WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Clinical Data Management and Pharmacovigilance: A Review

Parag Dani [1], Mr. Mahesh Kshirsagar[2], Dr. Gaffar Sayyed, Dr. Garje Sanjay*

[1]Student, Final Year B. Pharmacy, College Of Pharmaceutical Science And Research Centre Kada,414202,(MH),India.
[2]Guide, Department of Pharmaceutical Quality Assurance, College Of Pharmaceutical Science And Research Centre Kada,414202, (MH), India.

A B S T R A C T

Clinical research is a type of investigation where the main goal is to find a solution for a health issue or illness that affects people. Clinical research, however, is intricate and incorporates variables that affect how accurate the study's findings are. Documents pertaining to clinical research and data management become more important. The national and international regulatory agencies establish standard recommendations for the collection, storage, validation, distribution, analysis, and management of data obtained from clinical research. This study covers a wide range of topics related to clinical trial data administration, including the nature of the case record form, the data validation process, quality assurance during data collection, validation, database building, pharmacovigilance, the role of regulatory bodies, and more. Furthermore, pharmacovigilance—the scientific field concerned with medication safety—has undergone substantial research and is constantly expanding. Appropriate procedures are needed, and medical informatics techniques and interpretation play essential roles in this discipline. The trends of pharmacovigilance systems, particularly those related to data collection, detection, assessment, and monitoring, were examined and studied in this study.

Keywords: Clinical data management, pharmaovigilance, clinical trials, data driven approach, big medical data

1. Introduction-

Pharmacovigilance and clinical data management are significant procedures in the pharmaceutical industry that typically operate in conjunction with clinical trials to generate and analyze crucial data that can aid in the development of more superior and efficient pharmaceutical products. which can be applied further to models created by AI and efficient community pharmacy procedures.

1.1 Clinical data management:

The methodical gathering, organizing, and validation of data from clinical trials in order to guarantee correctness and dependability is known as clinical data management. It involves procedures like entering data, cleaning it up, and storing it in safe databases while adhering to legal requirements. In order to determine what data must be collected, the team will go over the study protocol during clinical data management. They then construct a system to collect, process, and store data using the relevant technologies. Electronic data capture (EDC), external data transfer and storage, data review software, and preprogrammed data listings for manual inspection are some of the possible components of this system. The data must be managed by the clinical data management team during the trial until it is prepared for analysis.

1.1.2. Main Goals of Clinical data management-

The two most important goals of clinical data management include:

1. Capturing the appropriate data based on protocol specifications
2. Ensuring a quality database is provided to the team at the time of database lock

Your odds of a successful trial outcome may be severely impacted by extended deadlines, missing data, and inaccurate data if you have inadequate cleaning quality and the wrong data points. Thus, it's crucial to carefully go over the study protocol to ascertain what information the statisticians and clinical team require, make sure the right instruments and techniques are used to collect the data, and make sure the data is effectively cleaned in a timely way before the database is locked.

Clinical Data Management (CDM) involves the systematic collection, cleansing, and oversight of subject data in accordance with regulatory standards. The primary objective of CDM practices is to ensure the delivery of high-quality data by reducing errors and minimizing instances of missing information while maximizing the volume of data available for analysis. To achieve this aim, best practices are employed to ensure that the data is accurate, reliable, and comprehensively managed. The use of software solutions that maintain an audit trail facilitates the identification and correction of data discrepancies.

