



The Power of ePRO

In the past few years, drug developers and regulatory agencies have become increasingly receptive to the use of electronic patient-reported outcomes (ePRO) devices in clinical trials. The vast majority of patient-reported outcomes are still recorded in paper-based diaries, but a broad range of appropriate, easy-to-use electronic technologies promise better patient compliance, increased data quality, and, potentially, fewer and/or shorter clinical trials.

Although all ePRO devices offer significant advantages compared with paper-based diaries, there is tremendous variety among these technologies. These include: interactive voice recognition (IVR) solutions; PDA- or wireless PDA-based solutions; Web browser-based solutions; Smartphone-based solutions; mobile phone-based solutions with short message service; and digital pen solutions. The

most common of these are PDA and IVR systems.

"We have used the three main ePRO technologies — handheld diaries, IVRS diaries, and site-based questionnaires — in every therapy area in which we are developing products," says David Conroy, clinical project manager, ePRO global business lead, at AstraZeneca Pharmaceuticals. "The drive to use ePRO at AstraZeneca comes from the technology's ability to facilitate the streamlined delivery of high-quality patient reported data. We continue to use these tools because of the strong benefits profile that they possess."

Handheld ePRO devices work on personal digital assistant (PDA) platforms. The interface presents to patients only the questions they need to answer in the order they ought to answer them. Depending on the study protocol, the devices might include diagrams on which patients would indicate where they experienced pain, for example.

To promote compliance, handhelds generally include alarms that remind patients to take their medications, complete diary entries, and submit the data to the investigators. In many cases, submitting data is a one-click process.

"Patients find our devices easy and convenient; they can stick them in their pockets," says Pamela McNamara, CEO of CRF Inc.

Some handheld ePRO vendors offer systems that integrate objective data from electronic measurement devices — such as peak flow meters and glucose meters — with reliable PDA-based diaries. Patients are unable to enter certain data into the e-diary unless they use the measurement device according to the terms of the protocol.

IVR systems, unlike paper diaries and handheld e-diaries, do not require patients to carry anything; the only hardware required is the patient's telephone. Patients report outcomes by dialing a toll-free number at predetermined times and encountering an applica-

From handheld **PDA devices** to **phone-based IVRs** to **digital pens**,



EPRO DEVICES HAVE A HUGE EFFECT ON TRIAL COSTS.

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● **DR. STEPHEN RAYMOND**

tion that delivers the diary questions. They enter responses using the telephone keypad, and their answers then go directly into the vendor's central database. Some systems allow patients to record messages.

"IVR systems help patients report their data on time and more accurately," says Keith Wenzel, ePRO product director at ClinPhone Inc. "IVR systems permit a patient to listen to his or her personally recorded health status, including voice inflections. This option helps orient the patient as to how he or she was feeling at the beginning of the trial, so he or she can better rate himself or herself at a later date, which has demonstrated a 16% difference in effect size."

Like handhelds, IVR systems can offer built-in reminders to promote patient compliance. Generally, at the end of each assessment phone call, patients are reminded of their next scheduled call. Automatic reminders can be sent in advance of scheduled calls via e-mail or text



In the early days of ePRO adoption, there were certain types of studies that the sponsors believed would be easier for patients. **TODAY, WE ARE COVERING VIRTUALLY ALL THERAPEUTIC AREAS WITH OUR STUDIES, INCLUDING SOME VERY COMPLEX ONES SUCH AS DIABETES AND NEUROLOGICAL DISEASE STUDIES.**

● **PAMELA MCNAMARA**

message to their cell phones, and, if necessary, the site may make a reminder phone call.

