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eClinical and Legacy Clinical Data Management Systems (CDMSs) and other Pre-existing Systems

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

Recently we received feedback about the topics covered in these articles, and based on that feedback our twenty-first issue explores legacy systems and EDC. In particular, we discuss specific considerations for a number of legacy and pre-existing computer systems that biopharmas have built to enhance the functionality of their legacy Clinical Data Management System (CDMS).

While pre-existing systems are a major factor when Biopharmas consider adopting or attempt to adopt recent technologies such as Electronic Data Capture (EDC), it is important that they not be an excuse not to pursue recent technology. Instead, a re-evaluation of the functions performed by these systems is what is truly mandated.

Introduction

In Issue 11 of *EDC Today*, *EDC Technology Old and New: Integrating Legacy Systems with EDC*,¹ we presented a discussion about legacy systems. Intended as an overview of different computer systems commonly used in clinical data management, we focused on a number of legacy and pre-existing systems biopharmas may already have in place when they begin to consider moving to EDC. In this issue, we will discuss how biopharmas might alter or upgrade their pre-existing systems when moving to an eClinical environment.

For any company to remain competitive, they must change. Changing to adopt new technologies and respond to external factors such as new FDA mandates (e.g., adoption of MEDDRA and Electronic Records) can insure a companies continued success. Unfortunately, deciding what the target of the change should be, managing that change, and decommissioning outdated systems is a difficult and challenging task.

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In the next issue of
EDC Today:

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In this issue we examine how pre-existing systems might be modified to optimize overall clinical processes and help keep companies competitive. We will look in detail at the following seven areas: Management and Monitoring systems, Central Laboratory and Assay Systems, Coding Systems for Medications and Adverse Experiences, Safety and Serious Adverse Event Systems, Drug Supply Systems, Randomization and Enrollment Systems, and Back-end Edit Check Systems.

Note that the following discussion may or may not directly apply to your specific situation. It is important to analyze all of your company's computer systems in light of strategic goals before determining your course of action.

Management and Monitoring Systems

Management and monitoring systems have often been described as Clinical Trial Management Systems (CTMSs). While some vendors produce and sell CTMS systems (such as eResearch Technologies' eStudyConduct™ and TrialTrac's TrialWorks™), CTMSs have generally been proprietary applications developed to keep track of various milestones of the clinical trial as it progresses, and also to keep track of investigator site documentation, patient enrollment progress, monitoring visits, and site payments. Some of these systems have been developed as Oracle applications; however, some companies also use Microsoft (MS) Access and MS Excel for maintaining this information. In general, the management application is updated after each activity is completed, and is generally passive in nature, in that data is added to the system and reports are run. More advanced applications developed by some companies include email messaging and perhaps even rudimentary scheduling of activities, sometimes in conjunction with MS Project.

Desirable workflow technology enhancements to existing CTMS software include making it more proactive, making it more real-time, and making it more available to the project team. Workflow and portals were covered in detail in Issue 12 of *EDC Today, Portals, and How They Can Make EDC Work Better*, but for our purposes, it suffices to say that clinical trial team members could work more efficiently if they had an updated list of tasks and documents for them to address when they got to work in the morning.² In addition to workflow, the CTMS could be integrated with the EDC system so many of the tasks that are performed in the EDC system can automatically update the CTMS in a real-time manner. Finally, better collaboration and scheduling of resources could be built into the CTMS. If calendaring technology is built in, meetings and tasks could be scheduled for all team members.

Certainly Web-enabling the CTMS could make it a more efficient management tool. However, the greatest impact is likely to be derived from the alteration of the CTMS from a passive tracking tool to a proactive planning tool. Companies that take advantage of new technologies and invest the time and effort to update their CTMS application will help their teams be more focused and more productive.

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Central Laboratory and Assay Systems

With traditional CDMS systems, the benefits of having a central laboratory perform the usual chemistry, hematology, and urine tests, as well as any “specialized” testing (e.g., monoclonal antibody allergy testing) have been obvious to many Biopharmas for some time. In addition to known costs, results can be transmitted in a standardized format, in uniform “units of measure”, and with high / low and clinical significance flagging already done. The Biopharma simply needed to develop a database loading mechanism and some sort of assay tracking system that tied the CRF assay labeling and dates to the results returned by the lab.

eClinical portals promise to simplify the process of managing (and perhaps controlling) data that is created or generated by a Central or Specialized Laboratory. If the CDMS system is still the “official location of the data”, any existing data loading software may continue to work without (extensive) modification. However, if the data are to be loaded into the EDC database (in an ASP model scenario), the EDC vendor should provide a tool to use to load Central Lab data. This tool should provide true “transactional” data import features. Management tools for tracking assay samples should be available at the portal, and tracking should be as “near real time” as it can conceivably be, and should be tied to the system used by the shipper (e.g., FedEx, United Parcel Service) so as to locate the whereabouts of any and all assays currently in shipment or those already delivered.

