Implementing ePRO Systems in Clinical Trials

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INTRODUCTION AND RATIONALE

Over the past few years, the clinical research industry has witnessed a significant change in the conduct of clinical research as patient-centricity in clinical trials has been recognized as a pillar to developing appropriate therapies and treatment regimens. This is reflected in the guidance by regulatory bodies such as the FDA, which advises use of Patient Reported Outcomes (PROs) when measuring a concept best known by the patient or best measured from the perspective of the patient (U.S. department of health and human services food and drug administration, 2009). The FDA defines PROs as any report of the patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else (U.S. department of health and human services food and drug administration, 2009). PROs can be collected in interview format by the research staff or self-administered by the patient via electronic or paper diaries. The adaptation of Electronic Diaries (eDiaries) is encouraged by regulators, mostly because of increasing evidence that it provides better quality data than paper due to the inclusion of time-stamps and data attributes.

Patient compliance is another important factor in obtaining quality data that is often a challenge with paper diaries. Since paper diaries are typically submitted by the patient during their next study visit, it is difficult to observe non-compliance in a timely manner and follow up with the patient to alter their non-compliant behavior before it is too late. It has been shown by Stone and colleagues that the subjects reported much higher compliance with a paper diary than was actually observed (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2003). While the patients reported 90% compliance, actual compliance was only 11 percent indicating a significant level of faked compliance. The same paper found that the actual compliance with electronic diaries is 90 percent. In addition, electronic diary submissions are recorded against the patient’s digital signature and are time stamped, making it impossible to fake entries and compliance. For this reason, ePRO has gained regulatory and scientific support as a preferred method of data capture in clinical trials. The FDA’s PRO Guidance states: “If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what steps are taken to ensure that patients make entries according to the clinical trial design and not, for example, just before a clinic visit when their reports will be collected” (U.S. department of health and human services food and drug administration, 2009).
Higher compliance with ePRO can be further driven by the use of reminders and alarms and enforced time windows for data submission, as well as identification of non-compliant subjects and timely follow up through real-time data monitoring capability. Time stamping and specified time ranges for making diary entries serve to eliminate backward and forward diary filling that has been noted as a frequent occurrence with paper diaries (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2003).

A common misconception and argument against ePRO utilization is that older patients are not tech-savvy and that diary compliance will be compromised as a result. In reality, studies have shown that older patient populations have higher compliance rates with ePRO than their more tech-savvy counterparts including teenagers and adults (Mongiello, 2012).

The timeliness of ePRO data can assist in motivating older and frail patients of poor health to participate in clinical trials, as the data can be utilized to make timely clinical decisions through symptom monitoring. This can provide patients with additional comfort that someone is watching over them and increase the safety of participating in the clinical trial, serving as an additional incentive for participation and increased motivation to complete diaries. In a COPD trial where patients reported their symptoms via EXACT-PRO Questionnaire, we have demonstrated significant success with this approach where an algorithm was incorporated to monitor symptom progression based on patients' responses. The system was able to detect all of the COPD exacerbations and patient compliance with daily responses was 99.9% (Johnston, et al., 2013).

Providing the patient with a mobile device to take home can also serve as a communication tool between the patient and the healthcare provider. In addition to providing symptom and disease related data, the device can incorporate instant messaging to deliver messages between the patient and the doctor where the patient sees the device as the extension of their care. The communication can be a mixture of automated messages, such as “Please contact your doctor if your symptoms worsen” as well as doctor-patient dialogue on symptom follow up (Singh, et al., 2013).

In terms of data accuracy with ePRO, utilization of real-time validation can decrease missing or unusable data by not allowing out-of-range entries and instructing the patient to input the data correctly. Use of eDiaries also eliminates unnecessary data through use of branching logic and displaying only relevant questions which is impossible with paper diaries.

