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An overview of clinical trial data management, its standards and recent trends

Abstract

Clinical trials help pharmaceutical/biomedical organisations to bring the drug/treatment/procedure from the development stage to the end user stage. Normally clinical trials consists of four stages Phase I – IV. During the Phase-III which involves human beings as the subject of trial, requires significant amount of data to be captured, cleaned, transformed, compiled, audited, analysed and reported. Traditional data management techniques may not be sufficient to manage the current clinical trials as they are conducted at different location results in high cost of collecting, storing and processing of data. Hence there is need for advanced technologies such as online/web based data management techniques to increase the efficiency in collecting, storing and processing of data and also to reduce the cost related to the clinical trial data. This paper starts with a brief overview of clinical trials, regulatory requirement, guidelines, and its different phases. It further discusses the traditional tools, techniques and standards to handle clinical trials data, software available for clinical trial data management and recent trends.

Keywords: Clinical Trial, Phases of Clinical Trail, Clinical Trial Data Management, FDA, ICH, Protocol, Case Report Form, eCRF, CDSIC, eSource, ePRO

1. Clinical Trials

Clinical trials are experiments conducted to study the efficacy and safety aspects of a drug/treatment/procedure which may or may not involve human being as the subject for the study [1]. The human beings involved in the study may be normal/healthy human beings or affected by a disease or condition. Clinical trial tries to provide solution to scientific questions and prevent or treat a disease or condition [2]. Clinical trials are conducted as a single centre or multicentre trial based on the requirement.

1.i. Food and Drug Administration (FDA)

Once the study is over, findings of the study are submitted to regulatory authorities for approval. In United States of America (USA), the Food and Drug Administration's [FDA] Centre for Drug Evaluation and Research (CDER) gives the final approval before it is marketed in USA while ensuring the new drug is safe and effective [3]. The application procedure for a new drug can be referred at FDA webpage [4]

1.ii. International Council for Harmonization (ICH)

Clinical trials involving medications/drugs are guided by International Council for Harmonisation (ICH) guideline for good clinical practice [5]. It aims to achieve harmonization at the global level to ensure the safe, effective and high quality medications [6]. Current ICH guidelines includes four categories namely quality, efficacy, safety and multidisciplinary guidelines

1.iii. Trial Protocols

Clinical trials are includes protocol[7] or plan which includes the trial background, objectives, design, patient recruitment, ethical consideration, adverse event reporting, study sample size and randomization schedule and statistical analysis. A sample trial protocol related to the University of Nottingham's Controlled Assessment of Salicylates and Azathioprine (CASA trial) can be referred at the trial's website [8]

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1.iv. Different phases of clinical trial

Clinical trial related to development of new drug for a specific disease or condition normally consists of four phases namely phase I-IV [9] which is described in the Table-1 below:

. **Table-1: Clinical Trial Phases**

Phases	Objective	Approximate number of study participants required	Type of study participants
Phase-I	To study the safety of the drug and determine the dosage of the proposed new drug	Less than 20	Most likely severely ill patients
Phase-II	To study the primary outcome (efficacy) in relation to the new drug under consideration. It also continue to study the safety aspect also	Less than or equal to 100	Patients with the disease or condition
Phase III	To study effect of new drug in comparison to the standard drug. It involves one or more group of patients wherein the new and standard drug is administered with the use of randomization schedule. It might be single centre or multi-centre study. It is usually includes at least two phase III trials which are required to confirm the effectiveness of the new drug	Less than or equal to 1000	Patients with the disease or condition.
Phase IV	To study side effect of the new drug and it is a post marketing surveillance study after regulatory approval is obtained	Less than or equal to 10000	General Population

During the pre-clinical trial phase pharmacodynamics and pharmacokinetics are parameters are determined for the drug and it mostly involve animals [9, 10].

2. Clinical Trial Data Management (CTDM)

Clinical Trial Data Management (CDTM) takes centre stage throughout the clinical trial process especially in the phase III of the clinical trial. Basic or Standard CTDM involves the following components [11]

2.i. Case Report Form (CRF) and its annotation

Case report from is a basic instrument used to collect the data for the clinical trial. The case report form's structured format helps the researchers to ensure the quality of the data collected. Case report form is prepared based on the clinical trial protocol and it adheres to the data validity requirements. The CRFs can be a prepared as simple manual form or web based online form which is useful in the case of multi central trials to make the data collection uniform across the centres. Data in the CRF are entered by the trained users and usually data entry errors are controlled by the automated validation at the form level itself such as preventing format errors such as text in the

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date field (Date of Birth will allow only the date of birth in the dd/mm/yyyy format) or the maximum/minimum value for a particular field or closed ended fields.

Annotated CRF provides details about where the data is stored or path of the data with respect to each section of the CRF so that every researcher who is involved in the trial has knowledge about the storage of data.