With the advent of eClinical systems, Central Lab and Assay tracking could become more tightly integrated. The Internet allows databases that are separated, physically remote, and with non-homogenous structures to be connected together, eliminating the need to transfer some of the data that is used in interim processing. Newer metadata description and data transfer mechanisms (such as XML and CDISC standardizations) promise fewer and easier data transfers.

Coding Systems for Medications and Adverse Experiences

A long standing processing challenge of CDMSs has been coding of verbatim text so that medical categorization and statistical number crunching and groupings could be performed. Many Biopharmas have expended a huge amount of effort seeking a solution to what is at best a difficult challenge and at worse, an intractable one. Adverse Event and Medication terminology expressed in an “unstructured” description needs to be coded, usually against a fairly complex hierarchical dictionary. Adding even more complexity are multi-national trials and the need for multi-lingual support. Over time, many proprietary Autoencoding solutions have been developed with varying amounts of success, with many systems having only “developmental expense” in common.

While an eClinical portal may not seem to offer much in the way of surmounting the Autoencoding challenge, it does offer some potential benefits, probably mostly in the area of resolving Autoencoding failures. With enhanced communications between investigator site, study monitors, and dictionary maintenance personnel, Autoencoding failures can be resolved, either by having the verbatim text clarified or by the addition or enhancement of the coding dictionaries. By having the more immediate data query responses available, the often-lengthy coding failure resolution process can be facilitated.

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The promise of eClinical systems, however, goes beyond the advantage of more immediate communication working to resolve coding failures. By reviewing the verbatim text and autoencoding it in near real-time, the process can remove frustrating delays and misunderstandings from the proceedings which helps makes the work more enjoyable. Another advantage of eClinical processing may lie in the replacement and unification of autoencoding technique and methodology, as EDC vendors seek to develop more broadly used, effective and more powerful, less proprietary coding systems.

Safety and Serious Adverse Event (SAE) Systems

The relatively slow collection of paper CRFs is a serious problem when trying to capture Serious AE information within the FDA mandated SAE reporting schedule. Where paper CRFs are subject to monitor review, source data verification, and collection for delivery to biopharma (sponsor) sites on an infrequent (e.g., monthly) basis, the FDA requires the SAE be reported to the study sponsor, safety officer, or their designee within 24 hours of the SAE. The sponsor, in turn, needs to provide the FDA with a completed report within as little as 3 or 10 days. This has led to the creation of standalone systems that deal with the expedited schedule that SAE reporting demands. These standalone systems often entail having to fax data to the sponsor and having the sponsor’s data entry staff enter it into a database separate from that used by the CDMS system.

The separation of CRF and SAE data means “reconciliation” must be done when a study is being including in a submission. All the AE information previously reported to the FDA needs to be “accounted” for within the CRF database. In the past, this reconciliation/accounting had often been done manually.

The promise of “near real time” data capture offered by an EDC system is two-fold. First, it could eliminate the need for a standalone SAE system altogether since the EDC’s eCRF database could be the single point of entry of all AE information. Since it would capture data swiftly enough to meet FDA reporting requirement deadlines, data would no longer need to be faxed. Second, since the SAE data is no longer in a standalone system but integrated with eCRF data, the tedious manual reconciliation process used by some Biopharmas is no longer required. Furthermore, the use of an eClinical portal to facilitate time-pressured communications regarding particulars surrounding an SAE is an added benefit.

Drug Supply Systems

Drug supply systems have generally been standalone systems that record information about a drug or study agent lot. Shipping information (such as lot numbers, shipment dates, recipients, quantities, and lot expiration dates) would likely be recorded. Sometimes the drug supply system is electronically integrated with the patient enrollment and randomization system allowing sponsors to monitor drug availability at sites that are expected to enroll patients. If needed, shipping notices can be generated and new drug shipments initiated. On the other hand, returned supplies (either supplies that are expired or supplies that are returned at the conclusion of the trial) are usually recorded manually.

