

ePRO: maximising the benefit and minimising the pain

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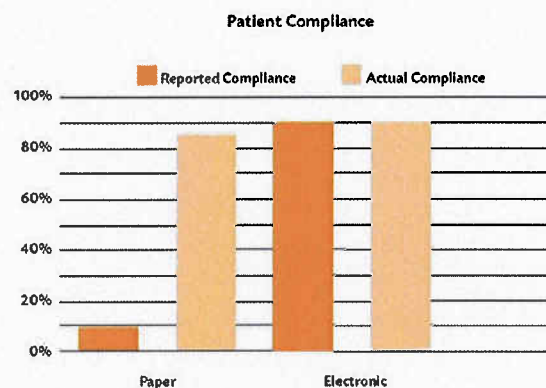
Today, many pharmaceutical and biotechnology companies use various forms of patient diaries in their clinical drug studies as a means of collecting patient reported outcomes (PRO). The various PRO instruments currently available provide invaluable endpoint data needed to bring new drugs to the market more quickly, while ensuring a drug's efficacy and safety. However, with a paper-based system, it takes many people to collect, perform quality checks, and process a multitude of diary entries to achieve the end result. The use of electronic PRO (ePRO) provides a number of advantages compared with PRO and promises greater efficiency in the clinical trial process: the elimination of paper data entry being the most obvious. In particular, the use of Interactive Voice Response (IVR) technology and Interactive Web Response (IWR) technology, both of which have been accepted by the FDA as a primary endpoint in new drug applications, is helping to revolutionise the collection of PRO.

A study sponsored by the National Cancer Institute (NCI) found that patient compliance levels were lower with paper diaries than electronic diaries.¹ The study also showed that a large discrepancy existed between the reported and actual compliance of using paper-based PRO but this does not occur with ePRO (Figure 1). Reported compliance with the paper diary was 90%, while actual compliance was 11%. Furthermore, actual compliance with the electronic diary was 94%. One of the many advantages of ePRO over paper-based PRO is the ability to time stamp records. The ability to time stamp confirms the date and time of a patient's diary entry. In the NCI study, the paper diary was prone to hoarding, defined as days when the diary was not opened but for which diary cards were completed: 32% of days contained no diary openings, but reported compliance for these days was 92%.¹ In addition, ePRO tools have the ability to deliver reminders to patients to prevent missed entries, increasing overall compliance and leading to higher quality and more accurate data.

EPRO USAGE

The requirements of Good Clinical Practice are such that all data collection must follow several explicit principles. The FDA requires that all data collected during a clinical trial is Attributable, Legible, Contemporaneous, Organised, and Accurate, known by the acronym ALCOA. It is apparent that paper-based PRO does not meet all of the ALCOA requirements while ePRO does (Table 1). Most industry observers estimate that 20–30% of current clinical trials use some type of PRO. The use of ePRO is increasingly widespread in trials that require PRO, growing from approximately 5% in 2002 to 15% in 2007, a significant increase, with more and

FIGURE 1



more sponsor companies requiring its use in clinical trial monitoring. In addition, regulatory approval is helping to drive its adoption and it is likely that within the next three–five years the use of ePRO will outstrip that of paper-based PRO. In contrast to the adoption of new technologies in other industries, which may create staff redundancies, the use of ePRO in the CRO industry has led to a redeployment of staff to ePRO-related activities. For example, staff formerly engaged in the quality control and data entry of paper patient diaries are now involved in the design, implementation, and monitoring of ePRO systems.

Doctors, site staff, and patients are usually willing to embrace the use of IVR technology because of the advantages it provides (Table 2). Because the system uses familiar and easy-to-use technology, there are no barriers to uptake. The advantages of IVR technology versus personal digital assistant (PDA) technology for the patient are numerous. IVR technology is easy to use since it simply involves pressing buttons on a standard telephone key pad. Training is minimal as patients are exposed to the underlying concepts in everyday applications. Importantly, it is easy for non-technical or elderly patient populations to understand. Patients can easily and quickly enter their responses and progress rapidly through the prerecorded diary questions. In contrast, PDA technology is less familiar to patients and requires more training, particularly for younger or elderly patients. In addition, PDA technology is more prone to technical difficulties or technology failures due to the more complex nature of the technology compared with IVR.



