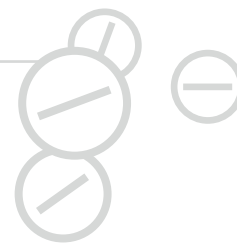




# Why Go ePRO?

By Phil Lee, President and Chief Executive Officer of PHT Corporation



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The improvement of data quality and the reduction of data variance are principal aims for clinical trials organisers around the world. With this in mind, Phil Lee of PHT Corporation explores the purported advantages of ePRO technology



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The age of paper in clinical research is ending. Electronic patient diaries are changing the nature and quality of clinical research relying on patient-reported outcomes. The following article details drivers for the increasing adoption of ePRO solutions, including improved data quality, real-time access to study data, proven return on investment, site tools for efficient trial management and a more engaging subject experience.

## PROBLEMS WITH PAPER

More than 20 years of research and experience have demonstrated the problems with self-reported subject data collected by paper diary methods. Recording responses on paper places the burden of properly completing the diaries on study subjects. Using paper, patients have to remember when it is the right time to fill in their answers; they are required to understand and follow any branching logic correctly, and to mark all visual scales and diagrams correctly; they are also tempted to write ancillary comments on the paper about their experiences, such as adverse events.

Even in the rare cases where a subject perfectly fills out a complete, logical and legible paper diary, there remains no way to verify the date/time that the entry was made. Numerous studies have objectively measured patients' completion of a task per the terms of the protocol (for example, completing a diary on time, or using a glucose monitor) as compared to the unverified completion as reported by the patient. Such studies show that significant discrepancies between actual and purported compliance with instructions for entry of data (see Table 1) commonly occur. This indicates that sponsors and regulatory authorities cannot depend on patients to honestly and accurately comply with the protocol.

These results give credence to the 'parking lot syndrome', which refers to the practice of subjects retrospectively completing batches of diaries prior to a site visit. One often-

cited study by Stone *et al* further revealed that subjects invent data by forward-filling their diaries. Findings such as these concern regulatory authorities who do not wish to base critical drug approval and labeling decisions on unreliable patient data.

## WHAT IS ePRO?

Electronic patient reported outcome (ePRO) solutions solve many of the problems associated with conventional paper diaries. The most common application of ePRO is implementing protocol-specific patient diaries and quality-of-life surveys on electronic handheld devices for use by subjects at home or at the investigator site. ePRO systems collect high quality, time-stamped data, thus providing researchers with more trustworthy insights into the experiences of subjects in the trial.

Handheld electronic patient diaries are mobile, convenient, private and easy to use. They support visual measures and scales, and the screens are usually touch-sensitive. Programmed controls, timestamps, alarms and alerts can be leveraged to guarantee any received subject responses are timely, complete and logical.

Most providers offer hosted ePRO systems to trial sponsors. These systems generally deliver a turnkey solution from diary design to study archiving. Products and services include the procurement and distribution of hardware devices (often PDAs), configuration of the diary, helpdesk support throughout the trial, and real-time reporting on patient compliance and enrolment.

**Table 1: Observations of Fake Data in the Literature – Observed versus Purported Measurements**

	Observed (Objective) Compliance	Purported (Written in Diary) Compliance	Discrepancies Between the Two	Number of Subjects
Stone A <i>et al</i> , <i>BMJ</i> : 324: pp1,193-1,194, 2002	11%	90%	79%	80
Jonasson G <i>et al</i> , <i>Eur Respir J</i> , 14, 1999	77%	93%	16%	163
Milgrom H <i>et al</i> , <i>J Allergy &amp; Immunol</i> , 98, 1996	58%	95%	37%	24
Spector S <i>et al</i> , <i>J Allergy Clin Immunol</i> , 7, 1986	47%	90%	43%	19
Straka RJ <i>et al</i> , <i>Pharmacotherapy</i> , 17, 1997	55%	71%	16%	68
Verschelden P <i>et al</i> , <i>Eur Respir J</i> , 9, 1996	N/A	N/A	22%	20
Chmelik F <i>et al</i> , <i>Annals of Allergy</i> , 73, 1994	N/A	N/A	58%	20
Simmons M <i>et al</i> , <i>Chest</i> , 118, 2, 2000	N/A	N/A	30%	101
Mazze R <i>et al</i> , <i>The Amer J Medicine</i> , 77, 1984	N/A	N/A	74%	19
<b>Averages</b>	<b>59 ± 13%</b>	<b>87 ± 11%</b>	<b>42 ± 21%</b>	<b>57</b>

## ePRO MARKET ADOPTION

ePRO solutions have experienced tremendous growth in adoption, especially over the past two years, as more study sponsors have realised the improvements in data quality and reliability a properly designed eDiary system can provide. By now, virtually all of the top 20 global biopharmaceutical companies have used ePRO technology and are investing in eClinical initiatives to decrease clinical development timelines and improve data quality.