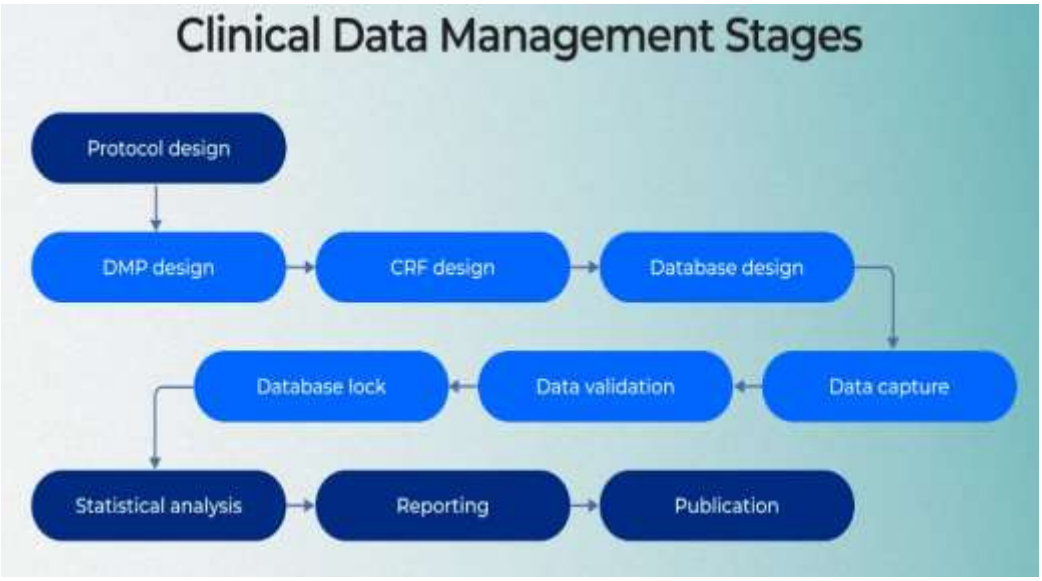
Furthermore, advancements in technology have enabled CDM to effectively manage large-scale trials and uphold data quality, even in complex study designs.

What defines "high-quality" data? Data of superior quality must be entirely accurate and suitable for statistical analysis. It should adhere to the criteria outlined in the study protocol and comply with its requirements. This implies that if a patient deviates from the established process and does not meet the necessary criteria, their data may need to be excluded from the final database. It is important to note that regulatory bodies may seek to review such information under certain circumstances. Additionally, clinical researchers are equally concerned about the presence of missing data. Ideally, instances of missing high-quality data should be minimal or nonexistent. Most importantly, high-quality data should only exhibit an arbitrary "acceptable level of variation" that does not compromise the integrity of the study's statistical findings. The data must also conform to the relevant regulatory standards established for data quality. (1)

1.2 Tools for CDM-

There are numerous data management software programs available; these are referred to as Clinical Data Management Systems (CDMS). A CDMS is now required in multicentric trials in order to manage massive volumes of data. Pharmaceutical businesses employ commercial CDMSs for the most part, while some are also available as open-source software. ORACLE CLINICAL, CLINTRIAL, MACRO, RAVE, and eClinical Suite are often utilized CDM tools. These software tools are essentially equal in terms of capability, hence neither system has a clear edge over the other. These software solutions are costly, and their proper operation requires a complex IT infrastructure. Furthermore, a few large, international pharmaceutical companies use specially designed CDMS instruments to meet their operating requirements. Some of the most well-known open-source tools are downloaded from their respective websites. (2)

Fig, (1) CDM stages (3)



