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The Final eFrontier

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Historically, clinical trial data were collected at the clinical research site on pieces of paper designated as Source Documents. These data were transferred manually by the site to paper case report forms (CRFs), which were then monitored against source documents by CRAs to basically see how accurately information could be copied from one piece of paper to another. At the same time that the CRA was verifying the accuracy of data transcription, they also had to evaluate how well the site was "following protocol." Once the paper CRFs were blessed by the CRA, the original forms were removed from the site and processed by data management.

In contrast to the above paper model, so-called remote data entry (RDE) appeared in the mid-1980s.^{1,2} RDE worked as follows: The company sponsoring the clinical trial would provide a computer to a site with a floppy disc and later modems. The site would collect the trial data in the patient record and then manually enter the data into the sponsor-provided computer via preconfigured data entry screens. The data, which were stored on the floppies, were monitored and eventually returned to the sponsor company via an overnight delivery for "data cleaning." Data lock would occur after completion of source document verification by the study monitors and signoff by data management.



Electronic Data Capture (EDC) is the current manifestation of RDE.³⁻⁶ While some EDC systems, like those used in paperless Phase I units, don't rely on paper at all but reference electronic source data, it is still the exception rather than the rule to have electronic source data.

When using EDC, sites still collect patient data in paper or electronic source documents, but in contrast to using paper CRFs, data are transcribed into Web-based data entry forms linked to a validated backend database. Data queries are managed electronically and are associated with either data fields or the overall data entry form. EDC data entry is no different than booking an airline ticket online; the main difference is that the EDC system allows for entry of agreed upon out of range or illogical data as long as a reason is provided why a data point does not follow a predefined rule.

Although not all EDC systems are as user friendly as maybe they could be, it is clear that the number of companies that insist on using paper CRFs are declining in the face of improved technologies and work flows.

Electronic records

In terms of the electronic medical record (EMR), in spite of underwhelming commitment by health care providers to adopt it, and despite a history of repeated disappointments with the implementation of health informatics systems, it seems adoption will finally happen with the American Recovery and Reinvestment Act of February 2009.

Key challenges to be addressed within the EMR and Health Information Technology (HIT) systems include poor connectivity, lack of interoperability among systems (including those faced with EDC), concerns about confidentiality of health information (exacerbated daily, it seems, by data breaches), hardware costs, training costs, and concerns about system downtime and its impact on medical practice.

Complicating these problems is the historical reality of the costs required for implementation. In 2008, it was reported that just 4% of physicians had an extensive, fully functional electronic records system, and 13% reported having a basic system.⁷ More recently, it was reported in 2009 that only 1.5% of U.S. hospitals have a comprehensive electronic records system (i.e., present in all clinical units), and only an additional 7.6% have a basic system (i.e., present in at least one clinical unit).⁸ Computerized provider-order entry for medications has been implemented in only 17% of hospitals. Larger hospitals, those in urban areas, and teaching hospitals are more likely to have electronic records systems.

Integration of EDC and EMRs

EDC allows users to enter, review, and analyze data in real time. The EMR allows users at a clinic or hospital to do the same for patient care data. The convergence of EDC and the EMR is inevitable and has the potential to improve the management of clinical research data and physician management of their clinical research operations.⁹⁻¹¹

While the EDC and EMRs are similar in both structure and function, as both focus on collecting patient data, adoption of both systems is still relatively modest. When properly designed, integrated EMR and EDC solutions should offer a convenient, cost-effective one point of data entry for the clinical sites to enter data. As a result, in the future, both traditional paper CRFs and paper source documents could be eliminated, and the whole concept of the CRF would need to be evaluated. The pharmaceutical industry will no longer focus on how well people can transcribe data from one medium to another; instead, companies will focus, in real time, on how well the sites are following the protocol and assuring a high level of data quality and patient safety.

There are a growing number of investigators performing clinical research who have also adopted EMRs. These forward thinking researchers are now faced with the dilemma that data entered within their EMR are not compatible with EDC systems, and that data needed to be collected for the clinical trial via EDC systems are not compatible with their EMR. With the advent of independently operating EDC and EMRs, it is wasteful of resources to enter clinical trial data into two incompatible electronic systems.

