Review Article

E-Clinical Technologies - Accelerating Clinical Trials with A Better and Defensible Data: Review of Challenges Addressed, Key Components, Benefits and Global Market Insights

Raju Sama*, Chaya Devi B, Vijaya Lakshmi N, Suresh A, Sathish M
Axis Clinicals Limited, 1-121/1, Miyapur, Hyderabad, Telangana, India.
*Corresponding author's E-mail: rajenderreddysama@gmail.com

ABSTRACT

As clinical trials continue to grow in complexity and global scope, the volume of clinical trial data is expanding exponentially. Innovative eClinical technologies are essential to manage these data requirements, reduce development costs, support faster "Go/No-Go" decisions for potential new products, and increase efficiency throughout the clinical trial process. EClinical technologies are a combination of technology, products, and services that work together as solutions to automate the management or conduct of clinical trials with the aim of replacing manual, ad hoc or paper-driven methods. EClinical technologies give life science organizations the ability to aggregate, standardize, and visualize their clinical data for powerful insights and advanced analytics. EClinical technologies are of different types, such as Clinical Data Management Systems, Clinical Trials Management System, Randomization and Trial Supply Management systems, Electronic Patient Reported Outcome and Electronic Trial Master File etc. The global eClinical solutions market was valued at USD 4.1 billion in 2015. The increasing demand for software solutions for clinical trials by the pharma and biopharma companies, expanding research and development, increase in the government grants to substantiate the clinical trials, and the rise in the number of customers for eClinical solutions are expected to boost the market in the coming future.

Keywords: Clinical trials, eClinical technologies, Demand, Market and Future.

INTRODUCTION

As clinical trials continue to grow in complexity and global scope, the volume of clinical trial data is expanding exponentially. Regulatory requirements for increased safety monitoring are also increasing the amount of study data that must be gathered, organized, and analyzed. Innovative eClinical technologies are essential to manage these data requirements, reduce development costs, support faster "Go/No-Go" decisions for potential new products, and increase efficiency throughout the clinical trial process. The industry has been on the verge of a technology explosion for a number of years. In the past few years, the clinical trial industry has made considerable progress in adopting technology as a way to streamline data collection, transmission, and monitoring.

eClinical is a term use to refer the electronic applications which are used in the Clinical Research. eClinical technologies are a combination of technology, products, and services that work together as solutions to automate the management or conduct of clinical trials with the aim of replacing manual, ad hoc or paper-driven methods.

eClinical technologies are of different types, such as Clinical Data Management Systems (CDMS), CTMS (Clinical Trials Management System), Randomization and Trial Supply Management systems, e-PRO (Electronic Patient Reported Outcome), Electronic Trial Master File (eTMF) and other common types of electronic solutions widely used in clinical trials.

Purpose of eClinical technologies

Clinical trials are being influenced by a number of factors like increasing competition, high costs of drug development and more stringent regulatory environment etc. As a result, pharmaceutical companies are faced with the tremendous challenge of conducting clinical trials. To overcome these, eClinical technologies came to picture

Advantages of eClinical technologies

- Provides to perform successful trials with quality data and shorter timelines, with reduced costs.
- Enables to both internal users such as CDM team and external users such as sites and CROs and Sponsor representatives.
- Provides us efficient planning, execution and tracking of clinical trials data from different geographical areas.
- Improves relationships with other than internal departments like clinical investigators, site coordinators and medical affairs.
- Facilitates compliance with regulatory guidelines for electronic records. The application used for eClinical trials consists of audit trail, security, access and authorization features with the compliance of 21 CFR Part 11.
- The collection of data from the investigational center will be directly captured into the study eCRF will give significant advantage in terms of time from data generation to date cleaning and database lock.

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eClinical Technologies that are Helping Evolve Clinical Trials

Clinical Trial Management Systems (CTMS)

Clinical trials management system is a software system, which provides a 'single source of the truth' for operational data related to the planning, management and reporting of trials. It consolidates, automates, and streamlines all operations associated with clinical development.

Challenges addressed

- Enhanced clinical research infrastructures and support via IT-driven enterprise integration

- Offered enterprise-wide solution to the clinical research community

- Replaced decentralized methods of recording clinical research activity

- Supported process and workflows to strengthen and support sites

- Ultimately reduced administrative redundancy.

