

Which ePRO Solution is Right for Your Study?

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Bringing Clarity to ePRO Options

Sponsors considering the use of electronic patient-reported outcome (ePRO) for their clinical trials can choose from a wide variety of diverse solutions. These choices include the very paper-like digital pen; telephone based systems such as IVRS; web based solutions; the well established flavors of device-based solutions (for both home and site use) and more recently, SMS based solutions using the subjects own mobile phone. When faced with this number of options, study teams may be tempted to fall back to the default and familiar choice of paper. Paper diaries have been used for thirty-plus years of clinical research, but they are not always the best choice. There are well-documented problems with the compliance and accuracy of at-home paper diaries.¹⁻² Today's ePRO options and technologies can successfully overcome these problems.²⁻³ Perhaps more significantly, clinical trial study teams are learning that issues with paper based data collection are minor in comparison with the task of establishing the validation status of the patient reported outcome (PRO) instrument selected. Whether a paper-based or electronic method is used to collect PRO data intended to support labeling claims, regulators are likely to review the psychometric properties of the data collection instrument.⁴⁻⁶ Some instruments meet the current requirements of validity, reliability and sensitivity to change, but there are a large number of instruments created during the 1990's that require further development and validation to meet the high standards demanded for regulatory approval in the U.S. for use as part of a claim.

The FDA will look for evidence that the data was collected "in accord with the protocol." The date or time of unsupervised entries in paper diaries cannot be verified, but ePRO tools provide a time-stamped audit trail.⁸

The regulatory review process makes it difficult to justify the use of paper for certain home-based diaries. Protocols often include specific time windows for capturing patient data. When patients are required to complete a morning diary between 8:00 and 10:00 a.m., for example, the regulatory agencies look for evidence that the data was collected "in accord with the protocol."⁴ The date or time of unsupervised entries in paper diaries cannot be verified. A time-stamped data entry point (as provided by the various ePRO methods) offers a significant advantage for studies that are designed to assess fluctuating symptoms such as pain, dyspnea, or cognition.

Compliance

The compliance to protocol requirement is critical to trial execution and increased compliance is one of the most valuable contributions of ePRO tools. In past years there has been considerable debate regarding how to improve the accuracy of patient-reported data. It is recognized that study subjects may not fully understand the importance of the timeliness of subjective data and the effect that recall bias has on their replies. Entering data points at home is substantially different from supervised data entry at the clinic. Regulatory agencies have come to recognize that paper-based diaries used outside of the clinic allow creative data entry and this raises concerns

about the accuracy of recall. Controlling the data entry event means that recall period can be restricted to the intended interval of time. A paper diary may appear to be 100% compliant, but may contain invented entries or entries made outside the required time periods. In most studies, an electronic diary yields over 90% compliance; the clinical study team can have confidence that the acquired data was collected at the correct time point and not, for example, in the parking lot prior to the visit.

One illustration of the importance of accurate recall and data entry compliance came from a small experimental study sponsored by an academic group¹. The study design required 80 adults with pain to complete daily diaries; one group used electronic devices to enter data while the other group used an experimental model of paper with hidden entry time stamp capability. The study results demonstrated the creativity of subjects who appeared to comply with instructions, yet actually made multiple data entries at false time intervals. The actual compliance of the paper-entry group was remarkably different than the apparent compliance; (11% actual versus 90% apparent). However, this finding cannot be extrapolated as representative of trial data collected on paper at the clinical site and overseen by staff. It is the unsupervised, home-based paper diary that is most at risk for creative data entries.

Study teams often design protocols, endpoints and desired label claims and then conclude that ePRO is the best way to collect patient-reported outcomes to support their trial. The team must also decide which paperless mode to use. As they review the variety of available modes, many factors can influence their choice. They may even decide to use more than one mode of electronic data collection. Among the factors that influence decisions are:

- the frequency of data collection
- the timing of data entry
- the number of PRO instruments required
- any instrument validation that must be conducted
- the indication being studied
- the characteristics, demographics and psychographics of the study population

Global studies often include regulatory and translation requirements and sometimes present logistical challenges, such as dealing with customs regulations or verifying the data transmission capabilities of the countries involved.

Other critical issues to consider include:

- the cost to the Sponsor
- the burden imposed on the site
- the potential impact on the patient's daily life

Some indications require special consideration of subject burden, such as a study in Parkinson's disease. The study team needs to ensure that the ePRO service provider can design an interface to accommodate special needs such as tremors, dyskinesia and micrographia.

