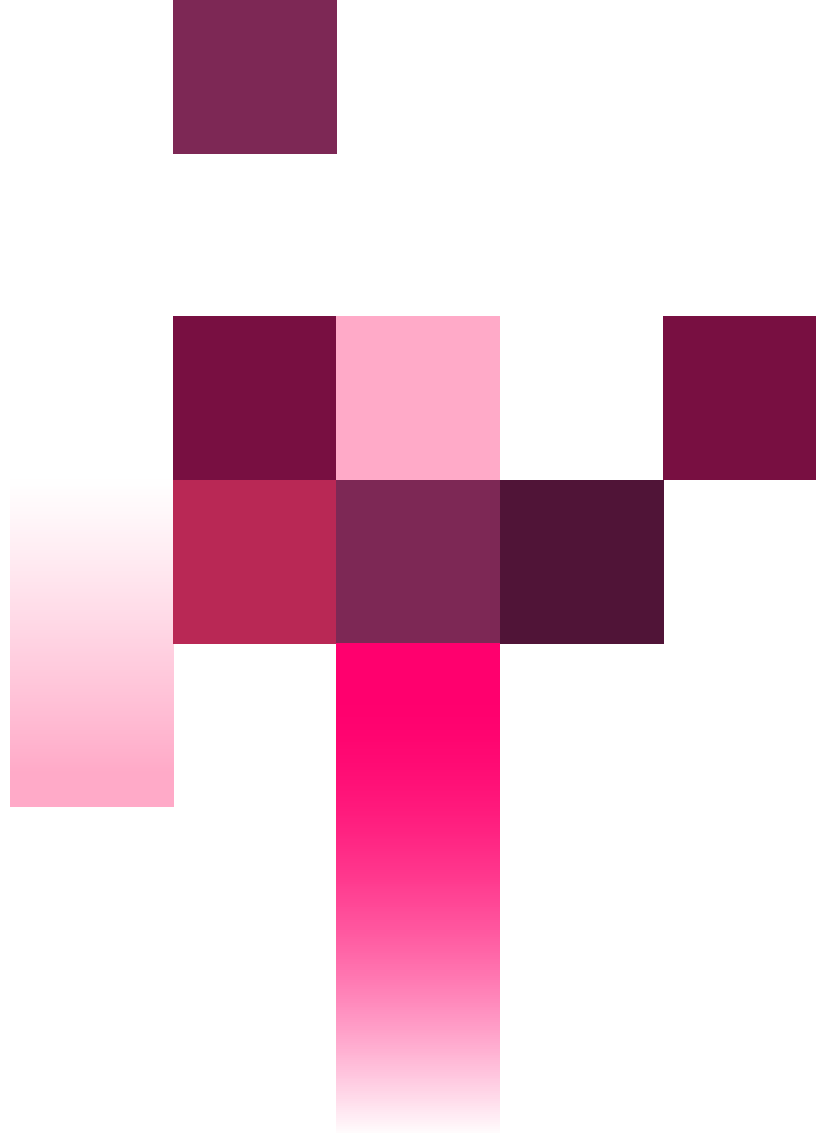




Using eCOA for the first time

Lessons Learned for Integrating ePRO in a Phase II Clinical Trial

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Electronic patient reported outcomes (ePRO) improve data capture, quality and transparency, but few people are experts at integrating ePRO into their clinical trials. Here are my “lessons learned” for integrating ePRO in a Phase II clinical trial, along with suggestions on how to plan and use these insights for future projects.

Introduction

The importance of patient-reported outcomes (PRO) is evidenced by their increased use in clinical trials and in drug and device label claims. In many cases, the best way to measure symptoms and functional status is through insights provided by the patient, but few people know how to go about integrating ePRO into their clinical trials. I completed a Phase II clinical trial using electronic PRO for the first time and identified the key decision points, responsibilities and lessons learned for incorporating ePRO into our clinical trial practices.

Study protocol and ePRO

FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims states, “If a patient diary or some other form of unsupervised data entry is used, the clinical trial protocol is reviewed to determine what steps are taken to ensure that patients make entries according to the clinical trial design and not, for example, just before a clinic visit when their reports will be collected.”¹ This is a critical requirement!

