

Managing ePRO

Patient Compliance in Emerging Markets



There is an increasing trend for pharmaceutical companies (sponsors) and clinical research organisations (CROs) to conduct clinical trials in the emerging markets, such as Asia (in particular India and China) and Eastern Europe, to the extent that many companies now have an established presence in these countries. Studies in these regions range from small early phase studies to establish the safety profile of a drug, to large late phase studies required for licensure of a drug in the country where the study is conducted or as part of a global, multinational study. Running clinical trials in these markets offers many benefits over the more traditional and established areas in Western Europe and North America. These include: access to a larger population of potential study patients with the disease being targeted, resulting in faster patient recruitment; a reduced cost of conducting the trials; and, compared to the European Medicines Agency and US Food and Drug Administration, fewer perceived regulatory constraints.

It is therefore important that electronic patient reported outcome (ePRO) technology and services meet the needs of clinical trials conducted in these emerging markets from the perspective of the trial patients, investigators, CROs, sponsors and regulatory agencies. This article outlines some practical considerations regarding ePRO technology and services, which are pertinent to studies conducted in the emerging markets.

Compliance Matters

For sponsors, ensuring compliance with a study protocol is very important in clinical trials, as this has an impact on the evaluable subjects at the end of a clinical trial to determine the safety and effectiveness of a drug. Study teams take care to ensure that the protocols are designed to meet the study endpoints, follow good clinical practices, and adhere to applicable regulatory agency requirements. These protocols are reviewed internally by the sponsor and externally by ethics committees. Similarly, study teams plan and design ePRO systems with close reference to the protocol and conduct multiple reviews and testing rounds to ensure that appropriate outcomes can be captured with minimal site and subject burden. The study medication itself often has a specific mechanism of action, and it's important that the patients follow the specific instructions they're given regarding when and how much medication they should be taking. Study medication intake and the actual collection of ePRO data is often done by the patient in an unsupervised environment. Therefore when a protocol calls for patient reported outcome measures and strict adherence to a medication schedule, an ePRO system plays an important role in ensuring a high level of compliance with the collection of data related to these activities.

ePRO Systems for Patient Compliance Management

ePRO systems can be set up for effective compliance management in a clinical trial. However, this requires careful planning by the sponsor, the CRO and the ePRO vendor. Here are the main components of an effective compliance management

process:

1) The patient eDiary

Subjects participate in clinical trials because they are motivated by the potential benefit the research might have for them or the wider community. They are usually quite good at doing what is asked of them, provided they have been given clear instructions in a language they understand, and tools that are easy to use. Patients are not research professionals; to get the best results, there are a few things to keep in mind. First, keep it simple for the patients. Don't expect them to remember what they need to do during the different phases of the trial. The eDiary can help them by acting like a personal digital assistant and actively guiding them throughout the trial. Some features that are useful here are alarms, real-time edit checks and conditional questionnaire navigation. Instead of asking the patient to make a choice, the eDiary can simply direct them: "It is time to complete your weekly questionnaire today. Click 'Continue' to proceed".

Essential in emerging markets is the provision of an ePRO tool that has instructions and questions in the most frequently used local languages. Care needs to be taken to ensure translations are accurate and questions can be interpreted in the same way in each language, especially for global studies.

ePRO tools must be simple to use so that training is not perceived as burdensome by the study investigators. Again, the eDiary can assist the site staff with the administrative procedures: "Subject setup is now complete. Please select 'Continue' to proceed with the subject training". A training module should be made available to the patients so that they can be trained and become familiar with the ePRO device and study questions. Simple instructions for the sites and patients in the form of a single-page quick reference guide, aimed at the local culture, can make the process easier. Questions for data collection purposes in the ePRO system also need to be short and simple, and should retain the meaning of the question in all languages. When forming the questions to pose, sponsors, CROs and ePRO vendors need to take into account the fact that many languages are inherently much longer than English, which often extends the length of the ePRO question on the device screen. Use of characters rather than Roman text usually requires a larger font size to ensure these more complex characters are easily readable.