In 2005, the Tufts Center for the Study of Drug Development issued a special report on electronic technology in the clinical trial industry stating that “the market for electronic data capture (EDC) technologies and electronic patient reported outcomes (ePRO) technology is expected to grow faster than its historical 23 per cent annual rate”. Recent research conducted by CDISC shows that 20 per cent of clinical trials collecting PRO data initiated in 2004 used ePRO, and that 80 per cent of sites have dedicated personnel trained on ePRO technology.

While ePRO technology has clearly entered the early majority phase of adoption, there is certainly room for continued growth, especially as technologies improve and sponsors use these enhanced capabilities to enable exciting new types of clinical research.

## THE ROI OF ePRO

Driving this remarkable and continually increasing growth in adoption amongst sponsors is the proliferation of proven success stories, as well as a more thorough understanding of the quantifiable benefits delivered by ePRO systems. First and foremost, ePRO improves data quality by providing timely data collected at the point of experience, which reduces data variance

and enhances the study’s ability to show efficacy. Since all subject responses are complete, legible and logical, study sponsors receive significantly more evaluable data than they would have on paper. By reducing data variance and providing more evaluable data, sponsors can decrease sample sizes in non-pivotal trials and draw better and more compelling conclusions in Phase III studies.

## REDUCED DATA VARIANCE AND STANDARD DEVIATION

To understand how these benefits manifest themselves in clinical research, consider a Merck Research Laboratories insomnia study – the first randomised study to compare the relative ability of eDiaries and paper diaries to show efficacy (1). In the study, subjects received an approved treatment for insomnia, and were randomised into two arms: one using paper diaries and one using an eDiary system.

The study results were presented at DIA 2004 and at the International Society for Quality of Life Research (ISOQOL) 2004 Annual Meeting. Key findings demonstrated that the eDiary provided data with a 35 per cent lower standard deviation than paper. While the mean values of the primary endpoint (change in minutes of sleep time) were statistically similar, the eDiary-collected data was much tighter around the mean and exhibited a more Gaussian distribution. In addition, the paper-collected data was clustered around 30-, 60- and 90-minute intervals, suggesting subjects estimated times rather than reporting them exactly.

Merck calculated that this reduction in variance would permit a sample size reduction of 56 per cent to achieve the same study power in similar trials. In practical terms, Merck calculated that they would require 101 subjects to achieve 90 per cent study power using paper diaries, as compared to only 44 subjects using an eDiary. Assuming a conservative total per-patient cost of \$6,000, this smaller sample size would suggest a potential cost saving of \$340,000. eSource solutions such as ePRO eliminate the need for (and cost of) double-data entry, queries, field-by-field source document verification and manual scoring at sites, thus reducing the time to diary database lock.

## BENEFITS OF REAL-TIME DATA ACCESS TO SITES AND SPONSORS

ePRO systems provide additional benefits beyond data quality, such as real-time access to study data. This enables sponsors to monitor the progress of their study across multiple sites remotely, ensuring enrolment and timeline goals are on track. Monitors can spend more time during site visits focussing on protocol compliance and the health and safety of patients rather than pouring over reams of paper diaries.



Figure 1: On-device Eligibility Criteria Calculations during Randomisation Screening



Figure 2: Validated Electronic Visual Analog Scales (eVAS) with Automatic Scoring



Figure 3: Intuitive Graphical User Interface with a Touchpad Screen

ePRO systems also enable site co-ordinators to stay informed about how their patients are doing in the trial. Sites do not have to wait until a subject's next visit to make important decisions regarding the subject's health, such as changing medication or reducing dosages. Further, sites are able to be more responsive in managing subject enrolment and compliance. Automatic scoring of eligibility criteria saves sites time and energy during the screening phase (see Figure 1), while compliance reports help co-ordinators identify non-compliant subjects in real time rather than waiting weeks or more until the patient's next site visit. This enables co-ordinators to call the patient before noncompliance becomes an issue for the trial.

Using paper diaries, co-ordinators need to be cautious about insisting that subjects complete every diary. Such encouragement may drive subjects to invent data or to complete diaries retrospectively or prospectively. eDiaries can prevent such practices, thereby empowering sites to encourage full compliance as strongly as they feel is appropriate.

### SUBJECT EXPERIENCES

Sites and sponsors aren't the only ones who prefer ePRO to paper, as subjects benefit from using eDiaries, too. On rating questionnaires and interviews, study subjects have consistently expressed a high degree of motivation to complete their eDiaries accurately and on time. They feel more connected to the site than

when using paper because their data is accessible to their clinicians. They are pleased to be contributing to the study, and they often appreciate that someone is listening to their symptoms and experiences on a daily basis. Most eDiaries use audible alarms to alert subjects when a response is due, and are programmed with front-end edit checks and other controls which make filling out the diary the simplest part of the subject's day.