1.3 The Designing of a Case Report form (CRF)-

In a clinical trial, the case record/report form (CRF) serves as the most critical document. It encompasses the data collected by the researcher concerning each participant involved in the clinical study or trial. According to the International Council for Harmonisation (ICH), the CRF, which is utilized to record the safety and efficacy of pharmaceutical products in test subjects, may be in printed, optical, or electronic format. The sponsor who initiated the clinical study is the primary recipient of this information. The CRF is developed following established procedures, and once completed, it undergoes a thorough review to ensure that all questions are pertinent and well-structured. Taking into account the language of the participants, the CRF proceeds to the printing stage. Upon completion of printing, the CRF is dispatched to the research sites, where it is handled by subject-matter experts, consultants, monitors, pharmacists, pharmacokinetics specialists, and contract personnel. After verification for completeness, the finalized CRFs are forwarded to the sponsor. Wright and Haybittle identified three essential elements of a CRF, given its specialized nature: content (what data is to be collected?), presentation (does the CRF include relevant questions?), and methodology (are there contingency plans in place if needed?). The data collected through the CRF must adhere to regulatory standards. The CRF should be distinctly identifiable as pertaining to a specific trial, with each participant's data collected individually, including the date, demographic details (age, sex, etc.), inclusion and exclusion criteria, dietary practices, administration of the trial product (dosage, timing) as per the protocol, and documentation of any adverse events along with the corrective actions taken. The success of a clinical study is significantly influenced by the CRF, making it crucial to develop multiple iterations and select the most effective version. CRFs can be produced electronically (eCRF) or in paper format. Moreover, since the data gathered in the CRF is pivotal in determining the success of a clinical trial, adherence to standard operating procedures is essential. (4)

Fig, (2) Deception of a well-designed and poorly designed CRF. (4)

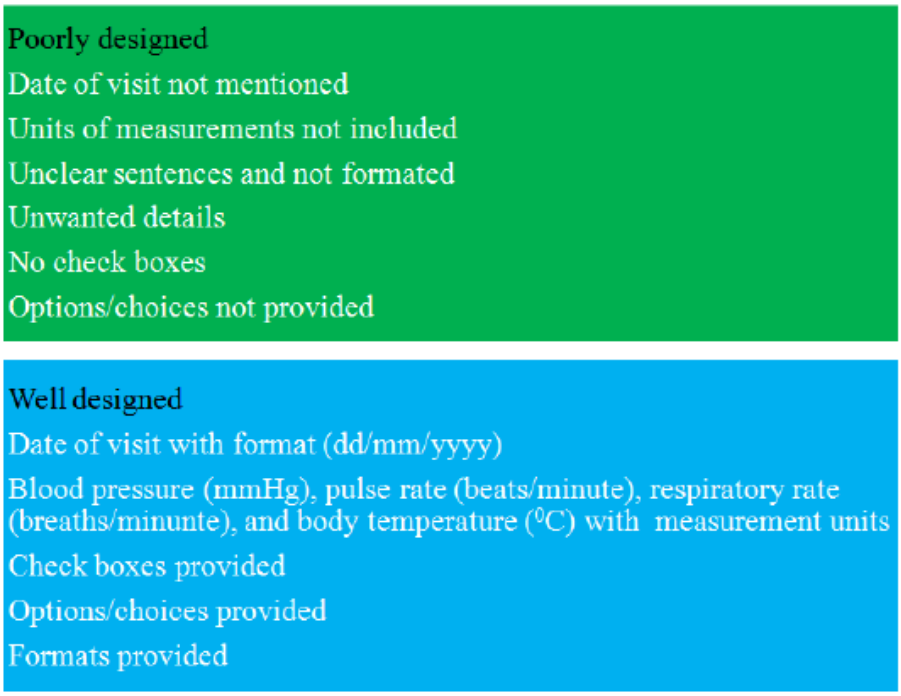


Figure 1. Depiction of a well-designed and a poorly designed CRF

1.4 Electronic Case Report Forms

As clinical trials become more intricate and numerous, the significance of electronic Case Report Forms (eCRFs) continues to grow. These digital instruments facilitate the integration of diverse data sources, including test outcomes and patient-reported results, while allowing for real-time data collection and ensuring adherence to international regulatory standards. By automating many previously manual processes that were susceptible to errors, eCRFs enable research teams to focus on their primary objectives—enhancing scientific understanding and efficiently introducing innovative therapies to the market. An eCRF serves as a digital alternative to the traditional paper-based Case Report Form, utilized for the collection and management of participant data in clinical trials. The primary aim of eCRFs is to promote accuracy, consistency, and regulatory compliance by optimizing the data collection process. Unlike paper CRFs, which are tangible documents, electronic CRFs are digital forms designed to collect and store clinical trial data online. This distinction highlights the advantages of electronic CRFs, which include improved data security, enhanced data monitoring, real-time data entry, and automated validation checks. (5)

