CASE STUDY

MERCK RESEARCH LABORATORIES REDUCES STANDARD DEVIATION WITH ELECTRONIC PRO

ePRO data deemed quantitatively superior to paper-based study arm

SITUATION

A formal clinical trial called the "Comparison Study" was the first parallel, controlled, randomized study to compare and quantify the differences in data quality between electronic and paper data collection methods. The primary objective of this study was to test the assumption that clinical data collected electronically would be of higher quality and more easily analyzed than those collected by paper.

Many differences between electronic patient-reported outcome (ePRO) and paper methods were expected to affect data quality (**See Appendix**), and the Comparison Study was motivated in part by curiosity to see whether such expectations held true when using best practices for data verification, site monitoring and data management for paper source records. The study also aimed to evaluate whether the two methods differed in their ability to reveal treatment efficacy.

The study, launched in 2002, was designed and funded by Merck Research Laboratories, and is still widely cited to this day as evidence of superior data quality and reduced standard deviation for electronic diary (eDiary) data as compared to paper data. ePRO services were provided by PHT Corporation (now part of ERT).

SUMMARY

The Comparison Study was a formal clinical trial performed by Merck to identify and evaluate differences in data quality and in the activities required of sponsor and site staff when using ePRO methods vs. paper methods for data capture.

IMPACT

- ePRO data were quantitatively superior in 5 categories
- Data variance for Total Sleep Time (TST) was significantly lower with electronic capture
- 41% lower standard deviation with ePRO

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SOLUTION

The trial was designed as a multicenter, parallel group, unblinded and 'usual-care' study for 90 patients recruited in the US. To qualify, patients met the DSM-IV diagnosis for chronic primary insomnia, and had been in treatment with FDA-approved prescription hypnotics for at least 3 months.

Patients were randomly allocated into two arms—one that used paper PRO (44 patients) and one using ePRO (46 patients). The study arms were stratified by age and education level. All patients were subject to the same drug, schedule of activities and PRO assessments.

Data quality metrics were defined and errors were tabulated for different categories, including logical inconsistency, missing values and failures to skip.

Patients completed daily diaries, including a Morning Questionnaire (MQ) (Figure 1) that captured the Total Sleep Time (TST) from the preceding night. These endpoint data were used to calculate the primary outcome measure (Figure 2).

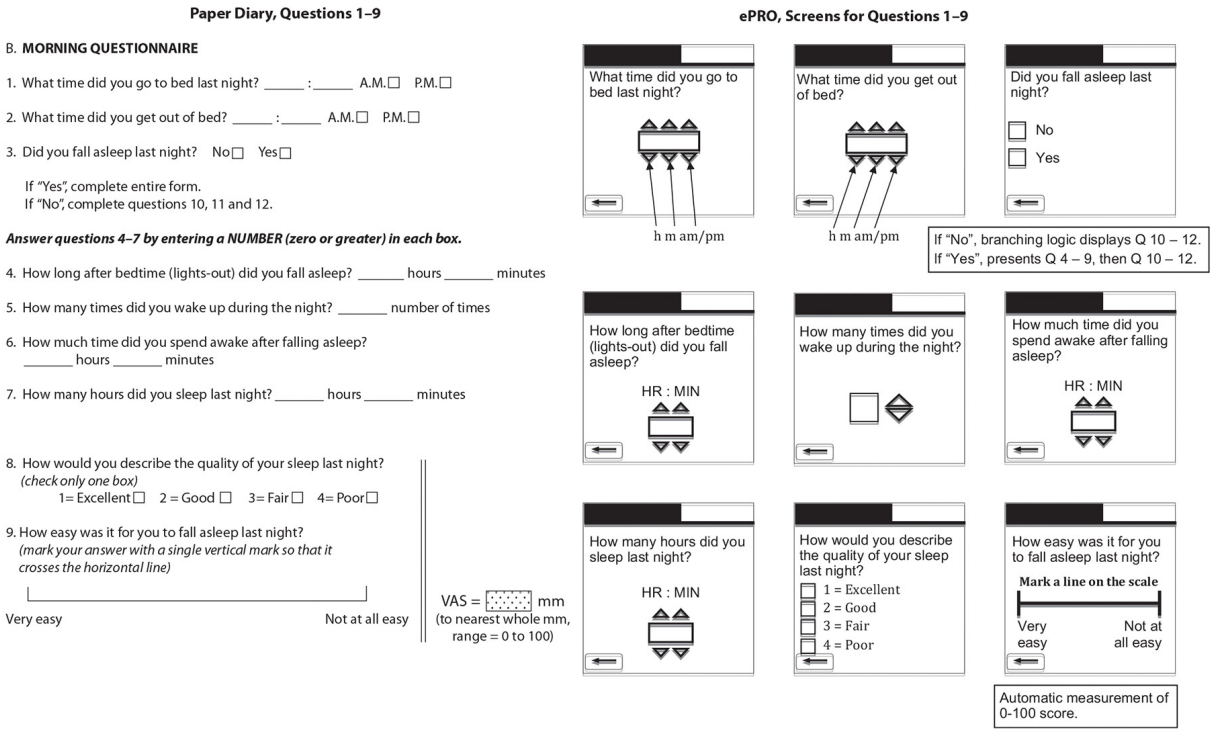

FIGURE 1. Comparison of representative images of the MQ for paper and ePRO[1]

