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Best Practices for Avoiding Paper Backup When Implementing Electronic Approaches to Patient-Reported Outcome Data Collection in Clinical Trials

Cindy Howry, MS[1], Celeste A. Elash, MS[2], Mabel Crescioni, DrPH, JD, LLM[3], Sonya Eremenco, MA[3], Paul O'Donohoe, MSc[4], and Tracey Rothrock, BS[5]

Abstract

Electronic data capture is fast becoming the preferred method of collecting patient-reported outcome (PRO) data in clinical trials. Data collection can be site-based (clinical study site), and typically collected on a tablet, or field-based (subject's typical environment such as home, school, or workplace), and most often accomplished with handheld devices, such as a smartphone. While site and study subject compliance with protocol-specific data collection procedures using these devices is critical to trial success, so is the robustness of the device hardware and the software these devices use to capture the trial data. Technology failures and/or site or subject resistance to the electronic data capture protocol may lead a subject to record data on paper, which can result in undesirable data challenges. As such, both site and subject compliance issues and technology-related factors must be anticipated to adhere to the ePRO data collection plan. The objective of this paper is to provide the technology industry's best practice recommendations for optimizing ePRO data collection in clinical trials by proposing the inclusion of a planned approach to data collection that includes viable electronic backup strategies so that defaulting to a paper-based backup becomes unnecessary.

Keywords

electronic patient-reported outcomes, ePRO, eCOA, questionnaires, paper questionnaires, measures, instruments

Introduction

With the advancement of technology and the acceptance and prevalence of personal electronic devices (eg, smartphones and tablets) by the public, the use of computerized systems to collect patient-reported outcome (PRO) data in clinical trials is commonplace and becoming the preferred and recommended method.[1-3] This movement toward electronic data collection has enhanced the quality and accuracy of clinical trial data, and regulators are encouraging electronic instead of paper-based data collection.[1-3] The current electronic options include telephone-based interactive voice response systems (IVRSs), provisioned device-based systems (such as handheld and tablet devices), web/Internet-based systems, and bring your own device (BYOD) systems in which an application is installed on the subject's personal mobile device. Data collection can be site-based (clinical study site), typically collected on a tablet, or field-based (subject's typical environment such as home, school, or workplace), which is most often accomplished with handheld devices such as a smartphone, or both approaches may be used depending on the study.

The advantages of electronic data capture over traditional paper-and-pencil methods are numerous and well documented in the literature[4-6] and include factors that enhance protocol compliance and data quality while reducing administrative burden and trial costs. Electronic data capture systems allow for more accurate and complete data, improved protocol compliance, avoidance of secondary data entry errors, easier implementation of skip patterns, reduced sample size requirements, and potential cost savings.[1] There may be circumstances, however, that arise with implementation of electronic systems, particularly in large, global trials, that may challenge the realization of a system's full potential benefits. In a recent publication,[7] the Critical Path Institute's PRO Consortium and ePRO Consortium outlined factors, including device loss or failure, that may lead study staff or study subjects to default to paper-based approaches rather than the intended modes of

[1] .assisTek, Scottsdale, AZ, USA
[2] Independent Researcher, Pittsburgh, PA, USA
[3] Critical Path Institute, Tucson, AZ, USA
[4] Medidata Solutions, London, United Kingdom
[5] Independent Researcher, Philadelphia, PA, USA

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Corresponding Author:
Celeste A. Elash, MS
Email: celash@comcast.net

electronic PRO (ePRO) data collection in clinical trials. The consortia also provided recommendations for preventing or resolving potential problems to avoid defaulting to paper. The objective of this paper is to build on those best practice recommendations for optimizing ePRO data collection in clinical trials by providing viable electronic backup strategies so that defaulting to a paper-based backup becomes unnecessary. In this paper, we (1) briefly address challenges to collecting complete data electronically related to subject or site resistance; (2) recommend strategies for mitigating the need for backup solutions and describe appropriate electronic backup solutions; and (3) outline the significant challenges created by the use of paper backups.

