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Clinical data management: Tools and regulations

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Abstract

Clinical data management (CDM) is that process in research which helps us to create high quality and statistically correct data from clinical trials. It helps us to reduce the manual work load as well as saves time and energy. There are certain members who are involved with CDM process, which helps to maintain the standards of process; those members should be highly qualified and experienced. Various processes involve in CDM process are CRF-reporting, data entry, data collection, data validation, discrepancy management, database locking, and medical coding. CDM process involves certain rules and regulation which need to be followed. There is an increase demand to improve certain regulations to stay ahead of competition by the means of capitalisation of product. It is the duty of CDM professionals to meet the demands of standards and protocols to maintain the quality of data and to adjust with the changing technology. This topic basically gives the overview of certain tools, standards and responsibilities in CDM.

Keywords: Clinical data management, Medical Coding, Clinical Data Interchange Standards Consortium (CDISC)

Introduction

Clinical data management (CDM) as the word suggest 'management and collection' of data during clinical trials. Clinical trials are usually performed to check the safety and efficacy of new drug. The data obtained from these studies are important for the outcome of the studies, therefore the data obtained should be of high quality and reliable. What do you mean by 'high quality data'? It should be absolutely accurate and suitable for statistical analysis. The main objective of CDM is that it reduces the manual work load as well as saves the energy. There are certain protocols for initiating CDM. If the person does not fulfil these requirements or in case of any deviation from the protocols, then we may think of excluding the patients from the final studies. Most importantly high quality data should possess only an arbitrary 'acceptable level of variation' [1] that would not affect the conclusion of the studies. To fulfil those requirements, certain software tools are used which helps in minimising the errors and data discrepancies and also provide easy identification. CDM plays an important role in clinical trials, as it helps to ensure that data generated is of high quality and effective. Therefore, at each step of clinical trial review is made.

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Clinicians involved in the management usually generate data on the daily basis which helps us to know that whether it should be continued or not. The same data can be used to generate alerts to improve the practice and to generate care activities to ensure that all appropriate care is given to patient or not [2].

CDMS should be reviewed regularly as it further helps in NDA submission, clinical planning, and process enhancement. A lot of money is invested during clinical trials, if the data generated is invalid or unacceptable then there would be lot of financial loss, therefore to avoid this loss proper review should be there. At each and every step of clinical trial data validation should be performed. This will ensure that data will be clean and safe as review and approval of drug is basically dependent upon the clinical trial data presented by various pharmaceutical companies, therefore all the practitioners and clinicians should be well educated and experienced.

This article basically gives an overview about how the data is managed during the clinical trial, about various rules and regulations (protocols) of CDM.

Roles and Responsibilities of CDM:

In CDM team, different role and responsibilities are allotted to different team members. About the educational qualification minimum requirement, should be graduation in life science and knowledge about computer applications.

There are certain lists of roles given below which can be review as a minimum requirement for CDM team.

Clinical data coordinator: The basic function is to coordinate processing of clinical trial data for certain protocols for analysis for registration and local studies.

Data Manager: Data manager is healthcare professional who collect, manage, evaluate and analyse the results of clinical trials. Regarding educational qualification post-secondary education, bachelor's degree or higher in clinical research.

Medical coders: medical coders transform the healthcare diagnosis, procedure, medical services and equipment into universal medical alphanumeric codes.

Quality control specialist: they basically perform testing and analysis to ensure that biomedical research or product meets the specifications of regulatory guidelines. Since the product being developed directly impact the lifestyle therefore it's important to do quality control studies.

Data entry associate: their main responsibility is to collect the information about patient's medical background and clinical trials.

