**ARTIFICIAL INTELLIGENCE IN MANAGEMENT OF CLINICAL TRIAL DATA**

**Abstract**: In the era of evidence based medicine thousands of clinical trials are conducted generating huge data from trial participants. Traditional trials highlighted ethical issues leading to patient withdrawal from trials, inadequate enrolments which gave rise to digitalisation with intent to promote authenticity, integrity in clinical research. Artificial intelligence is a boon in digitalization. It strengthened patient- physician relationships but it also contained some negative aspects which are being resolved. AI creates strong framework for clinical data management.

**Key words**: artificial intelligence,clinical data management, digitalisation, drug development

**Introduction and objective**

 Alan Turing, the founder of artificial intelligence (AI) defined it as the science and engineering of building machines, especially intelligent computer programs. In health care sector AI is combined with analytics (AIA). Computers programs which assist in simulating human behaviour are called artificial intelligence systems. Clinical applications of AI incorporate clinical decision making, automated surgery, patient monitoring and assistance, healthcare management etc. [1] Artificial intelligence (AI) uses huge data based on advanced machine learning techniques involving multiple layers of artificial neural networks (i.e. deep learning). [2]

Past trials highlighted ethical issues leading to patient withdrawal from trials, inadequate enrolments which gave rise to digitalisation with intent to promote authenticity, integrity in clinical research. Artificial intelligence is a boon in digitalization. It strengthened patient- physician relationships but it also contained some negative aspects which are being resolved. AI creates strong framework for clinical data management.

**Role of Artificial Intelligence in drug discovery and development**

Artificial intelligence (AI) has its own role in drug discovery and development. It has profound effect on drug development. Big data and machine learning in AI has increased annual sales in the health care system. [3] AI has promoted phenotypic drug discovery by allowing screening of compounds in cells or animal models without any prior information on biological target. Many pharmaceutical companies have started collaboration with AI companies and are adopting AI approaches for drug candidates, redrafting the new indications for already available drugs and in advanced stage of drug development also.[3]

Artificial intelligence (AI) utilises advanced machine learning techniques involving multiple layers of artificial neural networks (i.e. deep learning). AI has diverse role in drug discovery and clinical data management.

Traditionally clinical trials raised ethical issues resulting in patient withdrawal, inadequate enrolments with a consequent result of digitalisation with intent to promote authenticity, integrity in clinical research. Artificial intelligence is a power boost in digitalization. It has decentralised the clinical trials and strengthened clinical data management.

**Clinical Data Management (CDM)**

Clinical trials are conducted to collect data in response to research question for hypothesis testing. Data is the most important aspect of clinical trial. Research outcome depend on the quality of generated data. [4, 5] CDM is basically the collection, cleaning, and management of data obtained from trial participants but [4] in compliance with regulatory standards. CDM process is primarily conducted to provide high quality, authentic data with as minimum as possible errors and missing data. For this purpose good clinical practices are utilized and assurance is made that generated data is complete in all aspects, reliable and processed correctly. All this is facilitated by software applications which allow audit trail, provide easy identification and resolution of discrepancies in collected data. In large scale and complex trials sophisticated innovations in CDM ensure easy handling and high quality data. [4, 6]

 **High-quality data**

 Data which is accurate for suitable statistical analysis and complies with protocol-specified parameters and requirements is called high quality data. For a data to be high quality there are some requirements which are as below

1. Data should bear an arbitrarily ‘acceptable level of variation’ which would not affect the conclusion of the study on the ground of statistical analysis.
2. In case there is encountered deviation from protocol the participant should be excluded from final database and it may be audited by regulatory authorities.
3. Collected data should be free from missing data and minimal acceptable misses.
4. Quality of data should comply with applicable regulatory requirements. [4]

**Different CDM soft wares and their applications (Fig 1)**

**SAS Clinical software**

This software addresses unique needs of a new drug throughout drug discovery and development process. It generates a simple, easy and an integrated platform for assessment and management of data from several sources like CDMS, EDC etc. It helps in the automation and recognition of several processes to minimize manual intercession. Proper utilization of standards is assured by the proper use of the data. Data generated from SAS ensures compliance with quality standards and is less time consuming. [7, 8]

