



ePRO: The Site Perspective

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Featuring quotes and commentary from experienced **principal investigators** and **study coordinators** who have used our leading ePRO systems in over **270 clinical research studies** around the world.

Investigative sites are the cornerstone of

clinical research. When implementing eClinical products for site staff to use to improve data quality and processes, it is imperative that technology providers and study sponsors carefully consider the site experience. Improvements in systems for conducting and managing research are in jeopardy if these products make life harder for sites, rather than easier.

PHT regularly interviews and solicits feedback from principal investigators and study coordinators who have experience using our **LogPad®** and **StudyPad® Systems** in more than **270 clinical trials** around the world. Their collective insight provides firsthand knowledge into the benefits and challenges of using ePRO. Here's some of what we've learned so far.

About Sites

Sites that carry out clinical studies vary greatly in size, therapeutic specialty and number of enrolled subjects, but they usually share at least one common attribute: their staff values the time they spend with patients. Therefore, while some sites may be initially resistant to change, they appreciate using technology that lets them know how patients are feeling. Although sites often use multiple eClinical systems in each study, they are not particularly interested in technology itself. Proven ePRO benefits, however, such as the enhanced connection that the **LogPad** makes with subjects at home, motivates coordinators to support the switch from paper.

What Do Sites Like about ePRO?

Sites have been using paper diaries for years – so the switch from a familiar method to an electronic system presents both exciting benefits and new challenges. As ePRO becomes mainstream, in part fueled by the FDA's PRO Draft Guidance, more sites have become comfortable with the technology and have begun to realize the value advanced features provide. The following section details what sites report as the aspects they like best about using ePRO.

• Real-time access to current patient data

This is the most common benefit mentioned by sites. Real-time data access enables study coordinators to do three things that cannot be accomplished using paper diaries:

- 1.) **Review symptom severity data** and **respond** to email or web alerts when there is a need for intervention. This Improves safety monitoring and enhances the valued site-subject relationship.
- 2.) **Improve compliance.** When a subject is not completing required assessments, site staff can quickly detect non-compliance and address it by making a phone call or sending a message directly to the subject's **LogPad**.
- 3.) **Manage eligibility** by reviewing automatic calculations of enrollment and randomization criteria. (Sponsors use data summaries to track and compare enrollment across sites, which sites actually like because it showcases their recruiting efforts and results for the sponsor.)

"I think (PHT's **LogPad**) is a great tool to capture time-sensitive data. In daily symptom diaries, I think recall bias is a real problem and that it's difficult to assess actual compliance rates. The **LogPad** has worked out great – the patients have been very happy with it, and from our perspective it improves the accuracy of the data."

Nadia D. Hansel, MD, MPH, Instructor, Division of Pulmonary and Critical Care Medicine, John Hopkins University (Baltimore, MD)

• Confidence in the data received

Sites experience firsthand the problems typically associated with paper diaries (e.g. batch data entry, faked data, recall bias and forward-filling). They live in the world of trying to decipher illegible handwriting, marginal comments (which may include AEs), and illogical entries with inappropriate questions answered or skipped. Sites enjoy how ePRO fixes these problems, improves data quality and saves them time.

"From my perspective, (PHT's) **LogPad System** is a very innovative way to ensure that we're collecting valid, real-time data ... It's not retrospective, it's not a patient's recollection, but is valid and real-time data that's downloaded and monitored on a daily basis."

Jeff B. Hales, MD, Pulmonologist, Pulmonary and Medical Associates of Northern Virginia (Arlington, VA)

- **StudyPad: on-site eSource data collection**

PHT's StudyPad System, often implemented on larger-screen PDAs, allows study coordinators to administer standardized questionnaires to many subjects on a single, mobile device. These validated questionnaires automatically appear during specific visits as scheduled in the protocol. This eases the burden on sites who otherwise must remember and track exactly what questionnaires to administer at each visit. Most **LogPad** studies also include Health-Related Quality of Life questionnaires.

- **StudyWorks™ notifications and alerts**

PHT's eDiaries can perform calculations on the device in real time as data is entered. As soon as this data (or the results of automatic calculations) are transmitted, reports are generated in **StudyWorks** to provide instant access to clinically relevant parameters without requiring study coordinators to perform any calculations manually. These calculations can then trigger email alerts or notifications as specified by the sponsor.