A Planned, Rather Than Ad Hoc, Approach to Alternate Options for ePRO Data Collection

While electronic data capture is becoming the new gold standard for collecting PRO data in clinical trials, subject or site resistance to technology, or rare circumstances such as device loss or breakage, could result in refusals to use technology for data collection or inability to report data in a study leading to missing data. As such, the clinical trial design and development using an electronic system should include a plan to address such situations immediately to minimize potential data loss. Such a plan can be as simple as ensuring that sites and subjects are comfortable with the technology from the outset of the trial and have ready access to replacement devices in the event of loss or malfunction. More conservative approaches, such as developing an alternative electronic approach to data collection, for example, web-based backup, are viable, but costlier, and come with associated risks further described below. Any alternative approach to the main data collection method should be planned prior to study initiation to prevent missing data. There are several concerns underlying this recommendation.

Previous literature has focused on understanding subjects' resistance to technology or subjects' discomfort with using a device for data collection as one of these concerns. Some subjects might find technology burdensome, which may impact compliance and the completeness of the data set.[7] Clinical staff may also have resistance to technology or may find it burdensome and unintentionally convey this attitude to subjects when training them on the use of the device for the study.[7]

Another concern is that if the device stops working or the subject breaks or loses the smartphone or tablet, then the subject can no longer enter data as scheduled, potentially resulting in missing data that could impact the results of the study. In the past, when the technology was much newer and less robust, hardware breakage or failure was of concern with studies using ePRO data collection; however, with the explosive growth of consumer technology options in the last decade, the quality of hardware has improved significantly. Additionally, with the evolution of ePRO data collection software over the past decades, there have been substantial improvements in the reliability of software and the rigor with which it is tested by both vendor firms and their clients. Based on the experience of the vendor firms that participate in the ePRO Consortium, it is estimated that less than 1% of their clinical trial subjects are affected by issues related to total device failure, breakage, or loss.

BYOD solutions, whether app or web based, have their own unique challenges. Solutions dependent on an active Internet connection are obviously not suitable for those subjects without regular access. Offline solutions, such as a native-app, can sometimes be intentionally uninstalled from a subject's phone by the subject and may prove difficult to reinstall without guidance from site staff.

Negative attitudes toward electronic data collection technology among users, both subjects and clinic staff, can often be linked to previous experiences of device failures with older hardware or faulty software. Although data show that populations often thought to be resistant to new technology (eg, older adults or the technology-naïve) generally prefer electronic data collection to paper after using it,[8] it is still vitally important to ensure ePRO systems are robust and extremely user friendly. Feedback from subjects and clinic staff on the usability and preference for ePRO systems is overwhelmingly positive,[9-11] and these systems are generally designed to be user-friendly and intuitive. Additionally, training of clinic staff is vitally important as they typically introduce subjects to the ePRO system for the first time. Ensuring clinic staff are comfortable and confident with the technology when they are training subjects can have a significant positive impact on subject attitudes and willingness to use technology in the study.

Recommendations

It is the recommendation of the Critical Path Institute's ePRO Consortium that paper backups not be used in studies planning to collect PRO data electronically, particularly not in clinical trials for registration purposes, given the significant drawbacks of paper-based data collection. Paper backups are also not ideal in the site-based setting due to the challenges of setting up a parallel data entry system and are best avoided in these settings as well.

Strategies to Reduce the Need for Backups

Before presenting the alternatives to paper backups, it is important to reiterate that both the study sponsor and technology provider should take steps to minimize the need for any kind of backup in the first place. Adequate site and subject training can minimize missing data due to user error. In addition, the actual software application can be complex and require experienced developers and testers familiar with ePRO software design to program and test the software. Lack of planning, incomplete requirements analysis, and inadequate software design may result in faulty software.[12] It is important that detailed software design reviews are planned, and rigorous software testing is conducted to ensure the software is reliable and validated prior to study initiation to mitigate data loss due to software issues.