**EZ –entry**

It is a modification of EpiData software program incorporating several modules. Actions covered by this software are query management, revision tracking, data entry, import and export of data and finally quality control. It is user friendly and a secure system with user authentication manual where authorized user can access database and revision tracking manual where revision in the original database can be made and a new entry is recorded automatically in the system. Quality of data is ensured by field value check, data entry alignment and query forms. [7, 9]



 **Fig.1.Different CDM Soft wares**

**Oracle Clinical software**

 Information provided by this software is steadfast and protected. Key benefits are effective team work, speedy implementation, productive marketing and higher return on investment, industrial compliance, easy transition from paper to electronic data capture of the data etc. [6]

 **TCS CLIN-E2E software**

Tata consultancy services (TCS CLIN-E2E) software addresses all the four phases of clinical trials. The software captures the electronic data integrating the trial sites and the laboratories with the sponsors. Through this software the pharmaceutical companies are able to create CRFs which investigates the clinical data and monitors global trial sites. It can handle both paper and electronic CRFs. It creates study templates and CRFs that can be reused saving cost and time it has a greater compliance with 21 CFR part 11 of the GCP. [6]

**Cognos 8 Business Intelligence software**

This software has made CDM easy, simple and accurate. Data quality and performance is determined at personnel level and from collaborators. This software delivers a variety of business Intelligence capabilities and service oriented architecture (SOA) also. [6, 8, 10]

**Symetric software**

Symetric software provides a comprehensive understanding of day-to-day requirements for the workflow processes such as set of the database, data quality control and final export involved in clinical data management. This software has been fully loaded with completely integrated processes with data dictionary, full discrepancy management, classification of the missing data using special codes. It also provides benefit of interactive double-data entry verification, CRF tracking functions and query management. [6]

**Akaza's OpenClinica software**

It is an open source software and act as a collaborative model having modular architecture flexible for obtaining data for electronic data capture in the CDM system. It organizes clinical research in compliance with the protocol and trial site. It is secure and supports in proper management of the data with recurring patient visits. It provides tools for the import and export of data for the movement of clinical data sheets across excel spreadsheets. Other applications are interfaces for data query and retrieval, conformity with HIPAA (Health Insurance Probability And Accountability) privacy and security guidelines. It has Expandable technology framework developed using Java J2EE. [6]

 **Progeny Clinical software**

Progeny Clinical software tracks data from family history. The key features include family background, individuals and sample management, sub-pedigrees, custom display pedigrees, displays Haplotypes etc. [6]

**Sigmasoft's DMSYS software**

Sigmasoft is fully validated and affordable software. It provides high quality data management services for small scale and large scale clinical trials. Its unique application of short cuts allow the person to copy data entry sheets, forms, logic checks and other study structures and makes data easy to import/export from excel sheets. It serves rapid data cleaning, urbane error management functions and supports validation by its user validation project. [6]

**Process of** **Clinical Data Management**

**Data collection**

Data is collected either on Paper CRF or an electronic CRF (e CRF). Paper CRFs data is filled by an investigator as per the guidelines and data is fed into database by translated data entry. In case of the e-CRF the investigator or the designee first log in the CDM system and enters the data at the trial site directly. Data errors are minimally reported when data is collected by e-CRF mode and in case there is any discrepancy then it can be resolved earlier. Pharmaceutical companies opt for speedy drug development by preferring e-CRF options or remote data entry. [4, 11]

**CRF tracking**

Once the data is entered in data base, tracking is done to assure completeness and authenticity by Clinical Research Associate (CRA) under the guidance of CDM team. This team tracks CRFs for any missing, illegible data and maintains documentation. If any missing data or illegible data exist then the investigator is answerable. [4,11, 12]

**Data entry**

Double data entry is recommended for paper CRF as such data entry facilitates cleaner database and ensures better compliance due to minimal errors. Double data entry is performed by two separate operators since the pass entry by the second person facilitates verification and reconciliation of illegible data by recognizing transcription errors and discrepancies. [13, 14, 15]

**Data validation**

Next step after data entry is validation of data for compliance as per protocol specifications. It promotes identification of any pitfalls in the entered data. Data validation program (DVP) consists of edit checks as per logic condition mentioned to ensure data validity. Discrepancies may arise from inconsistent data, missing data, protocol deviations and range checks and can be resolved by investigators after logging into the system. During the entire course of CDM quality control is a continuous process and is performed at regular intervals. [10]