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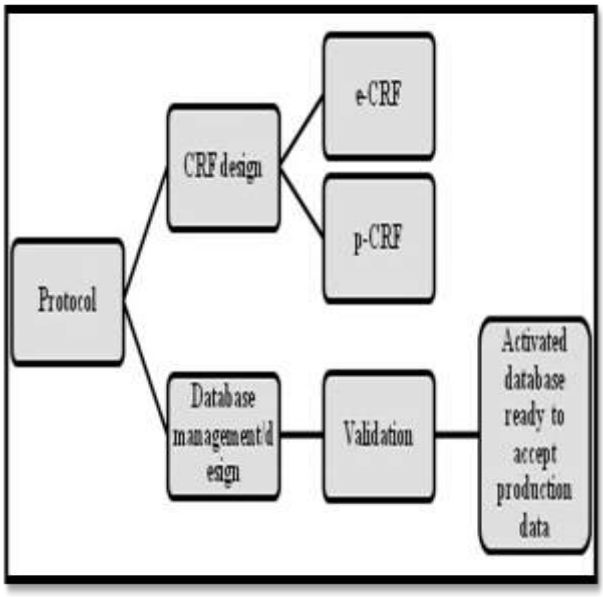

Fig. 1: Designing of Clinical Data Management Process

The CDM Process:

The CDM process is important because it help us to give error free, statistically accurate data. It is constantly being validated throughout the clinical trials. It include: CRF design and development, data management, SAE reconciliation, discrepancies management, data transfer, data entry, data validation report writing, statistics analysis.

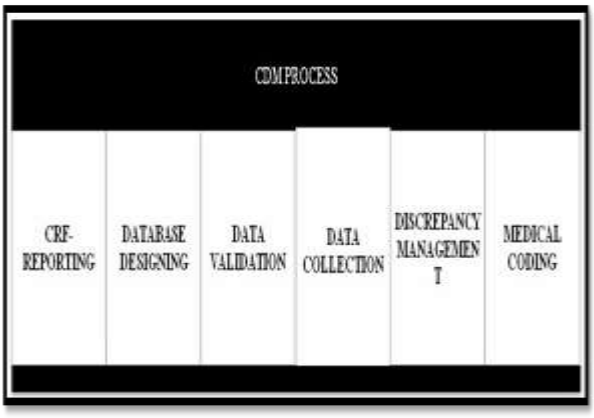

Fig. 2: Clinical Data Management Process

CRF- Reporting

A case report form is a trial document which contains information of the patients participating in clinical trials in a unified manner. Since on the basis of this form further reporting is done therefore it should be done carefully. It can be electronic CRF (e-CRF) or printed (p-CRF). In either case protocol should specify method of reporting. The design of CRF has direct impact on the quality of data being collected in the clinical trials. A proper design is essential to record all the data at appropriate time, since it is not always possible to go back and collect information at later stage. Unnecessary details should not be there only the details which are needed by the regulators should be there in specified and in unified manner. A good CRF should have following qualities viz. neither too much nor too little, precise, clarity in questions, negative questions should be avoided, and few open questionnaires and investigator signature as shown in Figure 1.

Database Designing

Database is referred to as the collection of views, schemas, tables, reports. Database designing is basically software which is used to analyse and capture the data .it gives the frame to the data obtained from the clinical trials. it runs according to the regulatory authorities and thus easy to use. 'System validation' plays a crucial role during database designing; this is to ensure whether the trials are running according to the regulatory authorities, In this aim, objectives , reports layout, full dummy structure are made before preparing actual data.

Data Collection

Data collection is gathering of relevant information during clinical trials like patient's parameter, questions, inform consent form and whatever is happening during trial it is basically collection of all that data. Case report form (CRF) plays an important

role; data is collected with the help of CRF. There are two types of CRF viz. e-CRF and p-CRF. Traditionally, p-CRF method is used, it is all paper based, all the data is handwritten and papers were maintained and then converted into database by means of data entry done in house. Then it is filled up by investigator. The main disadvantage of this type of CRF is, it is time consuming; moreover it is difficult to maintain paper documents, whereas in e-CRF, it gives us error free data and we can easily point out if there is any kind of discrepancies. Since today many of the pharmaceutical companies want to reduce time for drug development process therefore, they are opting for e –CRF.

CRF Tracking

CRA (Clinical Research Associate) is a health care professional who take care about the clinical research and clinical trials. They monitor that all work is in compliance with the trial protocol, they ensure the safety and protection of human beings. The inputs made in CRF are checked by CRA and then returned back to CDM team. Then this team track all the records. This is basically done to see if there is any page or data missing or any kind of discrepancies to ensure data is not lost.

