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ARTICLE

WITH THE MULTITUDE OF BENEFITS THAT ePRO PROVIDES, WHY ARE CLINICAL TRIALS STILL USING PAPER?

ESSENTIAL TIPS FOR MAKING THE SWITCH

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The electronic capture of Patient Reported Outcomes (PROs) and Clinical Outcome Assessments (COAs) has proven to be a valuable method for the collection of data, far outweighing the data quality of those collected via paper. An overarching question to be asked is, why are clinical trials that include PROs / COAs not using electronic data collection to optimise the integrity of the data and patient experience?

LESS THAN HALF OF CLINICAL TRIALS THAT INCLUDE PROs USE ELECTRONIC SYSTEMS TO CAPTURE PRO RESPONSES

To uncover the answer to that question, it is necessary to explore the reasons for the continued use of the collection of PRO and COA data via paper, look at the advantages of electronically captured PRO / COA data, and examine trends of the general population in the shift towards electronic devices. After having a better understanding of why key stakeholders are pushing forward the transition to electronic capture of PRO / COA responses, as well as what continues to hold back this effort, it can be identified how PROs and COAs can be integrated into an eClinical solution in order to reduce the burden to patients, sites, and clinical teams. In this identification, examining the electronic implementation in relation to each phase of a clinical trial, and evaluating the risks and associated mitigation steps in transitioning to ePRO / eCOA collection modes are also important steps for this transition.

REASONS FOR CONTINUED USE OF PAPER COLLECTION

It is estimated that less than half of clinical trials that include PROs use electronic systems to capture PRO responses.[1] Although some sponsor companies have embraced and incorporated ePRO and eCOA in their protocol implementation, many still continue to use paper PRO / COA. With the benefits and the higher data quality associated with ePRO, a common question is "why does paper PRO collection remain so prevalent in clinical trials?"

Here are the top five most commonly listed reasons for the continued use of paper-based PRO / COAs:

1. **Instruments Designed for Paper:** Many instruments, in particular those developed years ago when paper was considered the standard approach for capturing PRO data, were designed specifically for paper. If a PRO / COA instrument was designed specifically for paper, the instrument author may need to provide approval or have specific requirements for migrating the instrument to an electronic administration mode. Obtaining this approval or complying with the author's detailed requirements may result in unexpected delays and increased costs to the project. Further, the instrument could have wording that specifically refers to paper. For instance, the instructions may indicate to "circle the best response for each question on the paper with your pen or pencil." Thus, to migrate onto an electronic platform, there could be modifications required for the instrument to make sense on the electronic platform.

[1]Wilson, A. (2015). 'Benefits, Challenges and Best Practices of Clinical Trials: Paper vs. Electronic Data Capture.' *Open Health News*. http://www.openhealthnews.com/story/2015-03-11/benefits-challenges-and-best-practices-clinical-trials-Paper-vs-electronic-data-cap. March 11, 2015.

TRUE COSTS OF ELECTRONIC VS. PAPER

TRUE COSTS ASSOCIATED WITH PAPER-BASED PRO / COA USUALLY END UP BEING **MUCH HIGHER** IN MOST TRIAL SETTINGS

At a minimum, there are costs associated with the migration and equivalence testing when moving to an ePRO / eCOA mode. If the trial includes any translations, additional time and costs are incurred for any linguistic validation of translations on ePRO / eCOA platforms. Whereas, if the paper-based PRO / COA has been used before on other trials, paper PRO translations may already exist, seemingly providing an up-front time and cost savings for the trial.

2. **Inability to Determine True Risks of ePRO / eCOA:** Inexperience with ePRO / eCOA may lead to imagining risks that do not really apply, overestimating potential risks, and being swayed by 'ePRO experts' in their company whose experience with ePRO / eCOA comes from a clinical trial years ago. A time when industry standards and research results in literature were sparse, technologies were not as advanced as they are today, and regulatory guidance was limited or missing altogether. Putting heavy weight on unlikely risks is typically caused by limited or lack of experience in running a trial with ePRO / eCOA, and having limited or no ePRO / eCOA subject matter experts to help guide and support the clinical trial team in this transition. Due to lack of experience with electronic platforms and misguided perceptions, the perceived risks may seem larger than they actually are.

3. **Unknown True Costs of Electronic vs. Paper:** The costs associated with paper administration of PROs and COAs may appear to be much less than the actual costs. The true costs associated with paper-based PRO / COA (e.g., secondary data entry, data cleaning, delays in receiving trial results, costs of poor data quality, including additional patient recruitment or re-running the trial if overall results are jeopardised, etc.) usually end up being much higher in most trial settings.

4. **Level of Investment:** Dependent upon how a sponsor company chooses to move forward in their implementation of ePRO / eCOA, there may be up-front investment costs incurred, with the value being recognised later. The initial expenses for purchasing devices (e.g., smartphones, tablets, computers, etc.) or for acquiring new software, upgrading systems, or selecting new vendor(s) to support ePRO / eCOA data capture and integrating data with existing eClinical systems, may be substantial. The value of these investments may not be apparent for several months as the trial progresses, or years later as the trial concludes.