Patients also appreciate the privacy inherent with the personal handheld devices, which may actually promote more honest subject responses. In one female sexual dysfunction study, subjects reported 52 per cent more sexual encounters on the eDiary than they did on paper diaries. One theory for this difference is subjects were embarrassed to be completely forthcoming out of fear that their partner or children might find and read the paper diary.

Handheld-based eDiaries are mobile, graphical and user-friendly, which leads to high compliance from global patient populations of all ages and education levels. Sponsors often have questions about whether certain subject groups, such as the elderly, will be willing and able to use eDiary technology in a trial. Studies demonstrate that these concerns are largely unfounded – and that geriatric patients are, in fact, among the most compliant of subject groups. Figure 4 depicts compliance data from a low back pain study implemented by a PHT client. The results show that subjects aged 70 or higher had the highest average compliance in the trial. Although elderly patients are not

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generally tech-savvy, one theory on their high compliance is this patient population may have more time and dedication to follow the study exactly.

To make participating in an ePRO trial even easier for subjects, trial sponsors may take advantage of usability enhancements such as larger fonts and targets, devices with high resolution or bigger screens, and clip-on screen magnifiers. For example, in a trial investigating the gastrointestinal symptoms in autistic children, PediaMed worked with an eDiary provider to incorporate a Caregiver Module on the eDiary. This feature allowed parents to answer questions on their child's behalf, which in turn helped PediaMed better understand how the patients are reacting to the study treatment.

All together, ePRO solutions are rapidly transforming the quality of self-reported patient data in clinical research. Just as the impressive growth of ePRO market adoption is expected to continue, so will sponsors continue to explore the many untapped advantages and innovations ePRO offers over antiquated paper methods.

### CURRENT TRENDS IN ePRO SOLUTIONS

As sponsors and sites become more experienced with ePRO, they will begin to envision additional applications of the technology. Some recent trends seen in the industry include using ePRO to:

#### Ask New Research Questions Not Possible on Paper

Using measurement devices wirelessly integrated with an eDiary, sponsors can measure any number of objective physiological data streams, such as peak expiratory flow (PEF) scores, blood sugar level and activity level. This ensures subjects actually use the measurement devices and eliminates transcription error since the data is automatically transferred from the device to the eDiary. Combining objective and subjective measures can be valuable. Consider a study of efficacy for pain treatment following hip replacement. If a subject were to report the same level of pain before and after the surgery, researchers might mistakenly conclude that the therapy was ineffective. However, an activity meter might reveal that the subject went from barely walking to playing golf without increasing pain.

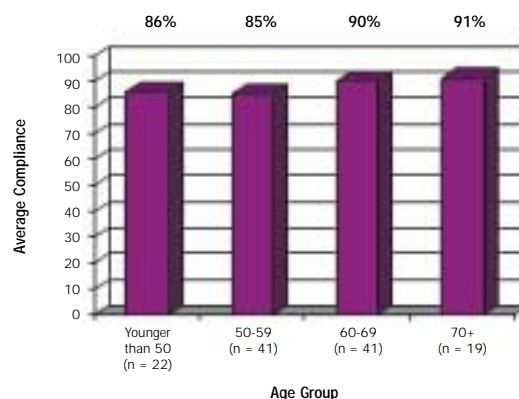
#### Make the Most of Adaptive Sample Sizing

This involves using real-time access to data and pre-scheduled interim analysis to adjust estimates on how many patients will be needed to prove efficacy, based on the actual variance of data received. This type of trial design makes use of established statistical procedures for interim analysis, and can be especially efficient when performed on up-to-the-minute results (2).

#### Implement Global Research Programmes

Sponsors are increasingly using ePRO in large-scale clinical programmes involving dozens of trials around the world, taking advantage of the multi-language and real-time update capabilities ePRO systems provide.

Figure 4: Average Compliance by Age Group (Low Back Pain Study, Subjects Aged 32-93)



### CONCLUSION

ePRO solutions improve data quality and reduce data variance for clinical trials around the world. Subjects enjoy using eDiaries because they are mobile, private and convenient. eDiaries alert subjects when a response is due, and patients of all ages find them intuitive and easy to use. Using the eDiaries, subjects feel more connected to the site (and the trial by extension), and are motivated to provide accurate data. All responses are complete, legible and logical. The time-stamped eSource data has lower variance than data collected on paper, which leads to smaller sample sizes and a better capacity to show efficacy.

Sites and sponsors further benefit from the advantages of real-time data access, which enables more efficient study management and reduces trial timelines. Site co-ordinators are more informed about the condition and experiences of the patients in their care, and are empowered to encourage compliance diligently. Sponsors are gaining more experience with ePRO and a better understanding of what is (and will be) possible using the technology. Exciting new trends include new data streams and research possibilities, adaptive sample sizing, implementation across global programmes, and more thorough data integration into other eClinical systems. ♦

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