Fig, (3) Electronic Case Report Forms Structure (6)

1.5 Pharmacovigilance:

Pharmacovigilance refers to the scientific discipline and practice dedicated to monitoring the effects of medications on patients. This area of public health aims to protect individuals from adverse drug reactions. It involves the collection, analysis, and interpretation of data regarding medication side effects. Additionally, pharmacovigilance encompasses the identification of new safety information and the assessment of the risk-benefit profile of pharmaceuticals. The primary objective is to ensure that the benefits of medications outweigh their risks, which is achieved by adhering to FDA recommendations through the drug safety department's implementation of a pharmacovigilance audit checklist. To identify potential hazards, it is crucial to gather comprehensive information on adverse drug effects. The overarching goal is to ensure that patients receive safe and effective medications. Pharmacovigilance also involves the ongoing study of a drug's effects after it has been released to the market, playing a vital role in ensuring the safety of pharmaceuticals. This information is essential for identifying potential risks associated with drug usage. (7)

Pharmacovigilance utilizes various large data sources, such as social media, medical literature, electronic health records (EHR), and spontaneous reporting systems (SRS). It comprises two primary systems: passive and active surveillance. Passive surveillance relies on SRS from patients and healthcare professionals; however, this method suffers from significant underreporting, with fewer than 1% of adverse drug reactions (ADRs) being documented. In contrast, active surveillance can leverage different databases derived from EHRs, which contain extensive patient information. This approach allows for the identification of new drug safety signals and the validation of indicators discovered through passive surveillance. From a medical informatics perspective, real-time monitoring of ADRs, enhancement of efficacy, and experimentation with various natural language processing (NLP) technologies are essential. Consequently, a systematic approach to medical informatics is required to implement effective methodologies within pharmacovigilance systems. The field of pharmacovigilance has evolved significantly since the World Health Organization (WHO) technical report published in 1972. Since that time, numerous research initiatives focused on patient safety have been undertaken, and a wealth of review articles has emerged in this domain. This article reviews the prevailing trends and assesses the comprehensive range of pharmacovigilance research conducted over the past decade. The key findings and limitations of these studies are summarized by categorizing them into sections that encompass all aspects from data collection to monitoring. Ultimately, we emphasize the critical role of medical informatics in active pharmacovigilance and related platforms. (8)

Fig. (4) Pharmacovigilance expertise (9)

1.6 Software used in Pharmacovigilance

1.5.1. Oracle Argus Safety

Businesses are increasingly focusing on a thorough understanding of product safety, beginning with clinical research and continuing through post-marketing surveillance. Oracle Argus Safety is a robust platform specifically designed to address the stringent pharmacovigilance requirements of the life sciences industry. The advanced database of Argus Safety supports informed decision-making, guarantees compliance with global regulations, and integrates safety and risk management processes. Organizations within the life sciences sector must ensure compliance with international laws, guidelines, and recommendations established by entities such as the FDA, ICH, EMEA, and various national authorities. The complexity of this landscape is heightened by extensive licensing agreements and the outsourcing of certain functions, making it increasingly challenging for the industry to meet its global reporting obligations. Companies depend on Argus Safety to effectively and proactively manage their regulatory compliance needs. By utilizing Argus Safety's advanced reportability features, which include comprehensive dashboards and analytics, managers and executives can gain insights into compliance and reporting key performance indicators. Additionally, Argus Safety's flexible architecture allows for the modeling of nearly any business process, enhancing case management and reporting compliance both internally and across license partner networks. With its powerful reporting engine, which enables clients to establish specific rules in line with legal requirements, Argus Safety streamlines reporting compliance. Coupled with advanced automation features such as "Auto/Force distribute" and "Auto-Submit," it ensures complete adherence and has the potential to lower regulatory reporting costs.

