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Sites and EDC:
Making EDC Site-Friendly

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In the next issue of ***EDC Today:***

Cleaner Data Faster: Using EDC to Improve Decision Making

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

EDC necessitates some changes at investigator sites, and site personnel may be initially resistant to these changes. Our fifth issue details the impact of EDC on investigator sites, examines many of the technological options for smoothly implementing EDC at investigator sites, and offers suggestions for making EDC more site-friendly.

With EDC, personnel at investigator sites enter data directly into electronic CRFs (eCRFs) with the use of PCs, laptops, or portable data assistants (PDAs) such as palm pilots. EDC software automatically flags errant or out-of-range data, prompting investigator site personnel to make data corrections or clarifications. Validated data is then transmitted from the investigator site to the sponsor's central database, usually via the Internet.

As EDC alters the traditional data collection process, it also impacts job functions and processes at investigator sites. Because of these changes in responsibility, some sites may be initially resistant to adopting EDC. Sponsors need to consider the sites they work with and be willing to address their concerns and demonstrate practical ways they can benefit from using EDC.

Investigator Site Operation

Though a clinical research study may provide extra income and a certain amount of prestige, it cannot detract from the primary focus of the medical practice — the effective, ethical treatment of their patients.

When designing an EDC-facilitated clinical trial, sponsors may need to carefully assess the investigator sites under consideration. Investigator sites and their personnel can vary widely in their computer literacy and technological savvy, in their overall experience and training in clinical research, in their knowledge of the disease or drug under study, in the quality of their facilities, and in their willingness and ability to embrace new processes and technology.

Amy J. Lampe and John M. Weiler from CompleWare in Iowa City, Iowa offer the following advice on choosing investigator sites:

> "Often, the investigative site is the last variable to be considered when a data entry technique is being evaluated. In some cases the investigative site is ignored altogether until the time comes to implement the technique. Only then may a sponsor realize that the data capture technique is unsuitable for the investigative site perhaps because the vendor has never worked with clinical trials previously and cannot function in the investigator's office…The investigative site generally is the point-of-capture for clinical data. Unless the concerns of the investigative site are considered, the data that are finally entered into the database may be of lower quality than the sponsor desires."[3]

Though some investigator sites are large hospitals, most are smaller clinics and private-practice offices. A single investigator – typically a physician who is compensated for recruiting patients and completing paperwork – often heads such smaller sites. The physician investigator is responsible for patient recruitment, following the study protocol, and ensuring patient safety.

In addition, investigator sites typically have a study nurse who draws blood and administers medication. Though study nurses may complete some or all of the CRF for the clinical study, a study coordinator usually performs this task.

The study coordinator may also have some patient contact, such as administering quality of life questionnaires or undertaking other activities that do not require a licensed physician or nurse. Because the study coordinator has clerical and technical skills and requires less medical training, he or she is "less expensive" than doctors or nurses.

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About EDC Management:
EDC Management was founded to assist biopharma companies plan, prepare for and implement Electronic Data Capture (EDC) strategies according to their data management goals and objectives. We do not sell or endorse any specific EDC software application or vendor.

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EDC and Site Considerations

Sponsors can help investigator sites prepare for EDC implementation. The key areas to consider are training, data entry, validation and security, Internet connectivity, physical space, and regulatory issues, which include source document management, FDA monitoring, and privacy concerns.

Training

Before using EDC, investigator site personnel will require thorough training in EDC-specific data integrity procedures. In particular, site personnel will require training on correctly following sponsor Standard Operating Procedures and Process Guidelines. Further, in order to satisfy FDA regulations, this training must be documented.

Whoever is responsible for data entry should receive training in EDC software. Though at the majority of sites this responsibility will fall to the study coordinator, at some sites the principal investigator, medical resident, or even a graduate study will have data entry responsibilities.

Data Entry

It is important to note that the effectiveness of EDC may erode if the person performing data entry does not have authority to correct data that has been flagged as potentially erroneous. For example, when medical residents or graduate students (who do not have this authority) enter data, physician investigators or study nurses must become involved with data validation.

Validation and Security

Though computer system validation and physical security have always been critical concerns at investigator sites, the implementation of EDC requires investigator sites to revisit validation and security issues. First, computer systems involved in processing clinical data must be validated. Although the sponsor is ultimately responsible for validating the computers used in its trials and for documenting that validation, the validation process will require the cooperation of site personnel.

Second, investigator sites will need to control access to computer systems used in clinical trials – both in terms of physical access and in terms of how passwords are created, used, and assigned. For example, in order to maintain effective audit trails, FDA regulations forbid the sharing of passwords. The time-honored practice at some investigator sites of keeping login passwords on notes stuck to computer monitors will have to change.