Proposed Alternatives to Paper

Suggested alternatives to paper backups are outlined below and summarized in Table 1.

1. Backup device: To minimize missing data that may occur due to loss, damage, or other device-related issues, backup devices should be available at the site and made readily available to study subjects. For site-based assessments, it is advised to have at least one spare device available at each study site, which will increase the associated hardware budget. In field-based studies, it is recommended that subjects be trained to contact the clinic site or help desk immediately if a device cannot be used as expected. If attempts to correct the issue over the phone are not successful, the subject may visit the site to obtain a replacement device, or it may be possible for the technology vendor to ship a replacement device from a local depot directly to the subject. This solution may be the most cost-effective in terms of data quality and up-front trial costs, as it does not require development of an alternative electronic solution.
2. Web- or app-based solutions: An alternative to offering a replacement device is to provide a web- or app-based backup system to capture the data in the interim until a replacement device can be deployed. This web-based backup system for sites or subjects would allow them to use their own Internet-enabled device to access and complete the measures. This solution relies on the assumption that clinic staff and subjects have a suitable device with which to access the web or install an app—an assumption that may not hold true depending on the geographic and demographic circumstances of subjects.
3. Telephone or IVRS solutions: Another option for capturing data electronically is IVRS. With this system, data are collected electronically with a date- and time-stamp including a complete audit trail. This solution might be desirable if the PRO measure contains only a few items and the response options are not lengthy or complex. If IVRS is chosen as a backup solution, sponsors should consider proactively conducting a quantitative measurement equivalence study to ensure equivalence or comparability of the data collected by the modes to be used in the trial given the potential differences in cognitive processing required of the subject with IVRS.[11]

Table 1. Case Scenarios and Proposed Solutions for Field-Based Versus Site-Based Studies.

Scenarios	Problem	Solution	Considerations
In a field-based study, subject's handheld device is unusable for any reason Examples: • Device is broken • Device is lost • Hardware/ software malfunction	Subject is unable to enter data	Solution 1: A replacement device should be provided to the subject as soon as possible. Ensure that each clinical site has access to enough backup devices to support "expected enrollment." Solution 2: To minimize data loss, provide a web-based or app-based backup with which the subject can record data until the replacement device is deployed. [a]	Consideration 1: Solution one is the recommended solution; however, data points may be missed before the replacement device arrives. Consideration 2: A web-based or app-based backup may facilitate collection of key data points that would be otherwise lost. However, use of mixed modes to collect primary or secondary endpoint data is discouraged due to potential risk of increased measurement error. Regulators may require evidence of equivalence of data collected via mixed modes, thus sponsors must weigh the benefits versus risks of increased variability or missing data.
In a site-based study, tablet device is unusable for any reason	Device is not available for use by remaining subjects that day	Solution 1: Ensure there is at least one backup device per site. Solution 2: To minimize data loss, provide a web-based or app-based backup with which the subject can record data until the replacement device is provided to the site.[a]	Consideration 1: Solution one is the recommended solution. Consideration should be given the cost-benefit ratio of providing a second device at each site, given the low probability of failure of site devices. Consideration 2: A web-based or app-based backup may facilitate collection of key data points that would be otherwise lost. However, use of mixed modes to collect primary or secondary endpoint data is discouraged because of potential risk of increased measurement error. Regulators may require evidence of equivalence of data collected via mixed modes, thus sponsors must weigh the benefits versus risks of increased variability or missing data.

[a] Interactive voice response systems may be a viable solution if patient-reported outcome instruments are succinct and amendable to aural responding. Issues of measurement equivalence must be addressed.

