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WHITEPAPER

WHY CHOOSE ELECTRONIC CAPTURE OF PATIENT-REPORTED OUTCOMES DATA INSTEAD OF USING PEN AND PAPER

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Patient-reported outcomes (PROs) are a form of clinical outcome assessment (COA) which are measures that assess how a patient feels, functions or survives. Patient-reported outcome measures (PROMs) are a report of the status of a patient's health condition that comes directly from the patient themselves, without interpretation of the patient's response by a clinician or anyone else[1]. In the assessment of some symptoms, clinical outcome assessments can only be truly assessed by the patient themselves – measures of pain, fatigue, or nausea are good examples. However, the use of patient-reported outcome measures (PROMs) have utility beyond these areas and are increasingly included in drug development programmes to provide patients' perspectives on their well-being, functioning, and experiences with treatment. They are also increasingly being used to support labelling claims.

Traditionally, PRO data has been collected using paper questionnaires during site visits, or paper diaries completed by the patient at home. With today's availability of smartphones, tablets, and other mobile devices, over 50% of clinical trials collecting PRO data use an electronic data capture solution. While PRO data collected on paper continues to be accepted by regulatory bodies, the quality and integrity of data collected in this way – especially in unsupervised conditions, such as at-home completion of symptom diaries – is under increasing scrutiny.

This article reviews limitations in the use of paper to collect PRO data and considers some of the advantages of electronic collection.

01 PAPER IS ASSOCIATED WITH GREATER MISSING DATA AND DATA QUALITY ISSUES

Paper completion of PROMs often results in data quality concerns. For example, one study reported that 44% of respondents completing the site-based SF-36 quality-of-life questionnaire either missed or marked an item ambiguously on the paper version[2]. Data collected in unsupervised conditions, such as home-based symptom diaries, are subject to greater data quality concerns.

Typical challenges with paper completion are illustrated in Figure 1. This example of a simple morning pain diary[3], completed at home, shows that the patient did not enter the date of their self-assessment, resulting in missing data. In addition, the response to the rating of pain severity is ambiguous and unclear as to the patient's pain level. Unsurprisingly, there is conflicting data in the response to question four: the patient indicated that they did not awaken in the night due to their pain, but they also reported they awoke 3 times. Finally, the patient has recorded extraneous data on the diary form, which could indicate an adverse event. Dealing with extraneous data requires careful consideration by data managers.

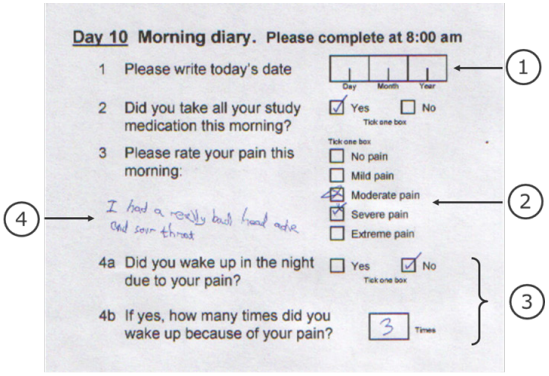

Figure 1. Data quality concerns with paper PRO data[3]

How ePRO helps:

Electronic solutions, such as smartphone apps (Figure 2), can be configured to eliminate many of the data quality issues seen in the paper diary example. Missing data can be eliminated by prompting patients for a response before advancing to the next question. The solution can contain built-in logic that eliminates conflicting and ambiguous data. For example, ePRO forms can enable only a single response to be selected, while questionnaire branching presents certain questions based on the answers to preceding questions, to eliminate conflicting data. Typically, the capture of additional comments and free text is not possible using ePRO.

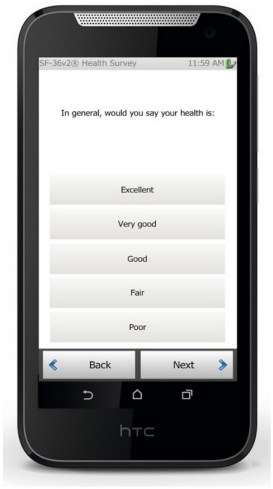

Figure 2. A typical smartphone ePRO solution, showing one item of the SF-36, reproduced with permission of Optum Inc., Eden Prairie, MN, USA (Now Quality Metric, Johnston, RI, USA)