For example, in a **Temple University** COPD disease management study, the **LogPad** automatically calculates a graded score based on symptoms reported. The eDiary instructs the patient to contact a pulmonary call center if the score exceeds a medically significant threshold. At the same time, site personnel review **StudyWorks** reports, which highlight in yellow the values that indicate a subject exacerbation. In this way, sites are relieved because they do not have to perform calculations by hand, which risks error and can be time-consuming, and because they receive reliable information about how patients are feeling between visits. This lets sites catch potential flare-ups before they happen.

Early results of the study are encouraging – patients enjoy the routine the **LogPad** provides, and site staff are pleased that hospitalizations are reduced. To learn more, download the **case study** and **TV news report** segment (featuring site and patient interviews) online at www.phtcorp.com.

PHT recognizes the value of active site notification, and has developed an exclusive capability to send email and paging alerts immediately to the principal investigator and medical monitor as pre-determined thresholds are reached.

“The main benefit of PHT's solution is the ability to review patient symptom data in real time. If we had used paper diaries for the study, it would have been difficult to know whether a patient was exhibiting early signs of an exacerbation and in need of call center intervention if those patients simply chose not to call when they should have.”

Carla Grabianowski, RN, BSN, CCRP, Research Nurse Coordinator, Temple University Hospital (Philadelphia, PA)

- **Randomization decision support**

The **LogPad** helps sites with randomization decisions by calculating a subject's performance in regard to eligibility criteria, such as symptom scores and diary compliance during baseline. Results are displayed on-screen for site review.

“One of the few patients who was dropped at our site was due to poor compliance with keeping the daily diary at baseline. It wasn't so much that he couldn't use the eDiary, but that he was distracted with different obligations and wasn't fully vested in the study ... Because key endpoints in this study include quality of life and other patient reported outcome data, poor diary compliance by patients would compromise the study outcomes. Thus for a long-term clinical trial requiring patient data, it is good to know up-front if the patient is fully vested, and the **LogPad** helps us identify and exclude noncompliant patients from the study.”

Jeff B. Hales, MD

- **More time, less paperwork**

It should come as no surprise that sites do not enjoy dealing with volumes of paper, or spending hours manually entering handwritten data into a CRF, which also invites error. Site personnel (who are busy interacting with patients) in a paper-based trial are also required to organize, collate, sign, manage and store reams of paper diary records. This presents a significant logistical challenge, especially when a site is running multiple trials concurrently. ePRO is a true eSource solution, which reduces physical data storage at the site to a single CD- or DVD-ROM study archive provided at close-out.

“I see what monitors have to do with paper diaries ... it's a lot of work. I see them doing it and I think, 'I'm glad I don't have to do that!' It's quite easy that everything is in the computer directly, and nothing is unreadable.”

Anne Jansen, Research Coordinator, Academic Medical Center (Amsterdam, Netherlands)

“One of the best parts of the **LogPad** is it means no more piles of paper in the office.”

Jeff B. Hales, MD

- **Attracting more subjects and studies**

Using eClinical technologies helps sites attract patients due to enhanced safety monitoring, and increases the site's reputation as a cutting-edge research facility. As the industry continues to adopt ePRO as the gold standard, leading sites will employ trained and experienced staff who know how to optimize multiple systems.

“Patients report feeling safer knowing that I can monitor their diaries between visits. This is especially true in pediatric studies. We've always been very successful in enrolling for pediatric studies, and I think it's because parents just feel so good about the fact that someone else is helping them manage their child's condition ... and the kids, they love (the **LogPad**). They can't wait to show it off to their friends.”

Pat Ridgeway, CCRP, Medical Research Associates of Central New York (North Syracuse, NY)

ePRO Challenges

While any change can create anxiety, the shift from familiar paper methods to electronic diaries is a fundamental change and sites need to be prepared. This section details some of the challenges of using ePRO as reported by sites, and discusses how PHT addresses such issues.

• Dealing with technical (transmission) problems

The primary technical issue subjects have with eDiaries has nothing to do with using the device to enter data. Instead, it is sending the data that can be a problem. Site personnel deal with this issue with reluctance, as they are not usually avid technology users. In fact, when asked, "What is your favorite technology product outside of work?" most coordinators did not have a response. Troubleshooting and solving transmission issues can therefore be a source of concern for sites.