Final Considerations

Despite reassurances regarding the robustness and acceptance of electronic systems, trial sponsors may still need to be reminded of the reasons to avoid paper as an alternative for electronic data capture in a clinical trial that is using ePRO technology. Despite the reservations raised herein by the ePRO Consortium, we acknowledge that paper backups are still being used. To further prevent their integration into a study and avoid compromised data quality resulting from paper-based data collection, study teams should keep the following considerations in mind:

1. *Access to paper versions of PRO instruments*: To minimize the likelihood that sites or subjects default to using paper data collection in an ePRO trial, sponsors should instruct sites to encourage subjects to contact them immediately if problems with data entry arise and discourage subjects from recording responses on paper. Additionally, sponsors should avoid providing any explicit or implicit permission to default to paper by limiting access to paper copies of the measure.
2. *Difficulty of reverting back to electronic data collection*: Once a site has switched to paper-based data collection, it can be difficult to move it back to the preferred electronic data collection mode for the trial. Therefore, it is important to prevent the switch from occurring in the first place because of the negative downstream effects.
3. *Impact on data quality from paper-based data collection*: When the same data are collected using paper and electronic-based modes, sponsors should consider impact on data quality as paper-based modes are generally poorer quality (missing responses, out of range data, etc) and may not be sufficiently comparable to be merged with the electronic data. The common argument that any amount of data is better than none ignores the impact on data quality of introducing paper to collect PRO data instead of using an electronic system of data collection. Ganser and colleagues[6] argue that paper-based PRO data can "result in untimely, unreadable, missing, illogical or otherwise faulty data" while Stone and colleagues[4] demonstrated the risk of so-called parking lot compliance, with paper diaries apparently demonstrating high compliance but having a per-protocol compliance of 11%, compared to 94% with the electronic system.
4. *Potential lack of comparability of data captured on different modes*: Sponsors must evaluate the risk of measurement nonequivalence of instruments captured with two or more different modes (ie, "mixed modes") of data collection.[11] Although there is increasing evidence showing equivalence between "visual" modes of data collection (ie, modes in which the data are read by the subject) that may support the use of an alternative mode as a short-term backup option,[13-16] sponsors are advised to weigh the benefits of reduced missing data against the potential risk of increased variability in the data due to use of both paper and electronic versions of a PRO measure, particularly in a field-based study setting. FDA has made clear that they will examine the comparability of data captured on different modes (ie, mixed-modes) within the same study.[2] Thus, depending on the clinical trial phase, the endpoints being supported with the data, and the amount of paper data compared to electronically captured data, there may be a need to demonstrate the measurement equivalence of the paper and electronically captured data a priori.[11] It is also possible to conduct post hoc analyses comparing trial data from both modes to demonstrate comparability, but there is still a risk that lack of comparability may be found, and some portion of the data thus would be unusable.
5. *Cost and complexity of including paper PRO data in an ePRO trial*: Regardless of whether measurement equivalence has been demonstrated, the statistical analysis plan must include methods for double-entry of paper data, as well as integration and analyses that are likely to be more complex and costly than expected. A paper backup may require creation of a separate data entry system and process, as electronic systems are not designed to allow manual data entry from paper.

Conclusion

As stated earlier, it is our recommendation to avoid using paper as a backup to electronic data collection. Effective training for study site staff and subjects is essential to avoid attitudinal- or proficiency-related reasons for defaulting to paper-based data collection. However, it still may happen for other reasons. Alleviating the temptation for sites to resort to paper backups by reducing access to paper copies as well as educating sponsors and sites on the data quality implications of using paper are important strategies for preventing defaulting to paper. Along with having replacement devices as readily available as possible, incorporating an alternative method of electronic data collection into trials during the study design phase can be critical to ensuring that a strategy for avoiding missing data is in place. In trials where an electronic system is being used to collect data for a primary or key secondary endpoint measure, developing a plan and strategy prior to study initiation that can be deployed in the event of hardware or software failure in the trial is crucial to reducing the risk of missing data.

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Declaration of Conflicting Interests

No potential conflicts were declared.

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ORCID iD

Celeste A. Elash, MS https://orcid.org/0000-0002-7825-9528
Sonya Eremenco, MA https://orcid.org/0000-0003-3956-0235

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