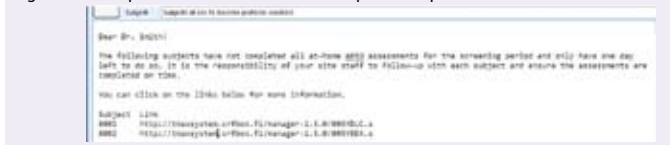
As often as possible, the ePRO systems should have close-ended questions in order to avoid collection of ambiguous data. Ongoing encouragement to patients can be given through an effective, but underutilized, method of simply giving them regular feedback on how they are performing during a study. For example, in an eDiary to be completed by pediatric patients, a weekly cartoon can be displayed to motivate them to improve on their compliance or to congratulate them on a job well done. Of course, these kinds of motivational tools must be appropriate for the population and culture for which they're being used.

2) Reporting system for study sites

Remote monitoring tools for use by investigator sites are an important part of the process to ensure patient compliance with ePRO data collection. This is especially important in studies where patients must fulfill a critical procedure at home, such as completing a particular questionnaire within a specified timeframe or collecting drug-related safety data. These remote monitoring tools allow the sites to proactively manage their patients. The sites can have access to reports that show the compliance for each of their patients. In addition, they can be automatically notified by the ePRO system via email or a report of poor or non-compliant patients, before they become protocol violators.



Figure 2: Example automatic notification of poor compliance



Another method that can be very effective is to encourage competition between the sites or countries participating in the study by highlighting sites whose patients have high compliance rates. Sites that are not on the list might make an extra effort to make the list, and sites on the list will do their best to stay there. This kind of report works really well if there is some reward involved, such as recognition in the study newsletter.

Figure 3: Example report to show investigator site compliance performance

Site	Compliance
Site 02 - Dr. Jones	100%
Site 03 - Dr. Carlson	99.5%
Site 12 - Dr. Smith	99.3%
Site 8 - Dr. Watanabe	98.8%
Site 3 - Dr. Bentley	98.4%

However, having compliance measurement and reporting tools in place doesn't accomplish anything by itself. Effective trial management is essential, and this usually starts at the site level with an investigator contract. To encourage good oversight of ePRO data by investigator sites, the investigator contract should include requirements for sites to review critical ePRO report(s) online at specified timepoints in the study. There should also be a requirement for the investigator site to make a phone call to potential non-compliant patients who are about to miss an important ePRO assessment at home. Once the investigators' ePRO responsibilities are defined, the reporting system should be designed to measure site performance in real time. In addition, the reliable support of a 24-hour helpdesk will assist the study subjects with any issues they may have related to the ePRO system.

3) Reporting system for monitoring and study teams

The monitoring clinical research associate (CRA) is crucial to ensuring ePRO compliance within a clinical trial, as they build a relationship with investigator site staff, train them in all aspects of the study, and act as the liaison between the investigator site and the study team. In emerging market countries, the CRA will also be aware of the cultural sensitivities and local understanding of a study. It is therefore essential that ePRO vendors, CROs and sponsors include CRAs from each country

in the user acceptance testing of the ePRO system, train the CRAs on all aspects of the study-specific ePRO system, and have ePRO tools designed to assist them in the monitoring of sites. This will ensure that they can provide additional support to the investigator sites as needed, and consequently this will improve compliance.

Some ePRO systems support reports where the CRA can see whether or not the site staff has reviewed a particular report according to the investigator contracts. This makes it easy for the CRAs to monitor the sites and provide additional support for sites to improve their adherence to the agreed ePRO responsibilities.

Figure 4: Site compliance report highlighting sites that have non-compliant patients and are NOT using the compliance reports

Site	Compliance	Non-compliant Patients	Compliance Reports Used
Site 0 - last week 2 weeks ago	98% (20%)	100 (10%)	100 (10%)
Site 1 - last week 1 week ago	98% (20%)	100 (10%)	100 (10%)
Site 2 - last week 3 weeks ago	98% (20%)	100 (10%)	100 (10%)
Site 3 - last week 4 weeks ago	98% (20%)	100 (10%)	100 (10%)
Site 4 - last week 5 weeks ago	98% (20%)	100 (10%)	100 (10%)

Study Region Impact on Compliance

While there are no hard rules for compliance expectations for different countries, there are certainly cultural differences and trends that can be observed from global compliance data.