One of the advantages of using EDC and EMR systems in lieu of paper CRFs and paper source documents is that sites can enter the data directly into intelligent systems, without having to write it down. There are no illegible fields or symbols that require interpretation. In addition, all missing and out-of-range data are flagged and require explanations at the time of data entry. Either before or during data monitoring, data discrepancies can be confirmed and addressed.

Even with data transfer standards, with the multitude of EMR systems and the complexities of clinical trials, it is not currently feasible for clinical sites or an EMR company to create the source document for each clinical trial within an EMR. It is also not feasible for the clinical site's EMR to export all of the clinical trial data directly into the pharmaceutical company's database, while at the same time maintaining the complete source document in electronic format.

Attempts are being made to standardize data entry forms that are compatible with EMR systems. The latest

iteration of Integrating the Healthcare Enterprise (IHE) profile is called Retrieve Form for Data Capture (RFD).¹² RFD is a system that demonstrates how an EMR system can transfer existing and incremental data for research purposes, such as exchanging it directly with an EDC system. However, to ensure that trial specific needs and regulatory compliance issues can be satisfied, sponsors should carefully assess policies around the EMR, as well as accessibility to EMR data, during the site selection process.

Regulations

An FDA Guidance was issued in 2007,¹³ which acknowledged an increasing use of computerized systems in clinical trials to generate and maintain source data and source documentation, and that FDA requirements are such that electronic source data and source documentation must meet the same fundamental elements of data quality and regulatory compliance that are expected of paper. FDA's acceptance of data from clinical trials for decision-making purposes depends on their ability to verify the quality and integrity of the data during FDA on-site inspections and audits. The guidance applies when source documentation is:

- Created in hardcopy and later entered into a computerized system
- Automatically recorded by a computerized system (e.g., an ECG reading)
- Recorded by direct entry into a computerized system.

From FDA's perspective, each study protocol should identify each step at which a computerized system will be used to create, modify, maintain, archive, retrieve or transmit source data. This information can be included in the protocol at the time the investigational new drug application, Investigational Device Exemption, or Notice of Claimed Investigational Exemption for a New Animal Drug is submitted or at any time after the initial submission. It is recommended that sponsors provide to FDA a detailed description of all anticipated uses of the computerized system in the clinical investigation, such as the actual transmission of data from point to point during each phase of the trial.

For example, a sponsor could provide to FDA a detailed diagram depicting the clinical data flow such as how data are captured and entered at the clinical site; how data are sent to both the redundant hard drives and the Web portal, allowing data to be viewed in real-time by study monitors; how upon trial completion the database will be locked; and how clinical investigators will only be able to access their site's data via a "read-only" access privilege.

The computerized systems should be designed to satisfy the processes assigned to these systems for use in the specific study protocol (e.g., record data in metric units, blind the study), and to prevent errors in data creation, modification, maintenance, archiving, retrieval or transmission (e.g., inadvertently unblinding a study). In addition, the data must be retrievable in such a fashion that all information regarding each subject in a study is attributable to that subject.

According to FDA, original data are those values that represent the first recording of study data, including, but not limited to:

- Hospital records, clinical and office charts, lab notes, memoranda, subjects' diaries or evaluation checklists
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies or transcriptions certified after verification of being accurate and complete
- Microfiches, photographic negatives, microfilm or magnetic media, x-rays
- Subject files
- Records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in a clinical trial.

FDA allows original documents and the original data recorded on those documents to be replaced by copies,

provided that the copies are identical and have been verified as such.¹⁴ A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original. As a result, each electronic system that deals with original documents has to be designed so that it:

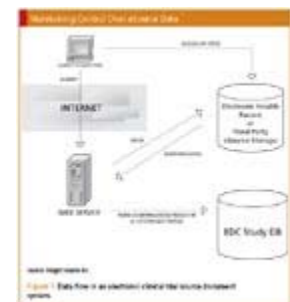
- Satisfies all requirements assigned to a protocol (e.g., data are recorded in metric units, the study blinded)
- Precludes errors in data creation, modification, maintenance, archiving, retrieval or transmission.
- Satisfies that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems
- Has audit trails or other security methods used to capture electronic record activities
- Documents who made changes to the data, and when and why changes were made to the electronic record.