To ensure success, the selected ePRO option requires balancing the protocol requirements with the data collection options and system capabilities. A particular approach may be suitable for some studies but problematic for others. The purpose of this paper is to identify current ePRO technologies and highlight their distinctive features that make them most suitable for a clinical trial. The following sections discuss the efficiency and effectiveness of various ePRO methods.

Home-Based ePRO - Personal Handheld Devices

The first devices used to collect data from subjects in their own homes were introduced about 15 years ago and were the custom built Swedish-made MiniDoc diaries. These devices, often called eDiaries, offered many advantages - including ease of use, the ability to limit data collection to the desired time interval and a solution to

the problem of subjects backfilling diary entries just prior to the clinic site visit. However, these devices had no remote communication ability; the data had to be off-loaded from the device at site visits. Handheld personal digital assistants (PDAs), popularized by Palm, were the next electronic devices used to collect patient-reported outcome measures. These devices had built-in sending capabilities and data could be transmitted on demand from the subject's own home (either wirelessly or using landline phone lines and a modem). Not only could sponsors ensure that data was recorded at the correct time, but the site staff and sponsor could now review data close to real time and thus monitor subject progress and safety more closely.

Advantages: Accuracy, Convenience, Privacy

Personal handheld devices are always available for data entry, regardless of connectivity, and create a time-and-date-stamped audit trail for data managers and regulators, meeting the FDA 21 CFR Part 11 compliance rules.⁸ PDAs allow for a very high level of standardization, ensuring that unnecessary variability is not introduced into the data due to differences in device characteristics such as screen size, font differences or overall usability. Personal handheld devices also allow full control over the user entry experience, because extraneous device functionality is disabled. Users will not receive phone calls or text messages from the eDiary device while completing their assessments. The ePRO provider handles the programming of the devices and manages the logistics and distribution of the hardware. The Sponsor decides whether to purchase or lease the devices. With the use of a hand held device for electronic patient-reported outcomes, the patient cannot record illegible or superfluous handwritten notes in the margin. Because eDiaries do not require site personnel to transcribe entries from paper forms, site burden is greatly reduced and the need for source data verification is eliminated. Real-time access to subject entries allow site personnel to monitor patient compliance and to intervene before a subject becomes a protocol-violator. When a study requires entries at specified intervals, the device is programmed to alert patients according to the protocol time and event schedule. When the protocol requires that patients report critical events (for example, when leakage occurs in an overactive bladder study), patients can enter the event on-demand and the event receives a time stamp automatically.

A personal handheld device offers privacy, a distinct advantage when recording a personal event or sensitive information. The device is discrete; a subject recording an event or completing an assessment appears to be checking email or responding to a text message. Subjects have much greater privacy with an electronic diary than they do with paper – there will be no chance of friends, relatives or neighbors accidentally or intentionally viewing diary responses and putting the subject into a potentially embarrassing situation. Anyone picking up the eDiary device will only see the login screen and will be unable to login to the device (without knowing the subject's confidential PIN code).

For many trials, the most user-friendly data collection solution may be a personal handheld device. It is typically a cost-effective solution for a Phase II or Phase III trial and can support almost all indications and types of data. Clinical teams should seriously consider this mode whenever it is imperative that data meet the ALCOA criteria: Attributable, Legible, Contemporaneous, Original and Accurate. This includes any study where the PRO data will be used in support of a labeling claim or where the primary endpoint is patient-reported.

Using hand held devices does incur a hardware expense and this may discourage their use in studies with large numbers of subjects and a low volume of data. Shipping devices can entail logistical challenges - especially if patient density per country is low and the countries selected have complex import and export procedures. A study team planning a small Phase I study may question the return on investment for testing and validating an eDiary solution. However, it is important to consider all of the costs associated with paper in order to reach the most informed decision. When the need (and cost) of source data verification is eliminated and your study team receives higher compliance and a larger amount of defensible and evaluable data, the improved results can make the use of hand held devices viable in even a small study.⁷

Site-based ePRO – Tablet PC ePRO

Site-based PRO assessments are used in many studies and can create high burden for site staff. In these cases, sponsors have the option to select an ePRO solution based on a tablet PC. This site-based solution enables many patients to use a single device kept at the site to enter their subjective outcome reports. This method ensures a high level of standardization and order of questionnaire administration that is important to the collection of defensible data.