The protocol in this proof of concept trial required patients to complete a daily questionnaire in the evening between the hours of 6:00 PM and 11:59 PM using a visual analogue scale (VAS) score as the primary data endpoint. Other protocol features included:

- A complex algorithm that analyzed patient criteria for enrollment and randomization (masked from both sites and monitors)
- The ePRO instrument calculated eligibility from data collected from the patient
- The algorithm processed patient data and once the algorithm calculations were complete, eligible patients were enrolled and provided with a bi-weekly schedule of study visits.

- Three different ePRO questionnaires were due for completion at different collection times:
 - Daily, between 6 PM and 11:59 PM;
 - Bi-weekly at every visit, activated at every visit and available until 11:59 PM; and
- The ePRO system collected patient diaries using either US English or US Spanish.

ePRO benefits

There are numerous benefits to using PRO, and very clear advantages of ePRO over paper-based tools. Although additional training for study sites is required with ePRO, the use of this technology offers cleaner data capture so study coordinators can spend more time with their study participants and potentially enjoy higher patient compliance. Electronic PRO eliminates missed, illegible or illogical responses.¹ Study coordinators are exempt from manual calculations and from spending precious time reviewing or deciphering patients' handwritten diaries.

Efficiencies are realized with accelerated data availability from electronic capture, including the elimination or reduction of missing data. Data collected by an ePRO system are in real time within the context of the patient's life. The electronic collection of diaries and questionnaires improves data quality for analysis and trial management. Depending on the study design, patients cannot back fill or forward fill diaries, because questionnaires can be programmed to appear and disappear at set times.

How ePRO works

A time and date stamp is created when the subject logs in, so an audit trail is created. Time and date stamps are "proof" that patients complied with the protocol and completed the questionnaire during the intended time. In my study, patients were asked to choose to receive their instruction in

English or Spanish, whichever language was most suitable to them, thereby eliminating the need to estimate how many questionnaires to print in each language for every site.

Selecting an ePRO system

Careful upfront planning can save time and money during study execution. With less than two months to set up the entire trial, I selected two electronic systems to collect study data: an interactive web response system (IWRS) and an ePRO system. Study planners noted that, in their experience, integrating IWRS/IWRS and ePRO resulted in fewer errors, minimized the number of data clarification forms (DCFs), and allowed better control of keeping study costs aligned with budgets. Each technology system captured the applicable study data.

If the patient met the eligibility criteria, the investigator logged into the IWRS and received a study patient number. The patient number was then manually entered into the ePRO device.

When the patient number was manually entered on the ePRO mobile device, the device was then given to the patient. The mobile device was used to collect patient data in transit.

The Clario ePRO system was selected because it offered a number of advantages to address the complexity of this trial. Each patient received a mobile ePRO device, a Wireless Pak for transmission, and in case the wireless transmission failed, a TeleCradle for analogue transmission. The mobile ePRO device was portable and lightweight, with a compact screen.

Two devices were ordered for each of the investigative sites, since expectations were to have no more than two active patients enrolled at each site at any one time. The working plan was that if one subject did not meet the criteria and had to be discontinued, the device would be reassigned to a new patient. The same held

true for those who finished the trial; once a patient completed the study, the device would be reassigned to a new study patient meeting the enrollment criteria. However, the initial plans were inadequate and it became necessary to reorder additional devices; in some cases, many more than two per site.

Careful up-front planning saves time and money

The study sites had several responsibilities for monitoring patients once they were enrolled. These included the daily checking of patient compliance through the Clario StudyWorks™ portal and contacting any patients at risk of non-compliance, or just needing to charge the batteries of their device. During training, site investigators or study coordinators were required to demonstrate an understanding of how to work with the ePRO device and to answer questions about the device (or, know when to refer questions to Clario Customer Care). Each patient was expected to receive 15 to 30 minutes of training from the study coordinator on how to use the ePRO device.