TABLE 1: ALCOA AND PRO

	ELECTRONIC	PAPER
Attributable	Unique use rfid, passwords, audit trails	Patient number written by patient
Legibility	Recorded in a database, reporting capabilities	Dependant on patient and nature of the PRO
Contemporaneous	Date and time stamps, logic and quality checks	Difficult to verify
Original	Data cannot be changed once recorded	Difficult to verify
Accurate	Date and time stamps, quality checks real time, logic flow	Difficult to verify

TABLE 2: IVR/IWR vs PDA vs Paper

	IVR/IWR	PDA	PAPER
Available 24 hours day/7 days a week	✓	✓	✓
Date and time stamped	✓	✓	✗
Documented high compliance	✓	✓	✗
Quality checks on data access	✓	✓	✗
Real-time data access	✓	✓	✗
Reminder options	✓	✓	✗
Enforce specific time/date windows	✓	✓	✗
Implement mid-study changes easily	✓	✗	✗
Familiar and simple technology	✓	✗	✓
Patients have the required equipment	✓	✗	✓
No distribution/management of hardware	✓	✗	✓

IVR TECHNOLOGY

IVR technology can be used in most therapeutic areas but is especially suited to research in disorders that are highly dependent on short assessments of self-reported data, for example gastrointestinal studies. The only limitation with IVR is that it is best suited to the use of binary (yes/no or true/false answers) or multiple-choice questions. IVR does not easily allow for open-ended text responses or diaries that require a visual display. However, Visual Analog Scales (VAS) can be adapted to IVR. Studies have shown that there is no difference in response characteristics when using a standard VAS versus one adapted for IVR². For clinical trials that require more detailed or subjective patient diary information, a PDA device will be more suitable.

Although there are many variables that need to be factored in when assessing limitations and intrinsic value, there are some standard practices that are based on extensive experience. A typical ePRO IVR diary will consist of five–eight questions. There is no technical limit to the number of questions that can be asked via IVR. However, a practical limit due to the amount of time a patient will be comfortable on a telephone is approximately 10–12 questions, assuming a maximum of 2–3 minutes to answer all the questions. These practical limits can be adjusted based on the frequency of the assessment. For example, a 20-question assessment once a day may be excessive but a 20-question assessment once a week may be acceptable. In a situation where a diary of more than 10–12 questions is frequently and consistently administered, an interactive web-based system (IWR) is more appropriate.

ePRO is particularly advantageous versus paper-based tools in studies that require either multiple daily diary entries or different diary questions on different days. Using ePRO, and taking advantage of the automation and nimbleness of an electronic system, the patient is not burdened with the protocol, day of the week, or logic flow of the diary. The ePRO asks the correct question based on the current time, day of the week, or previous diary responses. This allows the patient to focus only on the question being asked, improving the quality of the data collected. Ultimately, this flexibility and adaptability eliminates barriers and increases effectiveness of data collection across demographics and therapeutic areas.

ePRO ADVANTAGES

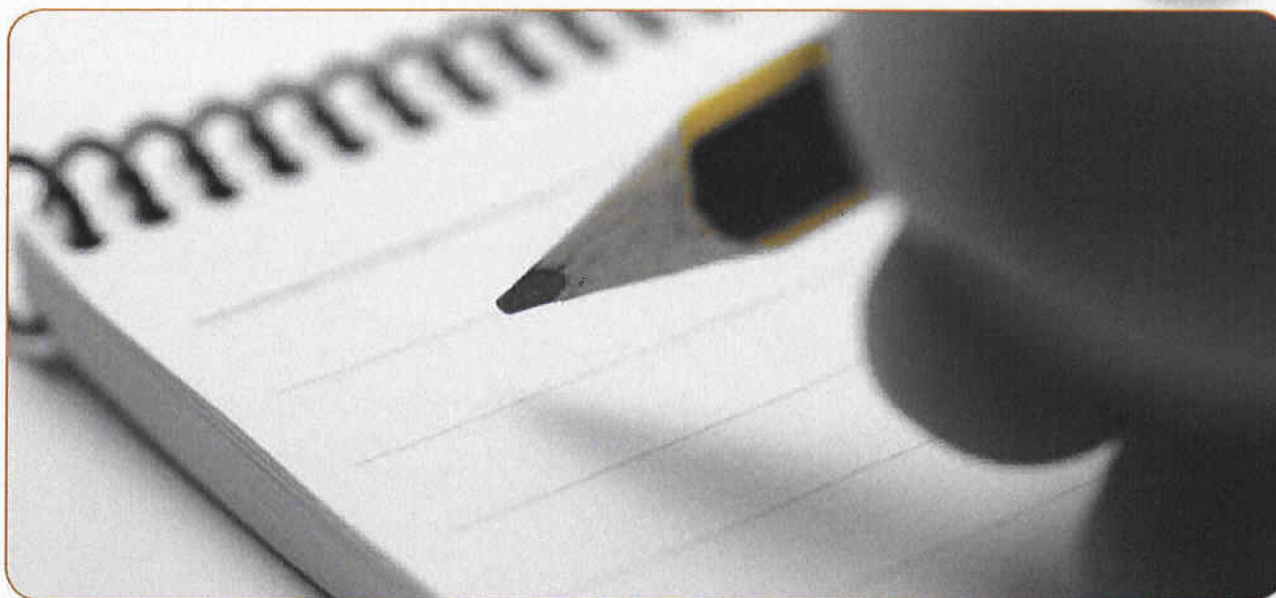
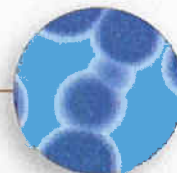
The biggest advantages of ePRO for a sponsor are the increased accuracy and quality of the recorded data compared with PRO. Because the data is collected directly from the patient, diary entries are made at the appropriate time and compliance can be monitored. The system can alert patients if they have not made a diary entry at the correct time and automatic reminders can be sent in advance of scheduled calls via e-mail or text message. Site staff and sponsors can also be alerted if a patient falls behind with compliance, enabling proactive approaches to correcting the problem and ultimately resulting in better data.