1.5.2. ARISg

Pharmaceutical companies widely adopt ARISg as a leading software solution for pharmacovigilance. Over 300 organizations worldwide rely on ARISg to manage their critical drug safety information. The software encompasses all necessary functionalities to address adverse event reporting and comply with the adverse reaction regulations established by various global regulatory authorities. ARISg supports a comprehensive range of pharmacovigilance activities, including CIOMS 1, MedWatch 3500A, and others, facilitating processes from case entry to the automated creation of submission-ready adverse event (AE) reports. It serves as a crucial component of an integrated pharmacovigilance and risk management framework, enabling companies to monitor their products and proactively identify potential safety concerns. With its customizable workflows and advanced technology, ARISg streamlines the management of adverse drug reactions. Users can configure a system that aligns with their business processes and standard operating procedures (SOPs) by automating the case routing according to their established workflow rules. Like all Aris Global offerings, ARISg is available in both on-premise and on-demand formats.

1.5.3. PvNET

With features including adverse event reporting, adverse drug reaction (ADR) data management, and regulatory reporting of ICSR (individual case safety report) that goes beyond simple compliance, PvNET is a complete pharmacovigilance solution and one of the top programs used in pharmacovigilance. PvNET assists in the integration of safety information from the beginning of development to the end of marketing, enabling users to make informed decisions. PvNET has successfully completed audits for medication safety across the board in accordance with GMP standards, 21 CFR compliance, and ICH E2B. (10)

1.7 Pharmacovigilance Companies

An essential part of the pharmaceutical industry is pharmacovigilance, which is the science and actions pertaining to the identification, evaluation, comprehension, and prevention of any negative effects or other drug-related issues. It is crucial to guarantee the safety and effectiveness of pharmaceuticals during their entire life cycle. A number of businesses have become leaders in this area by utilizing cutting-edge technologies and clever alliances. Due in large part to the COVID-19 epidemic and the increasing frequency of adverse medication reactions and safety concerns, the pharmacovigilance market is expanding significantly. The demand for pharmacovigilance services has increased as a result of the issues that the development of vaccines has brought up, including post-authorization safety monitoring and vaccine safety communication. The market is expanding due to factors such as rising rates of drug toxicity and adverse responses, increased rates of medication consumption and development, and an increasing tendency of outsourcing pharmacovigilance services. The expanding drug usage has also led to an increased demand for regular drug monitoring, which has boosted the pharmacovigilance business. Because pharmacovigilance services are being used more often, pharmaceutical companies are anticipated to have a significant market share in the pharmacovigilance market. This industry is expected to increase as a result of regulatory bodies' increasing demand for medical data. The importance of post-marketing medication evaluation in enhancing the characterization of drug safety profiles in practical contexts is another factor propelling market expansion. Moreover, collaborations between pharmaceutical firms and software suppliers in the market are also projected to boost market expansion. Nevertheless, a number of issues, including the high risk involved in data security, the absence of international regulatory harmonization, and the lack of data standardization for adverse event collection, could impede the pharmacovigilance market's expansion.

- Accenture
- Cognizant

- Laboratory Corporation of America Holdings (Labcorp)
- IBM
- ArisGlobal
- ICON plc
- Capgemini
- Wipro
- IQVIA
- Parexel International Corporation
- BioClinica Inc.
- Clinquest Inc.
- ITClinical,
- TAKE Solutions Limited
- United BioSource LLC,
- Bristol-Myers Squibb Company
- Linical Americas
- IMEDGlobal
- Boehringer Ingelheim International GmbH
- Novartis AG
- Sanofi (11)

Clinical data management and pharmacovigilance is done in the phases of the clinical trials, that's why the knowledge of clinical trials is essential.

