Vol 5 | Issue 3 | 2015 | 143-152.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

REGULATORY CONSIDERATIONS IN CLINICAL DATA MANAGEMENT

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ABSTRACT

Clinical data management (CDM) is a major cross-functional vehicle in clinical trials to ensure high-quality data are captured by sites staff through paper case report form (CRF) or electronic case report form (eCRF) and available for early review. The integrity and quality of data being collected and transferred from study subjects to a clinical data management system (CDMS) must be monitored, maintained, and quantified to ensure a reliable and effective base for not only new drug application (NDA) submission and clinical science reports but also corporate clinical planning, decision-making, process improvement, and operational optimization. The gradually increasing use of electronic data-capturing (EDC) technology and eCRF to collect data in clinical trials has grown in recent years and has affected the activities of clinical research operations for industry sponsors, contract research organizations (CROs), and clinical sites. This article focuses on importance of Clinical data management in clinical research.

Key words: Clinical data management (CDM), electronic Case Report Form (eCRF), Clinical Data Management System (CDMS), New Drug Application (NDA), Electronic Data-Capturing (EDC), Contract Research Organizations (CROs).

INTRODUCTION

It is recognized that clinical data are key corporate assets in today's biopharmaceutical industry, and that turning data into meaningful information is a critical core function for sponsor firms to make faster and more flexible assessments of compounds in development, design better clinical protocols when tailoring the appropriate target population with a specific indication, and enable innovative study initiatives and new clinical programs to ensure a robust clinical product pipeline. 1–3 EDC technology must comply with applicable regulatory requirements and offer flexible, configurable, scalable, and auditable system features. Transitioning from paper-based data collection (PDC) to EDC systems has produced many benefits, i.e., easing the burden associated with organizing paper CRF work and greatly reducing the time, cost, and stress required in bringing a product to market through technology-enabled efficiency improvement, such as the quick and robust interactive voice response system (IVRS) supported and integrated auto casebook creation, early data availability, and fast database lock via Internet-based user interface. Although EDC technologies offer advantages over traditional paper-based systems, collecting, monitoring, coding, reconciling, and analyzing clinical data. often from multiple sources, can be challenging. To realize the full potential of technology advantage in clinical research, both sponsor and site users need to change the way their offices and days are organized, how they enter and retrieve patient information, the process by which they issue, answer, or close queries, the standard operating procedures (SOPs), work practices, guidelines, and business documents, and the ways in which they relate to colleagues and CROs and interact with their patients.2 To address the challenges of the e-clinical environment and reap the benefits of technology, business re-engineering, organizational realignment, and management commitment are required to ensure that biopharmaceutical firms adapt

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to a culture embracing technology, and develop or revise existing legacy procedures to accommodate the re-engineered e-clinical processes and procedures.[1-3]

Scope and Objectives

It is now a known fact that the scope of data capture, CRF design, and CDM activity vary widely between different companies engaging in clinical studies. For small-size entities, traditional data entry from paper CRF at a central location or outsourced CRO may still be the most effective strategy when all factors are taken into consideration. Larger companies have turned to EDC technology to deal with ongoing clinical study challenges, and long-term benefits of pursuing EDC-enabled global strategies are being realized gradually. The associated changes in the CDM process and ensuing reorganizational structuring indicate that the roles of those employed in CDM become increasingly blurred with those of their colleagues in clinical monitoring, quality assurance, and application development.8 Moreover, the pace of technology development or optimization may be so rapid that additional consideration is required for any company planning to invest in new hardware and software for EDC technology in a changing operational environment.

Clinical Data Management

CDM refers to management of data capture & data flow processes in conduct of a clinical research. It begins with design of data capture instrument & data collection, continues with data QC procedures to assure quality of all aspects of process, & ends with database closure.

Once data have been screened for typographical errors, the data can be validated to check for logical errors. An example is a check of the subject's date of birth to ensure that they are within the inclusion criteria for the study. These errors are raised for review to determine if there are errors in the data or if clarifications from the investigator are required. Another function that the CDMS can perform is the coding of data. Currently, the coding is generally centered around two areas — adverse event terms and medication names. With the variance on the number of references that can be made for adverse event terms or medication names, standard dictionaries of these terms can be loaded into the CDMS. The data items containing the adverse event terms or medication names can be linked to one of these dictionaries. The system can check the data in the CDMS and compare them to the dictionaries. Items that do not match can be flagged for further checking. Some systems allow for the storage of synonyms to allow the system to match common abbreviations and map them to the correct term. As an example, ASA (acetylsalicylic acid) could be mapped to aspirin, a common notation. Popular adverse event dictionaries are MedDRA and WHOART and popular Medication dictionaries are COSTART and WHO Drug Dictionary.

