Electronic Patient Reported Outcomes and Integrated Systems:

EFFECTIVE SOLUTIONS FOR ENHANCED COMPLIANCE AND HIGH DATA QUALITY

Contributed by

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With all the elements that comprise a clinical trial — from design to enrollment to analysis — it is little wonder that success can be impeded by challenges along the way.

Use of Electronic Patient Reported Outcome Technologies

Low patient compliance and low data quality of Patient Reported Outcomes (PROs), such as patient diaries, can be critical challenges in clinical trials. Lack of patient compliance is a leading cause of missing data in PROs, and low data quality can also result in missing data when data are deemed inaccurate and unreliable. High amounts of missing data can lead to inconclusive trial results and introduce bias in the study. The FDA has encouraged the industry to identify ways to improve this issue in order to avoid inconclusive trial results.

Electronic Patient Reported Outcome (ePRO) tools have grown in popularity over the years and have expanded beyond the use of hand-held devices to Web, mobile Web, and phone. These tools enable study implementers to employ a number of techniques to minimize missing patient data and keep data quality high; such techniques are not possible with traditional methods of collecting patient reported data.

Regulatory View on Missing Data

Missing data are:"data not completed,""corrupted in reports & case report forms,""data not captured when subject withdraws" (CDISC, 2007)

Th FDA Guidance on PROs states:

- "Missing data can introduce bias and interfere with the ability to compare effects."
- "Missing data is a major challenge to the success and interpretation of any clinical trial."
- "When the amount of missing data becomes large, clinical trial results can be inconclusive. We encourage pre-specified procedures in the clinical trial protocol to avoid missing data."

Electronic Patient Reported Outcomes

With ePRO, clinical trial staff can enable hard edits that prevent patients from skipping items or pages. When patients fill out paper diaries, they can easily omit sections or questions (intentionally or unintentionally); with ePRO solutions, patients can be required to fill out all sections by prohibiting them to move forward until necessary entries are complete. The capture of extraneous data, such as when patients include additional information in the margins (which cannot be used in study results), can also be prevented with ePRO. Paper data collection methods also allow patients to provide both ambiguous data and contradictory data that would likely have to be counted as missing. To avoid ambiguous data (e.g., multiple responses for a question that requires a single response), a functionality in ePRO modality can be programmed to allow patients to provide only one response option where required. Contradictory data (e.g., patients responding that they did not take their medication in one question and later responding that they took their medication four times), can be addressed in ePRO with features such as branching and prompts.

The time accuracy of the data collected is also critical to the quality of the data, ensuring confidence in your trial results. This accuracy is affected negatively when patients do not complete their diary on the day or at the time of day that it is intended to be completed. Ensuring date/time accurate data when using traditional paper-based data collection methods is impossible, whereas date/time accuracy is one of the most significant benefits of ePRO solutions. ePRO solutions are able to stamp data with the date and time of completion to ensure that the responses are logged within the required time frame. ePRO solutions can also be programmed to only allow patients to record their information during pre-defined time frames to ensure that the information recorded is for the intended date and time. This solution essentially eliminates the challenges that exist with traditional paper-based methods:

prospective data completion where patients respond before they are supposed to, and retrospective data completion (aka the "parking lot syndrome"), where patients rush to complete their weekly diary entry just before their visit to the clinic.

Patient Reminders

In addition to the aforementioned ePRO data collection tools, clinical trial staff may use reminders that are sent directly to the patient through text and/or phone to remind them of their completion deadline and alert them if they miss it. This is appealing to many because it enables real-time communication directly to the patient that supports compliance prior to the patient missing the pre-defined timeframe for completion of their diary. It is a proactive compliance management tool rather than a reactive solution. There are a few things to consider when using this technology to get the reminder strategy correct:

- **Reminders are most powerful during the initial weeks of the patient's participation in the trial.** An Almac study indicates that patients begin to rely less on the reminders as their time in the trial increases. The percentage of patients who complete their diaries after receiving a reminder is significantly higher at the start of their participation than it is two or more weeks later. Consider allowing patients to cancel reminders after a certain period of time.
- **Reminders are most instrumental when patients are not required to register diary information on a daily basis.** It is much easier for the diary registry to become part of the patient's routine when daily diary entries are made, but very difficult when they are made less frequently.
- **Give the patient a chance to register diary information prior to receiving a reminder.** For example, set up the reminder system so that a reminder is only sent if the patient has not registered their diary 60 minutes prior to the close of the window. This will reduce the number of reminders that are sent, saving money and preventing reminders from becoming a nuisance for the patients. In a 2013 patient survey conducted by Almac, it was indicated that if patients perceive reminders as annoying, they are less likely to be compliant.
- **Consider using a technology that enables the patient to easily link or access the electronic diary system directly from the reminder vehicle for real-time response.**

IRT and EDC Integration

Data quality can also be compromised with the possibility for human error with data capture beyond PRO. This is combatted in a number of ways. In an attempt to make trials more efficient, many firms are choosing to adopt integrated data systems, combining electronic data capture (EDC) and interactive response technology (IRT) data (including ePRO). This provides immediate access to data, reducing error while constantly reconciling data and minimizing data redundancy. As integration solutions have evolved, the continuous challenge is to be able to allow the sponsor to choose best incase solutions from different providers while improving the level of data integration beyond a transfer or sharing of flat files. The good news is that integration best practices and experience have significantly evolved in the market enabling much more seamless integration between these providers.

There is continued growth in the adoption of IRT and EDC integration practices as more firms continue to implement integrated solutions. Not only have more firms adopted these solutions, they have sought solutions with wide scopes — solutions that encompass a broad range of systems. As scopes increase, so do opportunities for cross-functional benefits as systems and workflows are integrated. When systems and workflows are integrated, processes can be standardized, resulting in better solutions.

The complexity of clinical trials often means that information is shared across multiple systems: systems for screening and randomization, drug supply management, clinical supply management, and patient-reported outcomes. Historically, sites transcribed information manually among systems. Manual transcription is inefficient, time-consuming, and has a high probability for human error, leading to data discrepancies for sponsors. An integrated IRT/EDC system eliminates the need to log into more than one system, with data shared reliably between the two systems. With a successful integrated system, the site user should feel confident that the data shared between applications is not only reliable but high-quality and lacking in redundancy.

As integrated system use increases, so too must the scope of what an integrated system must accomplish. Systems share information and drive functionality in other systems. For example, drug supply management systems may need to reconcile damaged drug or incorrect dosage. Integrated systems can mitigate discrepancies in data by syncing all information coming from sites, data points, and systems — with large-scale global studies with many sites and data points, the possibility for discrepancy is enormous. Investing in an integrated system is more cost-effective than attempting to control for, detect, and remove discrepancies.

As the scope of integrated IRT/EDC systems broadens, it becomes increasingly important to standardize the system's requirements. Doing so reduces the need for change at the system level, encourages the use of standard data and message formats, and simplifies impact analysis during system amendments. It further creates a system of checks and balances. Ideally it should clearly delineate who to contact in the event of an error; who handles failures in business or technical validation; in which systems the data should be corrected; and how to ensure that any corrected data isn't overwritten by incorrect data in an adjoining system.

An integrated system can reduce human error, data discrepancies and redundancies, and streamline processes and workflow across systems, therefore leading to overall high-quality data.

While integrated systems can streamline processes, it is not feasible to develop an integration that can handle every scenario, particularly for large-scale global trials. Vendors should develop for the highest-value scenarios and ensure that systems communicate to users if manual intervention is needed. Integration should not be used to cover up gaps in data validation should they occur; it should validate the message and data formats and required data points.

Conclusions

Missing data caused by non-compliance and low data quality can undermine the efforts of a clinical trial by introducing bias. To increase compliance and maintain high-quality data, sites can deploy ePRO technologies and techniques designed to improve the reliability, accuracy and compliance of PRO data collection. An integrated system can reduce human error, data discrepancies and redundancies, and streamline processes and workflow across systems, therefore leading to overall high-quality data. PV

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