ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

OVERVIEW ON CLINICAL DATA MANAGEMENT, HISTORY, TOOLS AND PROCESS

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Received: 15-1-2022, Revised: 29-1-2022, Accepted: 31-1-2022

ABSTRACT

CDM is Clinical data management from which we can get high quality, reliable, and statistically sound data from clinical trials. Overall time required for drug development to marketing is decrease by this process. Team member must be participated in every stage of this process. For maintenance of quality standards team members have required knowledge of the process. CDM procedure includes designing case report form , CRF annotation, designing of database, entry of data, data validation, management of discrepancy; medical coding, extraction of data and database locking are observed for quality at different interval of time during clinical trial. In current scenario raised demand to improve standards of CDM to fulfil requirements of regulatory authorities and stay ahead of competition by faster commercialization of product. These demands can be meeting by CDM team by implementing regulatory compliant data management tools. Submission of data electronically is also mandatory for companies. CDM professionals must fulfil appropriate expectations and fix standards for data quality.

KEYWORDS

Clinical trial, Clinical data management, Medical coding, Database locking, Discrepancy management, MedDRA

INTRODUCTION

Clinical trials are used to obtain answers to research problems by providing data to prove or disprove a concept. In this procedure, data quality is quite crucial. Clinical data management is a crucial component in the clinical trial process. Knowingly or unknowingly most of researchers try their hands on activities of CDM. This article aids in the understanding of CDM processes and provides an overview of data management in clinical trials.CDM is process of collection management of data, cleaning of data according to regulatory standards. CDM process aims to provide data of high quality by keeping less number of errors and collect maximum data for analysis. [1] To fulfil this requirement, best practices are adopted which ensures that data is reliable, complete and processed correctly. This is done with the help of software tools that keep track of audit trails and aid in the detection and correction of data discrepancies. Sophisticated innovation [2] helps in handling of large trials and ensures quality of data in complex trial.
High quality data must be suitable for statistical analysis and absolutely accurate. High quality data should have no misses as missing data is matter of concern in clinical trial. Acceptable level of deviations is allowed in high quality data which will not affect the conclusion of study.

HISTORY

Clinical research has come a long way from the earliest reported study of legumes in Biblical times to the first randomized clinical trial of streptomycin in 1946.History of clinical research undergone through lot of regulatory, ethical and scientific challenges. In 1747, James Lind performed a scurvy trial. In 1943, the UK Medical Research Council conducted the first double-blind trial of Patulin for the common cold.This makes way easier for first randomized control trial which was conducted in 1946 of Streptomycin which used for pulmonary tuberculosis by MRC of United Kingdom. The ethical advances in human protection include Declaration Helsinki, Nuremberg code, Belmont report, and, 1996 International conference on Harmonization and Good Clinical Practice guidance. In 20^{th} century as government authorities recognized the need for controlling medical treatment clinical trials embodied in regulation. There may be new regulatory and ethical challenges as scientific advances occur which requires updates in legal and ethical framework of clinical trials.[3]

Roles and responsibilities in CDM

In CDM different team member have different responsibilities and role. Graduation from Life sciences and basic computer knowledge is minimum educational requirement. For medical coder minimum qualification requirement is medical graduate.

Data manager

Entire process is supervised by data manager. Data manager formulates DMP and Gives approval to CDM procedure.

Database programmer/Designer

CRF annotations are performed by database programmer, prepares study database and for data validation programmes audit checks.

Medical coder

Medical coder do coding for medical history, concomitants medication administration, co-illness, and adverse events

Clinical data co-ordinator

CRF designing and formulation, CRF filling instructions, preparation of DVP, management of discrepancy, preparation of CDM related checklist and guidelines is work of clinical data co-ordinator

Quality control associate

Accuracy of data entry and data audits are checked by quality control associate.