**Discrepancy management**

**Discrepancy management** is most crucial and attention seeking step. It includes review of discrepancies, assessing reason, followed by either resolving or declaring them as irresolvable. Discrepancy management facilitates data cleaning and collects adequate evidence for the deviations found in data. Approximately all CDMS have a discrepancy database where all discrepancies will be recorded and stored with audit trail. Discrepancies can be either flagged to the investigator site that require clarifications or closed in-house by Self-Evident Corrections (SEC). After solution the same will be updated in the database. In case of e-CRFs, the investigator can access the discrepancies flagged to him and will be able to provide the resolutions online. Discrepancies are reviewed by CDM team at regular intervals to ensure resolved and recorded as ‘closed’ but sometimes closure of discrepancies is not possible. [11, 12]

**Medical coding**

Most critical aspect in medical coding is right coding and classification of adverse events Medical coding is recognition and properly classification of clinical trial associated medical terminologies. Medical coding classifies reported medical terms on the CRF to standard dictionary terms already available online to attain consistent data and avoid unnecessary duplication. This is possible with technical expertise, skills understanding of medical terminology, understanding disease entities, drugs used and knowledge of concerned pathological processes. Medical Dictionary for Regulatory Activities (MedDRA) is used for the purpose of coding adverse events and other illnesses and WHO-ART is a dictionary for adverse reactions terminology. World Health Organization–Drug Dictionary Enhanced (WHO-DDE) is dictionary for coding medications. Customized dictionaries are also used by some pharmaceutical companies to suit their needs and meet their standard operating procedures. [4]

**Database locking**

Final data is validated after an appropriate quality check and assurance. The SAS datasets are finalized under guidance of statistician. Before data base lock a checklist is used to check completion of all activities. After approval from all stakeholders and extraction of clean database is locked and it cannot be amended in the database further, except by privileged users. After locking, data is extracted from the final database. [4]

**Players in CDM**

In a CDM team, different roles and responsibilities are attributed to the team members. The minimum educational requirement for a team member in CDM should be graduation in life science and knowledge of computer applications. Ideally, medical coders should be medical graduate but in the industry paramedical graduates are also recruited as medical coders. Some key roles are essential to all CDM teams as shown in table1.

|  |  |
| --- | --- |
| **Player** | **Role and responsibilities** [4, 16] |
| **Data Manager** | * supervises entire CDM process
* prepare the DMP, approves the CDM procedures and all internal documents related to CDM activities
* Controls and allocates the database access to team
 |
| **Database Programmer/Designer** | * performs the CRF annotation, creates the study database,
* programs the edit checks for data validation
* designs data entry screens in the database and validates the edit checks with dummy data
 |
| **Medical Coder** | * Codes for adverse events, medical history, co-illnesses, and concomitant medication administered during the study
 |
| **Clinical Data Coordinator** | * designs the CRF, prepares the CRF filling instructions
* develops the DVP and discrepancy management documents, checklists, and guideline documents
 |
| **The quality control associate** | * checks the accuracy of data entry and conducts data audits
* verifies the documentation
 |
| **Data entry personnel** | * tracks the receipt of CRF pages and performs the data entry
 |

**Digitalisation in drug development**

There has been reported a transformation in drug development due to expensive and complex nature of clinical trial and patient centric approach of drug trials. Safety and efficacy of experimental molecule is an important concern in clinical research. During the entire process of clinical trial, sponsors collaborate with clinicians and patients for detecting safety and efficacy of a novel molecule. Trials are usually designed in such a way that it is feasible and easy for drug sponsor to conduct the study as per his convenience but no consideration is given to convenience of patients which increases complexity in trials. But now the pharmaceutical industry is following a patient centric approach in drug development which has its unique advantages like patient is acquainted with disease, trial procedures, drug molecule, site of trial conduct and results from similar studies or trials. This results in quality talk between patients and physician. Contract research organizations (CROs) provide readymade repository of trial patients in the support of pharmaceutical companies by saving cost and effort. E.g. Digital Patient Unit program of quintiles helps to use real world patients for the speedy testing of inclusion/exclusion criteria and provide opportunity to sponsors to screen them and refer them to clinical trial sites if required. [17]