At the end of the clinical trial the data set in the CDMS is extracted and provided to statisticians for further analysis. The analyzed data are compiled into clinical study report and sent to the regulatory authorities for approval.

Most of the drug manufacturing companies are using Web-based systems for capturing, managing and reporting clinical data. This not only helps them in faster and more efficient data capture, but also speeds up the process of drug development. Perceptive Informatics, Medidata RAVE and Forte Research Systems' On Core eClinical are examples of Web-based data capture systems. In such systems, studies can be set up for each drug trial. In-built edit checks help in removing erroneous data. The system can also be connected to other external systems. For example, RAVE can be connected to an IVRS (Interactive Voice Response System) facility to capture data through direct telephonic interviews of patients [4-6].

Process

Source data are generated. Common examples of source data are clinical site medical records, laboratory results, and patient diaries. If paper Case Report Forms (CRFs) are being used, the clinical site records are transcribed onto the CRFs. Data from the CRFs, as well as other source data, are entered into the clinical trial database. Electronic CRFs (eCRFs) allow data to be entered directly into the database from source documents. Data from paper CRFs are often entered twice and and reconciled in order to reduce the error rate.

The data are checked for accuracy, quality, and completeness, and problems are resolved. This often involves queries to the clinical site. See more about data validation. The database is locked when the data are considered final. The data are reformatted for reporting and analysis. Tables, listings, and figures are generated. The data are analyzed, and the analysis results are reported. When significant results are found, this step may result in the generation of additional tables, listings, or figures. The results are integrated into high-level documentation such as Investigator’s Brochures (IBs) and Clinical Study Reports (CSRs). The database and other study data are archived. These steps are not strictly ordered. For example, it is common in longer studies to generate intermediate discrepancies and listings periodically to identify problems that need correction before study completion.

Basic Terms and Concepts

Source data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico technical departments involved in the clinical trial).

eSource data (electronic source data)

Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial. NOTE: "Permanent" in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trail.

eSource document

The electronic record used to keep together a collection of eSource data items for capture, transmission, storage, and/or display; and serving as a source document for a clinical investigation.

pCRF to eCRF transfer

In this scenario, clinical data are at first collected with a pCRF. This kind of documentation is in use, for example, in situations where the investigator is pressed for time or has to move between locations (e.g. emergency ward, operation theatre). In a remote data entry scenario, it is often not the investigator, but special assistance personnel who enter data from the pCRF into the eCRF. This transcription step must be quality assured. Type of personnel needed (i.e. for data entry, for data review, etc.) and criteria chosen to qualify them must be clearly defined. For using eCRF, specific training programs for investigators and assistance personal must be included.

Appropriate quality control steps have to be implemented and double data entry may be performed. pCRF transfer as well as status (arrived, reviewed, non correct, requested queries, correct, closed) must be clearly tracked. Personnel responsible for different phases of pCRF entry must be tracked as well as all the changes. Because the investigators signature is required, he is responsible for the correct transcription of the data. Appropriate workflow support should be implemented in the EDC system.

Data entry

The data entry process should be defined for the specific trial and specified in a Data Management Plan. For transcription from pCRF to eCRF different procedures are used:

- double data entry (one person)
- double data entry (two persons)
- single entry with second look
- single data entry with reading aloud
- single data entry with source verification

Double data entry is not required by regulations but "good practice". The data entry process should be chosen based on the skills of the personnel, the resources in the project and the reflected evaluation of key variables. Timelines of the data reported to the sponsor in the CRFs and in all required reports. Raw data should be collected wherever appropriate. The site should not have to derive or calculate any values. Special care should be given to the problem of differing laboratory ranges and/or units.

