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Clinical Research Related Documents and Data Management: An Update

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Abstract Clinical research is a way of doing research that is primarily aimed to solve a human health and/or ailment-related problem. However, clinical research is complex and involves factors that influence the accuracy of the study results. The clinical research-related documents and data management assumes increased significance. The data obtained from the clinical research is collected, stored, validated, distributed, analyzed, and managed according to standard recommendations as prescribed by the national and international regulatory agencies. The nature of the case record form, the data validation process, quality assurance during data collection, validation, database creation, pharmacovigilance, the role played by the regulatory authorities, and other aspects of clinical trial data management are discussed comprehensively in this review.

Keywords: *clinical research, human health, data management, case record form, regulatory agencies, pharmacovigilance*

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1. Introduction

Clinical research is a process of investigating the health-related aspects of humans. It includes the basic research that focuses on the relationship between the diseases, predisposing factors, therapeutic interventions, and prophylaxis [1,2,3]. However, in most instances, clinical research implies research being conducted to understand the usefulness of a novel therapeutic intervention or medical devices [4]. Clinical trials are lengthy processes that usually take years, and require huge financial expenditures, and skilled workforce [5,6]. Also, clinical research is conducted simultaneously in different selected centers (multi-centric studies), wherein the drug trials are simultaneously conducted [7,8]. During these circumstances, there will be clinical trial groups at each center, usually headed by a principal investigator. Because effective planning and implementation of a clinical study/trial is a crucial factor that decides the success of clinical research, the project manager is crucial to effectively plan the project budget, organize resources, and use the best processes to control and monitor the clinical study. Designing a perfect protocol, setting time limits, and following regulatory requirements assume significance while planning a clinical trial [9]. What, when, how, and who are planned before the initiation of a study trial. Clinical data management is a critical aspect, and therefore, extreme care needs to be taken while collecting the data. The case record form (CRF) must be carefully designed to include all the necessary elements and should be legible to the people designated to collect the data [10,11]. The CRF and clinical trial data may be managed using electronic/computer software wherever appropriate [12,13]. In cases of multi-centric studies, the data collected at the peripheral centers are appropriately communized to the central study site [14].

In this comprehensive review, we highlight the roles of regulatory agencies in clinical data management, designing an appropriate CRF, aspects of data capture, effective planning of clinical studies, data validation and quality assurance in data management, medical data coding, performance analytics, designing databases for laboratories, and pharmacovigilance.

2. The Role of International Conference on Harmonization (ICH)

The international conference on harmonization (ICH) plays a crucial role in unifying the registration requirements for novel medical products including medical devices and human therapeutics [15]. It helps the pharmaceutical companies to accelerate the process of licensing the new medical products, reduce the production costs, and to increase the patent protection times. ICH was first founded in 1991, in Brussels, under the umbrella of the United States of America (USA), Japan, and the European countries. The ICH conference is conducted once every two years with the participation from the member countries, observers from the regulatory agencies, like the World

Health Organization (WHO), European Free Trade Association (EFTA), and the Canadian Health Protection Branch, and other interested stakeholders from the academia and the industry. The expert working groups of the ICH ensure the quality, efficacy, and safety of the medicinal product (drug/device) [16]. The ICH guidelines on clinical data management include the 15 elements which ensure the quality, efficacy, and safety of clinical data management by the pharmaceutical companies during the drug design, discovery, and marketing process is shown in Table 1 [17].

Table 1. The ICH guidelines including the 15 elements

ICH code	Governing Topic
E1	The extent of population exposure to assess clinical safety
E2A	Definitions and standards for expedited reporting
E2B	Data elements for transmission of adverse drug reaction reports
E2C	Periodic safety update reports for marketed drugs
E3	Structure and content of clinical reports
E4	Dose-response information to support drug registration
E5	Ethnic factors in the acceptability of foreign clinical data
E6	Good clinical practice: consolidated guidelines
E7	Studies in support of special populations: geriatrics
E8	General considerations for clinical trials
E9	Statistical considerations in the design of clinical trials
E10	Choice of control groups in clinical trials
E11	Clinical investigation of medicinal products in children
M1	International medical terminology
M3	Timing of pre-clinical studies in relation to clinical trials

There are new rules and guidelines that are put forward by the US Food and Drug Administration (FDA), and the European Union (EU), which ensure that the pharmaceutical companies and the clinical data management groups adhere to the ICH requirements.

The European Parliament and the EU laid down ten provisions that include protection of trial subjects, ethics committee opinion, the commencement of a clinical trial, conduct of a clinical trial, exchange of information, manufacture, and import of investigational medicinal products, labeling, compliance with good clinical practice (GCP), notification of adverse events (AE's), and notification of adverse reactions.