MISSING DATA IS A WIDE-SPREAD ISSUE WITH PROs COLLECTED VIA PAPER, AND **CAN RESULT IN SIGNIFICANT PROBLEMS** IN DATA ANALYSIS AND REGULATORY SUBMISSION

5. **Fear of the Unknown:** In general, people are fearful of change. Typically, they do not move out of their comfort zone and are stuck in their usual way of doing things. In other words, if it's not broken, why fix it? The additional effort required for change and the potential learning curve associated with implementing new processes may be more than someone feels they are able to handle, especially when study teams are faced with the time constraints in the race to bring new products to market faster. Additionally, it might be difficult to determine who the key stakeholders are. If these stakeholders are not identified until late in the process, their input may result in additional delays, rework / effort, or unexpected costs.

ADVANTAGES OF ELECTRONICALLY CAPTURED PRO / COA DATA

In moving away from paper data collection, study teams should be made aware of how ePRO / eCOA offers many benefits to clinical trials, including higher quality of PRO data when compared to data collected via paper. Missing data is a widespread issue with PROs collected via paper, and can result in significant problems in data analysis and regulatory submission.[2-3] Electronic systems offer a solution to minimise the amount of missing data, as compliance is often higher when PROs are administered through an electronic system. Literature states that patient compliance with ePRO is usually >=90%, while paper compliance could be as low as 11-20%.[2]

Commonly cited benefits of ePRO / eCOA to clinical trial data include:[4]

1. **Increased Data Quality:** Direct electronic data entry eliminates time spent reviewing handwritten assessments for completeness (skipped responses or missing page[s]), logic and legibility, outliers / out-of range values, erroneous responses, and extraneous information written in paper margins.[5] Inherent in the nature of ePRO / eCOA systems, extraneous / erroneous information entry and errors stemming from secondary data entry are eliminated. With the ability to include ePRO / eCOA features like branching, validation to ensure only responses within valid ranges are entered, and prevention of skipping, the high-quality responses from electronic systems minimise data clean-up and queries.

[2]Stone, A.A., Shiffman, S., Schwartz, J.E., Broderick, J.E., Hufford, M.R. (2002). 'Patient Noncompliance with Paper Diaries,' *BMJ*, 324, 1193-1194 (2002).

[3]Gwaltney, et al, (2008). 'Equivalence of electronic & Paper-and-pencil administration of PRO measures: a meta-analytic review,' *Value in Health*, 11 (2), 322-323.

[4]Jose, N., Langel, K. 'ePRO vs. Paper,' *Applied Clinical Trials* Online. June 2010, http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=673674&pageID=1

[5]Arnera, V. 'Why Paper Diaries Should Be Banned in Clinical Trials,' *Pharmaceutical Executive Europe Digest*, March 2009, http://www.slideshare.net/challPHT/why-paper-diaries-should-be-banned-in-clinical-trials.

THE FDA HAS PRODUCED A GUIDANCE DOCUMENT FOR THE USE OF PROs IN CLINICAL TRIALS

2. **Optimised ePRO / eCOA Compliance:** Real-time monitoring and alerting for compliance allow sites and study teams to quickly identify patients and site staff who have missed assessments and need compliance encouragement or assistance. Similarly, the real-time safety monitoring and alerting notifies site and study team staff of potential safety issues that require immediate follow-up. ePRO / eCOA systems are easier to use, less burdensome than paper, and can include reminders on devices, via phone calls, or text messages, enhancing compliance in these areas.
3. **Accuracy of Data Collection:** Accurate date stamps provide certainty of the date and time when the patient or site has completed their assessment(s). Assessment windows may be set in electronic systems to ensure that assessments are completed only during these time periods, eliminating retrospective (backward-filling) or prospective (forward-filling) data entry.
4. **Integration:** Responses can be automatically uploaded into mapped electronic systems, allowing for easy integration with other clinical trial systems. For example, data integrated with eCRF, EDC, or IXR systems can provide information on AEs, calculate eligibility, or offer a 'one stop shop' solution with clinical trial reports accessible all from a single system. The integration of the data in these systems can help the trial run more smoothly and reduce the burden to sites and study team staff.
5. **Lower Data Cleaning Costs:** As with paper, the real-time entry and time stamps of electronic based systems reduce the need to clean data for missing or erroneous entries of date / time, secondary data entry errors, etc. The lag time associated to complete data cleaning is largely reduced with direct data entry, as there is no additional time needed for paper PRO / COA to be returned, manually entered with the potential for human error to be introduced, and reconciled. Higher data quality can therefore be achieved with ePRO / eCOA functionalities.