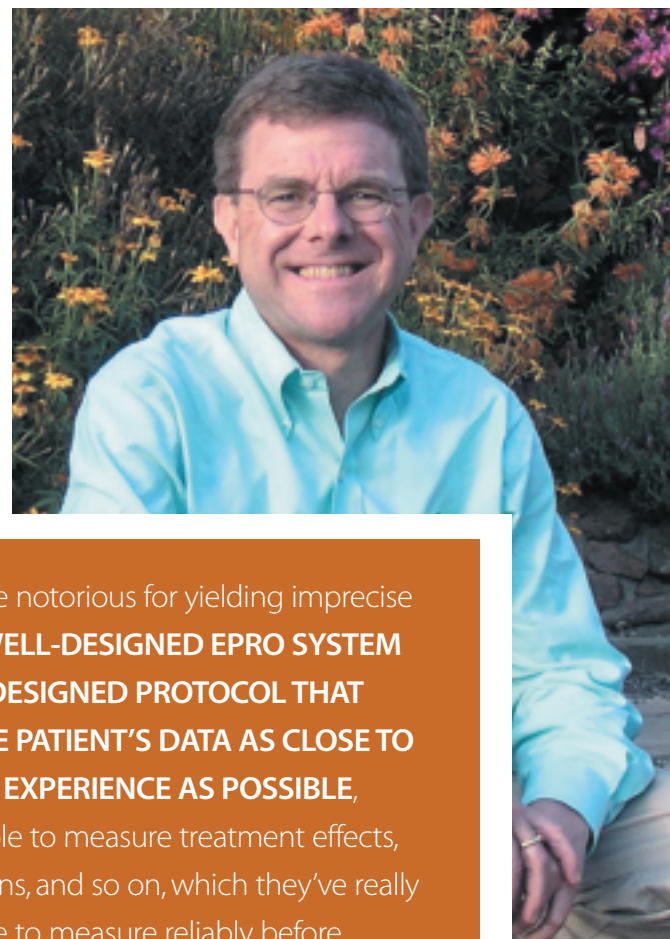
Like other ePRO systems, IVR systems routinely achieve compliance rates in excess of 90%, according to Mr. Wenzel.

"The most interesting aspect of ePRO is that it is FDA-recognized as a superior method compared with paper," says Glenn de Vries, cofounder and chief technology officer of Medi-data Solutions Worldwide. "The ePRO industry is beholden to device manufacturers and not software. In the next 12 months to 24 months, ePRO will become easier through e-mail-based questionnaires."

MEETING SPECIAL NEEDS

ePRO adoption was initially slow and limited to disorders that are highly dependent upon self-reported data, such as chronic pain or gastrointestinal problems. But experts agree that ePRO systems increasingly are being employed across a wide range of areas.

"There are several therapeutic categories that are dependent on self-reported data, for example, 68% of gas-



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● **DOUG ENGFER**

the **power of ePRO is its ability to support better science.**



There aren't any differences between IVR and handheld devices in terms of compliance. **IVR IS MORE COST-EFFECTIVE AND EQUALLY ADEPT, IF NOT MORE SOPHISTICATED, THAN HANDHELD SOLUTIONS.**

● **KEITH WENZEL**

triointestinal studies today use diaries, which is far more than average across therapeutic categories," says Doug Engfer, CEO of invivodata Inc. "Other areas that are reliant upon diary use include respiratory, pain, CNS, mood disorders, sleep, and endocrine disorders, such as diabetes."

In addition, ePRO devices have proven valuable across a range of patient populations. Devices can be configured to address the needs of special populations, such as elderly or terminally ill patients. E-diaries can be customized to display larger and bolder fonts, and buttons can be made bigger so that patients who might have trouble holding the stylus are able to touch the screen with their fingers without making an error.

CRE, for instance, reports compliance rates of more than 95% in trials with elderly/terminally ill patients.

"People are accustomed to using mobile devices," Ms. McNamara says. "We leverage that mindset with functionality that keeps the device simple and intuitive."

"Paper diaries are notorious for yielding imprecise data because of forward filling, back filling, and illegible data," Mr. Engfer says. "With a well-designed ePRO system and a well-designed protocol that captures the patient's data as close to the point of experience as possible, sponsors are able to measure treatment effects, timings, durations, and so on, which they've really never been able to measure reliably before."

One of the primary concerns with paper diaries is what experts call the "parking lot factor," the tendency of trial participants to forget to fill in their diaries until they are sitting in their cars outside of the investigative site. Patients then hastily record responses from memory, and those data are often compromised and unreliable.

Electronic diaries, on the other hand, prevent this type of faked compliance by incorporating alarms and reminders and by not accepting information outside of the windows of opportunity set by the protocol. Also, most ePRO systems collect patient data on an ongoing basis, allowing investigators to monitor patient compliance in real time.

According to Mr. Engfer, this function enables ePRO systems to serve as patient-management systems as well.