The ICH regulates the technical requirements of the pharmaceutical companies which conduct research and produce/manufacture medical drugs/devices for human usage. The ICH E8 deals with the general considerations of clinical studies. In this, the ICH details the systematic approach towards the conduction of a clinical trial/study.

It includes the first phase, the human pharmacology which deals with the pharmacokinetics and pharmacodynamics of the drugs, the tolerance studies, the drug metabolism, and its activity. The second phase deals the exploratory therapeutic studies, where the drug indication is studied, along with the dosage. The third phase called confirmatory therapeutics deals with establishing the efficacy of the drug, its safety, assessing the benefit to risk ratio, and establishing the dose-response ratio. Therapeutic use forms the final phase of the clinical study where the increased understanding of the benefit to risk ratio is obtained among the special population. This phase is aimed also to identify the potential adverse effects and confirm the therapeutic dosage of novel drugs [18]. Although the ICH was a developed nation initiative, the countries with emerging markets like India, China, Brazil, and others may choose to follow the regulatory requirements as suggested by the ICH along with their respective country's regulatory authorities [19]. The ICH E9 which deals with the statistical principles for the clinical trials emphasizes the importance of missing data, managing the missing data, investigating the sensitivity of the results of the trial, and recording the reasons for deleting the data [20].

3. The Designing of a Case Report form (CRF)

The case record/report form (CRF) is the most significant document in a clinical study. It contains the information collected by the investigator about each subject participating in a clinical study/trial. According to the ICH, the CRF can be printed, optical, or an electronic document that is used to record the safety and efficacy of the pharmaceutical drug/product in the test subjects. This information is intended for the sponsor who initiates the clinical study. The CRF is designed as per the protocol and later it is thoroughly reviewed for its correctness (appropriate and structured questions) and finalized. The CRF then proceeds towards the print considering the language of the participating subjects. Once the CRF is printed, it is distributed to the investigation sites where it is filled with the details of the participating subjects by the investigator/nurse/subject/guardian of the subject/technician/consultant/monitors/pharmacist/pharmaco kinetics/contract house staff. The filled CRFs are checked for their completeness and are transported to the sponsor.

Since the CRF is a specialized form Wright and Haybittle suggested three important aspects of a CRF that include the content (what information you wish to collect?), presentation (does the CRF include appropriate questions?), and methodology (are you ready with the alternatives if needed?) [21]. The data achieved/collected through the CRF must meet the regulatory requirements. The CRF must be identifiable as belonging to a specific trial, each subject's data should be collected separately, which includes the date, demographic characteristics (age, sex, etc.), inclusion and exclusion criteria, dietary habits, administration of the trial product (dosage, time) according to the protocol, and recording the adverse events and the corrective measures taken. Because the CRF assumes great significance for the success of clinical research, designing different versions of the CRF and selecting the best appears critical. The CRFs can be printed on paper, or electronic (eCRF). Also, because the data collected in the CRF decides the success of a clinical study, it is important to have standard operating procedures (SOP) for the CRF preparation to minimize the mistakes. Characteristics of a well-designed CRF is depicted in Figure 1.

Another important aspect of a well-designed CRF is its ability to generate precise data on each trial subject, and its user-friendliness [22].

