



The Paperless Trial – Past, Present and Future

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Electronic data capture (EDC) and the electronic health record (EHR) are radically changing the ways the pharmaceutical industry manages clinical research data and physicians manage their patients. EDC allows the users at clinical research sites to enter, review and analyse data in real-time, whereas the EHR allows users at a clinic or hospital to do the same. While these two functions are very similar in both structure and function, adoption of these systems is still relatively slow, especially in the US (1,2). From the clinical

research perspective, there is no functional integration of EHR and EDC (3). One result is that, whether the clinical trial is being performed using EDC or a paper case report form (CRF), there is a loss of efficiency when a study site has an EHR. While adoption of the EHR and EDC is still lagging behind, there is no question that EDC and the EHR are here to stay. When properly designed, EHR and EDC solutions offer a convenient, cost-effective approach for the clinical sites to enter data, manage data and generate reports.

In the pharmaceutical industry today, EDC offers clinical research associates (CRAs) the ability to review data prior to visiting the study site, monitor the data electronically onsite and resolve queries electronically. EDC also allows data managers to assure data quality more effectively by having online data validation checks. Project managers are also able to evaluate the study status in real-time. Back in 1997, Kelly and Oldham discussed the challenges for the implementation of an Internet-based clinical trial, as well as the obvious advantages of its use in drug development (4). Chadwick and Gisanti (5) gave a vision into the future and Garvey (6) addressed EDC as state-of-the-art technology. Several publications by Mitchel *et al* (1,7,9,10) documented many of the advantages of EDC over paper CRF-based studies.

PAST, PRESENT AND FUTURE

Historically, data management for a paper CRF-based clinical trial first included verifying the precision and accuracy of the data entered on the paper CRFs against the source documents. This is done at the study sites by the CRAs. Basically, this task evaluated how well the data were transcribed. In addition, the study monitor also made sure that the protocol was being followed and all protocol deviations and violations were identified. Monitors also assured that all regulatory documents were present and consistent with good clinical practice (GCP) requirements. The 'white' copies of the paper CRFs were then 'pulled' by the study monitor and delivered to data management. The data were 'double keyed' and the data entry compared for precision, using a 'data compare' program. Once data entry errors were identified and fixed, off-line (batch) edit checks were run for data validation purposes. Data entry items, which were illegible or clearly incorrect, or data errors identified as a result of the batch edit checks, were resolved via the query process, which could be manual or electronic. As a final step, once the queries were resolved, a QC person checked the data listings against the paper CRFs to assure that all of the data in the listings were matching.

Currently, with EDC systems, most sites still use paper source documents. However, instead of transcribing source document data to a paper CRF, the data are transcribed from source documents to the EDC system. Double-key data entry, and all associated tasks, have been eliminated. Interactive edit checks now exist at the time of data entry, which allow the data entry person to assure that any illogical or out-of-range data are actually correct. If not, the entries can be corrected or commented upon at the time of electronic data entry. In EDC systems, there are built in audit trails to track all changes to the database and electronic queries systems to manage query generation and query resolution. Batch edit checks still need to be run because not all queries can or should be run at the time of data entry.

One of the most promising entities within the field of biomedical informatics lies in the incorporation of clinical informatics and bioinformatics. In the not-too-distant future, EDC will be linked with the EHR, so that all information about a patient will be sourced electronically. When a patient is being

considered for a clinical trial, his/her EHR will be searched to evaluate inclusion/exclusion criteria. All baseline data already in the EHR will be 'pushed' into the EDC system, and all data related to the clinical trial will be entered once and then reside simultaneously in the EHR and EDC systems. This will allow the clinical site to maintain their source information about a patient for audit purposes, but at the same time allow the pharmaceutical company to have real-time access to the data. In our opinion, tools provided to the pharmaceutical companies by the EDC industry will still be used to create the data entry screens, but these screens will be rendered within the EHR to allow for full data integration. This will allow for standardisation across multiple EDC and EHR systems and the elimination of paper source documents.

The integration of the EDC and the EHR will benefit patients, physicians and pharmaceutical companies, by adding value to each sector while, at the same time, preserving the highest ethical standards. A customised virtual personal medical record, which is available anywhere anytime, enables continuity of care record, hence contributing to medical error reduction and to better informed decisions. It may also enhance the cooperation level of patients within clinical trials as it has a direct and evidently positive impact on the quality of medical care. Real-time, anonymous clinical data accessibility will enable the clinical researchers and the pharmaceutical companies to have an outstanding surveillance, audit trail and data analysis capabilities, in the pre- and post-marketing phases.