In complex study protocols that may include many different evaluations, a site-based ePRO instrument can ensure that subjects complete their assessments in the right order. The tablet is programmed with the schedule of events for each visit and the study coordinator need only be available to remind subjects to start the entries at the appropriate time – typically before any treatments are administered. When the volume of data required is limited and/or the number of patients is small, paper questionnaires remain a viable site-based option. If a study requires both patient-reported and clinician-reported outcomes (CLINROs), collecting that data on a tablet PC at the site can be an effective tool. This method also adheres to the FDA’s requirement for consistency in the tools utilized to capture all outcomes within any given study.

A site-based ePRO device can be appropriate for a Phase I trial or for collection of data from hospitalized subjects. A PDA device can be used in any setting, but when PRO data collection is needed infrequently, study teams often prefer a large-screen format at the clinic site. When implemented on an easy-to-read tablet PC screen, an instrument can include graphics, a large font size and large buttons - all of which can make entering data a more engaging task for those completing their outcome reports. The use of a dedicated tablet ePRO device at the site also eliminates issues of computer availability. Web-based ePRO without a dedicated device requires the subject to enter data via a browser at one of the site’s computer stations. These may not always be available and/or conveniently located to provide the subject a comfortable and private area to complete his or her assessments. The size of a dedicated tablet ePRO device also allows better usability for those with a physical impairment such as joint pain, limited fine motor skills or impaired vision. As with other ePRO devices, site-based tablets provide the advantages of legible data, the elimination of transcription errors and the provision of a time-stamped audit trail.

This site-based solution makes economic sense because many patients can all use the same device to enter their subjective outcome reports.

Interactive Voice Response

Interactive voice response (IVR) systems have long been used to randomize patients for clinical trials and to order and manage clinical supplies. They can also be used to collect patient reported data. The majority of patient reported instruments in use today were developed for paper. Creation of a version for use in IVR requires demonstration of equivalence and considerable validation effort because the psychometric properties of an instrument may be affected when the mode of administration is changed from a visual to an audible mode. This change of format is typically viewed as a moderate modification of an existing instrument because the available literature supporting the equivalence between IVRS and paper is still not conclusive. (Coons, et al., 2008) It could be time consuming and costly to perform the necessary studies to provide evidence of equivalence. In addition, in many countries people are weary of hearing recorded announcements and being prompted for responses via the telephone. IVR data collection is best suited for brief questions with simple responses. One example is a single daily question: "Did you take your study medication today? Press 1 for Yes. Press 2 for No." As the number of questions and the assessment frequency rises, compliance may suffer. In addition, the number of response options is best limited to 5 or fewer to avoid issues with short-term memory and the recall of the options. Another consideration is that IVR cannot accommodate visual analog scales (VAS) or graphical instrument models and may be too complex for a numeric rating scale.

When a Sponsor's study team determines that the questionnaire and the population are appropriate and the instrument has been developed for use in an IVR system, it can be a cost-effective choice. IVR for PRO is easy to deploy for simple daily questions, works anywhere in the world and requires only a telephone.

Interactive Web Response

As increasing numbers of homes have computers connected to the Internet, the potential for interactive Web response (IWR) diaries is increasing. For study subjects comfortable with a computer, it is perhaps the most user-friendly approach for patient reported data entry. Interactive web response can be an ideal way to recruit patients for post-marketing studies, especially among those who regularly surf the Web for information about their disease or condition. This approach is being used in experimental studies funded by the NCI.⁹

In industrialized nations, IWR has many of the benefits of IVR and SMS data collection without some of their downsides. As with other electronic methods, IWR's primary benefit is elimination of the need for data transcription at the site; data entered by research subjects goes directly into the ePRO provider's database.

Web-based data entry of a PRO is particularly suitable for studies that have infrequent data collection, for example, once a week or once a month. It has proven to be advantageous for sites that developed their own system to collect satisfaction data and even experimental submission of patient reported adverse events.⁹ Web-based systems can be combined with other types of electronic data collection. For example, patients in areas with high internet/computer penetration can use Web-based PRO and others, without such accessibility, can use a hand held device.

All methods have their limitations, of course, and IWR is no exception. The inability to standardize the IWR users' experience can be a drawback. Patients can connect to the Internet on computers with a variety of screen sizes and different browsers; they may connect on a public computer in a hotel or airport; they may sign on using the latest smartphone. These variable elements affect the look and feel of the questionnaire and may require additional work to assure equivalence (a part of validation),

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It is possible to present different layouts of Web ePRO for different devices. For example, a diary can be programmed to present an optimized user interface for those mobile device users and a regular web screen for full size PC users. This makes it possible to present instruments via the web. However, the study team should check the capabilities and qualification of their Web ePRO provider.