Data entry associate

Data entry in database and tracking receipt of pages of CRF is done by data entry associate. [4]

Tools of CDM

Clinical data management systems (CDMS) is software tools which are available for data management. Huge amount of data is handled by CDMs in trials. Commercial CDMs used by most of Pharmaceutical companies but some open source tools are also available. Clintrial, ORACLE CLINICAL, RAVE, MACRO and e Clinical suite are some of the commonly used CDM tools. These software tools are too much costly and require sophisticated Information. Some of the custom CDM tools are also developed by Pharmaceutical companies to suit their operational needs. OpenCDMs, OpenClinica, PhOSCo and TrialDB are commonly used open source tools. From their respective websites this open source software which available free of cost can be downloaded. These software tools ensure audit trail and helps for management of discrepancies. Multiple user ID can be created according to roles and responsibilities with limited access to data entry, database designing, medical coding or quality check. Each user have access only the respective functionality allotted to user ID and unable to make changes in database. For responsibilities where changes are allowed to make in data, Change made can be recorded by software such as time and date of change. During regulatory audit, auditors confirms that no false changes in data were made and can verify discrepancy.[5]

Regulation guidelines

There are several guidelines and standards for CDM which must be followed. There is need to maintain standard in electronic data capture as most of pharmaceutical companies relies on data which is electronically captured for evaluation of medicines. Electronically captured data must comply with Code of Federal Regulations (CFR), 21 CFR Part 11. This regulation is for electronically captured records which are created, maintained, modified, archived, retrieved and transmitted. This all process requires use of validated system for ensuring accuracy, consistency, and reliability of data with used of secure, computer generated, time stamped, audit trails for recording the data independently and time of operator entries, and actions that create,

modify or delete electronic records. For ensuring authenticity, integrity, and confidentiality of data adequate procedure and controls should be carried out. Data should be entered and processed as per 21 CFR Part 11 compliant systems if it has to be submitted to regulatory authorities. Contract research organizations and Pharmaceutical companies must ensure this compliance.

Good clinical data management practices (GCDMP) guidelines are published by society for clinical data management (SCDM) which provides the standards of good practice within CDM. In September 2000 GCDMP was first publish and then several revisions are done thereafter. Standards which supports acquisition, submission, exchange and archival of clinical data and metadata are developed by clinical data interchange standards consortium (CDISC) which is multidisciplinary non profit organizations. Data of data entered called as metadata. Which consist of individual data that made entry or done any change in clinical data. All the information such as time and data of entry/change and details about change recorded.[5]

The CDM process

Generally for answer the research questions clinical trial designed whereas process developed for delivery of valid, error free, and statistically sound database. To fulfil this need CDM process initiates early, even before study protocol finalization.

Review and finalization of study documents

For consistency and clarity protocol revised from database designing perspective. During these process personnel who are working in CDM identified data item which has to be collected and collection frequency with respect to visit schedule. First step of the process is translation of protocol specific activities into data being generated. The data type which has to be entered should evident from case report form (CRF). CRF must be user friendly, concise and self explanatory. For errorless data acquisition filling instructions along with CRF should be submitted to investigators. The variable is named according to the SDTMIG or the internal norms when using CRF annotation. Annotations are coded terms that are used in CDM tools to indicate the study's variables.

A Data Management Plan (DMP) is created based on these. The DMP document is a road plan for dealing with data in expected situations and defines the CDM activities that will be followed during the clinical trial. The database designing, data tracking guidelines, data entry SAE reconciliation guidelines, quality control measures, discrepancy management, data transfer or extraction and database locking guidelines. Along with the DMP, a Data Validation Plan (DVP) is created, which includes all edit-checks to be done as well as the calculations for derived variables. The DVP's edit check systems assist in data cleaning by finding discrepancies.

Data collection
CRF tracking
CRF annotation
Database design
Data entry
Medical coding
Data validation
Discrepancy management
Database lock

Table. 1 Activities in clinical data management [5]

Database designing

To facilitate CDM tasks for carrying out multiple studies clinical software application i.e. database are build. [6] These tools are developed such that it is easy to use and must be in compliance with regulatory requirements. For ensuring data security system validation is carried out. During system validation evaluation of regulatory compliance, user requirements, system specification are done. [7] Study details like objectives, visits, intervals, sites, investigators and patient are defined in database and for data entry CRF layout are designed. Before starting the real data capture entry screens are tested with dummy data.

Data collection

Collection of data with the help of CRF may exist in form of electronic version and inform of paper. Using paper CRF for collection of data response is traditional method which then translated to database by means of data entry done in house. According to guidelines investigator fills paper CRF. In e-CRF base CDM data is directly enter at the site by investigator or designee. e-CRF is advantageous as faster `resolution of discrepancies and less chances of error. In recent years, the use of electronic data capture (EDC) technologies and electronic clinical research forms (eCRF) to collect data in clinical trials has risen, affecting clinical trial activities.[8-10] e-CRF trial design allows robust management of data, visibility of real time data, analysi, reporting and global trial management and study scalablity.[15]

CRF tracking

Clinical research associate (CRA) monitors entries which are made by CRF for completeness and CRF handled over to CDM team after retrieval. The CDM team tracks the CRF's and maintain record. CRF team checks whether there are missing pages or data is lost. If data missing or illegal then issue resolved by obtaining clarification from investigator.