Internet Connection

In order to realize the full benefits of EDC, high-speed Internet connections may need to be installed at investigator sites. According to one recent survey, about three-fourths of practicing physicians have Internet access at their offices, but 60% of these use a dial-up connection rather than a high speed connection such as cable or DSL.[1] The highest speed modems (approximately 50 kilobits/second) for standard telephone connections are not effective when trying to transmit eCRFs. In addition, server and traffic delays on the Internet can further slow the data entry process.

Many physician investigators that use EDC have expressed frustration with the slow data entry process resulting from low speed connections. As James L. Coyne, CEO of CB Technologies, Inc., notes in his article "Untangle Your EDC":

> "Internet speed is a big concern because the data and forms must travel back and forth from the remote site to the Web server before being added to the central database. Before data can be entered, the investigator site must connect to the Web server. CRF pages stored on the Web server then travel through the Internet to the local site. The investigator site enters data and commits the form, and it is sent back over the Internet to the Web server. Once the page filters through the Web server, rules are checked and the form and data are either accepted or rejected. This can be an extremely time consuming process depending on the Internet connection speed and the amount of information being sent. Performance is such an issue in Web-only EDC, that some investigators are now threatening to charge a premium if they cannot get CRFs to refresh on the screen within 20 seconds."[2]

Sponsors may provide financial incentives for investigator sites to install high-speed connections, or in some cases, may even assist in the installation of these connections.

Physical Space

Finally, to the extent that different studies, study sponsors, or EDC technologies require investigator sites to use a separate, dedicated computer for each trial, investigator sites may have to create additional physical space for many different computers. Indeed, physical space limitations are a major consideration at almost any trial site.

Regulatory Issues

Source Document Management

With regard to investigator sites and EDC, one of the important regulatory issues that must be addressed involves source documents. Prior to EDC, federal regulations stipulated that investigator sites must retain the primary legal copy of the CRF with the original investigator signature. In the electronic environment (i.e., under 21 CFR 11), FDA guidelines allow the original eCRF to serve as the source document.

With Web-only systems, in which all software and data reside on the sponsor's computer instead of the investigator's system, a mechanism must be created to satisfy this requirement. With hybrid systems, in which the original, electronically signed eCRF resides on the investigator's laptop, that data is integrally linked to the sponsor's propriety software system and hardware.

Ultimately, the solution may be for the investigator to keep a certified electronic copy of the data as the "original" legal record. It would make sense for this data to exist in PDF format, both for its longevity and its portability to other software systems. It will not be feasible for the investigator to keep a paper copy of the data, as the FDA has stated that electronic records must be retained electronically, rather than converted to paper for long-term storage.

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FDA Monitoring

Another FDA guideline stipulates that all electronic records should be accessible to FDA monitors not only at the sponsor's facility but also at every investigator site. Fulfilling this requirement can be difficult, especially post-study, if the investigator has a certified copy that is not linked to the sponsor's system. Of course this is currently the case with the paper process, but the expectation is that electronic systems will offer greater access. Ideally, an FDA auditor sitting at any site should be able to view all patient records as if he were sitting at the sponsor's facility.

In the future, the FDA may even want direct ongoing access to data mid-study, via direct, secure links from the agency. They may also want an auditor to be able to check an investigator's eCRFs against the sponsor's database via a live link to look for errors or fraud. Whether or not this goal can be achieved in practical terms remains to be seen.

The Health Insurance Portability and Accountability Act (HIPAA)

This 1996 federal law, written by the U.S. Department of Health and Human Services, encourages the use of electronic records in the healthcare industry in order to eliminate cumbersome paperwork, but at the same time it establishes standards to protect the privacy of patient information. The lawmakers feared that electronically disseminated medical information could fall into the hands of employers or health insurers and be used to discriminate against individuals. The rule is scheduled to take effect in April, 2003.

At investigator sites, this rule may affect the process of source data verification. Study monitors must have access to electronic patient record systems in order to perform this function, but HIPAA restricts what information they can see.

So-called "smart charts" must also address HIPAA requirements. With smart charts, data are automatically shared between electronic patient charts, eCRFs, and record systems for billing and accounting in order to reduce the re-entry of the same data. Many investigators using EDC favor the concept of smart charts. In fact, on the EDMF survey, 67% of EDC-experienced investigators said they would enter data directly into the EDC system, rather than use an interim paper record such as a patient chart first, if a solution could be found to transfer eCRF data for inclusion into patient records.[6]

Addressing the Concerns of Investigator Sites

Sponsors should make a point of learning what investigators' concerns are regarding the implementation of EDC. For example, investigators may be uncertain about whether they want the added responsibility for data entry and management; they may not want their personnel to be distracted by these new duties from their normal responsibilities — primarily patient care. Further, if new equipment is installed at the site, investigators may be concerned about who will train site personnel to use the equipment, who is responsible for maintaining the equipment, who will monitor the site's use of the equipment, who to call for technical support, and finally, as previously mentioned, how to create the physical space to house the equipment. Finally, investigators may need assistance in addressing regulatory issues unique to the electronic environment.