1. More detailed information on this study is available in the chapter 'Data quality and power in clinical trials: a comparison of ePRO and paper in a randomized trial, Allen L. Ganser, Stephen A. Raymond and Jay D. Pearson' in ePro: Electronic Solutions for Patient-Reported Data ed. Bill Byrom and Brian Tiplady (Farnham etc.: Gower, 2010), pp. 49- 77. Copyright © 2010.

IMPACT

As hypothesized, the ePRO arm yielded superior data quality that could be more easily analyzed. Distributions from the paper arm showed greater variance and outliers, while the ePRO arm distributions showed little variance with fewer outliers (Figure 2).

Each data point indicates the change for one subject in mean TST between the washout week (no treatment) and week 4 of treatment.[1] Also plotted for each arm is the overall mean increase in TST (indicated by thick center bars) along with the ± 95 per cent CI and ±SD of that mean (thin upper and lower range bars). Results of the ordinary t test (unpaired, two-tailed, P<0.05) for the equality of means are given at the top.

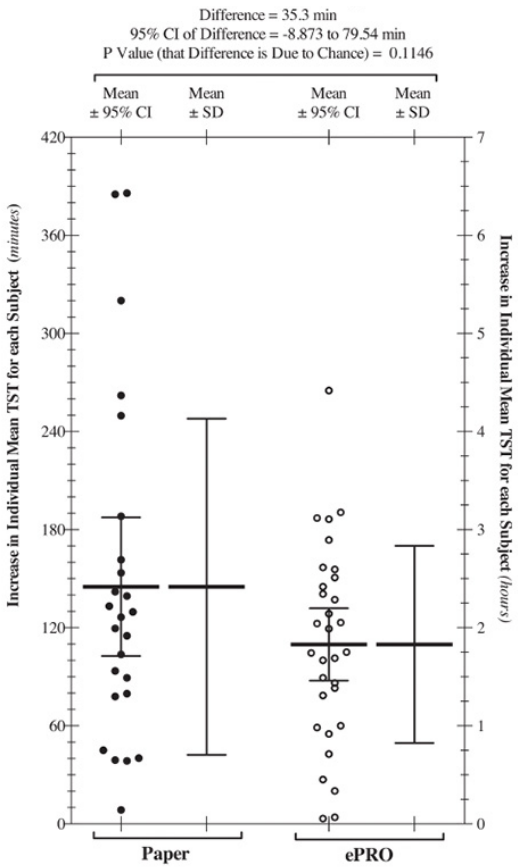

FIGURE 2. T Test of difference in means of individual changes in mean TST between paper and ePRO subjects

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Data quality findings

Clinical data captured and entered on paper records were found to have more data quality problems even though paper PRO data were monitored and cleaned in accordance with Merck best practices. The data captured and transmitted from ePRO handheld eSource records were more complete and more accurate as originally captured, and required fewer corrections.

The variance for the key efficacy variable (TST) was significantly less for the ePRO arm. Compared to the ePRO arm, there were three times more data point changes for the paper arm, and 50% more data clarification forms (DCFs) for paper (Figure 3).

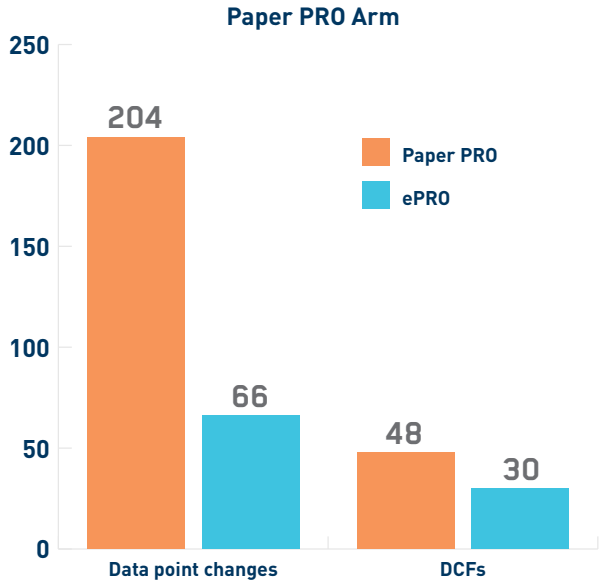

FIGURE 3. Data point changes and DCFs for paper vs. ePRO study arms

Treatment efficacy findings

Similar to other published studies,[2] this study found that the reduction in variability of scores with ePRO as compared to paper results in an increase in the study statistical power. Because of the 41% reduction in standard deviation, a result with the same level of confidence in the finding could be achieved with fewer than half the number of patients if using ePRO.

