



# ePRO – The Only Choice

**Finding a system that ensures patient safety while achieving regulatory compliance may have been a long term headache, but ePRO looks set to create a gold standard in collecting endpoint data, asserts Valdo Arnera of PHT Corporation**

Researchers around the world understand the critical importance of the patient's perspective in evaluating and assessing drug safety, efficacy and clinical outcomes. In the last decade, drug developers have collected patient reported outcome (PRO) data more frequently than ever before. An important goal in 2011 for sponsors across the industry is to collect higher quality PRO data in research trials. As such, the eClinical industry continues its educational programmes aimed at helping decision makers at drug developers, CROs and regulators to correctly evaluate the benefits and challenges regarding the safety, efficiency and financial benefits of automating PRO data collection in clinical research.

Today, 100 per cent of the top 20 and most of the top 50 biopharmaceutical companies are investing in eClinical systems and analytics, laying the foundation for automating PRO data collection. Sponsors are adopting industry-wide data standards and developing strategic outsourcing models to focus on core competency functions, including specific therapeutic area development, late phase development, marketing and sales.

## EMERGING GOLD STANDARD

Electronic patient reported outcome (ePRO) systems are among the most important eClinical technologies adopted for drug and device trials. ePRO is the capture of PRO data on a variety of modalities – handhelds, tablets, phones, smart phones, and the web. It offers researchers higher quality, less variable patient data for improved clinical data management. ePRO enables remote data monitoring via the web with real-time reports for study, site and patient data. Additionally, ePRO systems create electronic source (eSource) records which means there is no source verification required by monitors on the patient data. This eliminates the need for the time consuming and costly source document verification of paper diaries, questionnaires and clinical assessments that can easily be captured using an ePRO system. Overall, the rapid availability of current study data for online reviews allows for smaller, faster and safer clinical trials with better scientific conclusions.

## HIGHER QUALITY PATIENT DATA

The international clinical research community affirms the improvements in data quality provided by ePRO systems. Patient diary data collected electronically is time-stamped,

logical, meeting attributable, legible, contemporaneous, original and accurate (ALCOA) standards and reducing site administration, and provides patients with instant validation as they complete their daily questionnaires. Contrary to paper diaries, ePRO data collection ensures complete patient responses and prevents extraneous data. Patients must respond to each diary question in order to sign an affidavit required to complete the report. The structured nature of the electronic format prevents subjects from adding additional information to question responses. ePRO questionnaires branch logically based on subject response – for example, only subjects who report taking concomitant medications will see a question asking what quantities they consumed; subjects who did not take concomitant medications will not see the quantity question. ePRO measures automatically compute protocol-specific calculations, eliminating arithmetic errors. Calculations are often used to determine branching (for example, in the SCID), randomisation eligibility and symptom exacerbations (for example, in the ACQ).

The electronic format obviates manual double data entry by site personnel. The data standards that ePRO enforces also lessen the number of data queries, thus reducing cycle times and trial times. Final data analysis sets can be provided within days after the conclusion of a trial.

CRAs can use web-based clinical data management portals to perform remote monitoring of the ePRO trial, lowering trial management costs because CRAs spend less time travelling to sites just to go through the labour intensive task of source verifying PRO endpoints from patient diaries. Real-time patient data access is permission-based so only the appropriate clinical trial personnel can see patient data – thus CRAs can

see data for all the sites they monitor, whereas site personnel can only see their own patients' data. ePRO does not eliminate the need for accurate data review and monitoring, but it does enable trial sponsors to focus on higher value tasks rather than tedious source verification.

### **SPEEDIER, SMALLER, ACCURATE CLINICAL TRIALS**

ePRO technologies help to keep patient data at a much higher quality throughout the trial, across patient populations, and across the spectrum from Phase I to post-market. With advanced innovations, ePRO is an economically sound way to collect PROs efficiently for all types of trials. Clinical data management using ePRO systems has been shown consistently to reduce the variance of data collected on paper versus an eDiary. High quality ePRO data provide tangible benefits by reducing the number of subjects needed to prove efficacy. This means that sponsors and CROs can run eClinical trials with fewer patients. As an example, a pharmaceutical company estimated that they could have saved \$340,000 on just one trial when using ePRO versus paper to collect PRO data. Studies have shown that the data variance reduction in ePRO versus paper is evident in trials across a variety of indications, including asthma, urinary incontinence, chronic constipation and insomnia.