Figure 5: Global compliance metrics by region based on compliance metrics collected by CRF Health's ePRO system

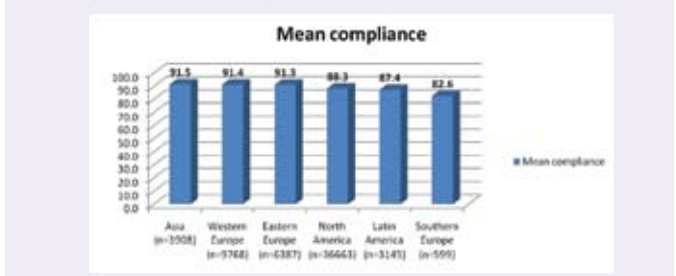


Figure 5, taken from CRF Health internal data, shows that the Asia Pacific region tops the charts in terms of compliance, but quite surprisingly, Western and Eastern Europe are not far behind. Southern Europe was separated into its own category because of the clear differences in compliance compared to the rest of Europe.

This data shows a difference between some of the regions, but it doesn't necessarily reflect a cultural difference. There is much more variation between different therapeutic areas than there is between different countries. For example, average compliance in vaccine studies conducted by CRF Health is 93.3%, while oncology has an average compliance of 87.2%. Part of the difference may be explained by the seriousness of the patient's condition; vaccine studies typically use a healthy population. The complexity of the protocol also plays a big part, as oncology studies often have long duration and more complex measures, while vaccine studies typically collect simple safety data in the form of injection site reactions and other systemic effects over a much shorter time period.

The good news for the pharmaceutical industry is that



some of the regions with the most compliant patients are also regions that are the most cost-effective in which to run clinical trials. However, deploying ePRO in these regions requires some consideration in terms of scalability and support. The ePRO vendors must be able to handle localisation of their software into various complex languages. For example, India alone has 21 official languages, and many of the Asian languages use complex scripts (fonts) that are not supported by all technology platforms.

Logistical considerations are another issue. Choice of device must take into account local communication networks (i.e. landline or wireless or a mixture of both) so that patients can reliably send their data in an efficient manner. In addition, companies not only have to deal with large distances and different time zones, but also must be able to deal with differing customs regulations in order to be able to import their technology into

some of these countries. The European Union and various trade agreements between countries in the west have made logistical matters quite trivial; the situation is completely different in Asia and some Eastern European countries, particularly Russia.

Once a study is up and running, the users will need support in terms of a helpdesk. Here again, subjects and investigator sites must be served in their local language or they will simply not use the helpdesk and their issues will not be solved in a timely manner. Providing reliable support in many languages across all time zones is a challenge that only the most well-established and reliable ePRO vendors can accomplish. It is important to choose an ePRO vendor that routinely collects and monitors helpdesk metrics to ensure the very best in service.

Conclusion

In summary, the provision of ePRO solutions for clinical trials in emerging markets is a great opportunity for companies to use advances in technology to ensure the highest compliance-to-protocol for the collection of their ePRO data. Sponsors, CROs and ePRO vendors need to provide a solution for studies in emerging markets that:

- a) Meets the logistical needs of the country, so that the devices can get into the country in time for study start and work reliably after deployment
- b) Employs a device that is simple to use - allowing for effective training and simplified data collection by patients
- c) Has questions that are simple to understand and answer, in local languages and with edit checks to ensure error-free data
- d) Provides suitable reports and alerts that will allow sites, CRAs and study teams to track compliance in real time – ensuring that small issues are caught before they become larger problems

One thing is certain: ePRO systems and technologies will evolve further in the future, but attention to these basic elements will help ensure improved compliance.



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.

Contributor: Deepankar Arora, Manager, Clinical Operations at GVK Biosciences Pvt. Ltd.