The Key Components

Study Start up:

- Investigator, site selection and management

- Investigator and site assessments

- User role management and access control

Study Management:

- Milestone and recruitment tracking

- Email notification for any study related events

- Drug shipment tracking and supplies management

- Subject, visit, CRFs and query tracking

- Monitoring visit plan, SDV tracking and reports

- Subject exemptions and deviations tracking

- SAE tracking alerts and notifications

- Study documents management

- Study progress tracking and status reports

CTMS Benefits

- Better strategic planning

- Strengthened compliance

- Overall reporting

- Improved workflow / processes

- Real time accurate online study information portal

- Improved human subject research activity throughput / volume

- Risk mitigation

CTMS solutions in market: Oracle Corporation, Medidata Solutions, Inc., Parexel International Corporation, Bio Clinica, Inc. (Bio Clinica), Bio-Optronics, Inc., Merge Healthcare Incorporated (An IBM Company), Data Trak International, Inc., Veeva Systems, Inc., DSG Inc. (Document Solutions Group), eClinForce, Inc., and Forte Research Systems, Inc. are the key players in the global CTMS market.

Clinical Data Management Systems (CDMS)

A clinical data management system or CDMS is a tool used in clinical research to store and manage data the data of a clinical trial. The clinical trial data gathered at the investigator site in the case report form are stored in the CDMS. To reduce the possibility of errors due to human entry, the systems employ various means to verify the data. Systems for clinical data management can be self-contained or part of the functionality of a CTMS. A CTMS with clinical data management functionality can help with the validation of clinical data as well as the help the site employ the data for other important activities like building patient registries and assist in patient recruitment efforts.

The CDMS can be broadly divided into paper-based and electronic data capturing systems.

Paper-based systems

Case report forms are manually filled at site and mailed to the company for which trial is being performed. The data on forms is transferred to the CDMS tool through data entry. The most popular method being double data entry where two different data entry operators enter the data in the system independently and both the entries are compared by the system. In case the entry of a value conflicts, system alerts and verification can be done manually. Another method is Single Data Entry.

The data in CDMS are then transferred for the data validation. Also, in these systems during validation the data clarification from sites are done through paper forms, which are printed with the problem description and sent to the investigator site and the site responds by answering on forms and mailing them back.

Electronic data capturing systems (EDC)

An EDC system is web-based software designed for the collection of clinical data in electronic format for use mainly in human clinical trials. In such CDMS the investigators directly uploads the data on CDMS and the data can then be viewed by the data validation staff. Once the data are uploaded by site, data validation team can send the electronic alerts to sites if there are any problems. Such systems eliminate paper usage in clinical trial validation of data. EDC replaces the traditional paper-based data collection methodology to streamline data collection and expedite the time to market for drugs and medical devices.

Challenges addressed by an EDC System.

Making the switch to an EDC system can help solve common challenges associated with other methods of data capture, such as:

- Efficiently managing time spent on data collection and review

- Ensuring compliance

- Finding what you need, when you need it

The Key Components:

Typically, EDC systems provide:

- A graphical user interface component for data entry

- A validation component to check user data

- A reporting tool for analysis of the collected data

Benefits of EDC

Benefits to subjects:

- Online and remote access training and help

- Electronic reminders of data requirements

- More accurate recording of data

Benefits to investigators:

- End-to-end applications are available

- Use standardized data/fields

- Build edit check processes to improve data quality

- Remote monitoring and data review

- Online and remote training and help access

- Consistent look/feel by system users

- Patient compliance and ease of use

Benefits to IRBs:

- Electronic transfer and review of research proposals

- Consistency among proposals o Potential for higher quality proposals

- Electronic informed consent software applications and processes

- Electronic tracking of reviews, requests for changes, and approvals/denials of research proposal.

Benefits to sponsors:

- Improved data quality and consistency

- Rapid access to data

- Rapid feedback to sites, contract research organizations, and clinical research associates

- Quicker path to product approval (or decision to discontinue research)

- Electronic submissions to regulators.

