

The Value of EDC in Early-stage Clinical Trials

William E. Gannon Jr., MD

Overview

While the value of electronic data capture (EDC) in late stage and larger clinical trials is clearly established in the drug and medical device marketplace, early-stage clinical trials can also significantly benefit from the use of EDC. Not only can data be collected faster and more accurately, safety signals can be detected earlier and the additional challenges that first-in-man studies represent can be more readily addressed.

Because EDC provides a more efficient, quicker, and thus a more timely process than paper case report forms (CRFs), it can help evaluate safety and efficacy better. It does this by supplying “real-time” data faster and more accurately, thereby providing the basis to move a new compound or device through the development process and to the market sooner.

Phase I and EDC: An unlikely pair?

Historically, early-stage trials have used paper CRFs for several reasons including:

- short durations and low subject counts
- paper is faster to deploy
- initial setup cost of electronic systems
- laboratory test results that are typically reported via paper
- training time needed for electronic systems
- familiarity with paper-based capture methods

As with any good system, clinical trial technology improves over time. What was once true in the world of EDC, no longer remains so. In fact, recent strides have not only improved the process, EDC has become a solution for what was typically the domain of paper, i.e. Phase I studies. Ramp up times for setup and training have been drastically reduced, lab results are easily incorporated, ROI studies have shown that the cost of EDC can actually be less than paper, and an increasing number of clinical sites and personnel are familiar with the process of EDC, alleviating training needs.

Moreover, consider that by using an EDC system starting with Phase I of a clinical-development program and using it through Phases II and III through the submission process, sponsors will have a consistent, familiar, validated system. This reduces the time needed to move to the next phase of development when the results from the current phase warrant. Finally, EDC allows multiple team members to have access to and use of, the data at the same time; all at a much earlier point in time than the use of paper CRFs allows. This creates a more streamlined process for evaluation and decision making.

With the ever increasing number of specialty Phase I clinics, e.g., oncology or biologic units, using an EDC system in these types of Phase I studies standardizes the reporting process, can allow for integration with the patient's electronic health record, reduces the number of queries to the site(s) for database cleaning and closure and creates a database for future patient recruitment in other studies.

Safety in Phase I Studies – EDC Can Help

As we all know, errors made in a trial can include enrollment of ineligible subjects through human error or missed or late arriving test results, incorrect allocation of collected samples to subjects, and continuation of subjects who exceed the protocol-defined safety ranges. The use of EDC has shown that these types of study errors can be prevented by providing real-time laboratory test results and validated stop-gap measures that detect when a safety issue occurs. Additionally, using an EDC system can provide a real-time status of the clinical study to the principal investigator, the CRO, and/or the Sponsor thereby enhancing monitoring capabilities and allowing for immediate review and response.

For example, in 2006, a series of serious adverse events (SAEs) in several subjects dosed too quickly occurred in an early phase study in the European Union (EU). As a result the European Medicines Agency (EMA) investigated and determined that “inappropriate study designs, incomplete assessment of available data, and a failure to reconcile inconsistencies in the nonclinical safety data may lead to inappropriate conclusions about human safety”.

The EMA offered a guidance that was recommended to be performed at an international level on how to “identify and mitigate risks for first in-human clinical trials”. This guidance has served as a “wake up” call to the industry and is assisting in setting new standards and processes for the conduct of all trials globally. One of the most important aspects of this guidance is the monitoring of the study and the timely reporting of information. EDC helps to improve both of these requirements.

Evolving Needs of Early Stage Trials—the Changing Landscape

In 2004, the FDA launched the Critical Path Initiative in an effort to modernize the scientific process used in clinical trials. As a result, adaptive study designs are being used more often in early studies, particularly in exploratory studies, with the hope of improving study efficiency through shorter durations, fewer subjects, and improved opportunity to detect an effect if one exists. While adaptive study designs offer the possibility of determining efficacy sooner and identifying safety issues quicker and with fewer subjects, they are more complicated to design and analyze, more difficult to implement, and require significant monitoring and rapid changes if necessary. An EDC system can easily accommodate adaptive study designs and provide a useful tool to better predict the safety and efficacy of an investigational agent, as well as provide a significant platform for use in the future development of the agent. The EDC system does this by accommodating protocol amendments, mid-study changes, and frequent exports of results for interim and ad-hoc analysis.

Another goal of early-phase investigations is to determine the lowest effective dose, typically by conducting dose-ranging trials. The most exciting development in this area is to make the trials adaptive, so that the balance of patients across the different treatment arms can be changed while the trial is still underway. For example, enrollment into the lowest dose group could be curtailed if the early data showed a lack of efficacy, or enrollment into the highest dose group could be curtailed if the early data showed signs of toxicity. This re-balancing directs more patients into the other treatment groups, which improves the precision in determining the correct dose when the study finishes. Decisions on adapting the balance across the different treatment groups can only be made if the data is timely, accurate and clean; this in turn indicates that EDC is a prerequisite for conducting adaptive trials.

Like many business endeavors, clinical development has become globalized. As a result, monitoring, evaluating, and reporting of these studies to the regulatory bodies involved has become far more complex. The use of an EDC system in global studies provides a unified framework for all the sites to follow, and enhances the capabilities of the Sponsor to monitor and evaluate all aspects of the study without necessarily being in that particular country. Additionally, most EDC systems are adaptable to US, EU, and other regulatory requirements.

A Tale of Two Trials: The Benefits of EDC

A recent Phase I study conducted at 5 clinical sites used an EDC system and a built-in randomization schema. Subject enrollment proceeded as planned with minimal requests for guidance from the Project Manager or Medical Monitor. Data collection was universal and collected in a timely manner with minimal queries to resolve. This study was completed 2 weeks early.

Another Phase I study conducted at 3 clinical sites used paper CRFs and had all enrollments coordinated through the CRO Project Manager. This study did not finish on time per the projected timeline, and due to the amount of time spent by the Project Manager and the Medical Monitor was over budget by 23.6%.

Summary

Today, the benefits of using an EDC system in early-stage studies far outweigh using paper CRFs, including:

- Quicker subject review and approval to participate in the study
- Rapid, efficient, and accurate evaluations based on real-time safety results
- Significantly fewer errors in data collection
- Expedited review and response resulting in improved and faster decisions; ultimately culminating in quicker progress from Phase I to Phase II
- Being able to use a validated and compliant EDC solution across the entire continuum of clinical development from Phase I through Phase IV.

Using an EDC system in early Phase I studies has significant benefits not only for that particular study, but for the entire clinical development program of a drug or medical device. Development success is measured by the ability to evaluate safety and efficacy quickly, accurately, and efficiently in as cost-effective manner as possible. Critical decisions to move a drug from one phase to the next are dependent on the data, and collecting those data through a validated and compliant EDC system will enhance the Sponsor's ability to make the best decisions possible.

William E. Gannon Jr., MD is a clinical trials consultant, and CMO of Capital City Technical Consulting. He has over 20 year's experience conducting clinical trials, providing regulatory expertise and medical monitoring services, and writing protocols. He has also participated in FDA Advisory Panel meetings, and filed several IND's. Dr. Gannon can be reached at WGannon@capcitytek.com.