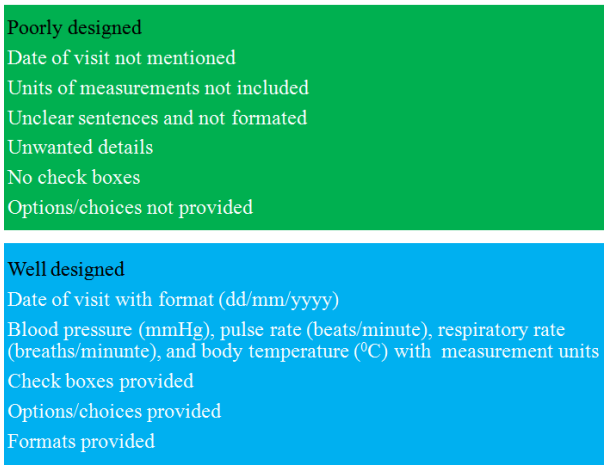

Figure 1. Depiction of a well-designed and a poorly designed CRF

4. The Nuances of Data Capture

Data capture is the process that involves the collection of data related to the clinical trial. The data collected may later be accessible to and be easily retrievable by the investigator and/or sponsor. There are different data capture methods available for the collection and storage of clinical study data. Manual entry of the data available on the paper (the CRF collected by the investigator at the trial site) into a database electronically by a trained data entry operator. Traditionally, data entry is performed twice by two different operators (the second time by an experienced operator) to enhance accuracy and minimize errors. The major drawback of the data entry process is the time, and this can be minimized by utilizing a better screen design of the database entry (making the page remarkably similar in look to the CRF which is used for the entry of clinical data at the trial site). Database management is the most critical element of the clinical trial/study which must be accurate, speedy, and secure. The data entry can be done at the investigation site (remote data entry), or the data collected in the CRF can be transported to a central facility where the data from different investigation sites is recorded. The drawback of a central data entry facility is the delay in time while the CRFs from various investigation sites arrive at the central facility. Also, there is a chance for missing CRFs during the transport and there is a possibility that the data entry operators may do errors while entering the data. Data from the investigation site is delivered to a central facility using fax, scanning technology, and by post/courier. The data entry can also be simplified by uploading the data directly into the software using the internet, removing the process of manual entry. The drawback with this process is the possibility of the data being stolen electronically using various software. The data entered in a systematic data entry form can be directly read by the computer software, which may reduce the time in the database management. The optical mark recognition, the optical character recognition, and the intelligent character recognition methods are used to increase the accuracy of the database management.

The drawback of remote data entry and software development for systematic data collection and retrieval is the associated cost. The cost of purchasing the electronic instruments like the computers, software's, and others like the fax machines, scanning instruments, and the cost of hiring the data entry operators and the training of the new operators. Since the data capture forms the core of both the clinical and the translational research studies, the electronic data capture (EDC) is superior to the traditional paper-based manual data entry (CRF). The EDC will improve the accuracy, timeliness, and cost associated with database management [23]. In a clinical trial, there are various times at which the investigator collects important data from the subjects participating in the clinical study. After a drug has been recommended to the study subject, it becomes important to collect/record the data regarding the dosage, the regularity with which the subject is asked to take the drug, and the subject's compliance with the study protocol. Recently, the use of a personal digital assistant (PDA), a drug compliance monitoring system with barcodes was successfully evaluated which investigates the management, investigator activities, and the patient aspects as shown in Figure 2 [24].

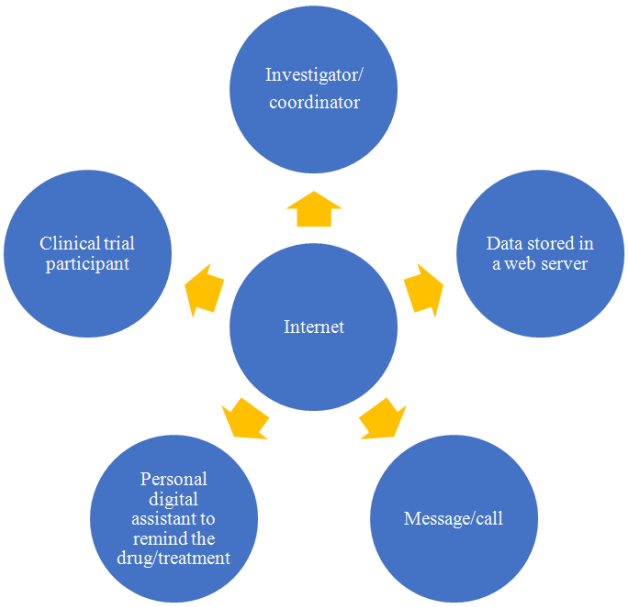

Figure 2. Depiction of the components of data capture

5. Significance of Planning and Implementation in Clinical Trials

Clear planning and performance of a clinical study/trial will impact its success. The clinical study majorly includes the collection and distribution of the trial data, which is done by the clinical data management section. The project manager is crucial to effectively plan the project budget, organize resources, and use the best processes to control and monitor the clinical study. The clinical study is conducted by a sponsor or a clinical research organization (CRO). A perfect protocol, time limits, and regulatory requirements assume significance while planning a clinical trial. What, when, how, and who are planned before the initiation of a study trial. Regular review of the project using the bar and Gantt charts, and maintaining the timelines assume increased significance

for success with the product (study report, statistical report, database).

The project undertaken to conduct the clinical trial must be predetermined with timelines and milestones. Timelines are usually set for preparation of protocol, designing the CRF, planning the project, identifying the first subject, and the timeline for recording the patient's data for the first visit. The timelines also are set for the last subject to be recruited in the study, the CRF of the last subject, and the locked period after the last subject entry. The planning of the project also includes the modes of collection of the data, the methods of the transport of the CRFs, patient diaries, records of severe adverse events, to the central data management sites (fax, scan, courier).