"By monitoring, measuring, and managing the patients' behavior in the study and their compliance with the protocol, these systems provide sponsors with a clear idea of whether the data can be evaluated," he explains. "As a result, studies are better managed."

Unlike paper diaries, ePRO tools generally include built-in, automatic audit trails with time and date stamps. According to Ms. McNamara, this feature can be particularly important in oncology studies with terminally ill patients, where researchers are interested in when data are recorded relative to when a patient has received treatment. In fact, she says, there recently have been situations in which the FDA would not accept paper data because the results lacked this level of specificity.

Additionally, data in paper diaries can be compromised by illegibility, incompleteness, and unanswered questions. Electronic diaries are expressly designed to prevent these types of errors.

"Because the data are, in a sense, all corrected automatically and forced to be legible, the number of fields that have answers is essentially equal to the number of fields that can be evaluated," says Stephen Raymond, Ph.D., chief scientific officer and quality officer at PHT Corp. "This might increase by 50% the total

FEATURES OF EPRO TOOLS

	DESKTOP PC	IVRS	HANDHELD DEVICES
Mobile	●	●	●
User-friendly	●	●	●
Documents 'actual' time of entries, verifying compliance	●	●	●
Simple assessments	●	●	●
Complex assessments, with branching	●	●	●
Active prompting (smart logic prompting)	●	●*	●
Systematically provides feedback to sites	●	●	●
Provides reporting tools for sponsor	●	●	●
Enforces 'within' range for sponsor	●	●	●
Prevents incomplete assessments	●	●	●
Prevents patients from reviewing previous entries	●	●	●
Manages 'timing' of entry of data (prevents forward filling)	●	●	●
Graphical interface	●		●
Multiple data entry formats (for example VAS, Checkbox, and so on)	●		●
Allows for dense sampling	●		●

Note: * Limited to reminders at the end of a call unless a patient-dedicated mobile phone is employed for receipt of incoming calls.
Source: etrials Worldwide Inc., Morrisville, N.C. For more information, visit etrials.com.

amount of evaluable data in comparison with paper. As a consequence of receiving near-perfect data, researchers get a lot more data that they can use.”

THE BOTTOM LINE

At \$300 to \$400 per patient for hardware alone, ePRO solutions can carry a hefty price tag for a trial sponsor. But the experts agree that the reliability of ePRO data could ultimately reduce the costs of drug development.

“I think ePRO devices can have a huge effect on trial costs,” Dr. Raymond says. “A trial has a fundamental value, which is that it assists the drug company and the regulators in making an appropriate clinical decision. This decision is based on science; so, in essence, the more science per trial, the greater the value of the trial.”

Pharma companies face about \$1.3 million in lost sales each day that a drug is delayed in getting to market. One way that ePRO can reduce the cost of trials is by saving time at the back end surrounding data management.

“A paper study can take anywhere from six to 10 weeks from the end of the trial to database lock,” Ms. McNamara explains. “We are leveraging five days from the time the last patient signs off to database lock, which is a huge time savings. This is in addition to, of course, the overall benefits of not having to manage all of the manual corrections of data errors.”

“The pharmaceutical industry has cadres of data-entry people, and the study team, includ-

The most interesting aspect of ePRO is that **IT IS FDA-RECOGNIZED AS A SUPERIOR METHOD COMPARED WITH PAPER.**

● **GLENN DE VRIES**

ing data monitors, are spending substantial amounts of time entering, reviewing, and reconciling data queries to paper-based data,” Mr. Wenzel says. “ePRO eliminates the need for data-entry personnel, and data-cleaning costs are negligible, which is a substantial savings.”

Additionally, the use of ePRO can allow sponsors to run smaller or fewer studies while obtaining the same results.

According to Mr. Engfer, Sepracor, one of invivodata’s pharmaceutical clients, determined that it would be able to run a replication study with half the number of subjects than originally planned.

“That has a massive impact on both the budget and the timeline for that follow-on study,” he adds. “The company calculated that it would save \$10 million based on the relatively modest investment made in e-diaries.”

Mr. Conroy, however, suggests companies should weigh the benefits and drawbacks of paper diaries and ePRO systems.



“They should carefully weigh cost versus paper, technology limitations in different regions of the world, and the limited formal regulatory guidance that exists for the ePRO tools,” he says. ♦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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