CHANGING ROLES OF CRAs AND DATA MANAGERS

With the advent of EDC and EHR's integration, the role of monitoring data within a clinical trial will change dramatically. No longer will there be a need to verify whether data transcription is correct. When data originally entered in the EHR is the only source document, logic and range checks will pick up any potential errors at the time of data entry. Audit trails will be required to identify those who enter and modify data. The reason for any data modification will be required as per 21 CFR Part 11. 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 as we know it will disappear. CRAs will become more like data managers and auditors. Utilising user-friendly web-based document management systems will also allow for all protocol-related study documents to be posted and signed online, so that that 'paper trails' as we know them will disappear.

DISCUSSION

One of the main advantages of EHR and EDC systems is that those who are familiar with the data (the clinical study site), enter the data directly into 'intelligent' systems. There are no judgements of intent and no guesswork. There are no illegible fields and no symbols which require interpretation. In addition, all missing data and out-of-range data are flagged and require explanations at the time of data entry. Either before or during

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

monitoring, data discrepancies can be confirmed. CRAs will assume some audit and data management functions. Sponsors should be aware that training must be adjusted as workloads are redefined.

When the integration of EHR and EDC systems is properly implemented, there will be major efficiencies in the monitoring of clinical trial data and data management processes. When managed properly, significant time- and cost-savings can be made by: eliminating double key data entry; automating the query system; reducing the time the monitor has to spend at the study site and interacting with the site coordinator; and by reducing the time from last-patient-last-visit to database lock. EHR and EDC systems are here to stay. Eventually, all companies will abandon paper CRFs and move into the electronic world. The first step is deciding 'what' a company actually wants to achieve in order to capitalise on the advantages of integrating EHR and EDC systems, and how to turn a 'concept' into a 'requirement'. The second major challenge is 'how' to do it. This involves system design, employee training and possibly employee redeployment. The third challenge, and one of the most difficult parts of implementing EHR and EDC systems, has nothing to do with the fundamental technology, but rather with making the necessary changes in structure, mind-set and culture within the sponsoring company as well as at the clinical study sites. Choosing the right people to manage and execute the process is key to the success of any programme.

CONCLUSION

The technology is ready and available. What the industry is waiting for are the innovators, trailblazers and 'risk-takers' to take the plunge. The pharmaceutical industry has reached a fork in the road. There will be those who will choose to stay where they are in the short term, and there will be those who will embrace the integration of EHR and EDC systems. The concept presented in this article has the potential to be the next revolution in the digital medical research era. It holds fundamental advantages for patients, their physicians and the R&D community, while emphasising the ethical issue of the patient's informed consent.

When the integration of EHR and EDC systems is managed properly, time is decreased for: database lock, statistical analyses, final study reports, regulatory submissions and, ultimately, market launch. In addition, time is saved, man-hours and costs are reduced, and the process of clinical research, data management, biostatistics and project management are

streamlined. However, in order to accomplish this, companies must be willing to take the necessary steps needed to reevaluate their workflow and resource allocations, as they move to implement EHR and EDC integration. ♦

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References

1. Mitchel J, Jurewicz E, Flynn-Fuchs K *et al*, The Role of CRAs in the Development and Implementation of Internet-Based Clinical Trial Applications: New Career Opportunities, *Monitor*, pp17-21, October 2005
2. Simon SR, Kaushal R, Cleary PD *et al*, Physicians and Electronic Health Records – A Statewide Survey, *Archives of Internal Medicine* 167: pp507-512, 2007
3. Bleicher P, Integrating EHR with EDC: When Two Worlds Collide, *Applied Clinical Trials*, 2nd March, 2006
4. Kelly MA and Oldham J, The Internet and Randomised Controlled Trials, *International Journal of Medical Informatics* 47: pp91-99, 1997
5. Chadwick B and Gisanti S, EDC 2001: A (Pharma) Space Odyssey, *Innovations in Pharmaceutical Technology*, pp92-95, 2001
6. Garvey A, EDC; State of the Art, *Innovations in Pharmaceutical Technology*, pp116-118, 2005
7. Mitchel J, You J, Lau A *et al*, Paper Versus Web; A Tale of Three Trials, *Applied Clinical Trials*, pp34-35, August 2000
8. Mitchel J, You J, Kim YJ, Lau A *et al*, Internet-Based Clinical Trials – Practical Considerations, *Pharmaceutical Development and Regulations* 1: pp29-39, 2003
9. Mitchel J, Ernst C, Cappi S, Beasley W, Lau A, Kim YJ, and You J, Meeting the Challenges of Internet-based Clinical Trials, *Applied Clinical Trials*, June 2004
10. Mitchel J, You J, Lau A *et al*, Clinical Trial Data Integrity. Using Internet-Based Remote Data Entry to Collect Reliable Data, *Applied Clinical Trials*, Supplement, pp6-8, March 2003