The preparation of standard operating procedures (SOP), type, and timing of the quality control (QC) procedures are also included under the project planning before the start of a clinical study. Review (budget, resources, quality of process, assessment), measure (turnaround times, training issues) and control (CRF collection and delivery, incentives, revising the process) are the three important aspects of the implementation of a clinical research project.

The European Medicines Agency (EMA) suggested the application of adaptive/flexible clinical trials for the success of clinical trials. The adaptive designs give way for the adjustment of drug doses in phase II/III trials and enable holding of the trial in cases of futility/unwarranted emergencies. The adaptive designs minimize the type I errors, increase the study integrity and accuracy of the results [25]. The role of planning and implementation of clinical trials in the field of radiation oncology was reported in a previous study [26]. Correct assessment of the study protocol at an early stage by appropriate regulatory authorities may contribute to reduced costs associated with the conduction of an unnecessary clinical trial. Multi-national and multi-centric clinical trials are complex and require scrupulous planning and implementation for their success as noted by a recent research report. Also, this study highlighted the implication of multi-national clinical trials when conducted in resource-constrained countries [27].

6. The Process of Data Validation in Clinical Trials

The major purpose of a clinical trial/drug development process is to generate quality and accurate data. The data management of the clinical study should be in tune with the study protocol and is required to satisfy the regulatory agencies that include the good clinical practice (GCP) guidelines, and the ICH. The data generated forms the basis for the submission of a new drug application (NDA). The clinical data validation is conducted systematically and is done by the investigator (CRF accuracy, legibility, timeliness, patient diary), the trial monitor (source data verification (SDV) verifies the CRF entries), and the clinical data management team/manager (statistical analysis, final reporting, edit check specifications (ECS)). Clinical trial data management (CDM) is a critical element of the clinical study which will decide its quality and accuracy. The quality of the clinical trial output depends on the CRF design, field monitoring guidelines, source data verification, missing data/CRF, electronic laboratory data, and data conventions.

The CRF must be designed as per the protocol, and it is beneficial to prepare different variants/versions of the CRF. The CRFs should contain the patient's treatment regimens, dosage, and all other essential details. The field monitoring guidelines invariably define the quality of data presented to the sponsor. The coordination between the monitor and the CDM to check the correctness of the data and its integrity delivers quality results. The integrity and the quality of the data depend on the SDV. It ensures the accuracy and the validity of the data presented by the investigator to the sponsor. The GCP guidelines emphasize the need to verify and track down the missing data/CRF. The date conventions are the aspect of different dates of the receipt of the CRFs in the case of the multi-centric studies.

Also, the electronic lab data generated must be identified as belonging to a subject by using unique identifiers and minimizing the potential errors. The lab values, their units of measurements must be decided at the protocol design time. Finally, the written SOPs concerning every phase/aspect of the clinical trial, and regular audits will assure the quality of the study. The data validation plan (DVP), along with the other measures used by the CDM ensure the required edit checks of the collected data regarding the study protocol and identify any potential discrepancies (missing data, incorrect data, deviation from the protocol) as shown in Figure 3 [28].

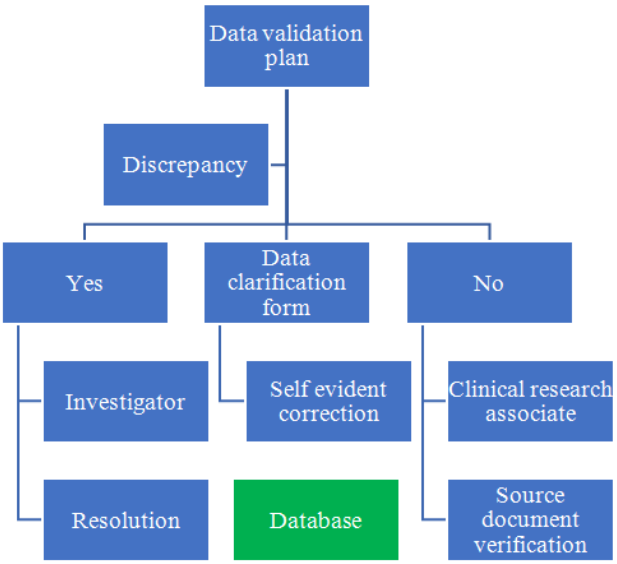

Figure 3. Flow chart depicting the data validation plan.

7. The Role of Quality Assurance and Clinical Data Management in Clinical Trials

Quality assurance, according to the ICH and GCP guidelines is necessary to be implemented during clinical research to generate quality and accurate data. Each element of the clinical research must have been conducted according to the SOP, which is written/determined before the initiation of the study and during the preparation of the

protocol. The audit team (quality assurance group) is instrumental in determining the authenticity of the clinical research. The audit, according to the ICH and GCP is an independent and external team that examines the process (recording the CRF, analysis of data, and interpretation of data) of clinical research.

