Data Management Redefined

Dr. Nimita Limaye

Abstract

Core perspectives on the traditional approach to CDM are rapidly changing and EDC and new eclincal initiatives are redefining the face of data management. Associated with EDC are not only the higher efficiencies, resulting in lower study costs, but its applications in key areas such as adaptive trials and clinical event adjudication; however the cost and effort involved in deployment and integration remain a deterrent. The role of the data manager may change to that of a data broker who manages the exchange of data from multiple sources, and semantic interoperability, data standards and data privacy will prove to be the defining factors. Simulation modeling, pharmacogenomics, personalized medicine and EHRs will no longer exist as silos and seamless data flows will be the drivers of healthcare solutions.

Key Words: CDM, EDC, eclinical, Personalized medicine, Adaptive trials, Clinical event Adjudication, Pharmacogenomics, Biochips, Semantic interoperability, HIPAA, GINA, Data standards

Clinical Data Management (CDM) was once perceived as the set of processes which resulted in clinical trial data being captured in an integrated, reviewed database. But this very perspective is in a state of dynamic flux today.

There has been a gradual but a succinct shift from the traditional methodology of capturing clinical trial data on paper and transcribing it into a database, the use of OMR (Optical Mark Recognition) and OCR (Optical Character Recognition) methodology, digital pens, data fax, etc to a quicker, more efficient process, namely, EDC (Electronic Data Capture), which brings significant cost savings to the clinical trial process. Reductions in query rates by up to 70% and a reduction in the time to database lock by up to 45% have been reported. Cost savings to the order of 60 – 65 million USD have been reported across the entire drug development program per drug along with a reduction in trial duration by up to 30%. [1]

Savings to the order of 6.2 million $ have been reported for a large phase III trial (with 2000 subjects, 200 sites and a 24 month study duration), in spite of a license fee of 1.5 million $ and a site internet access cost of 48,000$, with maximum savings resulting from a reduction in the number of monitoring site visits by 20% (about 3 million dollars), data entry and paper handling (3.6 million dollars) and data cleaning (1.2 million dollars). Savings were clearly higher for the larger phase III study as against savings to the order of 347,600 $ for a late phase II study clearly indicating the advantages of scale when it comes to EDC. [2]

Dr. Nimita Limaye
VP and Global Head, Strategic Data Services and Medical Writing, SIRO Clinpharm Pvt. Ltd. & Vice-Chair, Society of Clinical Data Management

Speed of data collection via EDC is also key to the implementation of adaptive clinical trials.[3] For example, CMed in May'09, announced a partnership with Tesella where CMed's Timaeus (the iDAM-intelligent Data Acquisition and Management solution which allows for the capture of multiple types of data within a single trial, including paper and web EDC, using an advanced wireless EDC appliance which is even capable of direct data capture from medical devices, e-source support etc.), would complement Tesella's FATES (Fixed and Adaptive Trial Execution System) allowing sponsors to see clinical data integrated from multiple sources in near real-time making the conduct of adaptive design clinical trials very practicable. [4] EDC also supports the review and assessment of clinical endpoints by Clinical Events Committees or by an IDMC (Interim Data Monitoring Committee) in order to achieve rapid, unbiased and centralized adjudication of dynamically updated data. The weeks spent on freezing the database and creating independent binders for review are now being replaced by efficient computerized systems that can provide the CEC members with the best available data integrated (from different sources such as CRFs or e-CRFs, site documents, images, external provider data) into a single interface to allow for the integrated, timely and comprehensive review of data.[5]

Thus the perception that EDC was just about a digitized electronic Case Report Form (eCRF) has undergone a sea change as realization set in that EDC is about the integration (of multiple applications involved in the clinical trial process, for example ePROs (electronic Patient Reported Outcomes), IVRS/IWRS (Interactive Voice Response System)/ (Interactive Web Response System), AERS (Adverse Event Reporting System) and CTMS (Clinical Trial Management System) and implementation (that beyond data management professionals there is a significant role for IT (Information Technology) to play as well). Integration would eliminate redundant steps, reduce the risk of validating data across two

systems and would thus cut costs as well. Semantic interoperability (put simply – the proper interpretation of transmitted data) is a must and eclinical software suites, for example, the Medidata Safety Gateway 3, an EDC-to-safety-system interface for the company's Rave system are driving the way. [6] On the other hand, Oracle has innovated by making its latest version, OC RDC 4.5.3 HTML-based; in this manner, it has addressed the PDF (Portable Data Format) technology issues associated with Oracle RDC (Remote Data Capture), (related to Adobe Acrobat reader and plug-ins) hence the implementation of software is no longer an issue at the sites and the sites only need their web browser for access.