### **BETTER, FASTER CLINICAL DATA MANAGEMENT**

ePRO allows sponsors to take advantage of the full benefits of running eClinical trials. Due to the high quality of ePRO data, there is no need for intensive cleanup by data managers, which can delay database lock for up to four months in paper diary trials. ePRO trials typically reach database lock within one week of trial completion, saving time, money and opportunity costs. ePRO can seamlessly integrate into EDC systems; sponsors using EDC systems and ePRO eliminate a rate limiting step in the trial process.

The use of ePRO results in faster decisions for Phase II programmes and faster analysis and NDA preparation for Phase III trials. In a recent trial, regulatory officials gave favourable preliminary advice for a drug to treat chronic constipation for women, but required more data about men. The company planned another study using a sample size of 1,026 male subjects to prove efficacy based on traditional paper variance statistics. Subsequently, they elected to use an eDiary instead of paper. The regulatory agencies later decided to approve the drug for men without further data. The drug company stopped the trial, but allowed the 322 already enrolled subjects to complete treatment. To the amazement of the clinical team, study power was reached with 69 per cent fewer subjects – representing less than one third the planned sample size (1).

### **COST OF SAFETY**

Real-time data access and clinical data management can greatly enhance patient safety. Study coordinators and CRAs can monitor symptom data on a daily basis, and the ePRO system

can use an advanced alert system to message both the sites and subjects if symptom thresholds are reached. By keeping better track of health status changes, sites can intervene quickly and change patients' dosages or remove subjects from a study if their condition is worsening. An unpleasant truth is that the side effects of oncology drugs can be more painful than the disease itself. In oncology trials, sponsors can use ePRO modalities to ask simple quality of life questions that identify patients who need immediate intervention. This quality of life information can have enormous value for care givers to learn about and respond to patient side effects between site visits and develop palliative care.

In drug trials for depression, sponsors can build alerts into an ePRO system to ask patients if they are having suicidal thoughts or feelings. With ePRO, researchers can easily trend patients' symptoms and sites can take action when a patient is feeling suicidal or doesn't complete an eDiary. These examples illustrate the importance of using ePRO systems to collect endpoint data and ensure patient quality of life and safety.

Collecting valid, reliable patient experiences and perceptions with ePRO gives researchers many more opportunities to share valuable information that can improve patients' outcomes across a wide patient population. The old way of thinking was that clinical trials could use ePRO modalities only if they had primary endpoint data. Sponsors understood that regulatory bodies want to see PRO data as a part of approval applications, but had the perception that using ePRO for other secondary or exploratory endpoints was too expensive and not important for the trial. Yet, the ePRO benefits of higher quality data and improved patient safety are true across all endpoints and therapeutic areas.

### **THE WEB – A VITAL PRO MODALITY**

The web is an important modality for collecting PROs, particularly for late-stage trials. With a web-based ePRO system, patients complete their questionnaires at any computer terminal and report precise quality of life information. The web ePRO modality offers high-quality, lower cost of research.

Sponsors don't pay for patients' laptops or internet access, so sites get immediate information on how patient quality of life is affected. Additionally, new web-based reporting tools can enable researchers to delve deeply and in real-time into patient population reactions to new drugs. Trials in the post approval arena – including comparative effectiveness programmes, studies aimed at understanding real world outcomes and long term safety – can immediately benefit from using web-based ePRO systems to collect and analyse high quality data from patients.