EDC solutions in market: Medidata Rave, Oracle® Clinical Remote Data Capture, InForm and OmniComm®, Perceptive Informatics, Forte Research Systems' OnCore eClinical, Aetiol EDC and Merge eClinical's eClinical OS are some of the commercial solutions. Besides rather expensive commercial solutions, there was more and more open source clinical data management systems available on the market are CARMEN, CRCNS, EEGBase, G-node, LORIS, REDCap and XNAT.[1-4]

A.   Randomization and Trial Supply Management (RTSM).

Randomization and Trial Supply Management (RTSM) are the activities associated with real-time processing and monitoring of enrolment, treatment allocation, dosing, dispensing and clinical supplies tracking. Randomization in clinical trials prevents bias in selecting which patients receive the investigational product or the placebo/comparator. It helps balance the allocation between patient groups (cohorts) based on predetermined criteria (for example age, sex and smoker/non-smoker). Technology used to support these processes is also known as IRT (Interactive Response Technology)

Challenges addressed

- Managing randomization and clinical trial supply chain management including study medication dispensing and inventory
- Monitoring real-time recruitment
- Managing emergency "unblinding" or "Code breaking"
- Performing calculations to ensure accuracy of dosing.

RTSM can also help solve difficult supply issues including adaptive trial design management, titration regimens or medication pooling across multiple protocols.

A new breed of RTSMs leverages cloud-based software-asa-service (SaaS) solutions that can be configured rather than programmed to meet the specific needs of a study. These solutions provide a web interface (IWR) and voice back-up (IVR).

IVRS (Interactive Voice Response Systems) and IWRS (Interactive Web Response Systems) both the tools processes are controlled by a central computer. IVRS is accessed via telephone and IWRS via web interfaces. Both the tools are very useful in Global trials for register new patients, randomize patients, obtain double blind medication, blinding, to unblind patients in Medical emergency etc... Now a day's most of the protocol uses IXRS (Interactive phone and web Response System) depending on the site convenient their might use the appropriate system.They are easy to integrate with the client's chosen electronic data capture (EDC) system or other eClinical applications. Because the general workflow of RTSM activities remains common across multiple studies, modern RTSMs enable simple configuration to comply with company standards or unique protocol requirements.

The benefits of RTSM

- Access to randomization and supply chain experts that can help you apply the correct methods for your studies.
    - Maximizing efficient use and minimizing wastage of limited, expensive clinical supplies, while maintaining the study blind.
    - Demonstrating full drug accountability.
    - Real-time reporting of recruitment, medication assignment and supplies inventory/location.

Components of a Successful RTSM System

- Selection of the right algorithm for the study from a comprehensive spectrum of validated randomization methods
- Centralized emergency code breaking via web and phone (IWR and IVR)
- Simulations and consulting to optimize the randomization methods
- Randomization methodologies for adaptive trial designs Trial supply management services include:
- Automated site and depot medication inventory control
- Real-time reporting of patient progress, medication assignments and supply location and status • Unique supply algorithms to optimize efficient use of available supplies
- Expiration date management and relabeling at depots and sites
- Pack-type substitution and multipack box handling within shipments
- Supplies management for adaptive trial designs Study teams and site can easily and quickly access administrative and management functions and data including:
- Supply administration to provide clinical teams with the ability to control and manage their trial inventory
- Site management to allow study personnel to view site-level and patient status in real-time
- Site inventory management to allow site users to easily view the status of their on-site supplies.

RTSM solutions in market: Medidata Balance RTSM, PAREXEL's ClinPhone® RTSM,Agile RTSM and *DATATRAK ONE® UX Randomization and Trial Supply Management™* (*UX RTSM™*)

Electronic Clinical Outcome Assessment (eCOA).

"A clinical outcome assessment (COA) directly or indirectly measures how patients feel or function and can be used to determine whether or not a drug has been demonstrated to provide a treatment benefit". There are tour types of clinical outcome assessments (COAs) that are used to provide evidence of a treatment benefit and that are typically used to collect data to support claims made to the regulators when seeking approval. Patient Reported Outcomes (PRO), Clinician Reported Outcomes (ClinRO), Performance Outcomes (PerfO) and Observer Reported Outcomes (ObsRO).

Electronic Clinical Outcome Assessments, or eCOA, employs technology such as Smartphone/Handheld Device , Site-Based Tablet , Web-based Portal , Interactive Voice Response (IVR) and/ personal computers to allow patients, clinicians, and their caregivers to directly report outcomes.

Factors that need to considered When Selecting eCOA Modality are Frequency of data collection (Daily, Weekly, at site, event), Type of data (Symptoms, Dosing, etc.), Use of data – primary or key secondary, Number of Instruments / Items per instrument, Burden Patient population – disabilities or impairments, Logistics and telecommunication support.

