Move Aside, Paper:

CAPTURING CLINICAL TRIAL OUTCOMES IN THE DIGITAL AGE

Contributed by

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There has been much discussion throughout the healthcare industry about providing a positive patient experience and encouraging patients to have more of a voice in their treatment options. Stakeholders have come to recognize that patients have valuable information to share about their experiences with diseases and medications, which should influence drug approvals and treatment decisions. The FDA, for example, has launched an initiative, "The Voice of the Patient," to gather patient perspectives across specific disease areas. The initiative allows the FDA to hear from patients directly about their conditions and the therapies they use to treat them.

The focus on patients' perspectives extends to clinical trials as well. Information reported by clinical trial participants is critically important to the success of studies designed to prove the safety and efficacy of investigational drugs. There is a growing demand for patient-reported data as proof points once products are on the market and payers require evidence of their health economic value. Patient data are collected via clinical outcomes assessment (COA) tools that can be either paper-based or electronic, the latter in the form of voice response systems, Web portals, specialized handheld devices, and smartphones. But why do we still use paper when we know anecdotally, at least, that an electronic format is more accurate, cost-effective, and faster?

The Scientific Realities of Patient Reporting

As part of Good Clinical Practice (GCP), any method used to collect patient-reported outcomes must minimize the burden on patients while providing feedback that is correct, dependable, and repeatable. Yet the process will always be limited by:

Patient compliance. Patients will report as directed—or not—based on their own internal motivation and regardless of the survey modality used.

Potential bias, independent of the survey modality. Patients want to get better and often say whatever they think will support the drug's approval. Moreover, patients want to please the Principal Investigator (PI) and so often say what they think the PI wants to hear.

"Parking lot syndrome." The validity of results diminishes the longer patients wait to report, and they do tend to put off their reporting. Patients make unreliable narrators when working from memory, often resulting in parking lot syndrome, whereby patients complete a weeks worth of diaries just before entering the PI's office for a study visit.

Misconceptions about Paper

Paper-based survey tools have been in use for decades and have successfully supported thousands of label claims. Paper-based instruments are held up as the standard against which all other modalities are measured.

Despite this history, paper cannot compare with e-solutions in speed or accuracy. Paper-based surveys cannot prevent patients from skipping questions, writing in margins, or providing ambiguous data. There is no way to tell if a patient completed the diary from memory. Errors can be introduced when interpreting patients' handwriting and manually entering responses into a database.

With all these limitations, why have trial sponsors been slow to adopt electronic solutions?

There are many reasons for this, but in all likelihood, the perception that paper is free stands out as a probable cause. While most trial managers never see a line item in their study budgets for paper, the cost is reflected in the corporate budget and, when added to the expense of purchasing the paper, printing diaries, binding, and shipping them to sites, it's a sizeable one. As one study leader with a large biopharma company noted, "We spend $14.7 million per year on paper for clinical trials, but it's not a line item in our trial costs."

For the most part, the cost of paper diaries is invisible. But electronic solutions do appear as a line item on a study's budget, which can be perceived as an added expense or just plain expensive. Companies must become attuned to the actual cost of using paper for patient-reported outcomes in order to make a fair comparison with the cost of electronic diaries.

The Benefits of Electronic Solutions

Studies have consistently shown that patient compliance for completion of patient-reported outcomes (PROs) and data quality is significantly higher when PRO assessments are administered electronically. Electronic solutions successfully:

- Reduce the tendency to report based on memory through automated reminders and the use of electronic date and time stamps
- Use checks and alerts to prevent data omissions and the entry of ambiguous or out-of-range results
- Provide seamless skip logic, preventing patients from erroneously answering the wrong questions
- Prevent patients from writing extraneous — and unusable — information in diary margins
- Reduce the number of monitors needed to input patient diaries
- Eliminate the data entry errors in transferring paper results into a database
- Provide immediate access to data in real-time reports
- Increase patients' willingness to report sensitive information

In fact, by improving the quality of the data collected, e-solutions actually reduce the number of cohorts needed to achieve the desired statistical power in a study. This could reduce the cost significantly.

The typical breakeven point for paper vs. eCOA is at 40,000 pages of incoming data. If a patient completes two diaries per day over a trial's lifetime, the number of pages can be

three times that amount, but there is no added expense when the diary is electronic. The costs remain constant because the hardware and software is already provided. Without the added expense of provisioning hardware, trial costs drop drastically.