- Format of data to be received from external systems agreed and standardized
- Data entry according to agreed instructions
- List of authorized persons for data entry
- -User training with data entry instructions/guidelines necessary Documentation of data receipt
- Audit trail for data entry
- Data received should be checked and any transfer problems identified
- Ensure blinding of information submitted to the data centre with regard to subject identifying information

Data processing

- All transactions to the database (insert, update, delete) must have a clear and complete audit trail
- Data only accessible to authorised personnel
- Site staff only access to data of their site
- Data handler familiar with GCP and will keep data secure and confidential at all times
- Coding performed using appropriate dictionaries
- Where auto coding is not possible, manual coding is performed
- Audit trail searchable and capable of producing audit trail reports.
- Coding conventions should be observed to ensure consistent coding within and between studies.
- Use of an auto encoder and synonym list where possible.

Data validation

The level of quality controls applied to data must be transparent. Any procedure involved in data cleaning, performed manually or automatically by validation check programming, has to be predefined in a Data Management and Data Validation Plan**,** preferably outlined in the protocol. In case of a change of validation rules during the conduct of a trial revalidation of all data might be necessary, requiring an additional and often labor intensive step.

- Data quality checks carried out according to agreed instructions and GCP and regulatory requirements.
- Manual checks (i.e. visual checks of CRFs with manual review of the data, e.g. medical consistency checks, lab

data pointing to an AE).
- Computerized checks (e.g. immediate checks during data entry or checks to be run in batches, e.g. at the end of a visit module or at the end of the CRF).
- Checking of missing, illogical and inconsistent data Complete documentation of data checks
- Errors reported to the appropriate person for resolution
- Final data checking.

Important documents for data management

Many documents are produced within a clinical trial. A common set of specific documents would greatly improve harmonization and interoperability. Several important documents to support compliant data management were identified:

- Study database validation plan, test plans
- Validation report
- Data management plan
- Annotated CRF
- Blank (unmarked) copy of CRF
- Mock Up CRF (optionally, for usability test)
- Edit specifications
- Data entry guidelines
- Site qualification, signature sheets
- Access control list
- (e)CRF training documentation
- Data validation plan
- Data review plan (for medical checks e.g. of medical consistency and AEs)
- Data handling report
- Database audit report
- Database lock documentation
- List of variables and reference values

Regulations, Guidelines, and Standards in CDM

Akin to other areas in clinical research, CDM has guidelines and standards that must be followed. Since the pharmaceutical industry relies on the electronically captured data for the evaluation of medicines, there is a need to follow good practices in CDM and maintain standards in electronic data capture. These electronic records have to comply with a Code of Federal Regulations (CFR), 21 CFR Part 11. This regulation is applicable to records in electronic format that are created, modified, maintained, archived, retrieved, or transmitted. This demands the use of validated systems to ensure accuracy, reliability, and consistency of data with the use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Adequate procedures and controls should be put in place to ensure the integrity, authenticity, and confidentiality of data. If data have to be submitted to regulatory authorities, it should be entered and processed in 21 CFR part 11-compliant systems. Most of the CDM systems available are like this and pharmaceutical companies as well as contract research organizations ensure this compliance.

Society for Clinical Data Management (SCDM) publishes the Good Clinical Data Management Practices (GCDMP) guidelines, a document providing the standards of good practice within CDM. GCDMP was initially published in September 2000 and has undergone several revisions thereafter. The July 2009 version is the currently followed GCDMP document. GCDMP provides guidance on the accepted practices in CDM that are consistent with regulatory practices. Addressed in 20 chapters, it covers the CDM process by highlighting the minimum standards and best practices.

Clinical Data Interchange Standards Consortium (CDISC), a multidisciplinary non-profit organization, has developed standards to support acquisition, exchange, submission, and archival of clinical research data and metadata. Metadata is the data of the data entered. This includes data about the individual who made the entry or a change in the clinical data, the date and time of entry/change and details of the changes that have been made. Among the standards, two important ones are the Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG) and the Clinical Data Acquisition Standards Harmonization (CDASH) standards, available free of cost from the CDISC website (www.cdisc.org). The SDTMIG standard describes the details of model and standard terminologies for the data and serves as a guide to the organization. CDASH v 1.1 defines the basic standards for the collection of data in a clinical trial and enlists the basic data information needed from a clinical, regulatory, and scientific perspective.

Specific FDA issues

The FDA is the US Government regulatory office for registration of pharmaceutical products. Here especially the Code of Federal Regulations (CFR) applies, which is the codification of the general and permanent rules published in the Federal Register by the agencies of the Federal Government. FDA regulation is relevant for EU projects in development of drugs considered for possible registration in the US Therefore, more specific regulation is available, e.g. for electronic documentation, the consideration of the US regulation is particularly helpful. However, it must be clarified, that in the EU it is not the FDA regulations which are governing, but the national implementations of EU directives or the EMEA implementations of EU regulations.

