementations of questionnaires used single item presentation, while larger screen implementations could have used either. The average correlation (ICC) between PDA scores and paper was 0.91, while the average correlation between larger screen devices and paper was 0.90. Thus their analysis suggests that using single questions per screen has little or no effect on the data obtained.

For some questionnaires, it is not possible to fit all the information needed to answer a question onto a small screen. If this is the case, some form of screen splitting may be used. There are two ways this may be done, and they have very different implications for the patient providing the data. The first is to place instructions for the questionnaire on an introductory screen, and then present the questions, one per screen. The second places the question text on one screen, and the response options on the next screen.

The difference between these two scenarios is highlighted by considering what the patient must remember. In the first case, the information to be remembered stays the same, at least for a section of the questionnaire. In the second case, the information is constantly changing, The second case imposes a much

greater cognitive load on the patient, and there is a consequently greater risk that the patient will fail to remember important information, thus affecting the quality of the resultant data. Empirical data on this issue is sparse, but one study has suggested that question-splitting may have an impact on data quality (Juniper et al., 2009). We would therefore recommend that in general, questions and their responses should be presented on the same screen. In addition, we suggest that critical information from the instructions, such as the assessment period, should be repeated on each question screen. These recommendations may well affect the choice of device size.

Moving in the other direction, larger screens allow more flexibility in design layouts. For example, question groups could be presented in a similar way to paper, and at the extreme a full A4 size device screen could allow exact reproduction of a paper page. It is important to note that making the screen appearance identical to paper does not mean that the ePRO application will be identical to the paper questionnaire. There are still significant differences, in particular in the method of navigation, and of changing responses once they are made. Thus issues of equivalence in migration must still be addressed. Moreover the similarity in equivalence data between large and small screen devices referred to suggests that any impact of single or multiple questions on equivalence to paper will be negligible. If there are advantages of multiple questions per screen, they will likely be found in convenience for patients, e.g. in simplifying navigation. Or patients may simply prefer one layout to another, or a larger screen with bigger text – this has not been systematically looked at.

Thus we consider an adequate device size to be one where all the relevant information required to answer each question be presented on the screen at an easily legible font size and where the use and portability features of the device make the most sense. There is no compelling scientific reason to use a size larger than this, though patient preferences may obviously influence this decision.

Summary and Conclusions

Site-based ePRO has a number of benefits, including

- Only valid in-range entries can be made
- Missing data can be reduced or eliminated
- Elimination of manual data editing and entry

With a minimum of training, systems are easy for patients to use, including the elderly, those unfamiliar with computers, and special-needs patients.

Modern ePRO systems are compliant with requirements on data security, privacy, and investigator responsibility for data

Extensive data supports the equivalence of ePRO systems with their paper counterparts.

A variety of device sizes ensures that questionnaire layouts convey sufficient information with good readability.

The amount of change and published evidence must be considered when migrating a paper instruments to electronic format. "Looks the same as paper" is not necessarily a supportable approach.

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