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Unit-IV

Clinical Trials

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UNIT – IV

Clinical Trials

Introduction to Clinical Trials

Clinical Study

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies:

- Clinical trials (also called interventional studies)
- Observational studies

Clinical Trials

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices, procedures, or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention.

Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases.

Clinical trials used in drug development are sometimes described by phase. These phases are defined by the Food and Drug Administration (FDA).

Observational Studies

In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.

Reasons for Conducting Clinical Studies

In general, clinical studies are designed to add to medical knowledge related to the treatment, diagnosis, and prevention of diseases or conditions. Some common reasons for conducting clinical studies include:

- Evaluating one or more interventions (for example, drugs, medical devices, approaches to surgery or radiation therapy) for treating a disease, syndrome, or condition

- Finding ways to prevent the initial development or recurrence of a disease or condition. These can include medicines, vaccines, or lifestyle changes, among other approaches.
- Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition
- Examining methods for identifying a condition or the risk factors for that condition
- Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness

Ethical principles of clinical trials

Ethical clinical research is guided by the principles of Nonmalificence, respect, beneficence and justice.

- Nonmalificence is the duty to cause no harm. This principle has its roots in the Hippocratic Oath. The ethical issue at the core of clinical research is whether the outcome of the research can be reasonably expected to provide benefit to society without doing any harm to the individuals enrolled in the trial.
- Respect for persons is embodied in informed consent, dictating that information is exhaustive and provided in a manner that is understandable, that the subject's cooperation is voluntary, and that all information pertaining to the subject is held in confidence.
- Beneficence is demonstrated by a thorough risk/benefit assessment, recognizing that benefits can be direct, collateral, and/or altruistic. Similarly, risks are considered in physiologic, psychological, and socioeconomic terms. For a clinical trial to be considered ethical, there must exist a sufficient body of scientific/medical evidence to justify exposure of individuals to the risks of the trial. There must be clear medical need, and the potential benefits to be gained by the research must be weighed against the possible risks to the participating person in both safety and effectiveness of the drug or intervention being studied.
- The principle of justice takes into account all the processes by which populations are selected for study to ensure that the results benefit the community, avoid exploiting vulnerable populations, and include individuals who may be likely to benefit.

Bias and Random Error in Clinical Studies

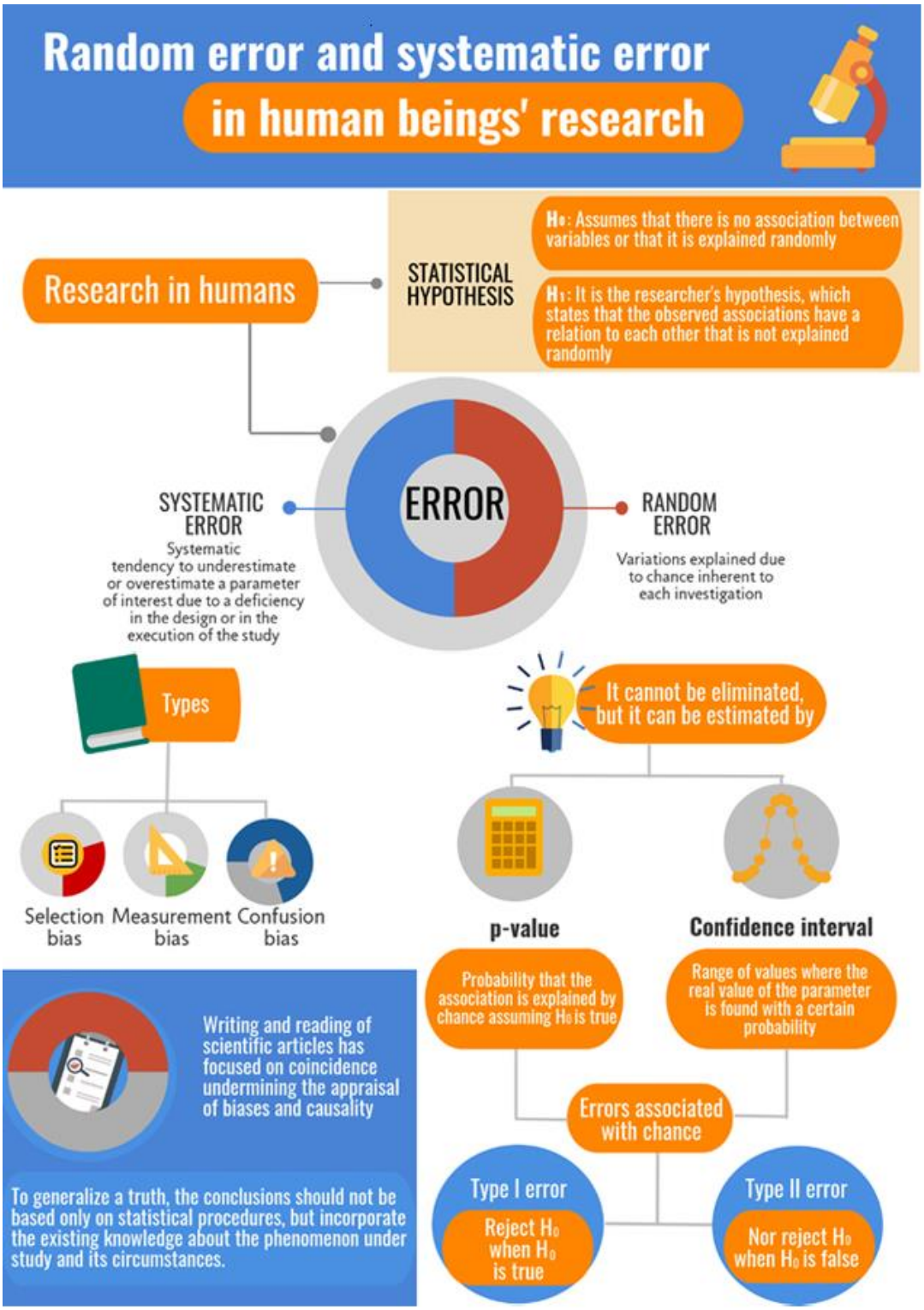
Systematic error (bias)

