

Technology Solutions for the Collection of Patient Reported Outcomes Data

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Many research articles have exposed the limitations of paper diaries and questionnaires in the collection of patient reported outcomes data. In a study comparing paper diary records to those secretly stored with an electronic peak flow metre, significant limitations were illustrated in paper diary data (1). It was found that 46 per cent of data recorded on paper were missing, but also that a surprising 22 per cent of paper data were invented by the subject, being entered onto the paper diary but not recorded electronically. Sometimes referred to as the 'car park effect', it would seem that individuals feel uncomfortable returning a blank diary and hence retrospectively complete a number of entries just before a clinic visit. More recently, a study using a paper diary with an embedded light sensor to record when the diary was opened and closed found that few subjects recorded data when scheduled, and in fact some subjects recorded data prospectively (2)!

These studies do not stand alone, the literature contains many other examples that criticise the integrity of paper diaries because they cannot assure the timeliness of data entry and guard against retrospective and prospective completion. The magnitude of missing and invented data can have a significant impact on the overall findings of the study. Empirical estimates suggest that four times as many subjects may be required in a study with 50 per cent missing data to achieve the same power as a trial with 100 per cent diary data (3). With the high rates of missing and invented data observed in studies using paper diaries, these studies may either be underpowered or may accommodate this additional noise by being designed with much larger sample sizes than necessary to detect relevant treatment-related differences.

The quality of paper diary data is often poor because paper diaries cannot prohibit the entry of conflicting or missing data. Some of these data quality concerns are illustrated by Ryan *et al*, where 44 per cent of respondents completing the site-based SF-36 either missed or marked an item ambiguously on the

paper version (4). Researchers using paper diaries that ask subjects to indicate whether they woke up during the night due to their symptoms and additionally to record the number of

Figure 1: Issues with Paper Diaries – Missing Data, Ambiguous Data, Conflicting Data and Extraneous Data

awakenings, will not be surprised when some subjects respond negatively to the first question and enter a non-zero response to the second (see Figure 1, page 79). It is not possible to query collected patient reported outcomes data, so statisticians must decide how such data should be processed and whether in fact, as is likely, conflicting data must be excluded from an analysis.

Electronic recording of patient diary data overcomes these issues. All electronic solutions have the ability to prevent entries outside predetermined time windows, and to record the time and date that entries are made. This addresses data integrity issues due to the timeliness of diary completion. In-built logic checks and questionnaire branching eliminates conflicting and ambiguous data. Datamonitor report that 25-30 per cent of all clinical trials collect some form of patient-reported outcomes data (5). Despite this, currently only three per cent of these use electronic diary solutions as a means of collecting such data. Although their report forecasts an increase in this figure, the uptake of electronic solutions is staggeringly low given the known and well-documented limitations of paper diaries.

BARRIERS TO IMPLEMENTATION OF ELECTRONIC SOLUTIONS

There are a number of reasons that sponsors may be reluctant to implement electronic diary solutions in clinical trials. First, researchers may feel that because they have achieved the required results using paper diaries there is no justification to change. In fact, there may be a feeling that by switching to a technological solution, this in some way acknowledges the limitations of previous data collected using paper. This is an understandable position, but one that is unlikely to be sustainable with the slowly increasing pressure of regulatory authorities for sponsors to defend the integrity and quality of these data. Recent EMEA guidelines in asthma request that if home recording equipment is used, reproducibility is particularly important, and an electronic diary record should be considered to validate the timing of measurements (6). In addition, some FDA speakers have stated off the record that diary data, when used as the primary endpoint, should be recorded electronically, although this has not yet featured in written guidelines.

Secondly, electronic solutions may be perceived to be expensive when compared to paper diary use. Although it is likely that an electronic diary will be more expensive than paper, few researchers consider the internal costs of processing paper diary records or the cost saving that can be accomplished by providing cleaner data, and therefore require fewer subjects to show treatment effects (when diary endpoints are primary). Without direct savings due to a reduced sample size, it is difficult to attribute financial value to an increased level of integrity or the quality of the data collected, but this realisation in itself is not a reason to ignore the possibilities.