While the beta-testing stage is now over and a spectrum of mature EDC providers have established themselves in the market, there are many who are still struggling to deal with deployment challenges and the need to move up the digital value chain. There is also a need to integrate EMR and EDC to minimize the re-entry of data by site personnel in two systems. However there are huge barriers that exist in making such initiatives commercially feasible as software packages and data standards often vary, and there are major concerns regarding the need to ensure data privacy as well. It is a no-brainer that the process will become 100% electronic and while there are huge costs involved, the question is not really about whether one could afford to go the EDC route, but whether one could afford not to go the EDC route.

While costs are clearly important, the user interface provided by the EDC solution has been rated as the most critical factor in an EDC solution. EDC is increasingly seen as strategically critical technology in driving the clinical development pathway in the pharmaceutical industry.

However CDM is being further redefined as data capture technology goes live in a wireless world. Thus researchers at the University of Florida have developed a tiny microchip with a digestible antenna added on to a standard pill capsule. When the tablet is ingested a signal is sent to the doctor. The pill communicates with a stand alone device worn by the patient which in turn signals a laptop or cell phone and intimates the investigator or family that the pill has been ingested.[7] Similarly, Novartis collaborated with Proteus Biomedical to have biochips integrated in to their blood pressure tablet, Diovan and these are reported to have directly enhanced patient compliance by 30 – 80%.[8]

Personal Health Systems which empower patients to continuously monitor and manage their health are being developed. For example, Heart Cycle is the European Union's (EUs) largest integrated project in this area. [9] This is about 'wearable computers', bio-shirts or wearable, portable or implantable devices that can monitor the physiological parameters of the patient (such as vital signs, biochemical markers) and potentially even allow for dynamic titration of medication as well. The Sensium Life Pebble uses Toumaz's nanotechnology (Sensium System on Chip platform) to enable continuous data capture of vital signs (including ECG, heart rate, skin temperature and physical activity) and wireless transmission at ultra low power. The data is transferred using a wireless datalink over a short range to a Sensium USB network adapter and yields clinical quality data that is ready for incorporation into an EHR.[10] Simulation modeling and *in silico* trials will again redefine the future. Denis Noble, Professor of Physiology at Oxford has developed a virtual human heart [11] and Entelos is partnering with the non-profit, Hamner Institutes for Health Sciences and the FDA to develop Drug-Induced Liver Injury (the most frequent cause of acute liver failure in the U.S.) Simulation Software, by creating a dual-species (human and rat) PhysioLab platform.[12] Similarly, the EU has funded the Virtual Physiological Human Network of Excellence (VPH NoE)[13] to enable a collaborative investigation of the human body as a single complex system, including patient-specific computational modeling and simulation of organs or systems; data integration and new knowledge extraction, and clinical applications and demonstration of tangible benefits of patient-specific computational models. Pricewaterhouse Coopers had projected in 1999 that the use of *in silico* technologies would bring products to the market at 50 to 66% of the average cost per drug. Meanwhile, Agendia has commercialized a US FDA approved tool for breast cancer prognosis, a 70-gene signature microarray, the 'Mammaprint', which has been reported to be 77 to 81% accurate. These measures thus signal a shift from empirical to predictive science.[14]

Semantic interoperability and the need to ensure data privacy would continue to become more critical. As pharmacogenomic data is now becoming a key driver of personalized, preventive and predictive healthcare, as of May 21, 2009, compliance of all new health plans with GINA (Genetic Information Nondiscrimination Act) is mandated and GINA has now changed the term "Protected Health Information" (PHI) coined by HIPAA (Health Insurance Portability and Accountability Act) to include genetic information.[15] Fujitsu PalmSecure™, a biometric authentication sensor, is being used by Carolinas HealthCare System (CHS) as a novel approach to register patient information and protect patient records and identity.[16]

Will data management companies also move to the role of healthcare informaticians serving as the connecting link providing blinded medical profile analyses of patient data to Pharma companies, as has been seen in the case of Healtheon which merged with WebMD, connecting patients, physicians and healthcare organizations, using advanced internet technology. Will data management one day involve the rapid processing of genomic data downloaded from a DNA chip such as the one being developed by IBM (costing between US$100 and $1,000) that would be used in handheld medical devices on which patients can deposit a sample to get their DNA read in a matter of seconds or minutes, to allow for rapid diagnoses, and personalized therapies that would be outlined within minutes?[17]

It has been said that there is no such thing as a science

fiction, there is only science eventuality. Biomedical engineering, personalized medicine, 'diagnostic partnering' and invasive computing are all technologies that are happening, but their success will be based on the appropriate and effective deployment of these technologies. The integration of bioinformatics and clinical informatics is also key to the future. Thus the traditional perspective of clinical data management would be redefined over a period of time as source data would change, data acquisition methodology would change, and standards and the entire processing methodology, as well as the turn around times may be completely revisited.

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