Initially, many patients called Clario Customer Care for training and questions on the ePRO device, either because they didn't remember some of the instructions once they had departed from the study site or the initial training wasn't intensive enough. The solution was to develop a study-specific Troubleshooting Guide to address the most common questions, with the aim of reducing the Customer Care call volume. It took approximately 10 days while waiting for the guide to be approved by the IRB.

Once patients received their ePRO device from the study coordinators or investigator, they were required to complete their diaries each day for two weeks. At the first visit following the initial screening, patient compliance was assessed with the touch of the button on the

ePRO device. With three separate questionnaires distributed at different points within the study, the potential for human error (and disseminating an incorrect questionnaire) was real. The ePRO system provided the right questionnaire to each patient at the right time and helped mitigate the potential for human error. If a patient withdrew early or completed the study, a final questionnaire was provided at the time of study withdrawal or completion.

Five key elements support study sites

1. An online Clario StudyWorks portal for the study coordinator to monitor patient compliance. StudyWorks provided full data access to the study team and selective access to monitors and site personnel;
2. An ePRO device training kit for study coordinators showed how to use the handheld with instructions for training their patients. Each patient was allowed to practice on the training device before being issued their own. Patients were allowed as much time and practice as necessary to feel comfortable using the ePRO device;
3. A 20-25 page site support guide, specific to the Phase II trial, included directions on how to log into StudyWorks, the expectations of each study visit and how to train and work with participants for ePRO study success;
4. Documents generated by our study team provided instruction on how to use the Clario ePRO system, and were approved by the study Institutional Review Board (IRB). Power adaptors, power cords, a universal pictorial step-by-step "getting started" card and support materials were supplied by Clario; and
5. The study archive of all data collected at the site was furnished at the end of the trial.

Lessons learned

1. Human errors occur

Data entered into and analyzed by the ePRO device determined eligibility, randomization and study medication kits. Since a single patient number connected the IWRS to the ePRO device, it was critical that the Sponsor Clinical Trial Manager ensured that the correct patient number had been transcribed from one system to the other. Discrepancies can only be resolved with Data Clarification Forms (DCF's).

Lesson learned: When two technology applications are used, such as IWRS/IVRS and ePRO, enable them to transmit data between the systems. These data can be transmitted electronically for eSource accuracy.

2. Study sites vary in enrollment rates

Don't forget that the success of any clinical trial is largely determined by the investigative sites that enroll patients, so have adequate ePRO devices when and where they are needed. Every study has high performing sites and low performing sites, and this trial was using ePRO for the first time. Costs add up quickly when ePRO devices must be shipped urgently overnight. Additional devices need to be on hand for keeping the high performing sites stocked.

Lesson learned: Order your ePRO devices wisely in the initial contract to keep trials and budgets managed and on track. Consider regional depots for additional devices that may be required in countries with challenging import regulations. The ePRO vendor should provide guidance on this.

Migrating paper instruments for ePRO implementation

The migration of paper-based instruments to electronic data collection modes must be properly planned and executed so that respondents interpret and respond to the PRO instrument's items the same way, regardless of the data collection mode. Too many PRO instrument developers are paper-centric and fail to contemplate alternative data collection modes when developing their items and selecting response scales. For example, a true visual analog scale (VAS) has descriptive verbal anchors at each end with an uninterrupted line in between. On a self-administered paper-based questionnaire, the respondent can be asked to place a mark or 'X' at the point on the line that best reflects his or her response; however, for an IVRS version of the same questionnaire, this must be converted to a numeric rating scale.²

3. Data transmissions vary

Find out up front if the patient lives in an area that supports wireless transmission of data. There are areas in the US (and other countries as well if you are considering using ePRO for global trials) that do not have adequate cellular reception to support wireless transmission. It's best to provide each ePRO device with a choice of transmission methods, both digital and analog, just in case. Having options avoids downstream frustrations for both patients and the investigative sites. However, in this experience, even on the occasions when disruptions with transmission did occur, the data were retained in the Clario ePRO device, so no study data were lost. In those circumstances, the investigative site transmitted data during the bi-weekly patient visits.