Thirdly, some researchers may believe that the validation of the electronic diary against its paper equivalent is a necessary and costly requirement. This may be seen as a barrier in terms

of the cost and time involved in instrument validation. When patient reported outcome data are primary endpoints or may be included on the labelling (such as quality of life); when the instrument used is a gold standard on paper; or when electronic data are to be pooled with data collected using the paper equivalent; this may be desirable. However, many bespoke instruments and secondary endpoints may not require such a rigorous approach. Validation studies can be performed rapidly and relatively inexpensively. Studies normally comprise a crossover in a small sample of both healthy volunteers (if appropriate) and patients, where both the paper and electronic diaries are employed for a short collection period.

Finally, electronic solutions may be perceived to be over-complicated for patients to use when compared to a paper diary. Certainly some patient populations may find certain technology solutions difficult – the elderly, for example, may find the use of a handheld device difficult or awkward to use. However, the variety of electronic solutions available means that an appropriate application should be available for most populations.

SELECTION OF TECHNOLOGY SOLUTION

When selecting an electronic diary solution for patient home-use, there are two broad types of solution available, each with unique advantages and limitations: handheld devices and interactive voice response (IVR) systems. Even within each class, the functionality and utility of solutions may differ widely. For site-based questionnaires, additional solutions are possible including the Internet, and tablet and touch-screen computers.

Handheld device solutions are, in effect, mini computers or ‘personal data assistants’ (PDAs) that are issued to patients entering a study. These devices have a small screen to display questions, and a number of buttons to control navigation through questions and to assign a response to a question. Data are normally stored locally, but can be submitted to a central computer either via a modem link at the patient’s home or at the study site. IVR systems are accessed by the patient who telephones into a central computer system via a toll-free number. Pre-recorded messages comprise the diary questions, and responses are made using the keys of the telephone keypad.

When selecting a technology solution it is important to consider that not every solution will be ideally suited to every study protocol or every patient population. It is therefore desirable for sponsors to establish a ‘toolkit’ of preferred solutions and an algorithm by which they can decide which solution to apply to a particular study. To determine the optimal solution it is helpful to consider the strengths and limitations of each technology.

Handheld device diaries have a number of advantageous features. Devices can be configured to beep or flash to remind the patient of a scheduled diary entry. The in-built

screen facilitates the entry of free text and visual analogue scale data, and can also be used to present on-screen tips during diary completion. Their main limitations centre on their ease of use, the requirement to deploy and maintain hardware, and connectivity issues. Equipment deployment and support is not a trivial problem. Customs importation issues may result in unplanned delays or expense; device malfunction or loss may result in loss of data and may place additional burdens on site staff and CRAs in managing the distribution, replacement and collection of devices; and battery failure may result in the loss of time and date and any non-transmitted data.

IVR systems have the advantage that they are easy to use, employing simple and familiar technology. Almost every patient in every clinical trial owns a telephone, making IVR a simple and cost-effective solution. Data are entered directly onto the central IVR database, eliminating download and connectivity issues and making all diary data available for review in real-time. The use of an IVR diary may be limited mainly by the nature of data collected. IVR diaries use the telephone keypad to enter data, making it ideal for collection of numeric, binary, ordinal scale, 101-point scale and categorical/multiple-choice data. However, it is not possible to simply incorporate instruments requiring free text entries or visual analogue scale (VAS) data using IVR applications. Although the VAS correlates well with ordinal and 101-point scales (7), it is not always possible to replace these scales, particularly when using validated gold standard instruments.

When selecting the technology type to employ in a particular study, sponsors may consider the following questions:

- ◆ Is the patient population unsuitable for either or both technology applications? As an example, elderly or arthritic patients may not be suited to handheld device diaries and patients with hearing difficulties, limiting their ability to use a telephone, may struggle with an IVR diary.
- ◆ Is the diary instrument unsuitable for either or both technology applications? For example, visual analogue scale data cannot be collected using IVR.
- ◆ Are the countries involved likely to have problems due to home telephone availability and connectivity? In countries where patients are unlikely to have a home telephone, IVR diaries may be inconvenient and it may be impossible to perform at-home data downloads from a handheld device. Paper diaries may provide the best alternative.
- ◆ Are the logistics of hardware deployment and support limiting to the successful management of the study? With many countries, many subjects, or few subjects per site, the handheld diary device solution may be particularly difficult to support.
- ◆ Does the study design make one or another solution significantly more expensive? When the

population and diary are suitable for administration using either technology, the decision may simply be one of cost.