Additional advantages for the CRO, sponsor, and site staff are that quality checks are built into the system and that patient ePRO data can be accessed and diary compliance monitored in real time via a web-reporting system. This immediate access to data increases the speed and efficiency of both interim and final data analyses. In addition, because decisions on the data can be made in real time, this helps in monitoring and driving the progress of a trial and the determination of patient eligibility for trial inclusion. Sponsors can monitor the progress of a global trial remotely, utilising real-time data on enrolment and patient compliance. In addition, staff can focus on important issues such as protocol compliance, adverse-event monitoring, and safety instead of tracking down missing paper diaries and performing manual reviews.

ePRO systems can also keep site staff informed of the progress of individual patients. The majority of ePRO systems will send automatic alerts to sites notifying them when a patient misses a key diary entry or when a patient's compliance falls below a predefined level. ePRO systems give the site access to a web-based portal that allows the site to see the real-time progress of each patient. Site staff can see patient diary results as well as keep track of each patient's progress.

ePRO PROVIDER SELECTION

The central database for an ePRO system is usually held by the CRO and information can be shared with the sponsor and trial sites via a secure internet or intranet. A system is usually based on a standard platform



that can be adapted for an individual sponsor or study. For the sponsor planning to use a CRO to conduct a clinical trial involving ePRO, they should investigate multiple providers and conduct an audit to ensure that QC processes are in place. Factors to consider in CRO selection include a good track record in the use of ePRO in a wide variety of therapeutic indications, the use of assessments that are validated for ePRO, the ability to use the technology worldwide, and the availability of backup systems in case of system failures.

There are many potential pitfalls to be aware of when utilising ePRO or selecting a vendor. A key factor is that a vendor should have technically and clinically or therapeutically trained Project Managers. The skill set is a unique combination given that the skills required to manage a technical project are very different to those required to manage a clinical project. The vendor should have a well-documented System Delivery Life Cycle (SDLC) that includes the appropriate processes for requirements gathering, testing, and implementation. Since it is almost certain that changes will be required during the life of the project, a vendor should also have, as part of the SDLC, a well defined change management process for implementing mid-study changes. A final potential pitfall to be aware of is the availability of suitable telecommunications technology with toll-free access numbers, although this is becoming much less of a problem.

CONCLUSIONS

ePRO, which can be used effectively by patients in a multitude of clinical trials from Phase I to IV, has a positive impact on clinical trials and drug development, speeding up the process of bringing new drugs to the market. Perceived barriers with specific patient populations, such as elderly, non-technical users, will be irrelevant if the proper technology is applied to the ePRO assessment. Overall data quality is vastly improved as quality checks are in place during data entry at the source. Importantly, patient compliance is significantly improved through the use of time stamping and electronic reminders. Ultimately, the biggest advantage of ePRO is that sponsors and site personnel have real-time access to data that is accurate and submitted on time, enabling improved and more rapid decision making.

NOTES

Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. "Patient non-compliance with paper diaries." *Br Med J* 2002;324:1193-1194.
Paice JA, Cohen FL. "Validity of a verbally administered numeric rating scale to measure cancer pain intensity." *Cancer Nurs* 1997;20:88-93



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Kris Gustafson has been with ICON since 2000 in multiple roles and positions. In January 2007 he was promoted into his current role as Global Head of the

Interactive Technologies business unit and the Lifecycle Sciences business unit. Prior to ICON, Kris was President and co-founder of Electronic Trial Management Technologies, a technology company specialising in IVR and IWR solutions for clinical trials, which was acquired by ICON in 2000. From 1995-1999 he served as Senior Director of Information Management at Applied Logic Associates. From 1990-1995 he worked as a Mechanical Engineer in the Nuclear sector.

Kris received his Bachelor of Science degree in Mechanical Engineering from Washington State University in 1990.



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