The FDA is primarily concerned about the following aspects of clinical trial data: attributable, legible, contemporaneous, original and accurate. The data reviewed by FDA have to be the original data collected at the investigator's site. The main requirement, therefore, is a robust audit trail. The FDA guidance for industry "Computerized Systems Used in Clinical Trials (CSUCT)" (1999) and the Electronic records/Electronic signature rule (21 CFR Part 11) including guidance are important in this

regard. In this context, it is important to note that the local implementation of the rules has to be taken into consideration, particularly where national regulations might conflict with FDA requirements (e.g. electronic signature as implemented in today's EDC systems might be inappropriate for German legislation).

The FDA is encouraging the use of computerized systems, but such systems have to meet certain requirements.

The key requirements include:

- system validation is crucial
• to ensure authenticity, integrity, confidentiality and non-repudiation of data and signed records
• to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records
- system validation has important components
• requirement specifications
• validation plan
• test plan
• traceability matrices
- requirement specifications are needed for
• system design
• edit checks
• archiving procedures
• audit trail design
• security access controls
• authenticity controls
• privacy controls
- the agency accepts three ways of signing
• digital signature
• biometric signature
• handwritten signature
- if data are collected electronically, they should be archived electronically
- The archived data should enable a reconstruction and evaluation of the trial.

Softwares Used in Clinical Data Management

Open clinica [7-9]

OpenClinica is the world's first commercial open source clinical trial software for Electronic Data Capture (EDC) Clinical Data Management (CDM). In just a few years since its first release, OpenClinica become one of the world's most widely adopted clinical trial software technologies powering research in over 100 countries. During this time, a rich community of innovation has arisen around OpenClinica making it both a robust and uniquely flexible platform used across diverse types of clinical research.

Progeny Clinical

Progeny Clinical is the ideal pedigree and clinical data management software solution for family-based studies. Since 1996, we've been providing research institutions and clinical genetic services worldwide the ability to draw pedigrees and track patient history data. You can configure the database to include unlimited fields, design data entry screens, enable security features to restrict access for specific users, run queries over the data, and more. All of this functionality integrates with Progeny Lab or Progeny LIMS so all users work off of the same database if you desire.

Query management

Query

A request for clarification on a data item collected for a clinical trial; specifically a request from a sponsor or sponsor's representative to an investigator to resolve an error or inconsistency discovered during data review.

Query management

Ongoing process of data review, discrepancy generation, and resolving errors and inconsistencies that arise in the entry and transcription of clinical trial data.

Query resolution

The closure of a query usually based on information contained in a data clarification. Before locking the database, there should be an agreed list of validation checks, which can be performed on the data for checking of consistency, etc. Queries as part of data analysis are not considered in this document.

- Queries should be created in accordance with customer requirements and documented procedures (data review guidelines and data validation plan) Defined procedure for self evident corrections performed by data management staff.
- Query resolution tracked and action taken within agreed time-scales.
- Action taken on queries is appropriate and edits are documented.
- All transactions to the database (insert, update, delete) must have a clear and complete audit trail.
- Adequate SOPs and working instructions for data changes take into consideration trial amendments, which may have consequences on the CRF.
- Ensure no duplication of queries
- Single checks with all variables, complicated checks with critical variables
- Queries are issued to sites within agreed time-scales
- Queries should have response within agreed time-scales
- Reports on query management.

Challenges in clinical data management

Although EDC technology and e-clinical systems have been implemented to enhance various aspects of the data management process, implementation has not been without difficulty nor has it been improved as rapidly as many had anticipated. The pharmaceutical, biotechnology, and medical device industry, as well as academia and the

government, have all started to learn about the technology advantages; some have gained implementation expertise in adopting or configuring it as a new data management tool. EDC acceptance seems strong, and there are few instances where sponsors have gone back to PDC studies when they have had the experience of EDC. Although the goal of data management will not change, i.e., assurance of clean data at the end of the study, there is no doubt that data management processes will evolve with the use of EDC and e-clinical systems.