1.8 Clinical Trials-

A clinical trial is defined by the World Health Organization as any research study that assigns human participants or groups of participants to one or more health-related interventions prospectively in order to assess the effects on health outcomes. As the name implies, clinical trials are a series of observations and experiments conducted on human participants for clinical research. They are conducted in an effort to find novel therapies, procedures, or diagnostic tools for the management, prevention, and detection of a range of illnesses. Clinical trials are useful in establishing the effectiveness and safety of new interventions as well as whether they outperform already recommended therapies.

Types of clinical trials-

Clinical trials can be classified into various ways One way is to classify clinical trials on basis of mode of study

1. Intervantional Study:- in this study researchers measure how the subjects' health changes. They give the research subjects a particular medicine and then compare the treated subjects with those receiving no treatment or the standard treatment. This is a type of a comparative study.

2. Clinical observational study:- in thisstudy the researchers observe the subjectsgiven with new medicine and measure their outcomes.

1.9 Phases of clinical trial

1.8.1. Phase 0 studies:

A clinical trial's phase 0 is typically conducted with less than 15 participants. Before beginning to use the drug at bigger levels for later phases, investigators must test it on humans in very modest quantities to ensure it poses no health risks. Before choosing whether to proceed with the trial or not, the researchers will probably conduct some further preclinical research if the medicine behaves differently than anticipated. (12)

1.8.2. Phase I studies:

this stage evaluates a medication's or device's safety. The testing process is currently in its early stages and could take several months to finish. Usually, between 20 and 100 healthy individuals participate in this phase. The goal of a phase 1 study is to ascertain the drug's or device's effects on humans,

including its absorption, metabolism, and excretion (ADME). This stage also looks into side effects related to dosage. Roughly 70% of experimental medications pass this stage of evaluation. (13)

1.8.3. Phase II studies:

Several hundred people with the ailment that the new drug is intended to treat participate in phase II of a clinical trial. Usually, the same dosage that was determined to be safe in the preceding phase is administered to them. For several months or years, participants are observed by researchers to assess the medication's effectiveness and provide additional data regarding potential negative effects. Even though phase II has a larger sample size than previous phases, it is still insufficient to show the medication's general safety. On the other hand, phase II data collection aids investigators in developing phase III methodology. According to FDA estimates, approximately 33 percent of drugs proceed to phase I trials.(14)

1.8.4. Phase III studies:

In phase 3 clinical trials, several factors are examined by physicians. They investigate if the novel treatment prolongs life and improves quality of life. They search for the presence of fewer (less) adverse consequences. They find out if fewer individuals with cancer returned after receiving the recommended course of treatment. In a phase 3 trial, participants are randomized at random to receive either the novel treatment or the standard therapy. Participants in randomization-based trials are not given the option to select their group. A phase 3 trial could result in a drug's success. If so, the researchers may approach the FDA to inquire about the possibility of providing the medication to other physicians for their patients as well. A phase 3 clinical experiment may occasionally be terminated. When the researchers notice that one group is performing noticeably better than the other, this is what takes place. Patients are kept protected in this way. Everyone is offered the new treatment if it proves to be more effective than the conventional course of care. If the standard treatment is working better than the new treatment, everyone is offered the standard treatment. (15)

1.8.5. Phase IV studies:

Clinical studies classified as phase 4, often known as post-marketing surveillance trials or late-phase trials, are conducted after a medication or medical procedure has received approval and is available to the public. The primary aim of these trials is to gather additional information regarding the long-term safety, efficacy, and optimal application of the treatment in real-world settings.

Key aspects of phase 4 clinical studies include:

1. Objective: Phase 4 studies evaluate the effectiveness of a treatment across a larger population and diverse conditions. They facilitate the identification of drug interactions, rare or prolonged adverse effects, and potential benefits in specific patient groups.

2. Sample size: In contrast to earlier phases, phase 4 studies typically involve a larger number of participants. With the medication already approved, the sample size can be significantly increased, enabling researchers to detect rare occurrences or effects that may not have been evident in previous trials.

3. Duration: Phase 4 studies are generally conducted over several years, often extending beyond that. This extended duration allows researchers to collect long-term safety and efficacy data, assess the treatment's enduring effects, and compare its effectiveness with other medications currently available.