While it has been demonstrated that ePRO methods can reduce variability around a treatment mean, and thus increase study power, "it should not be generalized that lower variation around a population mean will always result from the use of ePRO methods."[1] Nonetheless, given that accuracy of measurement of a variable includes the accurate measurement of its variation over time, it seems persuasive that ePRO is a better scientific method for PROs than paper.[2]

41%

REDUCTION IN STANDARD DEVIATION WITH ePRO

95%

STUDY POWER ACHIEVED WITH FEWER THAN HALF THE NUMBER OF PATIENTS USING ePRO

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2. McKenzie, S., Paty, J. and Grogan, D. et al. (2004). Proving the eDiary dividend. Applied Clinical Trials , 13(6): 54–68

APPENDIX

ePRO solutions for data quality problems with paper methods[1]

ASPECT OF DATA QUALITY	PROBLEM WITH PAPER METHODS	ePRO IMPLEMENTATION TO ADDRESS THE PROBLEM
Completeness (Were all questions answered? Were reports lost?)	Field(s) expected to be completed are empty in an otherwise complete report.	Completion checks disallow submission of reports with missing data fields.
	Accidentally missed fields cannot be distinguished from intentionally skipped fields ('ambiguity' of empty fields).	Accidentally missed fields are prevented while 'skip options' can mark fields that patients skip intentionally if, for example, they consider the item too embarrassing or if none of the response option fits the situation.
	Missing fields are completed after-the-fact, when study coordinators review paper records with patients, or when site monitors attempt to correct missing fields retrospectively when neither site staff nor patient can remember the situation.	Missing fields are prevented in ePRO reports that are available for completion only during scheduled time windows. Interim access to results supports timely resolution of data errors.
	Entire report is not completed and missing because of forgetfulness or refusal.	Alarms/messages remind patients to complete reports on schedule. Site personnel have timely access to completion compliance metrics and can thus encourage patients to comply.
	Finished reports are missing completely or partially because of loss by patient or investigator (for example, paper diary pages left on bus or misplaced).	A logging device can be lost or become inoperable, but only finished reports not yet transmitted will be missing; those already at a central server are not lost. Records stored centrally are backed up to protect against loss or destruction. Lost devices are replaced as easily as a set of blank paper forms.
Contemporaneous (timely)	Data entry is performed, but not when scheduled. Patients can misrepresent retrospective or prospective completion as if done when scheduled.[3]	Time constraint on the availability of questions is used to make it impossible for ePRO patients to complete scheduled diaries retrospectively or prospectively.
	No validation of time or date of entries.	All data entries are automatically time-stamped using a method validated to be accurate.

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3. Stone, A.A., Shiffman, S. and Schwartz, J.E. et al. (2002). Patient non-compliance with paper diaries. BMJ 324(7347): 1193–1194.

ASPECT OF DATA QUALITY	PROBLEM WITH PAPER METHODS	ePRO IMPLEMENTATION TO ADDRESS THE PROBLEM
Accurate	Transcription errors are made when manually transferring or scanning source data to either paper or eCRFs.	ePRO eSource data is automatically migrated to a central store and ultimately to the sponsor database by methods validated to be accurate and reliable.
	Intensity and impact of symptoms are not precisely rated because of recall difficulties. When patients are asked to assess their current symptoms, paper methods confound data that is current with prospective (guessing) or retrospective (from memory) data.	When ePRO assessments are intended to reflect the current state of the patient, they are captured in real time or close enough for memory to be sharp. Recall bias is minimized. For example, sleep latency is required the next morning when patients can recall the preceding night. ePRO prevents assessments made days later.
	Key behaviors required by the protocol, such as the schedule of taking study medication, are assisted only by static written instructions.	ePRO systems can request behaviors automatically at the appropriate time. Devices can also display recently logged events so that patients can, for example, avoid taking an extra pill or reporting taking a particular pill twice.
	Patients do not accurately interpret contingent instructions.	With a response of 'no' to 'Did you sleep last night?' ePRO skips the questions related to that night's sleep and presents subsequent items. ePRO systems can also automatically prompt patients for contingent behaviors (for example, 'you have escalated doses 4 days in a row, please call your study nurse').
	Annotations can show the proper formula to calculate a value to enter, but cannot assist in actually making the calculation and errors can occur in these derived fields (for example, BMI, median of total sleep time over a period of days).	Derived fields can be calculated automatically by validated methods.