Status of data management in clinical studies

Slow yet increasing EDC adoption combined with EDC technology improvement has demonstrated the reality and complexity of implementing re-engineered e-clinical processes along with new technology introduction. There is still the presence of PDC in a large number of sponsor firms, especially in Phase I clinical studies or studies sponsored by small-sized or start-up firms. Medium or large biopharmaceutical firms are tending to move into EDC, or have accumulated implementation expertise with the technology and associated e-clinical systems. It is not surprising that the traditional PDC and evolving EDC may coexist for a sponsor or CRO. To address the clinical operational needs, a sponsor firm or CRO may have a different set of procedures, standard work practices, guidelines, or business documents for PDC and EDC. Some sponsors may outsource the PDC data management functions to CROs in a complete fashion. Other sponsors may take a combinational approach whereby they would have an internal core team design the CRFs and come up with varied edit check specifications, but seek CROs to build the database and program those checks. To ensure that a standardized set of forms and edit checks are applied for cross-therapeutic clinical studies, sponsor firms must have the proper oversight and expertise to drive CRO data management or database design deliverables. There also seems to be an evolving trend whereby sponsor firms separate clinical database design (CRF or eCRF) and deployment functions into a specific unit from the CDM group due to the increasing sophistication of technology improvement, innovation, or clinical systems integration. It is also common for a different clinical programming unit to be set up for programming edit checks, listings, or reports for different functional groups. Increasing EDC computerization has enabled a paperless environment where key study variables based on protocols and electronic querying need to be transmitted between a clinic and a sponsor via a web browser entry. An

Independent CDM organizational unit with data managers designated to various therapeutic areas seems to be more beneficial to sponsors in terms of standardization, systems integration, and process consolidation than multiple CDM units affiliated with different therapeutic functions.

Roles and responsibilities

In this mixed PDC and EDC environment, clinical data managers and CRF designers should be involved in the earliest development of the strategies and tools for data collection. Table 1 lists potential CDM key activities prior to the planning of site initiation visit for a typical study. Through participation with the team during the design of the study, the data manager or study designer gains the necessary understanding of the required data from the protocol and the standards expected with respect to data quality. It is important for data managers or study designers to understand the varied sources of the data and the form in which the data will be retrieved, i.e., hospital records, laboratory test results, insurance and government records, private physician records, or e-diaries/patient-reported outcomes. It is increasingly recognized that the design of the CRF or eCRF is a key quality step in ensuring the data required by the protocol, regulatory compliance and/or safety needs/ comments, study scientific-specific hypothesis attributes, site work flow, and cross-checking of data items within a form or across different forms are addressed. CRF design is an interdisciplinary system engineering process requiring not only technical skills in utilizing the information technology (IT) tools but also expertise and scientific reasoning in the subject therapeutic areas. The original materials for this critical design are the draft yet stable clinical protocol, the corporate therapeutic unit standard forms, and clinical data acquisition standards harmonization (CDASH) guidelines. Such systems engineering work requires cross-functional team collaboration and input. It is mission critical that all functional teams including science, safety, biostatistics, regulatory compliance, and IT are represented in form review meetings and their feedback is incorporated into the revised and finalized forms. Systems development methodology and controlled process are followed for eCRF design and development to ensure regulatory requirements are met. Additionally, form design must always be tailored to the majority of end users and have their work flow taken into account. Any potential ambiguity in the CRF or eCRF must be avoided. In today's clinical research, the concepts and definitions are reasonably standardized. For each study, the definition of clinical terms, data entry guidelines, and data handling conventions require intensive effort and communication among all members of the study team to assure a meaningful and persistent set of data is compiled. Such information should be incorporated into written guidelines for CRF or eCRF completion. The use of the CRFs and guidelines should be thoroughly tested and reviewed by a pilot use at least among clinical data management or verification staff. Data edits such as ranges and cross-checks should be established with the participation of CDM, monitoring personnel, and scientists. This is especially important with EDC studies because the majority of such edit checks impact how queries will be issued and resolved.