Lesson learned: Ensure whatever ePRO device you select retains study data until transmission is possible. This is vital for preserving eSource data.

4. Site data improves with consistent support and training

Despite carefully scripted training and mentoring for our sites, reality sometimes trumps expectations. Clario Customer Care received a higher call volume than expected for general questions and ePRO training. Study sites should check StudyWorks on a regular basis for common troubleshooting tips.

StudyWorks also highlights patient data outliers and trends. Site-specific emails went out to each site every week to

identify patients where follow up with study coordinators was warranted (i.e., compliance, missed entry, low battery status, etc.). Additional ancillary training was provided throughout the course of the trial to address concrete, not hypothetical, questions arising from hands-on experience. Summaries of key messages were disseminated in bi-weekly newsletters so sites could learn from each other. We also scheduled regular “town-hall” meetings where, those who wanted to, could call in at a specified hour and ask questions, talk or share experiences with others. These outreach efforts paid off with very high compliance across all sites.

Lesson learned: Schedule at least two hours for an ePRO investigator meeting so everyone has plenty of time for hands-on training. Consider refresher training for sites and monitors to bridge any gap between the investigator meeting and first patient in. Stay involved. Ultimately, it's the sponsor's responsibility to keep sites and patients engaged as active participants.

Planning for success

Here are some additional suggestions to successfully plan for an ePRO study:

Your ePRO vendor

Select your ePRO vendor early and take time to understand their processes, document flows, and timelines. Get to know your Project Manager and Coordinator to establish who is responsible for what at each stage of the study, so handoffs are smooth.

Leverage the ePRO vendor's years of operational experience by including them during protocol writing and all planning phases so reasonable endpoint data and instruments (according to FDA and EMA guidelines) are used for protocol development.

Schedule time for modifying existing paper-based questionnaires for electronic implementation. A cognitive debriefing may be required.

If a combination of collection solutions is used, such as IWRS and ePRO, consider integrating these devices to eliminate the chance of manual errors. This will deliver fewer errors, reducing frustration and costs. Some integrations may increase the trial timeline, so plan accordingly.

More on UAT testing

Developing the User Acceptance Testing strategy cannot be left to the system provider or a third party. Rather, this is the responsibility of the sponsor. Those who wrote the protocol and provided requirements to the system provider at the start of the project should contribute toward verifying that these requirements have been covered.³

UAT does not involve target population subjects; it is conducted between the trial team and the ePRO provider. While both UAT and usability testing are necessary and important to the overall success of the trial, UAT is critical to determine whether the software complies with the user requirements documents and written specifications.³

Executing test scripts and ad-hoc scenarios determines whether the ePRO system is ready to go live. Once the clinical trial team has determined that the system is ready for production, they should prepare and sign a formal document that accepts the system as validated for its intended purposes.

Your clinical trial team

Assemble the core team early. Your data management, site management, and biostatistics colleagues need the same understanding of timelines as you to facilitate rapid approval of documents such as Confidential Disclosure Agreements (CDAs), ePRO contract, Statement of Work (SOW), Data Summary (DS) and Data Transfer (DT) Specifications, and User Acceptance Testing (UAT).

Review the vendor's ePRO Requirements Document carefully, as this determines what the trial will look like, and all that is required at each step along the way. Any change to this document later, even a minor modification, has an impact on the trial timeline. Further changes require that the ePRO vendor programs and tests trial changes in all languages.

While every document is important, the ePRO Requirements Document is the most important. More extensive protocol amendments can disrupt budgets and timelines. A thorough Requirements Document review allows for solid initial software deployment and avoids subsequent updates.

Test the ePRO device extensively during the user acceptance testing, and document the findings. These test results will be needed later for the test data transfer.

Your investigator sites

It's important to confirm and verify each site's mobile network and signal strength before determining which transmission devices to ship to the site for an ePRO study. If possible,

select "technology-loving" sites and study coordinators. If the site is ePRO naïve, be sure the study coordinator is familiar with electronic devices (especially computers and mobile phones). Consider adding an extra study coordinator if the study coordinator is not comfortable with the technology.