Maintaining control

It has always been possible to enter data directly into an EDC system without initially collecting data on paper source documents. However, one of the major stumbling blocks has been that when the data are entered directly into the EDC database, the site has no direct control over their source data, as they would when data are collected using paper. Of course, the site could always print out the data entry form and sign it as a certified copy of the electronic form, but this would be labor intensive and there's always the danger of losing patient records or suffering a fire or environmental disaster, which happened when Hurricane Katrina devastated New Orleans and its environs in 2005.

One solution is for the data to be stored or captured in a trusted third-party, 21 CFR Part 11 and predicate rule compliant database, where the data cannot be viewed without secure access or changed without a documented audit trail. There are a few ways to achieve this.

One solution is that all of the clinical trial data are entered initially within the 21 CFR Part 11 and predicate rule compliant EMR, and then "pushed" from the EMR to the EDC database. Another solution is for the data to be entered directly into an EDC system and then pushed into the EMR or to another trusted third-party environment, as one of the steps prior to the data reaching the EDC database (see Figure 1). Under either scenario, the eClinical trial record can be considered the source document associated with the patient record for a given clinical trial.



Maintaining Control Over eSource Data

Nuts and bolts

When EDC is integrated with EMR, all information about a patient will be sourced electronically. When a patient is being considered for a trial, his/her EMR will be searched to evaluate inclusion/exclusion criteria. All baseline data already in the EMR will be bound into the EDC system, and all data related to the trial will be entered once and then reside simultaneously in the EMR and EDC systems. This will allow the site to maintain their source information about a patient for audit purposes, and at the same time allow the pharma company real-time access to the data.

Tools provided to pharmaceutical companies by the EDC industry will still be used to create the data entry screens, but these screens will be displayed within the EMR. This will allow for full data integration and standardization across multiple EDC and EMR systems; thus the final elimination of paper source documents. In terms of the source documentation that must reside in the EMR, some data will come directly from the EMR database, while other data may come from the EDC database. The integration of the EDC and the EMR should benefit patients, physicians, and pharmaceutical companies by adding value to each sector while, at the same time, preserving the highest ethical standards.

Monitoring of trials

With the advent of EDC and EMR integration, the role of monitoring data within a clinical trial will change dramatically. When data originally entered via EMR is the only source of clinical trial data, online and real time logic and range checks should identify any potential data entry errors. Audit trails will be required to identify those who enter and modify data and the reason for any data modification will satisfy 21 CFR Part 11 and predicate rule requirements.

EDC-based query systems will still be needed to ask questions about the data. Online data management and batch edit checks will play a major role, while traditional monitoring will disappear. CRAs will become more like data managers and auditors and will assure that the protocol is being followed.¹⁵ Utilizing user-friendly Web-based document management systems will also allow for all protocol-related study documents to be posted and signed online. Paper trails as we know them will disappear, replaced by electronic trails.¹⁶ Furthermore, financial incentives for remote data monitoring includes the near elimination of costly and timely site monitoring visits.

So what are the challenges?

Validation. All software used within a clinical trial must be fully validated and comply with 21 CFR Part 11 and the predicate rule requirements. Most notably, entry of data into EMR systems, which will eventually be considered the source data supporting the eCRF, must be limited to authorized individuals with a unique ID and encrypted password, through authorized pathways (e.g., internal networks) with accurate and complete date and time stamps, as well as robust audit trails that can't be overwritten.

Thus the use and design of EMR and EDC software may be subject to evaluation during an FDA inspection as well as an FDA marketing application. Once there is no longer a paper source document for patient information, it is critical that all EMR software be validated to assure that the software performs as intended. Most likely this will require retrospective validation in most cases and a significant investment in infrastructure and quality practices. Of course, if the EMR software was developed under traditional software validation procedures, there should be nothing more to do than make sure that the documentation summarizing the design and testing procedures are accurate, complete, and adequate.