Future clinical data management [10-12]

The challenges to investigate clinical product candidate efficacy and safety efficiently and to adhere to regulatory requirements create the strong impression that widespread adoption of EDC technology is inevitable. Indeed, EDC and e-clinical systems have attributes attractive to the majority of biopharmaceutical firms and CROs in a competitive clinical trial industry. FDA has brought forward a critical path initiative in pushing SDTM adoption to enable electronic regulatory submissions for sponsors of human drug clinical trials. SDTM was initiated and developed by CDISC. The increasing usage of SDTM, the operational data model, analysis data model, case report tabulations data definition specification define.xml, the laboratory model, and maturing standards, such as CDASH and FDA protocols, has created an end-to-end solution for the industry to focus on moving data from the point of capture to regulatory submission, therefore boosting the adoption rate of EDC and e-clinical systems by biopharmaceutical firms. However, the apparent certainty of growing EDC adoption needs to be constantly re-examined due to considerations of a number of challenging issues.

Ongoing eHR and EDC integration

The first question is how the current standardization initiatives in reaching interoperability between differential clinical and e-health systems among several standard consortiums such as the CDISC, HL7, NCI, and FDA will play out on EDC technology. The recent Initiative Electronic Health Records for Clinical Research Functional Profile has produced a functional profile to identify critical capabilities for the conduct of regulated clinical research utilizing eHR systems and additional functionalities toward facilitating ease of use for clinical research professionals. Further, Roche Pharma Development and Genentech are currently conducting pilot projects focused on leveraging eHR in direct support of specific drug development programs/clinical trials. These projects include concept development (mining clinical data to understand targeted patient populations better), protocol design (using current real world clinical data to determine the impact of specific criteria on the feasibility of a protocol), and patient identification (having study sites identify potentially eligible patients directly from their eHR for proactive patient recruitment). It seems promising that clinical research benefits can be realized through an eHR system. From the technical architecture perspective, will modern EDC technology system offer a multi-tier web-based application framework so that even a new clinical or health standard definition causes minimum modification? This certainly presents a challenge call to EDC vendors to partner with biopharmaceutical firms and health care technology providers to offer flexible, configurable, scalable, and interoperable EDC solutions to meet future e-clinical research needs.

Balancing technology innovation with science advancement [13'14]

A second debatable question is how to balance the need for constant EDC technology, improving initiative, operational clinical support, and evolving clinical science advances. It seems reasonable that the effectiveness of the CDM function is crucial in this dynamic changing environment and hinges on science, technology, process, systems, collaboration, integration, and initiatives. Technology itself will present challenges as well as opportunities. As health care providers, health technology providers, and laboratory systems become more sophisticated and integrated, electronic data will be available from many more diverse sources and instruments. These data sources may not conform to the conventional approach of many large companies. Consequently, EDC technology and e-clinical systems have challenged traditional roles and responsibilities within clinical data management. It is increasingly realized that successful EDC implementation requires re-engineered clinical operations and culture change. Such a gear switch must obtain management support, contribution and collaboration on the part of multiple stakeholders, in which clinical science, CDM, and biostatistics play ongoing critical roles in ensuring deliverability and objectivity. Table 4 summarizes core principles for CDM to meet future challenges and what factors contribute to success in executing technology-enabled working practices and achieving quality data deliverables.

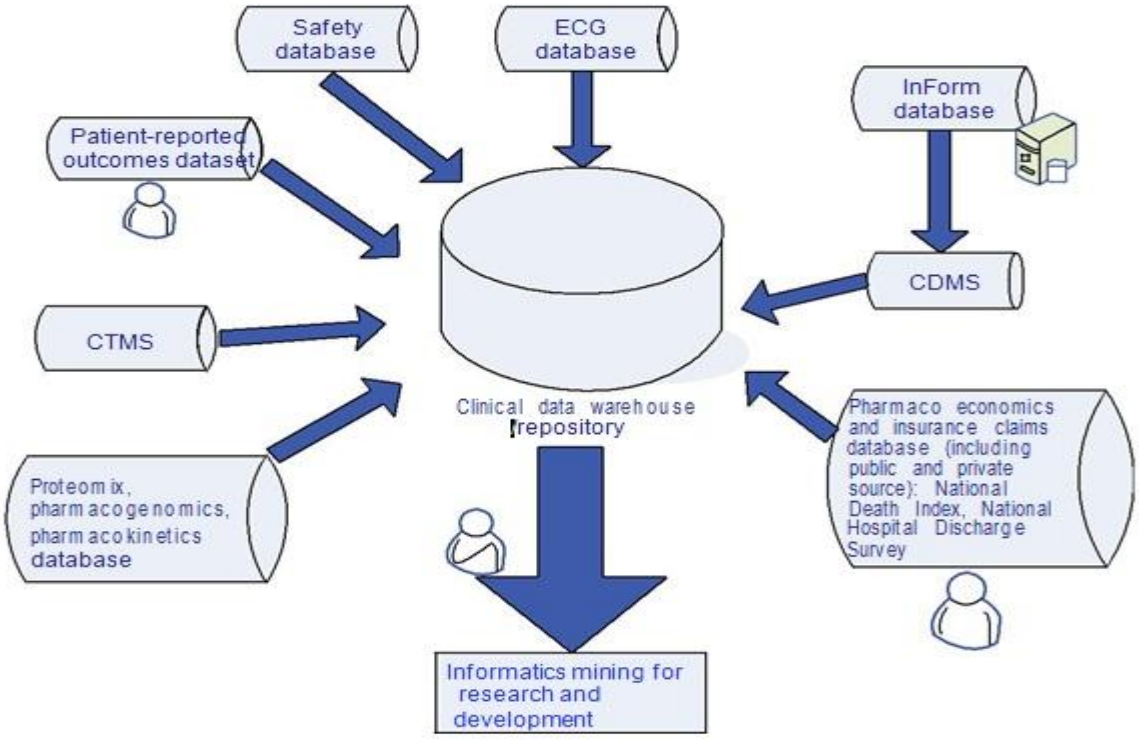
EDC technology pervasiveness with value-added cost benefit