TECHNOLOGY COST COMPARISON

The table below details the key cost drivers for implementation of an electronic diary solution using a handheld device or IVR application.

Table 1: Key Cost Drivers for Electronic Diary Implementation	
IVR Diary	Handheld Device Diary
<i>System Set Up</i>	
Complexity of diary	Complexity of diary
Number of patients and sites	Number of patients and sites
Languages	Languages
<i>Hardware Purchase/Lease</i>	
N/A	Number of patients and sites
	Duration of study
	Shipping costs to sites
	Device set up
	International power source and modem adapters
	Re-deployment of damaged/lost devices
<i>System Support</i>	
Number of sites	Number of sites
Duration of study	Duration of study
Length of diary questionnaire and frequency of administration	

Based on these key cost drivers, it is clear that handheld device diary solutions have significant start-up fees when compared to IVR. Hardware must be purchased or leased, configured, assembled (with peripheral hardware and/or foreign adaptors) and shipped before subjects can enter data. The IVR approach has none of these start-up costs; for IVR solutions, the key additional cost component is call volume, that is the length and frequency of patient diary calls. From this it is fair to assume that IVR will in many instances place less of a cost burden than a handheld device system.

REGULATORY REQUIREMENTS

Electronic diary solutions satisfy many regulatory concerns: subject identity is maintained; diary compliance cannot be faked; diary compliance can be measured; the timing of diary entries can be recorded; and data quality can be increased due to elimination of conflicting data.

Current regulatory concerns are focused on the availability of the data:

- ◆ Availability to an auditor and audit trail systems to demonstrate that data have not been corrupted or manipulated

- ◆ Availability to the investigator for ongoing review
- ◆ Availability in the future – will it be possible to audit and review the data in a number of years time?

Diary solutions using hardware retained by the patient must have robust in-built security to satisfy regulators that they are tamper proof, therefore demonstrating the integrity of the data they contain.

ICH GCP guidelines define subject diaries as source documents, which means that, in common with other source data, they belong with the investigator who is responsible for their retention. As a consequence, it is important that not only is a certified copy of the data provided to the investigator for retention at the end of the study, but that these data are fully available for investigator review throughout the study. This is facilitated using IVR applications because of the fact that data are written directly to a central database without data download from home or site. Data can therefore be made available to study site staff via real-time secure online reports or ad hoc reports, issued by fax or email following an investigator request via an IVR call.

Future-proofing is an important concern and means that technology is in fact only a small part of the decision-making equation. The EDC and eDiary business is a fast moving area – new technology and technology enhancements are rolled out in rapid succession. The concern facing sponsors and regulators is that the changes and enhancements to handheld devices and their operating systems means that devices employed in studies today may soon be obsolete. Unlike IVR, which has been delivered on a stable platform for many years, this may limit future availability and the ability to check data collected using handheld devices. In this climate of rapid change, the stability of the organisations behind the technology is an important consideration. Many device companies operating on the market two years ago are no longer in business today. It is therefore important that sponsors select a technology solution that is delivered by a stable company with an appropriate track record.

CONCLUSION

In clinical trials, interactive voice response (IVR) systems are commonly used to perform randomisation and 24 hour emergency code break and to provide a sophisticated method of optimising and managing the clinical drug supply chain (8-10). However, IVR has been used effectively in clinical trials to collect patient reported outcomes data (11-15), and in a similar way to deliver automated study pre-qualification screeners (16-18). In fact, as an electronic diary option, IVR systems have the advantage of being simple, easy-to-use, familiar technology, applied without the requirement of additional hardware to deploy and support. Not only do IVR systems satisfy current regulatory questions regarding the requirement for these (e)source data to be available for investigator review and approval, and for data to be accessible and readable in future, but they provide a highly cost-effective solution for the collection of quality patient diary data. ◆

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