The quality assurance personnel are adequately trained, become trainers if needed, should be good communicators, and must manage any kind of situation. The audits can be at the investigator sites evaluating the CRF data, the protocol, the personnel involved in clinical research (source data verification, monitors). Achieving quality assurance in a clinical study requires addressing issues like reviewing the available literature and procedures, designing an appropriate CRF and the preparation of protocol, recruiting the staff and clinical data management equipment and personnel, establishing the workspace, and infrastructure (computers, others). The audits during the clinical trials/study can be of diverse types. The source documentation audits to evaluate the data on the clinical trial according to the ICH-GCP essential document checklist before a drug is applied for licensing by the regulatory agencies like the food and drug administration (FDA). The results/findings of the clinical trial audits must be recorded, and a certificate of the audit must be issued so that the sponsor audited can understand the elements found in the audit that need improvements. The audits also consider coding as an important aspect that needs to be investigated for the maintenance of the quality control and the quality assurance of the clinical study.

Effective clinical data management in a clinical trial enhances data quality by identifying and rectifying errors in the process. The collection of data, its management, and storage of the clinical research data using artificial intelligence was reported recently [29]. The application of various software (Siebel Clinical, Oracle, ClinSource, Oracle, Phase Forward, DataTrack, Parexel, eResearch Technology, DataLabs, Nextrials, ClinPhone, CRF, in vivo data, BRAAN, DataLabs, Fast Track Systems, IRBWISE, ProIRB, IRBNet, SyTech, Wimmer systems, Oracle Clinical, Phase Forward, NetRegulus, Aris Global) in the clinical data storage, security and the management were also elaborated in the report. The workforce involved in the clinical data management and the systematic process involved is depicted in Figures 4 and Figure 5, respectively.

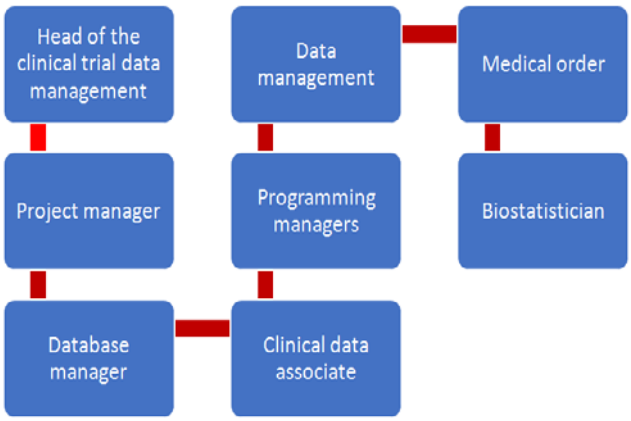

Figure 4. The personnel involved in the clinical data management.

8. Performance analytics in a Clinical Trial

Because the clinical study is a complex multi-step process, and that the process involves various groups, regular evaluation of the performance will contribute to the increased productivity, process cycle times, and quality output. The process flow differs with the type of the clinical study, the therapeutic medical drug/device evaluated, and the clinical phase of the study being conducted. The process flow broadly includes the data collection, and loading (pre-entry data review), data validation, data coding, and data editing. The clinical data performance measurement process involves status reporting (measuring productivity against resources), measurement and reporting quality, and measuring and reporting process cycle times.