To address these concerns, sponsors may want to provide a qualified instructor to the site to train personnel in the proper use of the new equipment and data entry procedures. Sponsors may also choose to designate a point of contact who investigator site personnel can call when technical problems occur or procedural questions arise. Finally, sponsors may want to consider increasing financial compensation to sites if the EDC implementation results in more work for the site. If the workload is increased but the compensation is not, investigator morale – and, in turn, data quality – may suffer.

Adopting EDC Technology

Choosing the best technological fit for investigator sites can make the transition to EDC run much more smoothly. Therefore, sponsors should understand the range of available technological options. Current EDC systems are based either entirely or partially on the Web and can be grouped into one of two categories based on this distinction: Web-only systems or hybrid systems.

Web-Only Systems

With Web-only systems, investigator personnel use a PC or portable computing device to enter data into a database on the sponsor's server. These systems, which are accessed with a standard Web browser, are the easiest to deploy and validate. With Web-only systems, one can transmit data from almost anywhere in the world – a particular advantage for sponsors with remote investigator sites.

Web-only systems provide a single, central source for all data and software applications: the sponsor's Web server. If changes must be made during the course of the study, those changes can be uploaded to the Web server, and investigators can access those changes immediately. Because all data and software reside on the sponsor's Web server and not the investigator site PCs, investigators do not need to worry about installing new software or tending to system maintenance. The central database provides sponsors with real-time data, and it allows easy management of data transmitted from multiple locations worldwide.

However, Web-only systems do have certain disadvantages, many of which are related to the Internet itself. With Web-only systems, investigators cannot enter data offline. If an Internet connection is lost or not available, personnel at the investigator site must wait to enter data until the connection is reestablished. With the high-volume of Web traffic, Internet performance is highly variable and uncertain.

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Hybrid Systems

With hybrid systems, data entry software and the data itself are stored locally on the PCs at each investigator site. This allows data to be entered offline, then transmitted to the sponsor's central database either in real time or at preset intervals. With hybrid systems, investigators can enter and access data even when an Internet connection is unavailable.

In order to communicate with the central database, hybrid systems do not require Hypertext Transfer Protocol (http), the communications protocol for the Web. Because the database does not need to be stored on a Web server, the entire system can be much more secure: for all practical purposes, the central database is invisible to the Web.

While eliminating many of the Internet-related problems associated with Web-only systems, hybrid systems also present certain challenges. Because data is stored locally on PCs at scattered investigator sites, copies exist at those sites and at the central data repository. If sponsors and investigators are to have access only to the most current data, a powerful synchronization engine must sort out this potential problem. Moreover, communications between remote sites and the sponsor's central database is also more complicated with hybrid systems than with Web-only systems.

Portable Data Assistants and Electronic Patient Diaries

Within the larger framework of a Web-only or hybrid system, small, portable devices for capturing and transmitting data at investigator sites promise to facilitate data entry and change the day-to-day routines of investigator site personnel. For example, as recently reported by *Computerworld,* PHT Corporation's acquisition of 3,000 handheld computers (with an order for 13,000 more on hand) for use in clinical trials, has already had a significant impact on the data collection process:

> "The handhelds are used by patients and doctors to answer questions once or twice daily during a drug trial. Users indicate whether they have taken the medication and whether there were any side effects, among other topics. Most inputs are made from a list of options, but the system supports software for handwriting recognition if comments are necessary.
>
> The handhelds are known as Esendant LogPads and communicate with PHT servers, usually through wireless modem. PHT has also developed a Web-based data capture and management reporting system. LogPad has been used by more than 12,000 patients and 900 investigators worldwide, PHT officials said."[4]

The *New York Times* recently reported on the use of electronic patient diaries in the clinical trial of an experimental drug for PMS. The first several paragraphs of the article, headlined "E-Diaries (Tap, Tap) Aid Drug Trials," effectively dramatize the effect of EDC on the paper process:

> "After 10 years as a research psychiatrist, Margaret Spinelli is used to having an office stuffed with paper, which fills every cabinet, closet, and shelf.
>
> She investigates new drugs for premenstrual syndrome, and participants in the studies must record their symptoms in daily diaries for several months. "You can have a collection of paperwork that's 18 inches high for each person," said Dr. Spinelli, an assistant professor of psychiatry at Columbia University's College of Physicians and Surgeons.
>
> At the moment, though, no more paper is piling up. In a trial of a PMS drug called PH80, delivered as a nasal spray, Dr. Spinelli's patients are keeping electronic diaries rather than paper ones.
>
> Every night, they enter their data on hand-held computers and send it via modem using a toll-free telephone number to a central database, where it is immediately available to researchers.
>
> Such electronic collection of self-reported data is creeping into clinical drug trials. Electronic diaries means less paperwork, quick responses to problems and, most important, greater accuracy; making the data more valuable scientifically."[5]

For sponsors, such portable devices may allow quick data capture, speedy validation and edit checking, and rapid detection of systematic errors. Further, missing data can be recovered quickly. By prompting patients to enter data at regular intervals, electronic patient dairies improve data quality by preventing so-called "parking lot" diary entries, in which patients, at the last moment, hastily fill out an entire week's worth of a paper diary from memory before submitting it to the investigator.

For investigator sites, PDAs can pose certain problems. PDAs can be difficult for patients to read, especially patients over 40. If the PDA screens are not backlit, the devices can be even more difficult to read, but backlit devices require more energy and need frequent battery recharges. PDAs also need a significant amount of maintenance. PDA data must be backed up – often many times a day – and that duty requires significant effort.

Finally, the use of these initially unfamiliar devices may distract personnel at investigator sites and detract from the caregiver-patient relationship. In fact, according to a recent survey of over 800 investigators conducted by the Electronic Data Management Forum, only 34% of investigators said they felt comfortable entering data directly into an EDC system in front of the patient in most or all circumstances.[6] As these devices become more commonplace, that attitude will likely change, but in the meantime it is important for sponsors to be aware of it.

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Conclusion

Sponsors can work with sites to calm fears, head off logistical problems, and smooth the transition to EDC. When a site is able to operate more efficiently, its costs go down. Even if the transition is difficult at first, savvy sites should be able to embrace EDC as a strategy to decrease costs and improve revenue and profits.

Sites with strong computer infrastructures and computer-literate employees who can perform electronic data entry in real time will likely be at an advantage over those that do not support computerized studies or that perform EDC slowly – i.e., relying on "scrap paper" or other intermediate methods of recording data such as a patient chart.

Ideally, personnel at investigator sites will spend more time entering data correctly the first time. Queries will come less often and can be handled faster. Over the course of the trial, site personnel should actually spend less time handling the data.

Skillful sites and site management organizations that invest in EDC can use their increased value to effectively market their services and raise or maintain their per-patient rates. Finally, sites that maximize the efficiency of EDC can spend more time on their primary pursuits: interacting with patients and providing quality patient care.

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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.

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Robert Pearsall received his BS in Electrical Engineering from MIT and his MS in Nuclear Engineering/Biomedical Instrumentation from The Ohio State University. He is Senior Consultant and Vice President for Business Development at Mousley Consulting, Inc. He has been involved with a variety of clinical data system projects for biopharma, including data management systems, electronic data capture (EDC), electronic submissions, validation compliance, and knowledge management. He was team leader and design architect for pilot projects in FDA/CBER electronic submissions.

Related ***EDC In Depth*** Research Reports:

5.1 "Adopting EDC Technology: Views from the Site Perspective"

When adopting EDC, biopharmas can choose among a range of products: from electronic patient diaries to smart charts to portable digital assistants. In this report, we detail the advantages and disadvantages of different products to help investigator sites understand the technologies and how they fit into medical practice and clinical research.

5.2 "Helping Sites Get Ready: Key Considerations of EDC Deployment"

Implementing EDC can be a significant undertaking for investigator sites, especially small, office-based practices. This report describes ways sponsors can help investigator sites smooth the transition to EDC. Critical areas include employee training, system validation and security, Internet connectivity, physical space requirements, and regulatory issues.

5.3 "Improving Data Quality with EDC: Key Process Changes at Investigator Sites"

EDC systems allow biopharma companies to achieve a fundamental business goal: producing better data faster. EDC achieves this by improving both existing technologies and existing processes. In this report, we examine how site-specific processes such as medical monitoring and safety reporting are affected by EDC.

5.4 "Beyond Technology: Legal, Ethical, and Financial Challenges for Sites"

Investigator sites choosing to implement EDC may face a range of unfamiliar legal, ethical, and financial challenges. In this report, we discuss investigator site responsibilities such as balancing patient care with research and negotiating privacy issues (e.g., compliance with the Health Insurance Portability and Accountability Act (HIPAA)). We also suggest approaches sites can take to meet the legal, ethical, and financial challenges unique to the electronic environment.

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