**mHealth** utilizes clinical practice under the umbrella of portable diagnostic devices. Such device has transformed health care delivery system from one that was health-systems generated to other which is remote and patient generated. This transformation increases opportunities for patient enrolments, outcomes and decreases cost. [8]According to World Health Organization mHealth is a triad of e-health and medical and public health practice facilitated by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants (PDAs) and other wireless devices. It is advantageous over traditional trial programmes in terms of safety, efficacy, real time quality data, real world evidence from continuous data, improved patient adherence and remote monitoring. [18, 19]

**Applications and limitations of mHealth**

1. Self-care and self-monitoring in terms of blood glucose levels, weight, and daily activity.
2. Managed care: Monitoring technology for instance as
* in Dementia: monitoring patient visits to the refrigerator or bathroom,
* in COPD: use of inhaler,
* in Ebola: vitals monitoring,
* in Diabetes: blood glucose levels,
* in Vaccines: body temperature,
* in Hypertension/diabetes: medical and physical activity adherence,
* Hospital at home: Bluetooth devices can be connected enabling patients to be at home, rather than in hospital. e.g. intravenous (IV) administration, dialysis at home, and webcams using two-way communication between patients and caregivers. The technology can also be used to link small hospitals into central hubs to provide expert care.

Limitations: lack of regulatory clearance, expensive, security of data issues. [18, 20]

 **Roche smartphone app**

Remote patient monitoring via Roche Pharma Research & Early Development (pRED) manufactured **smartphone app** for patients with Parkinson’s disease. This app is complemented with traditional physician assessments using the Unified Parkinson’s Disease Rating Scale (UPDRS) that measures disease, disability, impairment and symptom severity but restricted to the specific times when patients goes to physicians. The active tests include a series of 30-second long activities such as Voice test, balance test, Gait test, Dexterity test, Rest tremor test,Postural tremor test. Patients are asked to used the app throughout screening, dosing and follow-up, for a period of about 32 weeks. [21]

**HealthPatch MD i**s a wearable biosensor from collaboration of Vital Connect and Medidata for remote patient monitoring in an efficient way. Its sensors and advanced algorithm provide continuous measurement of electrocardiogram grading, respiratory rate, skin temperature, heart rate, physical activity, etc it enables near real-time review of patient's health metrics

**Iodine**, a new web-based application for cold and flu season from health information website. The app helps consumers to review >300 options related to medication for cold and flu and compare medications that can help cure their own symptoms. [17]

**Reg4all or Registries for All** from (Genetic Alliance and Sanofi) is matchmaker between patients and clinical trials. This tool provides privacy and flexibility with opportunity for patients to decide, which groups can have a view/access to their data thus empowering the patients. [17]

**Treato- treato c**aptures near real time comments from social media Facebook, Twitter, and patient forums using a combination of natural language processing algorithms, patient language dictionaries, and big data analytics. These captured comments help pharma companies to gain insights into patients’lives and focus their efforts in the correct areas of drug development.

**Electronic Health Records (EHRs) via HealthIT.gov**

In healthcare ii is critical to improve clinical outcomes, improve patient satisfaction and increase revenue generation. US government encourages the use of Electronic Health Records (EHRs) via HealthIT.gov and providing benefit in the form of incentives to doctors who are minimizing medical errors and give quality by meaningful use of EHRs. [17]

**Patient education tools**

Websites are accessible via mobiles or the internet for educating patients on diseases. for example **Agency for Health Research and Quality** maintained by US Department of Health and HumanServices ClinicalResearch.com, **WELVU** – Mobile First, an iPad- and iPhone-based educative tool providing medical illustration,quality scores, and health outcomes to engage patients, **Krames patient education** from StayWell, **ExitCare OnScreen**™ video solutions for patient education **MediGuard™** a Dose compliance tracking tools remindes for dose intake. In a trial retention of patients is the key to the success of the overall project. Acurian, a service provider for recruitment and retention services uses platforms such as Facebook and Myspace for patient referrals and retention strategies. The easier it is to be compliant to study schedule, the better is the retention till the end. [17]