Study coordinators are training the patients enrolled in the trial, so plan adequate time (preferably two hours) for the investigator meeting. The better they know how to use the ePRO device, how to charge it and transmit data, the better the patients will be trained. Better training means higher compliance.

Keep sites involved and informed. Remind them to check the study portal [StudyWorks] daily to monitor the Clario ePRO device battery level and patient compliance. Remind study coordinators that the sponsor can review the Support Center report online.

Consider publishing a monthly newsletter featuring anonymous questions/answers about the trial, or the most frequent questions addressed by Clario Customer Care. This is a very effective reminder for sites that are reluctant to ask questions of the sponsor.

Get to know your Project Manager and Project Coordinator and clarify who is responsible for what at each stage of the study, so handoffs are smooth.

Conclusion

The keys to a successful ePRO trial are to:

- Plan early;
- Pick an experienced ePRO vendor as a guide;
- Properly educate and allow hands-on training for users;
- Anticipate some human error; and
- Provide ongoing training and communication of best practices to the sites.

Ideally, it takes 6-8 weeks to set up and troubleshoot an ePRO system, not counting legal review, so allow plenty of time for contingencies.

Undoubtedly there is more upfront work required to use an ePRO, but in the end, proper planning can save time, money and frustration. An experienced ePRO vendor will be familiar with data transfers, communication, training and integration of the ePRO with other technologies, so it's important to pick a knowledgeable partner.

As more outcomes data are required for claims by regulatory agencies and payers, **ePRO is the way of the future.**

Paper or eCOA?

Which collection method for PRO data will best support your trial—paper or eCOA?

1 Will COA data be used to support a claim?	YES	eCOA Regulatory agencies recommend that the data collection method be capable of ensuring reports are done on schedule, as defined by the protocol time requirement. “If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what steps are taken to ensure that patients make entries according to the clinical trial design and not, for example, just before a clinic visit when their reports will be collected.” Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling claims’ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). December 2009.	eCOA - Provides regulatory agencies with proof that the protocol time requirements were met. - Provides on-demand data for evaluation or analysis. - Improves subject compliance when private or sensitive data is collected. - Enables smaller sample sizes.
NO 2 Is the COA data intended for an FDA/EMA/other agency Fast Track, Accelerated Approval or Priority Review?	YES	eCOA - eCOA on-demand data enables rapid access for independent evaluation or analysis, and is appropriate for any Regulatory body that will want to meet with the sponsor regularly to review the data (possibly for an expedited process). - Rapid access to data enables adaptive design and other trial efficiencies.	
NO 3 Are you collecting sensitive, personal data?	YES	eCOA - Patients welcome the opportunity to record without embarrassment, and appreciate that caregivers and family lack access to their personally revealing information. - Patients are more willing to provide more complete data. F. Malik and others, 2003, Capturing Quality of Life Using Electronic Data Capture, DIA Annual Meeting.	
NO 4 Is subject recruitment difficult?	YES	eCOA eCOA data has been shown to cluster to the mean value (lower standard deviation) compared to paper data, enabling smaller sample sizes in Phase II trials and more rapid, conclusive Phase III trials. Fried and others, 2007, Efficacy of Tegaserod in Chronic Constipation in Men, American Journal of Gastroenterology. McKenzie and others, 2004, Proving the eDiary dividend, Applied Clinical Trials. Pearson and Raymond 2004, Comparing ePro and paper collection methods for patients with insomnia, DIA Annual Meeting and at the International Society for Quality of Life Research (ISOQOL) Annual Meeting.	
NO Paper Paper is practical for supervised COA data collection where the patient population is abundant, COA data are not personal, or when there are no plans for COA data submission.			

Access at: <http://goo.gl/TAqQsj>

About the author

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Dascha Turner studied Clinical Psychology at the University of Basel, where she completed her training in 2001. Anxious to expand and build upon what she had learned, she pursued a career in the pharmaceutical industry where she has happily remained to this day. Her clinical trial experience includes the management of numerous trials, including the project management of the first ePRO trial of a leading pharmaceutical company.