4. Study design: Various study designs are permissible for phase 4 trials, including observational studies, registries, and randomized controlled trials (RCTs). Observational studies monitor patients in their natural settings without intervention, while randomized controlled trials may compare the treatment against other approved therapies or placebos.

5. Regulatory oversight: Although phase 4 trials occur after approval, regulatory bodies, such as the US Food and Drug Administration (FDA), continue to monitor these studies to ensure patient safety and assess any additional risks or benefits associated with the medication.

6. Post-marketing surveillance: Once a treatment is available on the market, its safety and efficacy are continuously evaluated. (16)

1.10 Clinical trials in India

India is regarded as a favorable destination for international clinical trials, accounting for approximately 20% of all clinical trials conducted globally. As the second-most populous country in the world, India has the potential to significantly impact international drug development efforts. Compared to developed nations, India presents numerous advantages, such as a large patient base, a well-educated workforce, a diverse array of diseases, reduced operational costs, lower drug prices, a supportive economic climate, and, crucially, the ease of establishing clinical sites due to the widespread use of English.

The Drugs Controller General of India (DCGI) serves as the equivalent of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). The DCGI is the federal authority responsible for all pharmaceutical-related matters in India, with the commissioner of the FDA holding a similar position as the DCGI. India adheres to Schedule Y for drug trials, which aligns with the Investigational New Drug (IND) regulations outlined in 21 CFR 312. Unlike the FDA, the DCGI operates without multiple offices or centers to oversee different product categories, personally signing each application submitted to its office. This includes applications for marketing approval of pharmaceuticals and medical devices, as well as for manufacturing and the import and export of regulated goods, not limited to clinical trial applications.

India follows the ICH E6 guidelines for clinical trials, and the Indian Council of Medical Research (ICMR) has developed a local version of Good Clinical Practices (GCPs) to address specific challenges faced in the country. An Institutional Ethics Committee (IEC) in India functions similarly to an Institutional Review Board (IRB) in the United States. Approval from the IEC, in addition to the DCGI, is required before enrolling any participants. The clinical trial application process in India typically takes about 4 to 8 weeks to initiate, whereas in the United States, various European countries, and Australia, the process may differ. (17)

1.11 Conclusion and Discussion-

Clinical data management (CDM) ensures high quality and regulatory compliance by methodically gathering, cleaning, and organizing data. It is essential to the success of clinical studies. The company wants to gather information in line with the methodology of the study. and offer a trustworthy database for examination. For test findings and regulatory submissions to be correct, all information must be complete and accurate. The design of the case report form (CRF), which guarantees the accuracy and consistency of the data, is crucial. The main goal of drug surveillance is drug safety. Drug monitoring evolved to include passive (e.g., spontaneous reporting) and active (e.g., electronic health records, NLP) monitoring of adverse drug reactions (ADRs). Incorporating medical data to improve medication safety is crucial. Leading software such as Oracle Argus Safety and ARISg along with companies like Accenture dominate this market, although challenges such as data security remain. Clinical trials required to advance clinical trials evaluate treatments over a period of time, from early safety testing (Phase 0) to post-marketing surveillance (Phase 4). India plays a key role in their development. world class medicine Providing a large group of patients and cost benefits under the supervision of DCGI to ensure safe and effective treatments.