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Although this is a promising ePRO approach, some experts have reservations about using it for pivotal studies. Because it is limited to those patients who have regular access to a computer, study designers must assess the risks to trial data from income-level stratification. At this point, the use most often cited as appropriate for IWR ePRO is post-marketing research.

SMS / Texting and ePRO

Texting, more formally known as short message service (SMS), is becoming ubiquitous among a large segment of mobile phone users. SMS-based data collection is typically not suitable for supporting labeling claims because of the difficulty in making it Part 11 compliant. Authentication, privacy issues, usability, reliability and instrument

validation are stumbling blocks. Still, SMS is both an efficient and effective way to accomplish other study requirements, such as reminders, notifications, and even recruitment.

Patients prescribed a recently marketed product can be recruited to take part in a Phase IV study in various ways. The Internet is the most obvious place to post a text message number and an invitation could be printed on the patient information insert with a new drug. Those who are prescribed the drug and see a recruitment notice can easily enroll in a post-marketing study by sending a text message to the number provided in the packaging.

And consider, for example, a vaccine study where text messaging can be used to send reminders: “Did you take your study medication today?” or “Remember to get your booster shot this week.” Reminders can be sent to alert the subject to an upcoming clinic visit and to avoid eating for 12 hours prior to the visit. Texting can play a useful ancillary role for certain studies that collect data using a web-based system or for studies that collect data only during site visits. Regulatory concerns are reduced when sending one-way reminders, alerts, notifications, or alarms - making SMS a good compliance management tool.

Although SMS has yet to fulfill its full potential as a data collection tool, some ePRO experts are working toward putting it to greater use in the future. From a regulatory standpoint, this is a challenge that may take a while to meet. Nevertheless, it is currently a cost-effective choice for post-marketing studies or simply as complementary support of other ePRO tools.

Digital Pen ePRO

In addition to the options discussed thus far, yet another viable solution for ePRO collection is a digital pen. This solution allows for the use of a familiar technology, pen and paper, with a digital component that permits subjects and sites to enter the required data items directly onto a paper form. This paper form and the accompanying digital pen, work together to capture what was written on the form in an electronic format. The pen senses where it has traveled on the form and collects the location of data items completed by the user. This electronic “picture” of what was written is then uploaded to a central server where the information is replicated onto a digital rendering of the original paper form.

The digital pen is quite often much larger than a traditional pen due to the internal electronic components. In most cases, the pen is required to be placed into a docking station for transmission of the data captured; however, Bluetooth technology is becoming more and more prevalent, increasing the use of wireless technology for capturing clinical trial data.

Having the ability to use an existing paper format for a given PRO instrument often eliminates concerns with additional validation requirements. Although there are several methods for accomplishing this data capture, the most typical involve having the forms printed on particular type of paper. The paper has a tiny grid of sensors imbedded in the paper stock that works with the pen to capture the handwriting or “brushstrokes” of the user. The use of a digital pen avoids some of the challenges commonly encountered when migrating a paper PRO to ePRO; the user interface remains relatively the same and the subject’s familiarity with pen and paper results in minimal training needs. However, there remain issues to overcome. Extraneous and illegible entries are possible; date and time stamping may not be as reliable as other electronic methods and source data verification is still required because the subject may try to use a different, non-digital pen, and the resulting data transmitted to the central server may only be a subset of the whole data as appearing on the paper copy.

No Easy Answers but Many Potential Solutions

When a protocol requires collecting patient-reported outcomes, the study team must consider many factors when deciding which method will provide the best data at a reasonable cost. Does the study have a great many patients

or only a limited number? Are there just two or three questions per data collection point or more? Are there potentially multiple time-points throughout any particular day that require data collection? Are those time-points the same every day (after meals, before bed, etc.) or at different times? Will sites be confined to English-speaking locations or will a study's global nature require that the instrument be translated into various languages? Will each translation fit on the page for any given device? These are some of the factors to consider.

Fortunately for study teams, the best way to determine the choice of an ePRO system for a new study is to talk with your trusted ePRO vendor or PRO advisor about your specific study requirements. Established, qualified ePRO vendors have the expertise and experience to guide your team to the best solution. At CRF Health, we can recommend the best approach or combination of approaches to fit your particular program needs.

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Glossary

ePRO electronic patient-reported outcome

instrument validated PRO questionnaire

IVR interactive voice response

IWR interactive web response

PDA personal digital assistant, an electronic handheld device with a visual display that allows a user to connect to the internet and may include touch screen technology

smartphone mobile phone with Internet connections and applications

SMS short message service (cellular phone text messaging)