[6]FDA guidance 2009: Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

[7]PRO Consortium: http://c-path.org/programs/pro/; ePRO Consortium: http://c-path.org/programs/epro

PATIENT PREFERENCES AND CURRENT TRENDS LEAN TOWARDS **ELECTRONIC SOLUTIONS**

RECENT REGULATORY AND EXPERT SUPPORT AND ADVANCEMENTS FOR EPROS / ECOAS

In the movement toward ePRO use in clinical trials, there is sufficient support from regulatory authorities, as well as guidance from consortiums with ePRO expertise to help sponsor companies make the transition. The FDA produced a guidance document for the use of PROs in clinical trials that includes a section for considerations in using electronic modes of administration, as well as providing endorsement for the use of ePRO in clinical trials.[6] Additionally, the PRO and ePRO Consortiums were formed and are currently collaborating to produce PRO assessments across multiple therapeutic areas to be available on various electronic platforms.[7] The ePRO Consortium is conducting instrument migrations to electronic platforms, drafting guidance documents, and providing education for ePRO implementation in clinical trials.

PATIENT PREFERENCES AND TRENDS

In a 2013 survey conducted by Almac on subjects with recent ePRO and / or paper PRO experience with at least one clinical trial in the past two years, significantly more participants (77.3%) noted a preference for ePRO than compared to the 22.7% who selected that they preferred a paper mode ($X2=9.9$, $df=2$, $p<0.01$).

It is also easy to see the shift towards electronic devices outside of clinical trials in the general population's daily routines. In 2015, there were 2.6 billion smartphone subscriptions globally. By 2020, globally there are expected to be 6.1 smartphone subscriptions.[8]

With patient preferences and current trends leaning towards electronic solutions, and with the clear benefits that electronic data collection provides, sponsor companies that have historically been content with using paper will need to shift toward the use of electronic modes. For sponsor companies most familiar with the paper data collection approach and transitioning to ePRO / eCOA, the burden to study teams, sites, and patients can be minimised by putting an integration plan in place. There are recommendations to keep in mind within each study phase in order to achieve a successful integration plan (see Table 1).

[8]Lunden, I. (2015). '6.1B Smartphone Users Globally By 2020, Overtaking Basic Fixed Phone Subscriptions,' http://techcrunch.com/2015/06/02/6-1b-smartphone-users-globally-by-2020-overtaking-basic-fixed-phone-subscriptions/

Table 1. Considerations for Successful ePRO Integration Plans

PHASE	ROLE	STEPS FOR THE INTEGRATION PLAN TO MINIMISE BURDEN AND ENSURE SUCCESS
Set-up:	Study Team	- Review wording of assessment questions and response options to ensure it is appropriate for electronic administration. For ease of comprehension, text should be on a 5th grade reading level or lower - User Acceptance Testing of the ePRO / eCOA instrument and integration with any other electronics (if applicable) - Detail up-front efforts and costs associated with setting up ePRO / eCOA system and processes, including any translations
	Site	- Receive training on how to complete eCOA assessment - Receive training on how to train patients in completing ePRO assessments
	Patient	- Not applicable
Maintenance / Management:	Study Team	- Review reports and / or alerts and follow up with sites when compliance rates are low - Review safety alerts and follow up with sites when triggered (if applicable)
	Site	- Train patients on how to complete ePRO assessment - Documentation to provide to patient for ePRO use and support - Troubleshoot ePRO / eCOA access issues with study team or vendor - Download software (e.g., new versions) as needed - If eCOA: Time required to complete assessment(s) during office visit - If ePRO: Review reports and / or alerts and follow up with patients on non-compliance - Review safety alerts and follow up with patients when triggered (if applicable)
	Patient	- Time to complete assessment - Receive training on how to use device (if applicable) - Download software (e.g., new versions) as needed
Close-Out:	Study Team	- Request final data transfer - Ensure any last reconciliation is completed - Request eClinical database lock - If ePRO: Provide access to patient responses (primary source data) in the event of a regulatory audit
	Site	- Ship devices back to study team / vendor (if applicable) - If ePRO: Ensure there is access to patient responses (primary source data) in the event of a regulatory audit
	Patient	- Not applicable

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MIGRATION TO ePRO / eCOA OFFERS TIME AND COST-SAVING BENEFITS

ADVANCING INTO THE TECHNOLOGY OF TODAY

Although some have embraced and incorporated ePRO and eCOA in protocol designs, many continue to stay within the confines of their comfort zone and use paper-based PROs / COAs. Migration to ePRO / eCOA offers time and cost-saving benefits, while effective strategies can be implemented to minimise any risks associated with the transition. For further support, the multitude of educational opportunities and guidance documents available today can also help sponsors in their move to ePRO / eCOA.

In this age of technological advancement, including an integration plan in clinical trials can help to alleviate many of the obstacles in transitioning from paper to ePRO / eCOA, while also mitigating potential risks and minimising burden to patients and clinical trial personnel.

Get the discussion started today!

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