A third unanswered question is how, exactly, the modern EDC and associated clinical systems will recruit the major-ity of small- to mid-sized companies, pharmacies, health care providers, and academic communities who still use labor intensive PDC tools and prefer not to change due to cost, concerns, or skepticism about EDC technology. As yet, no clear strategy has developed to assist these entities with the cost of installing, configuring, and maintaining these systems or for convincing them that they can function effectively within the new practice regimes that EDC may offer and support, with better improved return on investment compared with the PDC manual systems. Addition-ally, convincing top pharmaceutical companies with well established systems and processes to switch to modern sophisticated EDC systems or commit all studies to EDC can be both challenging and exciting. One needs to possess at least the following assets to succeed: ability to demonstrate enhanced system functionality and configurability, an understanding of business requirements, a commitment to customer service, ability to assist with data migration and system knowledge transfer, ability to offer consultation in preparation of new standard operating procedures or modification of existing ones, and ability to demonstrate

cost saving advantages in the long-term. The most difficult item seems to be aligning or adjusting existing processes to fit into the new system.

The biggest uncertainty concerning EDC technology and e-clinical systems is how much data warehousing or integration effort is required for a sponsor to take advantage of the vast variety and huge amount of data available, including (but not limited to) clinical data collected via CRF or eCRF, data captured through e-diaries, laboratory data generated via 2D or 3D imaging diagnostics, produced via central laboratory instrumentation, safety data stored in corporate safety system, patient data captured via eHR, "omics" data accumulated in translational research spectrum and how mining such data may break through the barriers that constrain productivity to bring new insights into the study of disease and human populations. Such challenging development may be an appropriate option for some biopharmaceutical- firms only. Undertaking such enterprise level initiative requires top management vision, accountable resource or consulting commitment, a long-term clinical development strategy, and close partnership among all therapeutic units. Effectively translating this knowledge into clinical intelligence and improved patient care and efficient utilization of such vast informatics data are holding potentials to advance the conduct of science and design new clinical programs for future medicine. Such novel strategies based on multiple sources of data attributes may open up new opportunities, transform how clinical medicine is practiced, and offer earlier interventional measures in the treatment process to stop diseases before they occur. The framework for this data-driven personalized vision is centered on the model of predictive, personalized, preemptive, and participatory medicine. Practicing medicine in this way will help us move more quickly to understand the fundamental causes of diseases at their earliest molecular stages so that we can reliably predict how, when, and in whom a disease will develop due to individual genetic compositions and difference in response to environmental changes/stresses. In order to realize this individualized approach and incorporate informatics into a sponsor data warehouse, the rigor to improve and innovate will be primary, the standardization and integration secondary, and patience and collaboration critical. Creating a standards-based and interoperable clinical development data repository/data warehouse in which corporate management, clinical science and safety staff can perform data mining and quality improvement in identifying process optimization, setting clinical product candidate priority, detecting safety signal, and reducing cost to accomplish corporate financial and professional goals will be paramount to widespread adoption of modern EDC technology and e-clinical systems and to assessing their transformative potential.