02 PAPER IS ASSOCIATED WITH REDUCED DATA INTEGRITY

Patients completing paper diaries at home may be tempted to fill up the missing diary entries of a sparsely completed diary in the doctor's office parking lot just before their next study visit. Because patients are unlikely to accurately remember the full nature of their health status and symptoms from many days ago, the accuracy and integrity of data collected in this way is questionable. In fact, there are two sources of bias we need to consider when data are captured in this way. Recall bias is the error in measurement due to the inability of a patient to accurately remember their health status at a point in the past. And, response shift is when a change in perception about health status in the past occurs because of an improvement or worsening of health status at the current time. How far back a patient should be able to complete a daily diary, for example, will depend on how accurately patients can recall their status over time.

An understanding of this "parking lot effect" is important in being able to design data collection solutions that are able to demonstrate the integrity of PROM data collected, and helps to support the use of PROM endpoints in regulatory decision making and within medication labelling. A compelling example of this phenomenon was published in the British Medical Journal in 2002[4]. Researchers supplied patients with a paper diary including a hidden light-sensitive microchip that recorded each time the diary was opened and closed. This enabled the researchers to identify whether diary entries were recorded at times scheduled by the protocol or outside the protocol times, such as just prior to a clinic appointment. While the paper records appeared to have 90% completion across the 21-day interval, when the timings of completion were assessed relative to when the diary was opened and closed, the true compliance was in fact only 11%. On 32% of days, the diary binders were not opened, and yet 96% of those days had diary entries completed. In addition, two of the 40 patients were found to have completed the diary ahead of time!

Because of examples like this, regulators have since paid closer scrutiny to the integrity and contemporaneousness of PROM data. The US Food and Drug Administration, for example, state in their PRO Guidance that "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."[1]

How ePRO helps:

Electronic recording of patient diary data overcomes these issues. All electronic solutions have the ability to prevent entries outside predetermined time windows. Take a daily diary for example. This ePRO solution may be configured to allow a patient to record data for the previous day but not beyond that. Solutions also include alarms and reminders to help patients remember to complete their diaries at the required times. This addresses data integrity issues due to the timeliness of diary completion. ePRO solutions also automatically record the time and date that entries are made, providing full demonstration of the timeliness of PROM completion.

03 PAPER DIARIES ARE LESS ABLE TO SATISFY ALCOA+ CONSIDERATIONS

Throughout Good Clinical Practice (GCP) guidelines, we understand that source data collected should meet ALCOA+ requirements as a means of ensuring its reliability. ALCOA requires data to be Attributable, Legible, Contemporaneous, Original (true copy), and Accurate; with ALCOA+ including the additional attributes: complete, consistent, enduring and available.

Figure 3 shows some of the ways an ePRO solution is able to satisfy ALCOA requirements. With paper, it's more difficult. Attributability with a paper diary could be supported by, for example, confirming that no change in handwriting style was observed over the completion period. Legibility, however, is harder to manage, and although good diary design should aim to eliminate the need for free text writing, free text in paper diaries may still be needed when entering numeric data, for example. The contemporaneousness of data collected in an unsupervised setting, such as an at-home daily diary, is impossible to demonstrate when a paper diary is used – it's impossible to prevent the parking lot effect – or prove that even prospective completion hasn't occurred. Originality is harder to demonstrate using paper diaries – undocumented changes to the data recorded are hard to identify and mitigate. Finally, accuracy – both paper and electronic diaries are subject to the need for honest completion, but paper again falls down due to the potential for uncontained retrospective completion which may introduce recall bias or response shift and affect the accuracy of the measures collected.