"Some patients are not really used to working with computers, maybe some older patients, and when (the eDiary doesn't send), it asks to send it again. You only have to press OK and it will send again. But if you're scared and don't know what to do, then people don't do that. They don't read it, see an error and want help."

Anne Jensen

>>> **PHT Tips:** As ePRO technology matures, more reliable transmission solutions continue to emerge. For example, PHT's **SimpleSend™** family of transmission options enable either analog or wireless transmission from any of our eDiaries. This enables us to address problems that can emerge due to subject location, restricted service, absence of standard phone lines, etc. We partner with leading worldwide cellular network providers **Cingular Wireless** and **Swisscom** for reliable wireless transmissions. Coupled with our **Site Telecom Assessment** service, SimpleSend now substantially mitigates the risk of transmission errors.

In case these errors (or other technical issues) do occur, our internal **Study Support Center** is always available to resolve the matter quickly. PHT supports subjects directly as needed, but strongly recommends sites maintain the relationship with subjects to minimize the disclosure of private health information. Sites are best prepared to deal with patients who might report AEs or other clinical information during a support call.

PHT recognized from the beginning that no transmission system is perfect, so our eDiaries were designed to accommodate transmission failures. PHT allows completed reports to be stored on the device – therefore, sites should train subjects to continue to complete diaries as they normally would, even if a prior transmission did not go through or if an error message appeared. Subjects simply need to choose "OK" or "Continue" and fill out diaries as required. When they next transmit successfully, all stored reports will send automatically.

• Assigning devices

Paper diaries do not need to be assigned to each subject. In contrast, one-to-one assignment of a particular device is a benefit of the **LogPad** as it helps show attributability of eDiary data to each individual. It is also, however, a technical step the site must undertake while the patient is present. The assignment process is straight-forward, but if a technical problem arises (e.g. a communication issue), it can frustrate the coordinator, who wants to appear reliable for the subject.

"(Having technical issues during a visit) is definitely what the study coordinator doesn't want to have happen in front of the patient. Don't forget, you're asking these patients to trust you to take an investigational product, so you (want to appear confident), because you're handing them drug."

Pat Ridgeway, CCRP

>>> **PHT Tips:** Sites should test transmissions from their location prior to FPI by simply tapping the "Test" button on the LogPad. PHT's global **Site Telecom Assessment** service also minimizes risk. All **LogPads** to be assigned on any given day should be fully charged and configured properly in advance. This way, assignment will go smoothly. PHT's **Study Support Center** is always available to answer site questions, but it is preferable to avoid issues altogether.

• Training subjects how to use the eDiary

ePRO providers cannot train subjects around the world in person. Sites have always served as the trainers of subjects concerning PRO, and now we rely on them to educate patients on how to use eDiaries, as well. Sites with the least amount of technical issues usually report having spent an average of **15-30** minutes with each patient during assignment to walk through the diary and to explain how to transmit reports from home. Sites have traditionally high turnover, and new personnel need to be trained as the study is on-going.

"Each person is a little different. I think those that grew up with technology have an easier time learning any sort of eDiary than others who've had it as a part of daily life since day one. So you try to standardize it so everybody gets the same education, but sometimes you have to tailor it for your audience ... but it's pretty easy to do that."

Study Coordinator (Oklahoma City, OK)

>>> **PHT Tips:** Most ePRO providers include graphical setup and troubleshooting instructions for subjects and sites, as well as a level of help desk support. PHT provides each site with a study-specific **Site Reference Manual** and a **Training LogPad**. The Trainer device enables coordinators to show all diaries and questionnaires and lets subjects practice data entry until comfortable with the **LogPad**.

In order to keep site personnel up-to-date and to train replacement staff, PHT and **ePharmaSolutions** have teamed to develop **Web SiteLearning™**, a comprehensive eLearning program which features animated instructions, interactive certification exercises and full documentation.

• Overly restrictive eDiary designs

As **Dr. Barbara Marino** described in the March, 2005, issue of *Insights*, one common mistake is **over**-designing the eDiary. Restricted time response windows eliminate unplanned recall bias and forward-filling, but if the windows for completion are set too narrowly, subjects may not be able to enter their diaries in the allotted slots with consistent frequency. This could negatively impact convenience, lower compliance and frustrate site personnel who want subjects to stay in the trial.