Systematic error or bias can be understood as the systematic tendency to underestimate or overestimate the estimator of interest because of a deficiency in the design or execution of a study. This bias undermines the study's validity (internal or the degree of agreement between the study results and the true value of the population parameter, and external or the degree to which the results for one study sample can be extrapolated to other populations). Biases can be associated with any phase of a research study but tend to skew the results in the same direction

Random error (chance)

Random error is associated with variations resulting from chance that are inherent in all research and cannot be eliminated; this type of error can therefore influence results, even when biases have been properly controlled, and compromise the reliability of the investigation. Three main factors are associated with random error in study results: the degree of individual and inter-individual variability, the sample size, and the magnitude of the differences (with the likelihood of it being caused by chance falling as the difference found in the comparison increases).

Diagram of random error and systematic error



Phases of Clinical Trials

Clinical trials are categorized as Phase I to IV trials. They are generally described as follows:

Phase 0 (Preclinical animal studies)

Phase I (small number of participants, normally between 6-10 healthy volunteers, or very sick patients for whom treatment options are lacking)

Phase I studies are designed to allow scientists and medical doctors to understand what effects an investigational compound has in human subjects. The goal is to study what happens to the compound in the body from a safety and tolerability point of view after it is swallowed, injected or infused. .Study participants are monitored for the occurrence and severity of any side effects that they may experience.

Phase II (once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups of patients, generally 20-300 depending on the type of disease)

Phase II studies are designed to begin to evaluate the safety and efficacy of an investigational medicine in patients, and often used to determine if different dosages of the treatment have different effects. The patients are given various doses of the compound and closely monitored to compare the effects and to determine the safest and most effective dosing regimen. In many instances, multiple Phase II studies are conducted to test the compound in a variety of patient populations or indications.

Phase III (carried out on large patient groups, 300–3,000 or more depending upon the disease being studied)

Phase III studies are designed to confirm the safety and efficacy of an investigational medicine. Large numbers of patients are generally involved in order to adequately confirm benefit and safety. These studies, as in the earlier phases, may involve one or more 'treatment arms', which allow for the safety and efficacy of the new investigational drug to be compared to other available treatments, or to be tested in combination with other therapies. Information obtained from Phase III studies is used to determine how the compound is best prescribed to patients in the future.

Phase IV (also known as Post-Marketing Surveillance Trials)

Phase IV studies take place after the medicine has received regulatory approval (market authorization) and are designed to provide broader efficacy and safety information about the new medicine in large numbers of patients, subpopulations of patients, and to compare and/or combine it with other available treatments. These studies are designed to evaluate the long-term effects of the drug. Under these circumstances, less common adverse events may be detected.

Randomization and blinding

- **Randomization:** A process based on allocation of subjects to treatment groups by chance, aiming at removing the potential bias in treatment assignment whether conscious or subconscious. This will greatly enhance the validity of the trial.

- **Blinding** is when the investigator and/or the study subject do not know which subject is taking which treatment. The investigator, the participant, and sometimes even the evaluator are all kept unaware (blinded) of the outcomes of the trial.

    1. **Single-blinded study:** either the investigator or the subject tested is blinded to the intervention allocation.

    2. **Double-blinded study:** both the investigator and the subject tested are unaware about of the intervention allocation.

    3. **Triple-blinded study:** even the evaluator is also not aware of the process.

Single Centre Trials

Single centre trials are usually set up in a particular hospital, clinic or general practice. They are usually small-scale studies, cheaper to conduct than multicentre trials and therefore generally easier to obtain funding for. Single centre trials provide the flexibility of approach necessary for clinicians and scientists to develop new treatments and can provide an important source for new therapeutic ideas. In a single centre trial the clinical investigators are often continuously involved and maintain enthusiasm throughout.