Challenges addressed

- Increasing patient compliance and reducing the patient's burden of participating in the trial
- Eliminating transcription time of assessment data and source document filing costs
- Intrinsically cleaning data
- Providing real-time data visibility
- Helping in having fewer source documents to validate
- Helping in generating electronic DCFs
- Ensuring Faster database locks
- Designing processes gets trials up and running quickly
- Can be tailored to support study protocols and satisfy regulations
- Reporting tools are user friendly, and help ensure accurate and complete data
- eCOA solutions can be scaled, which contributes to effective, efficient results
- Can be integrated with eCiinical systems or medical devices, which contributes to better healthcare delivery and management

Benefits

- More data for less money, statistically fewer falsified data points Reduced burden on site, potential savings on site stipends Front end edit checks reduce DCF and improved data quality Proactively see study progress and site/patient compliance allowing to minimize recruitment overages and reduce study costs Reduced site monitoring load Fewer and faster resolved DCFs No impact to critical path and Better, Defensible Data/Reducing Regulatory Risks eCOA data Meet the ALCOA Standard

eCOA solutions in market: CRF Health - TrialMax®. [5-8]

B. Electronic Trial Master File (eTMF).

An electronic trial master file (eTMF) is a formalized means of organizing and storing documents, images and other digital content for pharmaceutical clinical trials that may be required for compliance with government regulatory agencies. The term eTMF encompasses strategies, methods and tools used throughout the lifecycle of the clinical trial regulated content. An eTMF system consists of software and hardware that facilitates the management of regulated clinical trial content. . In an

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eTMF, documents and content are stored centrally on a computer server, typically using a document management system and exchanged with others through either a corporate Intranet or a secure internet connection that can be accessed with auditable security.

Challenges addressed:

- Reduced business risk - systems provide confidence that you have met agency regulatory compliance requirements
- Enhanced document quality - automated systems have been proven to make fewer errors than manual paper handling processes; ability to implement automated quality control processes
- Improved team productivity - sharing, viewing documents anytime, anywhere from any device is faster than manual paper retrieval
- Reduced auditing and reporting costs - automated reporting and retrieval of ECM based systems can significantly reduce auditing and reporting labor and travel costs

Benefits:

Use of an eTMF system can provide cost savings, time savings and risk reduction for organizations conducting clinical trials.

- Growth in Regulations: State, Federal and industry regulations continue to grow and evolve
- Risk Management: Significant risks and penalties for non-compliance, including fines, and customer lawsuits
- Product Quality: Enhanced product quality through easier audits and management
- Accelerate Clinical Trials: Electronic document sharing with clinical trial stakeholders: e.g., Investigators, agencies, and clinical research centers can help resolve issues faster and accelerate clinical trial milestones
- Cost Savings: Save document mail and overnight courier costs; save document physical storage costs; save administrative staff document handling and management costs
- Time Savings: Anytime, anywhere access to documents helps move business operations forward faster than manual, paper-based processes

The required components of eTMF systems.

- Published, standards-based terms available in machine readable format
- Automated digital signature capture option to minimize paper handling
- Limiting system access to authorized individuals
- Use of operational system checks
- Use of authority checks
- Use of device checks
- Determination that persons who develop, maintain, or use electronic systems have the education,

- Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- Appropriate controls over systems documentation
- Automated document audit trail and workflow history (time stamping of records)
- Record export to a portable format such as PDF or XML
- Validation of the system
- Web standards - Most ECM systems support XML, HTTP or other web standards to exchange, view and manage eTMF content

Although the FDA and other regulatory agencies have defined the requirements for electronic document and record systems that store clinical trial essential documents, no government agency has defined how eTMF content should be classified, or the standards for metadata that may used in content indexing, or the electronic format(s) that should be used to model, store or exchange eTMF data.

eTMF solutions in market: CareLex, Forte Research, Fujitsu, HL7, Mayo Clinic, NextDocs, Oracle, Paragon Solutions, Phlexglobal, Safe-BioPharma, SterlingBio, and Sure Clinical. [9-12]
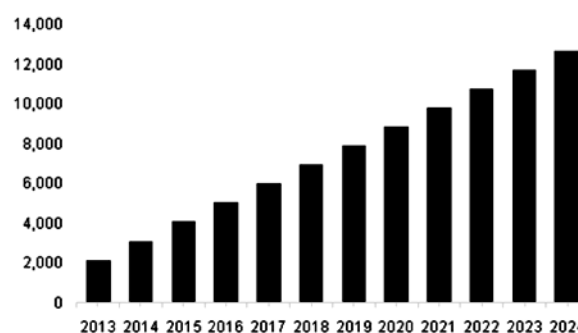
Global eClinical solutions market, 2013 - 2024 (USD Million)