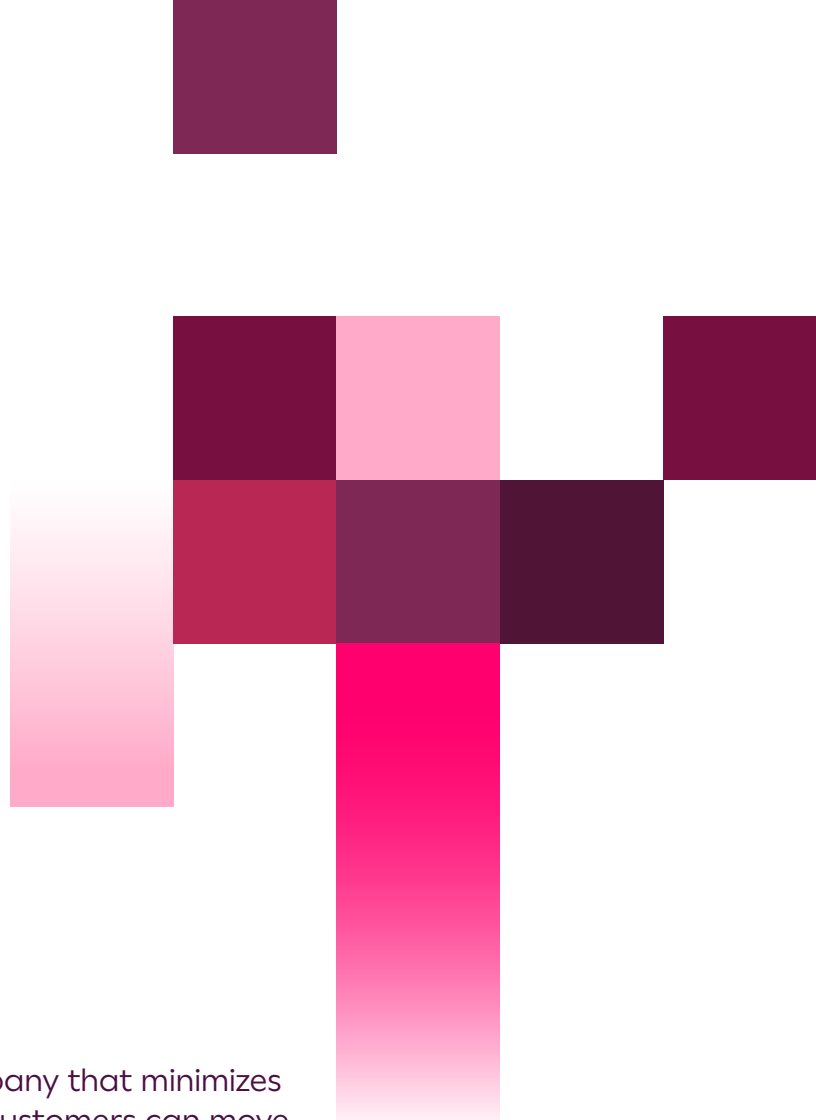
She has served as an Expert Clinical Supplies, Planning & Coordination responsible for the Supply Chain Management of clinical studies

(Phases I – IV), designing of labels and texts and the validation of a new method of package identification. Dascha assisted in the validation of a Timaq-specific tool called TimaqView™.

Please note that the author's views and opinions expressed are personal and should not be attributed to any organization. Dascha Turner can be reached at D.Turner@gmx.ch.

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About Clario

Clario is a global data and technology company that minimizes uncertainty and risk in clinical trials so that customers can move ahead with confidence. With nearly 50 years of clinical and therapeutic experience, Clario balances knowledge of what works with a vision for what's next, so we can adapt without compromising standards.

Powered by the company's EXPERT® technology platform, Clario's solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. Since 2014, more than half of all FDA drug approvals came from Clario-supported studies. Pharma companies, biotechs and CROs have relied on Clario solutions in 10,000+ studies spanning more than three million patients to date. By identifying trial risks before they become problems, Clario enables customers to bring clinical treatments to patients quickly — and with confidence.