The eCOA Landscape

Sponsors can choose from among a number of electronic modalities for collecting patient-reported data, each with its own strengths and challenges, as summarized in Figure 1.

Figure 1: An Array of Modalities, Each with Strengths and Challenges

Modality	Ubiquity/ Global Availability	Affordability	Data Quality	Convenience for Patients	Ease of Development
Paper	◐	●	◐	●	●
Voice	●	●	●	●	●
Web	●	●	●	●	●
Specialized Handheld Devices	◐	◐	●	◐	◐
Tablet	◐	◐	●	◐	◐
BYOD (App)	●	●	●	●	◐
BYOD (WAP)	●	●	●	●	●

Interactive Voice Response (IVR) Systems

Interactive Voice Response Systems (IVRS) are the oldest electronic solution, but that doesn't make them outdated. They may just be coming into their own, given the ubiquity of cell phones even in emerging markets. Patients are given a toll-free number and use voice prompts to report their information. Voice response is ideal for instruments with fewer than 10 questions and can accommodate all types of survey questions. There's no learning curve with IVRS and they are extremely cost-effective, as there's no hardware to provision.

Web Portals

This modality, like IVRS, is widely available to patients and very inexpensive for sponsors. Patients log on to a computer and access a portal to complete their survey. Study managers can easily render questions on a website to appear just as they do on paper, simplifying equivalence testing. And for those patients who have smartphones or tablets, this solution becomes one part of a bring-your-own-device (BYOD) approach.

Tablets

Some trials have provided patients with tablets installed with a data-collection application. The format of surveys presented on tablets is faithful to paper versions (similar to the Web solution). Unfortunately, the hardware itself is still expensive. If a tablet were lost or misplaced, a replacement would need to be swiftly furnished, which has both time and cost implications. Hardware must also be shipped to study countries and clear customs. The investment could be justified if used for by clinicians to collect patient data (ClinRO).

Patient Smartphones and Tablets: BYOD Solutions

Sponsors can arrange for patients to provide data via their existing smartphones: either through a dedicated application that patients download or through WAP/WEP accessing a Web portal. Leveraging assets the patient already has reduces patient burden and proves especially cost-effective for the sponsor.

These options are appealing because pharmaceutical companies wouldn't have to provision devices to patients all over the world, and the devices wouldn't have to be pre-loaded with instruments. Subjects can receive a stipend to cover data costs in the same way sponsors remunerate subjects for subsistence and travel.

Proprietary Handheld Devices

A number of years ago, some clinical trial service providers created specialized data collection software to run on personal data assistants (PDAs). The idea behind this method — allowing patients to report via a mobile device — was groundbreaking then, but will likely be phased out in favor of a BYOD solution moving forward.

Simply stated, furnishing patients with a separate device is both costly and inconvenient. Proprietary devices must be leased, programmed, shipped, and re-provisioned if lost, and as trials become increasingly global, shipping devices becomes increasingly complex.

What's the Best Choice?

There's no universally applicable solution. The best modality depends on a number of factors, including:

- The actual assessment to be used
- The disease state measured
- The length and complexity of the instrument
- The infrastructure for cellular signals and Internet connectivity in target trial markets
- The size of the patient population to be surveyed

Given the rapid advancement of technology options, it seems that paper solutions are destined to give way to digital ones. This will likely occur when:

- Decision-makers become attuned to the true cost of using paper solutions.
- HEOR professionals begin driving patient-reported research. They'll need a modality that is inexpensive enough to use with many patients and that will deliver quantitative data. IVR systems and BYOD fit the bill. The use of both will likely explode in the next few years as HEOR's interest in them grows.
- A body of evidence is formed as proof that these modalities have been successful in meeting regulatory requirements. Currently, sponsors are reluctant to share their success stories in using electronic modalities, but all could benefit by pooling information on their experiences, perhaps through a neutral party that serves as a clearinghouse for the information.

Technology is ever-evolving. Already, there are new, exciting innovations on the horizon, such as wearable health tracking devices that could conceivably become an effective means of collecting patient data. In the short term, however, eCOA solutions such as IVRS, web portals, tablets, and BYOD are poised to supplant paper, becoming equally ubiquitous, familiar, and proven. And perhaps most important, these solutions will inject the "voice" of the patient into treatment pathways, helping to drive greater efficiencies, increase accuracy and ultimately improve trial outcomes. PV