**Application of Digitalisation tools in CDM**

Digital technologies can transform the future of clinical trials. Digital technologies can facilitate participation by clinical research staff, increase the amount and quality of data collected in trials., digital technologies fastens cycle times for products in development. [22, 23]

**Facilitators and barriers in Digitalised CDM**

**Enrolment in trial** : Recruitment in a clinical trial is a most critical point of consideration since more than two-thirds of trial sites fail to accomplish original target. Digital approaches such as websites and online patient communities, social media and mining unstructured patient data (e.g., electronic health records, lab results) can facilitate in recruitment procedure with minimal cost and efforts. One suitable example of enrolment tool is Antidote which retrieves data from clinicaltrials.gov and addition of AI (machine learning) and minor human intervention generates structured eligibility criteria for single or multiple trials. It fabricates pre-feasibility questionnaire into easily understandable language for patients. By completing such questionnaire they can easily sift through several studies and choose on eof their interst. [22, 23]

**Participants to collaborators**

Digital technology has transformed Participants from subjects to collaborators while increasing patient engagement in the clinical research minimizing research mistrust and addressing patient-centric concerns. Digitalization measures patient-centric endpoints — such as quality of life or the ability to perform specific daily activities and receive patient feedback via online surveys and focus groups to reshape the final treatment. [22, 23]

**Multiple visits**

**Mutilple visits** to clinical sites for assessment is somewhat problematic, inconvenient and increases cost factor. Digital technologies has reduced travel time of trial participants and increased convenience. This factor affects willingness and ability to participate. Virtual trials leverage social media, e-consent, telemedicine, apps and biosensors for patient communication making data collection easy from homes, reducing or even eliminating the need to travel to sites. It was found that about 50% of clinical trials can be conducted either partially or completely virtually.one example of Roche used an app connected to smartphone sensors to remotely monitor and compare readings with in-clinic assessments in multiple sclerosis (MS) study. The app guided patient’s performances such as hand and wrist turning, gait, balance exercises and cognitive tests to assess their neurological activity. The data was generated in the form of trends in patient’s disease progression. Results from remote patient monitoring were found more sensitive as compared to in-clinic assessments. [22, 23]

**Improved treatment adherence by digital tools**

Digital technologies improve treatment adherence in the form of self-reporting and assurance about consumption of prescribed drugs which is verified by blood investigations but sometimes may require extra visits to trial site. Digital adherence tools such as smartphone apps and text messaging can record patient health data, answer their queries in real time, remind them to take medication and plan site visits. Even facial recognition tools can confirm adherence. [22, 23] Clinical data managemententails utilization of many software tools and form a component of Clinical Data Management Systems (CDMS). Most Commonly used CDM tools are ORACLE CLINICAL,CLINTRIAL, MACRO, RAVE, and eClinical Suite etc. (table. 2) where huge amount of data is generated as in case of multicentric trials, CDMS is most crucial to handle such data. [4]

**Table 2: Commonly used Clinical Data Management (CDM) tools**

|  |  |  |
| --- | --- | --- |
| **Software**  | **Applications**  | **Reference** |
| BRAAN, DataLabs, Fast Track  | at the stage of Clinical Trial Development for designing Protocol and execution |  [7]  |
| Oracle clinical  | for study monitoring and reporting,cost tracking,document management, adverse event reporting |
| Oracle, Phase Forward, DataTrack, Parexel,eResearchTechnology, DataLabs, Nextrials,ClinPhone, CRF,  | invivo data, electronic data, electronic patient diariescapture, case report forms,  |
| SyTech, Wimmer systems  | during study completion and regulatory Filing,data analysis |

Every information obtained from study participants is sensitive and should be protected. Security of data is most essential aspect of clinical research. Privacy and confidentiality of the data should be maintained in compliance with the informed consent. With AI there are chances of lack of transparency also which need to be resolved. [24]

 **Conclusion**

AI tools have proved their performance in drug discovery and development. AI tools have similar fuctions and demand sophisticated information technology and infrastructure. Some softwares can be downloaded free of cost from respective websites. Pharmaceutical companies are in collaboration with AI companies. This collaboration is a boon for clinical research industry but this has generated some ethical issues also. Ethical guidelines in the medical field regarding the use of AI are being established by many international authorities.

**Conflict of Interest: Nil**

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