ASPECT OF DATA QUALITY	PROBLEM WITH PAPER METHODS	ePRO IMPLEMENTATION TO ADDRESS THE PROBLEM
Logical (consistent, not out of range)	Response data are factually incompatible (for example, patients respond that 'no' they didn't sleep but also report a number of hours slept).	Software applications detect logical inconsistencies at the time of data entry and allow for corrections. The sequence of questions automatically branches depending on previous responses, so that illogical items are not presented.
	Patients fail to follow instructions on how to answer a question, such as checking both responses to an either/or question or marking more than one option of a multiple-choice item where a single option is required and some options may be logically inconsistent.	ePRO system allows only one response to either/or questions and to multiple choice or rating questions that require only one answer from a list of options. For example, 'Did you sleep last night? ☐no ☐yes' and 'How would you describe the quality of your sleep last night? (check only one box) ☐1 = Excellent ☐2 = Good ☐3 = Fair ☐4 = Poor'
	Out of range values are entered (for example, total sleep time is greater than time in bed).	'Soft' range checks can alert responder to values likely to be out of range. 'Hard' range checks disallow values deemed impossibly out of range.
	Past, present or future dates can be entered, regardless of instructions.	Selection of dates or times that are known to be inappropriate is prevented at the moment of data entry by programmed date checks.
Conforming (to protocol)	Patients may forget that they have already done a report and re-do it.	If only one report is scheduled, ePRO devices allow only one report to be completed for a particular scheduled report time.
	When a patient receives a set of paper forms that replaces a lost set that had been partially completed, the patient may begin with the wrong report.	ePRO replacement devices automatically guide patients to complete the next available appropriate report.

ASPECT OF DATA QUALITY	PROBLEM WITH PAPER METHODS	ePRO IMPLEMENTATION TO ADDRESS THE PROBLEM
Original (not duplicated)	Study data are first recorded to a record that cannot be demonstrated to be original such as scraps of paper for writing measurement values or notes where dates, times and other contextual information are often not recorded.	ePRO capture devices used by patients and observers are the first mode of capture for study data. By regulation, the temporal context and authorship must be part of each record.
	Resolution of a data mismatch between a manually compared paper CRF with paper sources may not be traceable.	ePRO records are eSource documents. The eCRF fields in ePRO systems are automatically populated from eSource data, and each field in the clinical database is therefore traceable to the original eSource.
Attributable (Did anyone but the patient write in the diary?)	Data pertaining to a patient becomes associated with another patient. Source data may not include necessary identifiers and may be sorted incorrectly.	Devices with unique codes (analogous to credit cards) are assigned for the sole use of a patient. PIN or other access codes, given only to the identified user, are required for data capture. Phone numbers or IP addresses used during capture or transmission are logged. Handwritten or digital signatures are linked to eSource records. Current interim data is available for site staff to review so that data content not matching a patient's status can reveal erroneous attribution.
	Actions on data (capture, edits, approvals, etc.) may not be linked correctly to the person performing the action (for example, improperly signed or dated source documents, CRFs, edits to data).	ePRO system identifies users and links all actions on data to an identified and authorized person via a computer-generated audit trail. The action cannot be completed without attribution.

ASPECT OF DATA QUALITY	PROBLEM WITH PAPER METHODS	ePRO IMPLEMENTATION TO ADDRESS THE PROBLEM
Unambiguous	Ambiguous date formats (for example, 05/07/09 entered for July 5, 2009 could be interpreted as May 7, 2009).	Date fields are entered from a calendar, date 'spinner,' or other control that reveals month and day unambiguously and presents them in the order that is locally appropriate.
	Blank day or month numbers appear in date records where fully specified dates are required; am or pm are missing from time entries.	Devices require capture of complete dates for some fields, but could truncate full dates to hide the day and month and/or allow capture of partial dates for others. Date and time conventions are set at field, form, or study levels.
	For time entries, inadvertent use of am or pm, or confusion about whether midnight is 12:00 am or 12:00 pm.	Intelligent ePRO software can request assurance of am or pm entries or correction of inappropriate use of am or pm time indications.
	Differing database standards across studies hamper combining data for analysis (for example, a yes or no response may be transcribed with 0 vs 1, 1 vs 0, or 1 vs 2 codes).	Multiple coding conventions can be supported in each study. CDISC or other standards can be enforced for original source data so that data from similar studies can be pooled for meta-analysis.
	Response mark is made between two check boxes.	Selection of response options are displayed in real time so that the patient resolves any ambiguity at the time of capture.

ABOUT ERT

ERT 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, ERT balances knowledge of what works with a vision for what's next, so we can adapt without compromising standards.

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