References

1. What Is Clinical Data Management? A Beginner's Guide from the Firma clinical research retrieved from https://www.firmaclinicalresearch.com/clinical-data-management-guide/
2. Data management in clinical research: An overview by Binny Krishnankutty, Shantala Bellary, Naveen B.R. Kumar, and Latha S. Moodahadu Indian J Pharmacol. 2012 Mar-Apr; 44(2): 168–172. doi: 10.4103/0253-7613.93842 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326906/
3. clinical data management: process, benefits, and software solutions by evgeniy altynpara and diana chabanovska retrieved from cleveroad website- https://www.cleveroad.com/blog/clinical-data-management/
4. Clinical Research Related Documents and Data Management: An Update Venkataramana Kandi , Sabitha Vadakedath American Journal of Pharmacological Sciences. 2023, 11(2), 35-43. DOI: 10.12691/ajps-11-2-2 Received September 09, 2023; Revised October 10, 2023; Accepted October 17, 2023 retrieved from https://pubs.sciepub.com/ajps/11/2/2/
5. Comprehensive Guide to Electronic Case Report Forms (eCRF): FAQs, Benefits, and Best Practices by Corrine Cato retrieved from https://www.cloudbyz.com/resources/clinical-operations/comprehensive-guide-to-electronic-case-report-forms-ecrf-faqs-benefits-and-best-practices/
6. clinical data management: process, benefits, and software solutions by evgeniy altynpara and diana chabanovska retrieved from cleveroad website- https://www.cleveroad.com/blog/clinical-data-management/
7. Introduction to Pharmacovigilance: How Drug Safety is Enforced By Pharmacovigilance ByDr.Heba Yehia retrieved from https://www.pharmacovigilancefoundations.com/pharmacovigilance-introduction/
8. The 2011–2020 Trends of Data-Driven Approaches in Medical Informatics for Active Pharmacovigilance by Hyunah Shin 1,Jaehun Cha 1,Chungchun Lee 1,Hyejin Song 2,Hyuntae Jeong 2,Jong-Yeup Kim 1,3,* andSuehyun Lee 1,3,* Appl. Sci. 2021, 11(5), 2249; retrieved from https://www.mdpi.com/2076-3417/11/5/2249\
9. The Importance of Pharmacovigilance for Labs retrieved from https://www.propharmagroup.com/thought-leadership/the-importance-of-pharmacovigilance-for-labs
10. Software used in Pharmacovigilance by ClinSkill retrieved from https://www.clinskill.com/software-used-in-pharmacovigilance/
11. Pharmacovigilance Companies (2024 - 2029) retrieved from Pharmacovigilance Companies - Top Company List (mordorintelligence.com) https://www.mordorintelligence.com/industry-reports/pharmacovigilance-pv-market/companies
12. What Happens in a Clinical Trial? Medically reviewed by Deborah Weatherspoon, Ph.D., MSN — Written by Jill Seladi-Schulman, Ph.D retrieved from Clinical Trial Phases: What Happens in Phase 0, I, II, III, and IV (healthline.com) https://www.healthline.com/health/nocebo-effect#takeaway
13. Clinical Trials: A General Review by Akhilesh Tiwari,Megha Joshi January 2016 DOI:10.15520/ijcrr/2016/7/12/215 retrieved from https://www.researchgate.net/publication/349534334_Clinical_Trials_A_General_Review

14. What Happens in a Clinical Trial? Medically reviewed by Deborah Weatherspoon, Ph.D., MSN — Written by Jill Seladi-Schulman, Ph.D retrieved from Clinical Trial Phases: What Happens in Phase 0, I, II, III, and IV (healthline.com) https://www.healthline.com/health/nocebo-effect#takeaway

15. What Does Phase 1, 2, and 3 of a Clinical Trial Mean? retrieved from What Does the "Phase" of a Clinical Trial Mean? | Memorial Sloan Kettering Cancer Center (mskcc.org) https://www.mskcc.org/cancer-care/clinical-trials/what-does-phase-clinical-trial-mean

16. Clinical Trial: Phase 4 retrieved from Clinical Trial: Phase 4 (thepharmadaily.com) https://www.thepharmadaily.com/courses/clinical-data-management/clinical-trial-phase-4

17. Clinical Trials: A General Review by Akhilesh Tiwari,Megha Joshi January 2016 DOI:10.15520/ijcrr/2016/7/12/215 retrieved from https://www.researchgate.net/publication/349534334_Clinical_Trials_A_General_Review