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These systems can benefit by tracking tools offered by FedEx and UPS. These tools can automatically update the drug supply system with information such as what supplies have been received at the investigator site and who signed for it. In addition, a Web-enabled tracking system can inform investigator sites when shipments have been scheduled for their particular site. Furthermore, if the drug tracking is integrated with an EDC system, additional drug supplies can be ordered based upon patient consumption.

There are several benefits of enhancing drug supply systems. Certainly improving the delivery logistics insures that drug supplies are available at a site when the site is ready to enroll a subject and administer study material. This availability helps to insure smooth patient enrollment and study progress. An ultimate goal might be to help insure that the investigator site, which has the ultimate responsibility of tracking the supply of experimental substances, has direct online access to the drug tracking system so they can track their own internal inventory as well.

Randomization and Enrollment Systems

Typically randomization and enrollment systems are implemented with manual telephone systems where a phone operator records enrollment information and disburses enrollment and randomization information. Many companies have also implemented these systems using Interactive Voice Response (IVR) technology. In general, these systems have been standalone systems where the investigator site calls when they have a patient to enroll and/or to be randomized, and they receive the patient identifier, randomization code, and the treatment strata that the patient is assigned to.

To some extent, these systems are often isolated to protect blinding of patient information. However, only the blinding strategy and assignments need to be kept isolated. Consequently, when moving to an eClinical environment, patient enrollment and randomization can be more tightly integrated. For example, if EDC is used, when investigator site personnel initiate a new patient, the patient identifier could be readily assigned. In addition, when consent information is entered for that patient and the patient meets all enrollment criteria and is intended to be dosed, the randomization code and treatment strata can be automatically generated.

The advantage of rethinking how enrollment and randomization are performed is that the process becomes more seamless. It may be that biopharmas still want to collect data for patients that do not meet study criteria and are not treated or randomized. In both cases, the process followed by the investigator site can be the same. The process is simplified since the site does not have to record the randomization strata information in a separate place.

Back-end Edit Check Systems

With a legacy CDMS system, edit checks are run after the data has been entered into the database. The edit checks may be part of the CDMS package (such as validation rules in Clintrial or consistency checks in eData Management) or they may be run as Oracle PL/SQL™ programs or as SAS™ programs. In all instances, we say these edit checks are run on the back-end, since they are run after data entry personnel perform “heads down” data entry with little or no data validation checks at data entry time. After the data is in the database, edit checks are run on the data. The discrepancies that result from data that is found to be in error are then printed to a Data Clarification Form (DCF) and sent to the investigator site.

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Although biopharmas may have a complete library of edit-checks and a good process for printing the DCF forms, back-end checks are not as efficient as data validation that is done when the data is entered. So moving forward, many companies probably should invest in converting as many of their library edit checks as possible to screen level validation checks. In addition, the DCF form process can be changed. Depending upon the eClinical environment, it may make sense to raise data errors within the EDC software itself, or if that is not possible, within a portal messaging framework.

Since back-end edit check systems were developed for paper-based collection of clinical trial data, they share the inefficiencies of the paper-based system. These check systems and their accompanying libraries represent many hours of effort. Getting cleaner data into the database in the first place and using the entry system to aid the investigator site in correcting erroneous data is a huge step towards optimizing the clinical data collection process. Unfortunately, back-end edit checks will still be needed since some are too complicated for screen level programming. Nevertheless, making it completely electronic can optimize the DCF process.

Conclusions

Biopharmas have legacy CDMS systems in use and have developed a number of auxiliary systems to accomplish functions that are not part of their CDMS application. These biopharmas are faced with questions about what to do with their pre-existing computer systems when they adopt newer and hopefully more efficient computer applications.

However, legacy systems should not be used as a reason for not adopting more efficient computer applications. Nor should the protestations of an overly protective in-house developer that the “time has come” for the system he or she has created. While it is human nature to be proud of ones accomplishments and want to continue to use the systems one has built, all computer systems have a definitive lifecycle. As the new applications may or may not contain some of the functionality of the pre-existing applications, time should be spent revisiting these applications and either upgrading them to work in an eClinical environment or replacing them completely.

The need for the business to maintain its competitive position should be the driving factor in change. As new technologies allow better collaboration and quicker communication between clinical team members, legacy and pre-existing systems should evolve to use the new technologies.

References

¹ EDC Today™, Issue 11, “EDC Technology Old and New: Integrating Legacy Systems with EDC”

² EDC Today™, Issue 12, “Portals, and How They Can Make EDC Work Better”



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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