PURCHASING THE RIGHT TOOLS

Industry Insights

The global eClinical solutions market was valued at USD 4.1 billion in 2015. The increasing demand for software solutions for clinical trials by the pharma and biopharma companies, expanding research and development, increase in the government grants to substantiate the clinical trials, and the rise in the number of customers for eClinical solutions are expected to boost the market during the review period. Moreover, factors such as the presence of a large population, growing customer base, low operating costs, and shift of resources from Sponsor companies to CROs are propelling the growth of this market, especially in the Asia Pacific countries. The emerging markets, including Korea, China, Taiwan, and India, have become pleasing destinations for the outsourcing of clinical trials due to the presence of a large population& low service costs.

However, factors such as the high implementation cost, lack of awareness of clinical data sciences software in the research community, and scarcity of skilled research professionals are expected to hinder market growth.

Product Insights

The eClinical solutions market is segmented on the basis of product (clinical analytics platforms, Electronic Clinical Outcome Assessment (ECOA), Electronic Data Capture (EDC),Clinical Data Management Systems (CDMS), clinical data integration platforms, safety solutions, Clinical Trial Management Systems (CTMS), Randomization and Trial Supply Management (RTSM), and electronic Trial Master File (eTMF)),delivery mode (web-hosted, licensed enterprise, and cloud-based), clinical trial phases (phase I, phase II, phase III, and phase IV), and end-user application (consulting service companies, medical device manufacturers, hospitals, contract research organizations, and pharmaceutical & biopharmaceutical companies).As of 2016, the industry is estimated to be led by the EDC and CDMS segments, whereas the eCOA segment is anticipated to witness the highest growth rate during the forecast period.

Regional Insights

On the basis of geography, the eClinical solutions industry is categorized into North America, Asia Pacific, Europe, Latin America, and the Middle East and Africa. As of 2015, North America was estimated to dominate the market followed by Europe. One of the key factors attributing to the growth of the North American market is the increasing number of clinical trials being conducted in the region.

Some other factors influencing the growth of the market are intensive R&D activities resulting in the development and launch of new products, increasing government grants for clinical trials, and the rising prevalence of lifestyle diseases. In terms of growth rate, Asia Pacific is anticipated to witness a rapid growth in the global market. The increasing participation of emerging economies in the clinical trials is expected to fuel the growth of the market in the near future.

Competitive Market Share Insights

The key players in the market include Oracle Corporation, Parexel International Corporation, Medidata Solution, Inc., BioClinica, DataTrak International, Inc., CRF Health, ERT, eClinical Solutions, Merge Health Incorporated, and OmniComm Systems, Inc. In order to attain a competitive edge in the industry, the major players are actively involved in organic as well inorganic growth strategies. Agreements, collaborations, partnerships, and new product launches are some of the key strategies, which are implemented by the market players.[13]

CONCLUSION

As clinical trials continue to grow in complexity and global scope, the volume of clinical trial data is expanding exponentially. eClinical technologies are essential to manage these data requirements Implementation of eClincal technology in a study helps us in many ways such as real-time data access, clean data at any given point of time, immediate resolution to queries, locking patient data when clean. Additionally, the Last Patient Last Visit - Database Lock timelines can be significantly reduced (i.e.) from conventional 8 to 10 weeks for paper studies to three to four weeks for an EDC. The global eClinical solutions market was valued at USD 4.1 billion in 2015. The increasing demand for software solutions for clinical trials by the pharma and biopharma companies, expanding research and development, increase in the government grants to substantiate the clinical trials, and the rise in the number of customers for eClinical solutions are expected to boost the market in the coming future. Oracle Corporation (U.S.), Medidata Solutions, Inc. (U.S.) PAREXEL International Corporation (U.S.), BioClinica, Inc. (U.S.), CRF Health (U.S.), DATATRAK International, Inc. (U.S.), ERT (U.S.), eClinical Solutions, Inc. (U.S.), Merge Healthcare Incorporated (U.S.), and OmniComm Systems, Inc. (U.S.) are some key players operating in the global eClinical solutions market.

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Source of Support: Nil, **Conflict of Interest:** None.