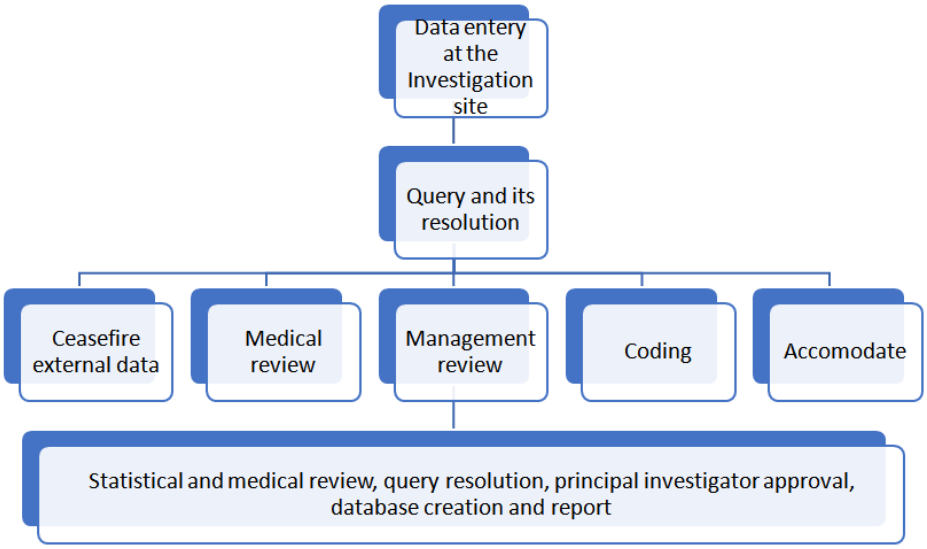

Figure 5. Flow cart depicting the process of clinical data management

Since clinical studies/trials involve huge financial obligations, they are considered as projects which are meant to be completed in a specified timeline. Reporting the process timelines/cycles is the job of the project manager/team leader. Measuring the performance process assumes increased significance for managing and responding to the process flow. The project managers, therefore, maintain timesheets and measure the timelines of various process flow cycles daily. The baseline times for each process flow are set considering the previous projects by the project manager/team leader.

The timelines are set for the entry of the CRF, validation, and generation of the query during the CRF visits and the data coding requirements. It is only after the timelines are set, that the budget of the project is finalized. Application of timesheets for the collection of data daily will ensure that the data management personnel will learn about the time required to complete each process cycle. Achieving the desired goals in a stipulated time limit is important to optimize the process performance and maintain in-stream processing. Clinical studies performed in multiple sites warrant special attention [30]. Since performance metrics appear to be vital for the success of a clinical study and its quality indicator/assessment, setting the goals on metrics and assessment assume increased significance.

9. Role of Medical Data Coding in Clinical Trials

During a clinical study, a huge amount of the data is collected, entered, analyzed, and is available for assessment to all stakeholders who relate to the study. Coding may be defined as a process of entering the data into a database. This entry is usually conducted by using codes (numeric, alphabetic, or alphanumeric). Medical codes can be universalized depending on the country in which they are used as in the case of the UK, where it is called as National Health Service (NHS), and as the Systemized Nomenclature of Medicine (SNOMED) in the United States of America (USA). Considering that a huge volume of data is generated in a clinical study, the use of medical codes becomes even more essential, as it saves time, and helps to summarize and understand it. Coding facilitates easy data management, record a stores data (saves time and space), eases data search and retrieval, allows data manipulation and analysis, and it standardizes and improves reproducibility.

Although medical coding saves time and is useful for clinical data management, it has drawbacks. It is quite time-consuming as the data entry operators must be well versed with the terminologies. Also, the terminologies need regular updates, and the addition and removal of the terms require professional competence. In medical coding, the terminologies are standardized based on the system disorders (32 system/organ classes) using preferred terminologies and the included terms. The medical coding for the adverse reactions is available as the World Health Organization-Adverse Reaction Terminology (WHOART) and managed by the WHO Uppsala monitoring center, which is used both by the regulatory authorities as well as the pharmaceutical industries. The coding system for a thesaurus of adverse reactions terminology (CoSTART) is maintained by the US FDA, and the terms (glossary terms-identifying various related conditions) used are represented by the long alphabetic coding symbols. Also available is the international classification of diseases wherein a code is given to the disease of a system (Ex. ICD-1-Airway disease). The WHO and the USFDA recommend the use of MedDRA-The medical dictionary for regulatory activities for all types of pharmaceutical research of all phases for the drugs as well as the devices.

Since the data generated from a clinical trial is of huge quantity, and the same trial may be conducted simultaneously at different centers, uniformity of the medical terms assumes great significance.

A recent study had elaborated on the utility of the most used medical coding methods in clinical data management [31]. The MedDRA and the WHO-DDE (WHO drug dictionary enhanced), along with the other medical coding dictionaries like the COSTART - Coding Symbols for Thesaurus of Adverse Reaction Terms, ICD9CM - International Classification of Diseases 9 Revision Clinical Modification, and WHO-ART - World Health Organisation Adverse Reactions Terminology are standardized medical coding dictionaries available currently in the market. Other drug dictionaries include the WHO-DD (WHO-drug dictionary), WHO-DD enhanced, and the WHO herbal dictionary.

10. Designing Database for Central Laboratories

Because a huge quantity of data is generated during a clinical study, database management appears crucial. Minimizing the inconsistencies and to improve the handling of the raw data generated at the trial site is important to design an improved methodology for data management in the central laboratories. The organization of economic cooperation and development (OECD), and the good laboratory practices (GLP) recommend guidelines and regulations on data management using computer systems (Annex 11). The US has its own guideline on data management using computers listed under the FDA's 21CFR113, and the US environmental protection agency's good, automated laboratory practices (GALP) and the ISO-9000 series' 9000-3 also guides regarding the use of the software in clinical data management. Data entry appears critical, and the data entry operators need to understand that they must just enter the data, and not bother about their validity, which is later checked by the investigator.