2.ii. Data validation

Once the data is stored in the database, data is to be validated against the set protocol of the clinical trial. The CRFs which confirms to the validation requirement only be processed for the next level.

2. iii Data Auditing

Data to be audited for any deviation found in the data and if it is found, it should be recorded with reason for deviation.

2. iv Clinical Coding

Standard Clinical Terminologies to be used when representing the diseases, drugs and other clinical parameters.

2. v Database freezing

Once data is validated and audited, the database is to be locked before the start of the statistical analysis to ensure the validity results.

2.vi. CDISC – Clinical Data Interchange Standards Consortium

Clinical Data Interchange Standards Consortium (CDISC) is a non-governmental organization which aims to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare [12]. The standards has [13,14] foundational standards, and data exchange standards which covers the different stages of clinical trials starting from the planning stage to the data analysis stage including the data exchange part. The following Table-2 provides the details about CDISC

Table-2: Clinical Data Interchange Standards Consortium (CDISC)

Standards	Components	Elements	Description
Foundational Standards	Planning	Protocol	Provides standard format for study protocol
		Study Design	Provides formats of interchangeable and machine readable study designs
	Data collection	Clinical Data Acquisition Standards Harmonization(CDASH)	Defines set of data collection elements formats
		Laboratory Data Model (LAB)	Defines formats for transferring data between laboratory and study site
	Data tabulation	Study Data Tabulation Model(SDTM) Standard Exchange Of Non-Clinical Data (SEND)	Provides formats for tabulation data it contains three main classes namely events, intervention and findings in a trial

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	Statistical Analysis	Analysis Data Model (ADaM)	Provides data structure for analysis. It contains three classes namely Subject Level Data Analysis, Basic Data Structure and Adverse Event Analysis Dataset
Data Exchange Standards	Data Transfer	Study/ Trial Design Model - eXtensible Markup Language (SDM-XML)	Used to transfer data between organizations using XML
		Operational Data Model	Provides standards for data transfer
		Define eXtensible Markup Language (XML)	Describes the metadata during the transfer

2.vii. Software used in Clinical Trial Data Management – Electronic Data Capture (EDC)/Clinical Data Management Solutions(CDMS)

The following table provides details of software available to manage the data in a clinical trial

Software	Description	Link
SAS	Commercial Package	www.sas.com
Velos	Commercial Package	http://velos.com/velos-eresearch
Medidata Rave	Commercial Package	https://www.mdsol.com/en/products/rave
Openclinica	Open source software	https://www.openclinica.com/
ONCORE	University of Wisconsin Institute for Clinical and Translational Research software	https://ictr.wisc.edu/oncore/
WebDCU™ system.	Medical University of South Carolina web based software	https://dcu.musc.edu/Solution/WebDCUoverview.aspx
REdcap	Available free for institutions that join the REDCap Consortium.	https://projectredcap.org/software/
CTMS	Mayo Clinic 's Clinical Trial Management System (restricted access)	http://www.mayo.edu/research/labs/clinical-trials-management-system/about
Penn CTMS	University of Pennsylvania Clinical Trial Management System (restricted access)	http://www.med.upenn.edu/ocr/about-ctms.html

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3. Latest Trend in Clinical Trial Data management

The clinical trial data management has evolved over time from using manual collect and analyse data(paper based) to capturing the data electronically and analysing the data using advanced statistical software. Currently the emergence of technology tools such as wearable device, eSource technology, emergence of cloud computing, text mining and social media have greater impact on the clinical trial data management in terms of reduced time, tasks and cost [15].

a. eSource Technology

eSource technology helps to electronically capture the patient data. Patient measurements are directly fed into eCRF without the need of manual entry into CRF. Real time data collection is possible with the help of eSource technology and it helps in avoiding duplication of data, reducing the data entry time and data entry errors [16]

b. Electronic Patient Reported Outcome (ePRO)

Electronic Patient reported outcomes helps to achieve more accuracy and compliance in the data collection and reducing the duplication of data [17]. The ePRO are collected through the devices provided by the clinical trial organizations with the required software or bring your own devices approach for study participants to report the outcomes.

c. Wearable devices

Wearable devices such as wristbands, clothing tags monitor and collects the data related patients vital signs and physical activities respectively in a real time environment [18, 19]. It helps in reducing time, cost and repeated visit of patient to the clinical trial site

d. Cloud Computing

Cloud computing technology provides reduced Information Technology infrastructure requirement through the shared pool of computing resources such as servers and databases. Some of the benefit of the cloud computing are it is available as service, available everywhere and scalability. Clinical trial organizations are yet to adopt the technology fully due to the factors such as security and lack of control [20]

e. Use of social networks

Social media groups are useful in providing awareness about the disease or its treatment. It also helps in recruiting study participants for a clinical trial [21]

4. Conclusion

The paper provided an overview of clinical trial, data management in clinical trial, related standards, software used in clinical trial data management and the recent trends in clinical trial data management

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