>>> PHT Tips: Sponsors should work closely with the ePRO provider's experienced scientific design team to optimize tradeoffs and create a pragmatic eDiary. PHT understands that sponsors know their scientific objectives best; it is our job, therefore, not to alter the science, but to customize an ePRO solution to best reach those goals.

• Managing inventory and multiple systems

A portion of sites may not have adequate physical space to store eDiary systems easily before they are assigned. Similarly, shipping and receiving devices can raise issues. Sites also have to manage multiple systems, log-in's, URL's, etc., in each trial. It can get confusing even for seasoned technology users.

"I have so many user IDs, PINs and passwords that I have to keep a spreadsheet. I have a spreadsheet. You're going to ask, 'How secure is that?' Don't worry... it's user ID and password-protected, as well."

Pat Ridgeway, CCRP

>>> PHT Tips: If physical storage space is at a premium, shipments of equipment can be staggered to re-supply certain sites on a regular or on-demand basis. The good news is, once the devices are assigned, the eSource data and documents require no storage space, and the entire **Study Archive** consists of durable CD- or DVD-ROM(s). Helping sites manage disparate eClinical systems across their trials is a wider issue; this is one of the key reasons PHT frequently solicits comments from sites on usability and training. We continually strive to understand their needs and challenges, which enables us to design ePRO products that make their lives easier – not harder.

Site Acceptance of ePRO

In a 2004 CDISC survey, 40% of study sponsors listed resistance from sites as a reason for delay in adoption of data collection technologies. These concerns, however, now seem to have been largely unfounded. Perceived difficulties and anxieties about using technology to replace paper appear to be dissipating rapidly. According to the survey, **73% of sites prefer ePRO** to paper – and that was in 2004. Sites appreciate technology's ability to improve upon current paper processes, as only 7% of sponsors listed sites as "satisfied with paper" as a reason to delay ePRO adoption in the industry. Clearly, the entire industry welcomes a proven and superior alternative to conventional paper methods for collecting and managing PRO data.

PHT has found that sites are most satisfied with ePRO when they understand not only how to use it, but **why** the decision to use eDiaries was made. By explaining the benefits of data quality and real-time patient monitoring at the Investigator Meeting, sponsors can achieve site buy-in up front and create excitement and enthusiasm behind the move to ePRO.

Final Thoughts

As compared to a few years ago, sites now demonstrate a stronger understanding of ePRO's data quality and reliability improvements. PHT alone has implemented over **270 trials** with **tens of thousands** of global sites. Even those coordinators who claim to favor familiar paper processes invariably admit they would choose to use ePRO every time if not for concerns about technical problems. It is incumbent on ePRO providers to minimize issues and make it easier for sites and subjects around the world to accomplish their important work.

"Because the data is eSource, and is collected and downloaded directly into the study database, it removes the opportunity for error in the transcription of data from paper to electronic formats. There are no mistakes, such as accidentally keying in one decimal point wrong."

Jeff B. Hales, MD

"I think (the **LogPad**) is a novelty, once people got over the slight nervousness of using it. It sticks in your mind in a way that a paper diary perhaps wouldn't. It bleeps you, it prompts you, it stays in your memory."

Study Coordinator with elderly patients (Cambridge, UK)

"With **StudyWorks**, we can monitor on a daily basis what the (patients') symptoms are. You can obviously see any change in their symptoms and be alerted to potential problems in a more timely fashion ... With paper, there is a much higher workload going through every daily diary entry with a patient and having to record that information. With the **LogPad**, it's all automatic, and doesn't take away from the data management person's time."

Nadia Hansel, MD, MPH

"I think (with the **LogPad** and **StudyWorks**) you're getting a true picture of it, as they're living it, right then."

Study Coordinator in (Oklahoma City, OK)

"Believe it or not, I have watched patients writing in paper diaries from my office window ... And how valuable is that data? It's recalled from five days ago, six days ago? Who really knows?"

Pat Ridgeway, CCRP

Learn more about sites at www.phtcorp.com

To learn more about the Site Perspective Using ePRO, read the **Asthmatx** case study at www.phtcorp.com. Also, stay tuned for our **new web site** in early 2007, which will include a **recorded site webinar by Dr. Hales**.