Data entry

According to guidelines prepared data is entered but this is only applicable in case of paper. Two operator separately enters data i.e. double data entry is performed.[12] Second pass entry is carried out for

reconciliation and verification by identifying the errors and discrepancies caused by illegal data also cleaner database can be obtained by double data entry.[13]

Data validation

Data validation helps for testing validity of data. To identify discrepancies in data edit check programmes is written which are entered in database for ensuring data validity. With help of dummy data, edit check programmes initially tested. Missing data, incomplete data, inconsistent data, deviation, range check from protocol can cause discrepancy. During CDM process quality control is carried out.

Discrepancy management

Discrepancy management is also known as query resolution. It includes discrepancies review, reason investigation and resolving them with documentation proof or declares it as non resolvable. All discrepancy databases always present in CDMS where all discrepancies recorded and stored with audit trial. Discrepancy management helps in collecting evidence for data deviations for clarification. Discrepancies are either flagged to investigator or closed in house via self evident corrections(SEC) without sending DCF to site, Depending on type spelling errors are mostly found SEC. DCF file sent to site if discrepancies required clarification from investigator. Investigator will write resolution or explanation what happened in the case data discrepancy. Investigator can provide resolution online. In case of e-CRF for ensuring all discrepancies is resolved all discrepancies are reviewed at regular interval by CDM team. Management of discrepancy is most critical activity in CDM process.

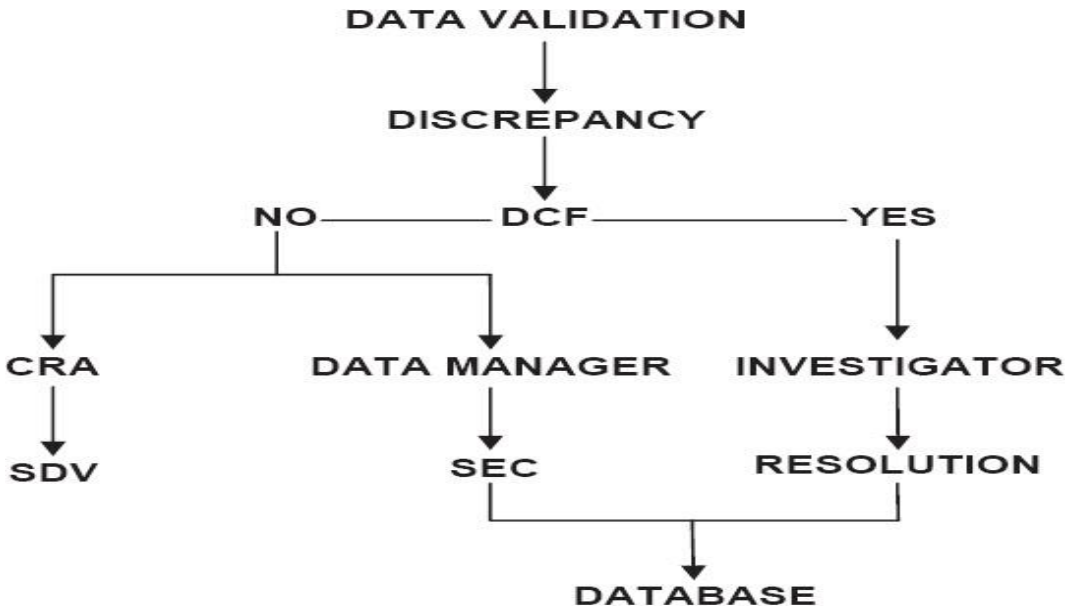

Figure. 1 Discrepancy management [5]

Medical coding

Medical coding is the branch which helps in determining and classifying medical terminologies which are related with clinical trial. This classification is done with help of medical dictionaries which are available

online. This activity requires understanding of disease knowledge, knowledge of pathological process and drugs which are used. It also needs knowledge about hierarchy of classification and structure of electronic medical dictionaries. Adverse drug reactions which are occur during study are coded using available medical dictionaries.