Data changes in the EMR post-transfer to the EDC database. If data that are entered directly into the EMR are to be pushed into an EDC system, there would need to be controls when these original data are modified. For example, the EDC system must be alerted that the gender was changed from male to female due to a data entry error at the time of the original patient visit to the clinic.

Queries. Once data are received by the EDC database, edit checks, separate from those that already exist in the EMR database, will be generated based on either visual review of the data or software-generated edit checks. The ideal system will allow queries to be sent directly to the EMR so that sites can use one system for data entry and query resolution.

Data entry. To satisfy source document requirements, it is critical that all data sent to the EDC database is also housed in the patient's EMR database. These data should also be accessible in a user-friendly manner for review by industry and regulators. There should be no data in the EDC database that is also not available in the EMR database. That means that data should also be able to be pushed from the EDC database to the EMR if there are no corresponding data fields in the EMR database that exist in the data entry form.

Audit trail. There must be an audit trail of all changes and reasons for changes within the EMR database with date and time stamps that cannot be overwritten.

Changes to the protocol during a study. The EMR needs to be designed to allow for both minor and significant changes to a protocol during a study. Who supports the EMR is another question for this

nonexhaustive list.

Integration with data sources outside the EMR. Not all trial data will be sourced in the EMR. For example, medical imaging and electrocardiogram files may be stored in other locations. As a result, cross reference to other source data needs to be a part of the EMR and EDC integration.

Conclusion

The technology to integrate EMRs and EDC is ready and available. What the industry is waiting for are the innovators, trailblazers, and risk-takers willing to take the plunge. The pharmaceutical industry has reached a fork in the road. There will be those who choose to stay where they are in the short term, and there will be those who embrace the integration of EMR and EDC systems.

When the integration is managed properly, time is decreased for: database lock, statistical analyses, final study reports, regulatory submissions, and ultimately market launch. In addition, hours and costs will be reduced and the process of clinical research, data management, biostatistics, and project management will be streamlined. However, in order to accomplish this paradigm shift, companies must be willing to take the necessary steps needed to reevaluate their workflow and resource allocations as they move to implement EMR and EDC integration.

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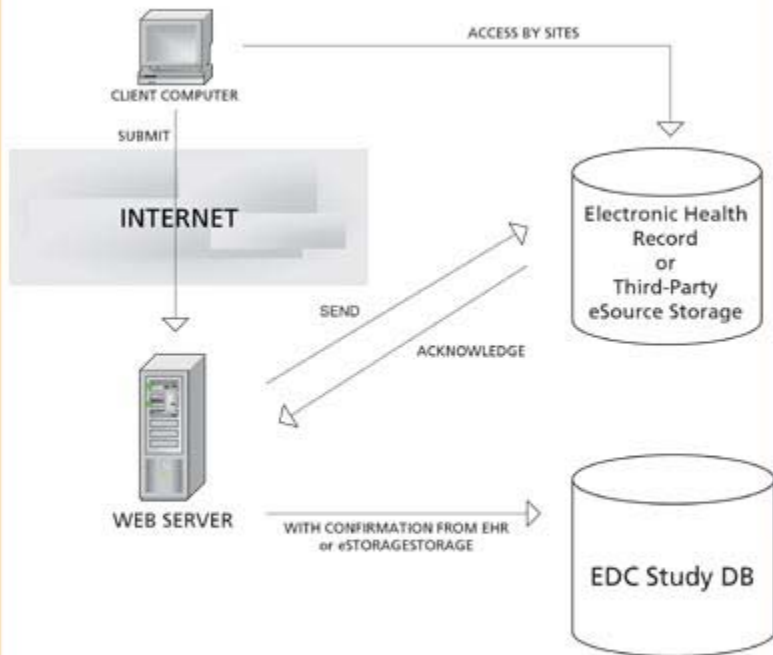
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Source: Target Health Inc.

Figure 1. Data flow in an electronic clinical trial source document system.