**Is ePRO Worth it?**

A major hurdle to overcome in ePRO implementation is the initial time and monetary investment for electronic system planning and setup. However, what most research teams tend to overlook are the returns derived from time savings and reduced labor costs as a result of ePRO use over paper, as well as increased patient compliance and potential patient safety benefits. It is critical to evaluate the attributes of the trial and consider the setup process for ePRO prior to deciding on the data collection method. Several factors have to be carefully weighed, including the disease being studied, number of patients needed, duration of the study, number of instruments being used, frequency of diaries, as well as overall costs of ePRO vs overall costs of paper. Electronic diary use tends to be more favorable for trials involving diseases where the quality of life is compromised, where the patients are experiencing pain, discomfort or restrictions in terms of their daily functioning and activities. It has also been demonstrated
that sensitive information such as sexual behavior is more likely to be completed via electronic diaries than paper diaries, perhaps due to increased privacy or anonymity perceived by the patient while completing the questionnaires electronically (Lim, Sacks-Davis, Aitken, Hocking, & Hellard, 2009). Therefore, in instances where the patient is to submit data that is sensitive or embarrassing, ePRO may be the only option to obtain reliable results.

**WHICH ePRO SOLUTION TO USE?**

Electronic diaries can be delivered via a variety of methods and across a myriad of different devices including computers, tablets, smart phones, etc. The device chosen must be compatible with the patient group being studied. Numerous patient factors as well as characteristics of the instruments to be used need to be taken into consideration when deciding on the appropriate ePRO device.

Factors such as screen size, patient dexterity, and technological proficiency in terms of device use, appropriate reminders and daily diary commitments greatly influence both the ability of the patient to complete the diaries effectively as well as overall patient compliance in the trial.

Apart from being appropriate for the patient population, the screen size has to accommodate the instrument that is to be delivered as an eDiary. For example, if the instrument involves graphics and diagrams that will be too small to view on a smartphone, perhaps tablet is a better choice. Visual Analog Scales also have to be accommodated with an appropriate screen size to ensure proper visibility.

Overall device size may also be a factor, especially when the patient may need to carry the devices with them at times. Typically, smartphones are easiest. However, if the instrument or screen size required needs to be larger than a smartphone, tablets are often a viable alternative. Tablets are also the top choice for ePRO completion at research sites as they provide a good balance of portability and screen size and allow for patients to conveniently complete their ePROs in the waiting room or the doctor’s office.

**BRING YOUR OWN DEVICE (BYOD)**

While the conventional provision of ePRO is to provide patients with a handheld device dedicated to study use, an emerging alternative is the Bring You Own Device method. The adoption of the BYOD approach is driven by the widespread use of personal smartphones and tablets and the ability to leverage the use of the subject’s own internet or data plan. However, the utilization of BYOD raises a number of operative and scientific concerns that will need to be sorted out before it becomes a routinely used method.

There are two ways for patients to submit data through their own devices. One is to utilize their web browsers, a process that can provide very different experiences for the patients based on the combination of device and browser used. Functionality can vary across different browsers, and an even more significant concern is the transmission of data via an open internet connection.
An alternative approach is to utilize a study specific ePRO app. With the exception of potential screen size differences across devices, the app would display the ePRO instruments in a consistent manner on all devices (Yeomans, 2014).

Native apps will allow for data entry while the device may not be connected to the internet which may be an advantage in some areas with poor connectivity (Coons, Eremenco, Lundy, & O’Donohoe, 2014). However, they pose a set of concerns with the Research Ethics Boards as the data is stored on the device itself, a feature that raises concerns over potential data loss and compromise of patient privacy in the event of device loss. Security measures have to be evaluated to ensure that the patient data is stored with a satisfactory level of security and in line with the relevant laws and regulations.

A challenge in both instances with app utilization is ensuring the wide range of devices and operating systems that are available are accommodated. Typically, apps are developed for the most popular operating systems such as Android and iOS, which still creates a risk for excluding some countries and populations.

In contrast with dedicated devices, the BYOD approach provides less control over the devices as app notifications and updates cannot be pushed on the patient’s personal device. In other words, the patient has control over their device, and the app has to be accommodating to the environment. If the patient shuts off the sound on their phone, they will be able to ignore audio alarms that may be automatically setup on the app. The subject may also delete the app anytime, and the methods to alert research staff of such actions is limited. These factors can be a significant threat to patient compliance in the study.