Data Validation

Data validation is the process of reviewing the accuracy, completeness and the logic. To validate a data means to check the CRF which is submitted, to ensure accuracy, in accordance with the protocol specification. The CDM guidelines provide us the basis according to which errors, typographical mistakes, unwanted data are identified. Validation of data occurs throughout the whole process of clinical trial at each stage data is validated and entered into the database, in order to control the errors and inconsistencies in data. In addition to this data editing staff will monitor which pages are received and which are still missing, and data that is received from some outside source. The process of checking or validation is first done on dummy data and discrepancies are identified. Discrepancies are the data which shows deviation from the protocol specified.

Discrepancy Management

Discrepancy is the data which is not executed according to the expected range of value or those which shows deviations from the protocol. Discrepancy management is the process of managing the unsystemic data. Cleaning and correcting discrepancies ensure that data is complete, accurate and follows study protocol.

Discrepancies raised in the Validation Process: Remote Data Capture (RDC) checks and monitor patient data at the following times:

- As you enter data or when you save a CRF, RDC implement simple edit checks and then flags any data entry errors. You can correct these discrepancies at any point of time during the data entry process.
- During the patient validation process, RDC implement complex edit checks, typically relating to values that do not correlate across CRFs. You can easily implement patient validation after you complete the data entry for a visit.[3]

In a Broadway there are two kinds of discrepancies as system generated discrepancy and manual discrepancy. In system based these are automatic created by RDC onsite, whereas in manual based these are generated by users only RDC do not have a role in it. You can add a manual discrepancy to a CRF section or to a field. You can resolve discrepancies as they are raised, or defer their resolution for later.

Medical Coding

Medical coding is the process in which different medical terminologies are converted into single standard code to maintain the uniformity. Data generated during clinical trials are recorded in case report forms either in the form of paper or electronically. In this various information is collected including medical background, adverse events. In multicentre clinical trials there are trial sites which involve different investigators, medical professionals from different backgrounds. Thus use different medical languages in the form, therefore due to involvement of different professionals from different background there is a possibility of understanding the data in different manner. Hence it is necessary to interpret this data uniformly in a standardize format and this is done by using various medical dictionaries most commonly used are MedDRA Medical Dictionary For Regulatory Activities and WHO-DDE World Health Organisation Drug Dictionary Enhanced.

MedDRA: It is a medical coding dictionary developed by ICH International Conference on Harmonisation. This is an open dictionary anybody can use it, before this there was no such kind of dictionary, it is used for coding medical terminologies generated during clinical trials except animal toxicology , therapeutics signs and symptoms ,causes, diagnosis , coding of medical history ,

surgical procedures . Med DRA is divided into five levels.

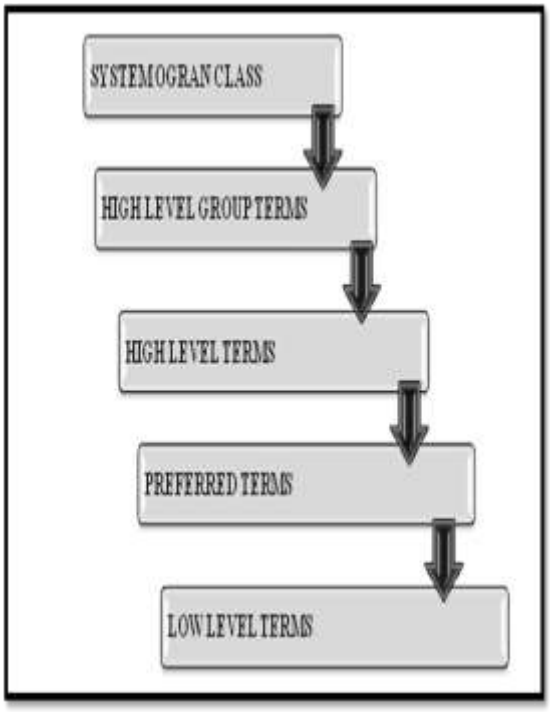

Fig. 3: Levels of MedDRA

WHO-DDE:

The WHO Drug Dictionary Enhanced is most widely used dictionary for the coding of medicinal products. It is used by various pharmaceutical companies, clinical research organisation (CRO) for the identification of the drug names, during their safety surveillance period. As in multi-centric clinical trials, different investigators, medical practitioners are from different medical backgrounds so they might be able to use different terms for a same adverse event, therefore medical coding is required to convert these different terms into a single standard code. As the name suggest it is locking of database. After all the data validation, quality check, clean data is extracted and sent for further statistics analysis. After the locking of data nobody is able to make any changes in the database until or unless if there is any critical issue or some important operational reasons, only privileged users have right to modify the data. However, this requires following certain protocols and documentation process with proper valid reason of why you are modifying your data.

Tools for CDM:

Tools are used to identify, monitor, estimate, analyse certain activities. Many software tools are used in clinical data management. These are referred to as clinical data management system. These are used to handle a big amount of data.

Some most commonly used tools are:

- **Oracle Clinical:** oracle clinical enables managing of all the data that has been recorded during clinical trials in a single system, upgrading accuracy, visibility and data integrity. Some benefits include improving efficiency and productivity, lower down the total cost of ownership, reduces risks and IT burden.
- **Clintrial:** The clintrial software is basically used by various companies for the determination, collection, management of data recorded at the time of clinical trial. Clinical software permits various pharmaceutical companies to unite all their clinical data collection, regardless of pre or post marketing. Some more are macro, rave and eclinical suite. In terms of functionality these software tools are more or less same; there is hardly any advantage of one tool over other. Moreover they are expensive.

Certain multinational companies used open source tools which serves the same purpose in terms of functionality, which include OpenClinic, OpenCDMS, TrialDB and PhoSCo. These are free of cost.

Regulation and Guidelines for CDM:

As compared to other areas in the clinical research CDM has certain guidelines and protocols which have to be followed. Today all the big pharmaceutical companies rely on the electronic captured data method for evaluation of medicines, therefore there is need to follow certain protocols and rules. These electronic records have to comply with the Code of Federal Regulations (CFR), 21 CFR PART 11. [4]. This protocol is applicable to those records or data which are electronically determined, analysed, modified and transmitted.

Good Clinical Data Management Practices (GCDMP) is a current industry standard for clinical data management that consist of best business practice and acceptable regulations. It was published in September 2000 and then revised year after year. The version 2009 is the currently followed GCDMP. During clinical trials all the information regarding laboratory or any other must be collected and converted into digital form for analysing or reporting purpose. Why there is a need of GCP? It is required so that public get assured, protection of right, safety and well-being of trial subject, reliable data based on scientific quality standards.

Clinical Data Interchange Standards Consortium (CDISC) is a multidisciplinary, non- profit

organisation that develop certain standards with the mission to serve globally. Among the standards two important ones are Study data tabulation model implementation guide for human clinical trials (SDTMIG).It provide standards for organising and formatting data to streamline process in collection, management analysis and reporting, [5] clinical data acquisition standards harmonisation (CDASH) standards. Its main focus is on data collection not data reporting.

Conclusion

Today pharmaceutical companies are evolving at a great rate; therefore there is an increase demand of CDM. In recent years, regulatory authorities and other organisation who are working with clinical data have seen the critical need for more robust data standards [8].which in future lead to better and more appropriate science. Moreover we need to make certain more amendments, follow them in order to obtain high quality of data. To meet all these predictions there has been shift from paper based work to electronic capture method. Addition to this, there is an increase in technology like patient recruitment, data measurement, data collection, communication, data review. However, development on technological site has led to increase the speed and quality of data standards. Challenges: From industry view, the work of CDM professionals or practitioners is not only to maintain records, CRF report forms, data validation, CRF tracking, data entry, data collection but also to contribute to the subject recruitment, extrapolate trial information for future use, with respect to medicine safety and efficacy, subject profile/drug price [9]. The biggest hurdle is to meet the changes which are occurring with the pace of development. Apart from these, CDM is emerging as a standard based clinical research entity by maintaining the balance between the past amendments and future expectations.

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