### **PAPER: INACCURATE & EXPENSIVE**

Cost is a major driver during the consideration of a PRO modality. Often, sponsors compare the surface costs of paper PRO to the total costs of ePRO. Pricing models are typically developed based on experience with paper trials. These trial budgets include 'built in' or assumed trial costs which ePRO

solutions eliminate. In most cases, thorough analysis of all the costs (and additional labour) relating to paper diaries shows that ePRO solutions are more economically viable. ePRO systems diminish or nullify several key costs associated with paper:

- ◆ Source verification on paper diaries and questionnaires
- ◆ Queries on diary and/or questionnaire data
- ◆ Double data entry
- ◆ Data management and extra sample sizing costs to deal with missing and illogical data
- ◆ Storing and archiving paper data
- ◆ Site and CRA time to review handwritten diaries or perform complex calculations
- ◆ Printing, reprinting and shipping all paper diaries
- ◆ Data management time spent on trial cleanup after LPO
- ◆ Higher sample sizes to accommodate for highly variable and or incomplete data

## REGULATORY VIEWPOINT

In a July 2005 reflection paper, the EMA discussed the consequence that health-related quality of life (HRQL) might have in drug development. The paper stated, “The basis for the approval of a new medicinal product is its efficacy and safety in the given condition. Therefore, in the drug evaluation process, the first step for the regulators is usually to assess efficacy and safety of a given drug by using the established efficacy endpoints...” (2). The PRO final guidance, issued by the FDA in December 2009, also advances the steady movement toward eDiaries as a replacement for paper diaries in clinical trials (3). The document provides constructive support for collecting PRO and ePRO data with scientific rigour. It establishes that FDA reviewers will evaluate protocols with respect to the targeted labelling claims, an endpoint model, a conceptual framework of PRO instruments and the content validity of PRO items.

The guidance shows that the FDA understands the pivotal role of PRO and ePRO measures in establishing clinical benefit, and is aimed at ensuring sponsors collect PRO data using good science. The guidance would indicate the value of ePRO instruments in statements like this: “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” (3). While ePRO systems can easily capture valid proof of data entry times, collecting such data is quite challenging with paper PRO measures.

## THE BOTTOM LINE – AN APPROVED DRUG

The ultimate return on investment is a safe and efficacious new treatment or therapy developed rapidly, and before the competition, that exceeds the current standard of care. ePRO systems enable better scientific conclusions because regulatory authorities recognise the validity and trustworthiness of ePRO data, which may prove to be the difference between an approval and a request for more data. ePRO enables eClinical trials that are less expensive, more accurate, and safer than paper trials. It

## About the author



**Valdo Arnera** is General Manager, Europe, at PHT Corporation, the leading provider of PRO and ePRO solutions worldwide. Valdo has more than 22 years of experience in the pharmaceutical industry in France and Africa. He began his career in the industry as a clinical pharmacologist in a Ciba-Geigy company, where he was responsible for Phases I and IIA. He founded the first European central clinical laboratory dedicated to clinical trials, SciCor (now Covance Central Laboratory) in 1992. Very active within the DIA, Valdo has been the chairperson and the track chair of several DIA conferences and is a member of the DIA Advisory Council for Europe, as well as the Annual Meeting Program Committee. His numerous industry recognitions include a 2009 Lifetime Achievement Award and inclusion on the list of the most inspirational people in the pharmaceutical industry.

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offers unique opportunities for improving clinical data management, including:

- ◆ ALCOA patient data that is time stamped and complete through the use of alarms, branching logic and edit checks
- ◆ Real-time access to diary data between visits for enhanced safety and compliance monitoring
- ◆ Reduced data variance for improved quality of study results and reduced number of patients to show efficacy
- ◆ Compatibility with adaptive trial designs
- ◆ Reduced standard deviation for more conclusive planned interim analyses
- ◆ Libraries of experience and metrics with data including compliance and data variance or standard deviations for specific indications

The use of ePRO systems to collect the best patient data possible enables smaller trials, ensures patient safety, and achieves regulatory recommendations for collecting clinical trial data. The accurate, immediate, easily shared information made possible by ePRO is creating a gold standard in collecting patient primary and secondary endpoint data.

## References

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