The inconsistencies in the data, which majorly arise from the similarities of the patient's name, age, sex, and date of birth remain as it is as noted by Murphy's rule. The inconsistencies also may arise from the wrong entry of the three different entries of the same patient as that of the first entry of a new patient. For foolproof database management, the software must ensure that the changes are not made in the entered data and that if the changes are made only under a specific cause, then the operator must be identified along with the time and the date of corrections. The applicability of a robust information management system is an essential aspect of the clinical study to generate and efficiently manage the data as noted

by a previous study. This study elaborates the efficacy of the laboratory information management system (LIMS) for the management of biological material like the deoxyribonucleic acid (DNA) database [32]. A previous study had highlighted the significance of long-term storage, security, upload, and retrieval while managing the high throughput primary lab data [33].

11. Clinical Data Management, Epidemiology, and Pharmacovigilance Its Significance in Clinical Trials

In tune with the guidelines and the regulations recommended by the FDA, the ICH (ICH: E6), GCP, and other controlling authorities like the GALP, good, automated manufacturing practices (GAMP), it is important to validate the computer systems involved in the clinical trials. According to the association of clinical data management (ACDM), validation is the process of assessing the computer systems for implementation, operation, and monitoring. This confirms that the entire process runs in a specified manner and the results are accurate. The audit group guarantees that the computer systems were designed in a secure manner (in-house/vendor). The audit also makes sure that the SOPs related to the software development/design, changes/versions, training material, the capability of the personnel, security, problem identification and management, system backup and restoration procedures, decommissioning plan, and others are adequately specified and implemented.

There are two types of validation, prospective and retrospective validation.

In the validation, the heads of all the concerned departments/processes are involved that including the Statistical personnel, Data Management group, Clinical QA team, IT managers (software and hardware), clinical research associates, Monitors, Database Administrators as well as a Project Manager. The study of a new drug, its efficacy, and the safety (large, simple, safety trials (LST)) among a large group of people (heterogeneous group) is called pharmacoepidemiology. Although the cost of the drug includes all the costs associated with the safety testing before the drug is marketed, the real concern is the quality of the patient's life after consuming the drug. Clinical research and therapeutic drug development is a financially huge project and due to increased competition with the generic drug manufacturers and due to the increased cost of production, the pharmaceutical industry is in a delicate situation.

Re-engineering is the process of fundamental re-thinking, re-design of the pharmaceutical project to radically improve the cost, quality, and speed of service. Thus, re-engineering not only reduces the cost but also minimizes the time associated with production/manufacturing without compromising the quality. Conducting an effective re-engineering process needs clinical researchers to set a target in terms of the time of completion, effectively communicate the target timelines with the personnel, and keep in mind both the internal and external customer requirements. During the clinical research, there is a need to form the solution development teams in the diagnostic phase. These teams will ensure that the targets of various clinical processes are achieved like the last patient last visit (LPLV). Improving the efficacy of the drug and its safety require the conduction of experimental designs (randomized control trials (RCT)), and the non-experimental designs (observational studies). Study validity is measured to confirm the data integrity and quality and is done by various methods. Spilker described five types of measuring validity that includes the construct validity (measure reflects what it is meant to measure), criterion validity (measure results are same for tests, scale, or questionnaire), discriminant validity (measure can detect the minutest but a significant change), content validity (significance of each part of the test/questionnaire to get the intended the result), and face validity (correctly measures what it is supposed to measure). The assessment of the interactions of the drugs and their effects in humans is called pharmacovigilance (PV). PV includes the detection, assessment, understanding, and prevention of ADRs. PV plays a critical role all through the production of the drug, its testing, pre-marketing assessment, and for the full life of the drug during the post-marketing period. The pharmacovigilance process can be depicted in Figure 6 [34].