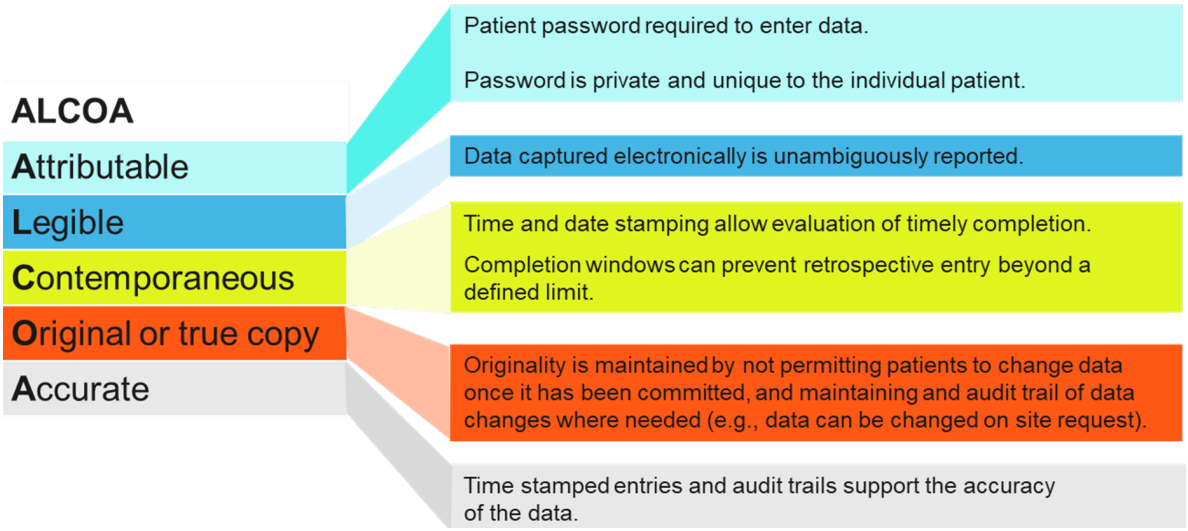

Figure 3. How data collected using ePRO solutions can satisfy ALCOA requirements

04 PAPER DATA IS ASSOCIATED WITH GREATER VARIABILITY AND LOWER STATISTICAL POWER

Some studies have indicated paper collection of PRO data is associated with higher data variability and lower-powered statistical tests compared to ePRO. One study, for example, showed that the estimates of mean change from baseline in total sleep time measured using a sleep diary were similar between electronic and paper diaries, but the standard deviation of the change from baseline was significantly greater with the paper data.[5] Increased variability is associated with a reduced ability to detect treatment-related effects when they exist.

How ePRO helps:

Using ePRO, the reduction in missing data, enhanced data quality, and improved timeliness of data recording may be associated with reduced data variability and high-powered statistical tests.

CONCLUSION

Collection of PRO data on paper is associated with significant limitations, and electronic collection of PRO data is always recommended in clinical trials.

In addition to the advantages discussed above, ePRO enables data recorded by the patient to be visible to investigators and sponsors between clinic visits. This enhances patient monitoring and oversight in clinical trials. Further, in addition to patient oversight, real-time data on ePRO completion rates is valuable to help identify and proactively manage patients failing to remember to complete diary data regularly. Too much missing data means that statistical analyses may be less robust and less able to support reliable inference making. In addition to compliance reports flagging poorly compliant patients to sites and CRAs, audible alarms and notifications built into an ePRO solution can help provide timely reminders to patients and drive complete datasets.

As the smartphone, tablet and desktop technology typically used to collect ePRO data is now commonplace and well accepted, there is no reason to accept the reduced data quality and integrity associated with traditional, pen and paper data collection.

Read more in:

Byrom B, Muehlhausen W. The case for ePRO. In: Electronic Patient-Reported Outcomes: An Implementation Handbook For Clinical Research, Second Edition, pp.5-12. ISBN: 979-8387922077. https://a.co/d/4trld2i

REFERENCES

01 FDA. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Guidance for Industry. Clin Fed Regist. 2009;(December):1-39.

02 Ryan JM, Corry JR, Attewell R, Smithson MJ. A comparison of an electronic version of the SF-36 General Health Questionnaire to the standard paper version. Qual Life Res. 2002;11(1):19-26. doi:10.1023/A:1014415709997

03 Byrom B. The Clinical Trial Process: Technology in Clinical Trials. In: Davies M, Kermani F, eds. A Quick Guide to Clinical Trials. 2nd ed. BioPlan Associates, Inc. Rockville, MD, USA; 2017:217-246.

04 Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. Br Med J. 2002;324(7347):1193-1194. doi:10.1136/bmj.324.7347.1193

05 Ganser A, Raymond SA, Perason JD. Data Quality and Power in Clinical Trials: A Comparison of ePRO and Paper in a Randomized Trial. In: Byrom B, Tiplady B, eds. EPRO: Elecronic Solutions for Patient-Reported Data. Gower, Farnam, UK; 2010:49-78.

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