Fig. 1. A sample list of potential computer data sources, database, and datasets feed data into a corporate clinical data warehouse/repository to enable informatics mining capability



Abbreviations: ECG, electrocardiogram; CDMS, Clinical data management system; CTMS, Clinical trial management system

CONCLUSION

The competitive pressure in today's marketplace is forcing the biopharmaceutical industry to seek better ways of reducing drug development times and increasing productivity. The market acceptance of EDC technology has fueled new demands for improvement, configurability, and intelligent features. The need to improve clinical efficiencies and accelerate study times continues to grow, driving industry sponsors to seek an e-clinical environment that provides and promotes flexible eCRF trial design, build, and speedy deployment, robust data management, real-time data visibility, reporting and analysis, and global trial management and study scalability. Shortening the clinical trial lifecycle by collecting quality data more quickly and accelerating the availability of data are solutions to a critical path bottleneck that the industry has been working on for many years. Adopting EDC technology and e-clinical systems in the clinical trial process offers a solution with some claimed success stories. This has led to the growth of a new industry of clinical software vendors, offering a host of systems from EDC to IVRS, ePROs to CTMS, central coding application to safety signal detection, and clinical data warehouse initiatives to race towards e-clinical realization. The availability of near-real time data through the use of EDC has opened the door to the development of an integrated e-clinical environment. Yet, PDC-based clinical studies represent a fair percentage of studies in many organizations. Where EDC is being used at scale, operational benefits are being realized. The near-real time data, increasing standardization among multiple stakeholders, and integrated clinical environments have produced a paradigm shift in the clinical development model from research hypothesis, patient experience, through to analysis and SDTM submission. EDC technology and e-clinical systems have the potential to meet the challenges of providing powerful support to identify and discover the increasing range and potency of medicines. However, there are issues, concerns, and challenges in implementing and configuring modern EDC solutions. Clinical research -professionals need to anticipate proactively, embrace attentively and prepare for the further diversified challenges from both systems and business engineering perspectives in the world of Internet medicine.

Appendices

Appendix I: Terms and abbreviations

AE – Adverse Event
CDISC – Clinical Data Interchange Standards Consortium
CDMS – Clinical Data Management System
CONSORT – Consolidated Standard of Reporting Trials
CRF – Case Report Form
CSUCT – Computerized Systems Used In Clinical Trials
CSV – Comma Separated Values DBMS – Database Management System DDE – double data entry
DM – Data Management
DMP – Data Management Plan
EC – European Commission
ECRIN – European Clinical Research Infrastructures Network eCRF– electronic Case Report Form
EDC – Electronic Data Capture
EDP Electronic Data Processing EMEA – European Medicines Agency
FDA – Food and Drug Administration, US Department of Health and Human Services GCP – Good Clinical Practice
ICH – International Conference on Harmonization
IVR – Interactive Voice Response
MedDRA – Medical Dictionary for Regulatory Activities
NIHR -- National Institute for Health Research
ODM – Operational Data Model (CDISC) pCRF– paper Case Report Form
PDF – Portable Document Format QM – Quality Management
RDE – Remote Data Entry SAE – Serious Adverse Event

SAE reconciliation – the process of investigating clinical data and safety data in order to detect discrepancies (e.g. review of CRF and SAE data) and the process of resolving those discrepancies
SAS – Statistical Analysis System
SDTM – Study Data Tabulation Model (CDISC) SOP – Standard Operating Procedure
STATA – Data Analysis and Statistical Software
SUSAR – Suspected Unexpected Serious Adverse Reaction
VPN – Virtual Private Network
XML – eXtensible Markup Language

Appendix II: Regulatory documents

- ICH Topic E6: Guideline for Good Clinical Practice Guideline, Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), EMEA, January 1997
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Commission of 4 April 2001, No. L 121 p. 34
- Directive 2005/28/EC of the European Commission laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products. Official Journal of the European Commission of 9 May 2005, No. L 91/13-L91/19
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, Official Journal of the European Communities of 23 November 1995, No L. 281 p. 31.

US-based documents

- FDA, Guidance for Industry. 21 CFR Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003)
- FDA, Guidance for Industry. Computerized Systems Used in Clinical Investigations (CSUCT) (May 2007)

Draft Documents

- EMEA. Reflection on expectations for electronic source documents used in clinical trials. London, 17 October 2007 (draft).

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