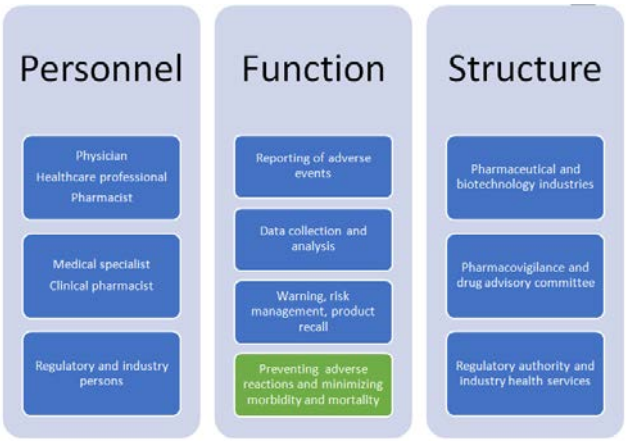

Figure 6. Depiction of the elements of pharmacovigilance

12. Current Perspectives

A recent study had highlighted the ICH Q6A guideline document which emphasizes the impurity limit setting of the drug substance/drug product. This guideline states that the specifications should focus on useful characteristics ensuring the safety and efficacy of the drug substance and drug product [35]. The recent ICH guideline documents also emphasize the management of the purity of the drug substance (ICH Q3A, Q3B, Q3C, Q3D, Q6A, Q6B, M7, and ICH S9). The mutagenic and non-mutagenic impurities in the drug substance/drug products and their management.

A recent study had evaluated the application of SMS-based reminders in healthcare delivery to ensure the standard quality, and accuracy of the clinical study [36]. This study had observed that such a reminder system could help increase the attendance of the study subject and improve the adherence to the medication. Improving the performance and the quality of a clinical trial, an interactive data visualization tool along with the data obtained from Covance's central laboratory was found beneficial as noted from the results of a previous study

[37]. The data which is stored in the electronic health records need to be extracted and standardized by not disturbing the integrity of the data. A recent study had evaluated the process of validation that includes the extraction, loading, and transformation (ETL) [38].

Despite the enormous growth of digital health solutions, the clinical research personnel are still low in confidence. A recent study had suggested that there is a need for an objective, transparent, and standard-based assessment of digital hearth services [39]. This study recommended the use of end-user necessities and assessed the technical, clinical, and cost factors for finding digital health solutions. The use of mobile applications (Apps) to manage medications among the patients was evaluated by a recent study [40]. The pharmaceutical drugs recommended to the patients as medicine require careful monitoring with respect to the regularity, side effects, and clinical outcomes among the patients. This app was evaluated for its efficacy to empower the patients with a chance to influence the clinical outcome. The patients take the help of the mobile app to incorporate the medicine in their daily routine, assess its side effects and benefits.

Advancements in information and communication technologies have improved the accessibility, cost-effectiveness, and quality of health care services as noted by a recent research report [41]. Digitalizing health care as suggested by the WHO includes the concepts of eHealth (using the electronic, communication, and information technologies in health care), telemedicine, and mHealth (using the mobile). The ICH S9 document guideline emphasizes the need to understand the disease being treated and the patient population involved, the pharmacologic, genotoxic, and carcinogenic potential of the drug substance/product, duration of the treatment, impact of the impurity reduction on the manufacturing costs, and the dose-comparison in clinical and non-clinical studies [42]. In multi-centric studies, it is important to harmonize the data capture and therefore a multi-technique approach was designed for retrieval, and to analyze the reasons for failure to record the missed results [43].

The application of information technology and the significance of EDC were recently evaluated by a study from the United Kingdom. This study had evaluated their use in both the clinical study and pharmacoepidemiology. It was noted that the EDC and the use of information technology improved the accuracy and are cost-effective [44]. Considering that the clinical trials are plagued with inadequate and poor-quality reporting, it is important to consider both internal and external validity during the planning and implementation stages [45]. As evidenced from the available research studies it is imperative that the clinical research is costly and involves phases and is a lengthy process. Assessing the integrity of the clinical data, its reliability, and monitoring a clinical trial appears a huge task. A recent study had proposed an improved system called the blockchain-based system to make the clinical research results more trustworthy [46]. Blockchain technology is advanced software that ensures security and unfalsifiable transaction history, which is used on the internet and banking systems [47].

13. Conclusion

Clinical research has been in huge demand courtesy of the current Coronavirus disease (COVID-19) pandemic caused by the novel Severe Acute respiratory distress Syndrome Coronavirus (SARS-CoV-2) that resulted in huge morbidity and mortality throughout the world. Traditionally, clinical studies are conducted for a lengthy period that was previously noted to take decades for the discovery and manufacture of novel drugs and devices. However, the large-scale mortality and the hitherto unknown virus as experienced through the discovery of SARS-CoV-2 have been instrumental in fast-tracking clinical research and enabling the development of vaccines against the virus. This was possible with the improved infrastructure and the availability of advanced technology. Among the components of clinical research, clinical research data management is a significant element that allows the manufacturers to collect, analyze, and submit the clinical data derived from research to successfully get approval from the regulatory authorities to market pharmaceutical drugs, vaccines, and devices.

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