Patient Compliance, ePRO and the Role of the Care-giver

Sponsor companies are increasingly required to employ methods for patient-reported outcomes (PROs) that ensure timely, accurate and attributable data collection, as well as to improve patient compliance. In many drug trials, electronic patient-reported outcome (ePRO) systems, particularly electronic diaries (eDiaries), have been shown to be an effective and superior method of driving patient compliance when compared to paper-based methods. ePRO systems can be set up for real-time completion, eliminating errors or bias due to patient recall. The quick availability of data allows sponsors to track compliance closely and intervene with remediation measures when required. ePRO can also be used whether data is being reported by patients themselves or by their care-givers, such as in the cases of pediatric studies, and when studying diseases with severe motor symptoms or cognitive impairment.

Patient and Care-giver Compliance

A common misconception is that eDiaries would be too complex or time-consuming for some patients (for example elderly) or their care-givers to use for PRO data collection, resulting in poor patient and protocol compliance.

Metrics-based ePRO vendors that measure patient compliance-to-protocol tell a different story; the elderly are actually one of the most compliant groups, with an average of 92 % compliance, whereas the presumably most 'tech-savvy' groups of teenagers and adults have the lowest compliance rates, implying little correlation between technical expertise and ePRO compliance.

Several reasons for this may be that:

- Elderly patients generally have more time, whereas adults and teenagers have busy schedules
- Elderly patients are typically more concerned about their health
- Care-givers of elderly patients may be more concerned about the patient's health and are therefore more compliant
- Older generations may be more compliant when receiving and following instructions
- Modern ePRO technology and good diary design can be intuitive for the patient

Similarly, compliance in infant and children populations is also high, most likely because parents want to provide the best care for their child and comply with instructions to ensure this.

Which ePRO attributes enhance patient and care-giver protocol compliance? What is critically important to ensure patients and care-givers are compliant with data entry, medication intake and the visit schedule?

Proactive eDiary Design

A key principle is to keep the ePRO design simple, to avoid completion difficulties and confusion. The device should guide the patient or care-giver in a logical way to perform all the required tasks at the correct times.

Simple design elements that ensure data entry with minimal errors and allow for fast completion include the use of:

- o Audible alarms with instruction texts, such as: "It is time to fill in your evening diary"
- o Questions with pre-set answers ("Yes" or "No")
- o Radio buttons or drop-down single answer selection from a list of options
- o Soft edit checks for clinical values, with normal ranges and upper and lower data entry limits that trigger data error alerts
- o Avoidance of free text data entry

For studies with more complicated requirements, eDiaries can be designed to capture specific events. For example, in a hemophilia trial, eDiary design can capture bleeding events and associated self-injections and utilise reminders for follow-up treatment efficacy questions to be answered in line with protocol requirements, as shown in Figure 2. Such a design allows patients or care-givers to rely solely on the eDiary to guide them on what to do at any given time, therefore providing more proactive support than they might get in a normal clinical setting.

eDiaries can also be used to provide reminders about the expected duration of forthcoming visits, together with what patients need to take to that visit and the tests planned for that visit. They can even remind patients to fast before a blood draw visit. These design elements make the eDiary device more than just a data collection tool, but also a personal clinical trial assistant for the patients, care-givers and study sites.

Active Remote Monitoring

Remote monitoring tools for the investigator sites and study teams add another layer of checks that help to improve patient compliance. When study protocols have a specific study medication intake schedule or limits for rescue medication use, sites need to be able to track medication intake remotely in order to be able to intervene when problems are observed, as non-compliance with the study medication regimen is a significant issue for many studies. Real-time access to the patient's reported medication intake data, via reports such as that in Figure 4, together with automated email alerts when issues are detected, can help minimise this.

Figure 1: CRF health proprietary ePRO compliance metrics

Age	N	Average Compliance	STDV
Elderly	5,910	92.3%	14.2
Adult	48,197	88.7%	18.1
Children	1,256	92.6%	12.5
Teenage	46	85.9%	24.2
Infant	7,687	93.6%	12.2

Figure 1: Sample timed follow- efficacy question

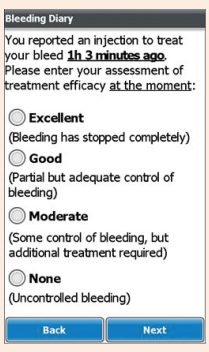


Figure 3: Visit reminder screen

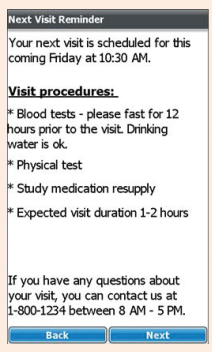
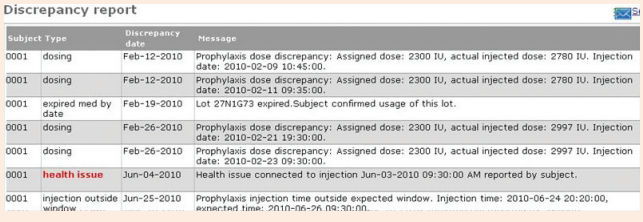


Figure 4: Sample medication compliance tracking report



Challenging Study Populations

With diseases that result in significant motor symptoms or impact on cognitive abilities such as Parkinson's, Alzheimer's or multiple sclerosis, ePRO systems might seem complicated and be considered less user-friendly than paper-based data collection.

Recently CRF Health and Oxford Outcomes coordinated a focus group of patients with Parkinson's disease to investigate this aspect. After basic orientation, patients who were able to use an eDiary preferred this method over paper. Some patients with severe symptoms could not use either method, but commented that their care-givers would prefer the electronic version. Similar, if not even more positive, results were collected in a usability test with twenty patients with multiple sclerosis using a large-screen tablet PC device. Many individuals from both groups noted that one of the key benefits is the ability to easily correct data entry mistakes with the electronic device.

eDiary designs can accommodate both patient and care-giver functionality on the same device. When a care-giver is involved, it is even more important to have clear instructions in the eDiary that will guide them to follow the study and ePRO data entry schedule more closely. It is also important that the ePRO system used has a care-giver module that fulfills all the regulatory requirements for this type of data entry. All eDiary users must have their own user accounts so that the data can be attributable.

In conclusion, in studies where care-givers enter the PRO data on behalf of the patient, such as studies with infants or subjects with Parkinson's disease, dementia or Alzheimer's disease, compliance can be maintained at consistently high levels. Proactive eDiary design, visit reminders, and active remote monitoring are critical functions and necessary requirements to maintain high levels of patient compliance in all patient settings, including those that rely on care-giver support.

Rohini Beavon, PhD is Director of R Beavon Solutions Limited in the UK and is currently a freelance clinical research professional to the pharmaceutical industry. She has worked in the pharmaceutical industry for 12 years, most recently for Pfizer (formerly Wyeth) as a Clinical Project Manager and Clinical Scientist and was educated at the University of Liverpool and the University of Surrey. Email: Rohini.beavon@RBeavonSolutions.co.uk

Kai Langel has worked with CRF Health since the company's inception in 2000 and is one of the pioneers in the ePRO industry. During this time, Kai has been involved in all aspects of ePRO operations from system design to deployment and support. Kai spent 5 years in the United States where he was responsible for building CRF Health's technical delivery team. He is currently based in Europe in a consultative role providing advice and guidance to both customers and CRF Health's internal teams on technical, operational and regulatory issues. Kai is a true global ePRO expert, having worked both in the United States, Europe and more recently in Japan and Asia. Email: Kai.langel@crfhealth.com