For coding of illness or coding of adverse events medical dictionary for regulatory activities (MedDRA) is used and for coding medications World Health Organization drug dictionary enhanced (WHO-DDE) is used. For adverse reaction terminology WHO-ART dictionary is used. Medical coding helps to avoid data duplication and maintain uniformity in process. [11]

Database locking

Data validation is finally run after proper quality check and quality assurance. By taking consultancy from statistician database are finalized if no discrepancies found. Before locking database, It must be ensures all activities completed and prelock checklist used for ensuring this. This process is done because database unable to changed after locking. Database is locked once approval is obtained from all the stakeholders and after that extraction of clean data is done for statistical analysis. In case of critical issue privileged person can able to modify data after locking database but it needs proper documentation and an audit trial is maintained. Extraction of data is done from final database afterlocking and followed by its archival.

CONCLUSION

CDM has emerged in response to the growing need from pharmaceutical companies to expedite the drug development process, as well as regulatory agencies to put in place quality system to ensure the provision of high-quality data for accurate drug evaluation. To fulfil the demands, a gradual shift from paper-based to electronic data management systems is taking place. For improvement of data quality professionals from CDM should ensures the quality standard.[14] CDM is being speciality in itself which must be evaluated by means of process and systems which has to be implemented and standard being followed. Standardization of data management process and development of regulation will be the biggest challenge with respective to regulatory perspective. In changing operational environment planning and implementation of data management system will be biggest problem. Inspite of all these CDM is evolved to become standard based clinical research entity by maintain balance between business demands and constraints in existing system expectations.

ACKNOWLEDEMENT

I wish to thank Mrs.Archana Gawade (Board of Directors Elite Institute) for all her help and guidance.

REFERENCES

1. Gerritsen MG, Sartorius OE, vd Veen FM, Meester GT. Data management in multi-center clinical trials and the role of a nation-wide computer network. A 5 year evaluation. In Proceedings of the Annual Symposium on Computer Application in Medical Care 1993 (p. 659). American Medical Informatics Association.
2. Lu Z, Su J. Clinical data management: Current status, challenges, and future directions from industry perspectives. Open Access J. Clin. Trials. 2010 Jun 22;2:93-105.

3. Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res. 2010 Jan;1(1):6.
4. Ottevanger PB, Therasse P, Van de Velde C, Bernier J, Van Krieken H, Grol RP, De Mulder P. Quality assurance in clinical trials. Crit. Rev. Oncol./Hematol.2003 Sep 1;47(3):213-35.
5. Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: an overview. Indian J. Pharmacol. 2012 Mar;44(2):168.
6. Fegan GW, Lang TA. Could an open-source clinical trial data-management system be what we have all been looking for?. PLoS Med. 2008 Mar;5(3):e6.
7. Kuchinke W, Ohmann C, Yang Q, Salas N, Lauritsen J, Gueyffier F, Leizorovicz A, Schade-Brittinger C, Wittenberg M, Voko Z, Gaynor S. Heterogeneity prevails: the state of clinical trial data management in Europe-results of a survey of ECRIN centres. Trials. 2010 Dec;11(1):1-0.
8. Pavlovic I, Kern T, Miklavcic D. Comparison of paper-based and electronic data collection process in clinical trials: Costs simulation study. Contemp Clin Trials. 2009;30:300–316.
9. Lu ZW. Information technology in pharmacovigilance: Benefits, challenges, and future directions from industry perspectives. Drug, Healthcare and Patient Safety. 2009;1:35–45.
10. EI Emam K, Jonker E, Sampson M, et al. The use of electronic data capture tools in clinical trials: Web-survey of 259 Canadian trials. J Med Internet Res. 2009; 11: e8.
11. Lu ZW. Technical challenges in designing post-marketing eCRFs to address clinical safety and pharmacovigilance needs. Contemp Clin Trials. 2010;31:108–18.
12. Cummings J, Masten J. Customized dual data entry for computerized data analysis. Quality Assurance (San Diego, Calif.). 1994 Sep 1; 3(3):300-3.
13. Reynolds-Haertle RA, McBride R. Single vs. double data entry in CAST. control clin.Triale 1992 Dec 1;13(6):487-94.
14. Haux R, Knaup P, Leiner F. On educating about medical data management. Methods Inf. Med. 2007; 46(01):74-9.
15. Babre D. Medical coding in clinical trials. Perspectives in clinical research. 2010 Jan; 1(1):29.