**PREPARING FOR IMPLEMENTATION**

The key to successfully implementing an ePRO system is adequate planning prior to the onset of the trial. All of the stakeholders including CRO, sponsor and ePRO vendor representatives have to act in concert and discuss key trial attributes that have to be reflected in the ePRO solution, including diary delivery schedules, attributes of the instrument, ePRO devices, all while keeping the patient demographics in mind. You should expect a series of “prototype” solutions as the details are ironed out and ePRO development advances. Being a very visual and hands-on solution, ePRO is best tested via prototypes where the stakeholders can get hands-on experience utilizing and testing the device prior to deployment. To obtain high compliance rates, it is necessary to consider the patient population and which device and diary delivery schedule fits best within their daily routines. Therefore, the development process is very much a “walk in the patient’s shoes”.

To drive patient compliance, patient rewards have to be carefully planned out. Depending on the demographics, additional functionalities can be placed on the device that are valuable to the patient but not a privacy or a security issue from a trial perspective. This can include additional health monitoring in the older population and perhaps games for the younger patients. It is beneficial to include functionalities that can serve as motivation for the patient to carry the device with them if frequent diary submissions are needed.

Another approach is to see how the technology can be leveraged to increase patient safety while participating in the trial. As discussed earlier, knowing that their disease progress is being monitored behind the scenes by a medical professional can act as a strong motivational factor for patient
participation, and appropriate messages can be incorporated based on algorithms to alert both the patient and medical team to follow up on certain patterns in disease progression and elicit timely follow up.

Taking advantage of real-time data and validation can bring tremendous benefits to the trial if planned and incorporated properly. Discuss the incorporation of point-of-entry validation for acceptable ranges for patient answers including precise numerical values to ensure that the patient is alerted if a mistake is made. Correcting the data at point of entry is important not only to obtain clean data, but especially in instances when algorithms are developed to drive further action based on those answers.

Algorithms can also be implemented in other components of the system, such as participant screening in the trial. When eligibility is determined on a set of answers or attributes pertaining to the patient and their health, logic can be implemented to ensure that no errors are made by research staff while enrolling participants. For example, we had previously been involved in a trial with Aquinox Pharmaceuticals that assessed eligibility based on an average pain score over several days prior to enrolment. The system was automatically calculating the average pain score and would inform the coordinator if the patient had a sufficient number of submitted pain diaries as well as an average pain score that satisfied the range required for trial participation. In the event one of these criteria was not met, the system did not allow the coordinator to enroll the patient, avoiding a potential protocol deviation that would have to be documented after the fact.

It is beneficial to start contacting vendors early on in the planning process to understand the workflows, timelines and capabilities of their systems. If the trial is deployed in multiple countries and languages, special considerations for shipping and configuring devices across borders have to be accounted for in the timelines and budget, as well as diary translations. As all patient-facing materials have to be submitted for ethics approval, set clear timelines for development of the ePRO interface and instructional materials so that ethics submissions can be done in a timely manner.

It is critical to discuss the vendor’s data transmission and data storage capabilities as it an important factor in ethics approval and the supporting documentation that needs to be prepared and submitted. If the data is not stored on the device and is instead securely transmitted via an internet connection, documentation on transmission processes and encrypting will be necessary, as well as attributes on the security and accessibility of the server where the data will reside. In case of native apps or any other instances where the data may reside on the data collection device for a period of time, outline the documentation need and obtain the supporting documentation on the internal processes as early as possible to ensure timely REB approval.

**CONCLUSION**

It is becoming evident that electronic data collection provides additional benefits over paper such as point-of-entry validation, automated reports and notifications, health monitoring capabilities, greater privacy over paper, increased patient compliance, and regulatory advantages. Perhaps the most important for all stakeholders is the rapid collection of data, which enables the sponsors to bring their products to market sooner as well as allowing patients to benefit from new therapies sooner rather than
later. Based on these added benefits over paper, ePRO should become the standard approach for patient data collection in clinical trials. For a successful ePRO implementation strategy, you will benefit from contacting ePRO vendors early on in the planning stages to properly address all attributes of the ePRO solution for a feasible implementation plan.

If you are considering an ePRO solution for an upcoming study, we would be pleased to share our expertise and insight and can be contacted as follows:

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Works Cited
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