Many single centre trials often recruit too few patients to be scientifically viable. A trial with only a small number of participants carries a considerable risk of failing to demonstrate a treatment difference when one is really present i.e. type II error. Often a single source of participants may be insufficient to make a clinical trial of viable size. This problem may be clear-cut from the beginning but on other occasions it may linger on with too few participants and finally peter out as enthusiasm wanes. Thus, it is important to recognize early on whether a single centre trial is feasible and scrutinize the ethics, organization and relevance of it carefully.

Multicentre trials

Multicentre trials are carried out for two main reasons. Firstly, a multicentre trial is an accepted way of evaluating a new technology more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time frame. Multicentre trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centres with a large number of subjects per centre or, in the case of a rare disease, they may have a large number of centres with very few subjects per centre.

Secondly, a trial may be designed as a multicentre (and multi-investigator) trial primarily to provide a better basis for the subsequent generalisation of its findings. This arises from the possibility of recruiting the subjects from a wider population and of delivering the technology in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. The involvement of a number of investigators also gives the potential for a wider range of clinical judgements concerning the value of the technology. Such a trial would be a confirmatory trial in the later phases of technology development and would be likely to involve a large number of investigators and centres. It might sometimes be conducted in a number of different countries in order to facilitate generalisability even further.

Multi-centre trials are considerably more complex (e.g. co-ordination, quality control, data management) than single center trials and therefore it is essential to have efficient central co-ordination of all trial activities. They are also very expensive to run both in terms of personnel and resources and therefore require adequate funding from the onset. If a multicentre trial is to be meaningfully interpreted and extrapolated, then the manner in which the protocol is implemented should be clear and similar at all centres. Furthermore, the usual sample size and power calculations depend upon the assumption that the differences between the compared treatments in the centres are unbiased estimates of the same quantity.

Data Management

Data

Data is information such as facts and numbers used to analyze something or make decisions. Computer *data* is information in a form that can be processed by a computer.

Aspects of Clinical Data Management

The five aspects of Clinical Data Management (CDM) are

1. Key team members
2. Standard Operating Procedures (SOP) in Data Management
3. Clinical Data Management (CDM) process
    - Data Validation Plan (DVP)
    - Discrepancy Management (DM)
4. Medical Coding
5. Quality
    - QA (Quality Assurance)
    - QC (Quality Control)

Along with these above aspects, some others include

1.Electronic Data Capture (EDC)

2.Locking

3.Data Entry

Key team members and their responsibilities for data management in clinical trials

In order to achieve efficient data management, you need to have the following key members as below to drive each function systematically.

- Data Manager
- Database Administrator

- Developer/Programmer (Database)
- Clinical Data Associate
- Quality Assurance Associate
- Medical Coding Associate

Data Manager

- A data manager is a person who is responsible for administering the whole CDM process and preparing the Data Management Platform (DMP).
- He also performs the approval of CDM procedures and all internal documents for data management.

Database Administrator

- The database administrator is the one who works upon the software databases in order to find ways to store, manage, organize, troubleshoot, keep databases up to date, and manage clinical trial data.

Database Developer/Programmer

- The database developer/programmer is the one who performs the Case Report Form (CRF) annotation, creates the study database, and programs the edit checks for data validation.
- He is also responsible for designing the data entry screens in the database and validate the edit checks with dummy data.

Clinical Data Associate

- The Clinical Data Associate (CDA) or Clinical Data Coordinator (CDC) designs the Case-Report Form (CRF), prepares instructions for CRF filling, develops the Data Validation Plan (DVP), and also manages the discrepancy.
- The CDA also prepares the CDM-related documents, checklists, and guideline documents.

Quality Assurance Associate

- The quality control associate checks the accuracy of data entry and conducts data audits. However, sometimes, there is a separate quality assurance person to conduct an audit on the entered data.
- Additionally, the quality control associate verifies the procedure documents that need to follow.
- The data entry personnel will track the receipt of CRF pages and performs data entry into the database.

Medical Coding Associate

- The medical coder assigns codes to diagnoses and procedures using ICD (International Classification of Diseases), CPT (Current Procedural Terminology) codes, or other similar platforms.
- The medical coder will do coding for adverse events, medical history, co-illnesses, and concomitant medication administered during the study in data management.

Standard Operating Procedures (SOP) for data management in clinical trials

- Standard Operating Procedures (SOPs) are uniformly written procedures, which contain instructions to record routine operations, processes, and practices that one need to follow in a clinical trial.
- These SOPs play an integral part in clinical research and help to handle the standard practices and daily processes to execute the research tasks concerning institutional, federal, and state guidelines.
- The SOPs should contain adequate detail to guide the research staff through a particular procedure, and thereby it helps to establish uniformity in the everyday functions of the department. Each SOP will have a specific aim.

The key elements of an SOP include

- The objectives of the SOP,
- Definitions of significant terms and acronyms,
- Defines the list of responsible individuals and
- Details that outline the procedures with attachments of examples wherever applicable or necessary.

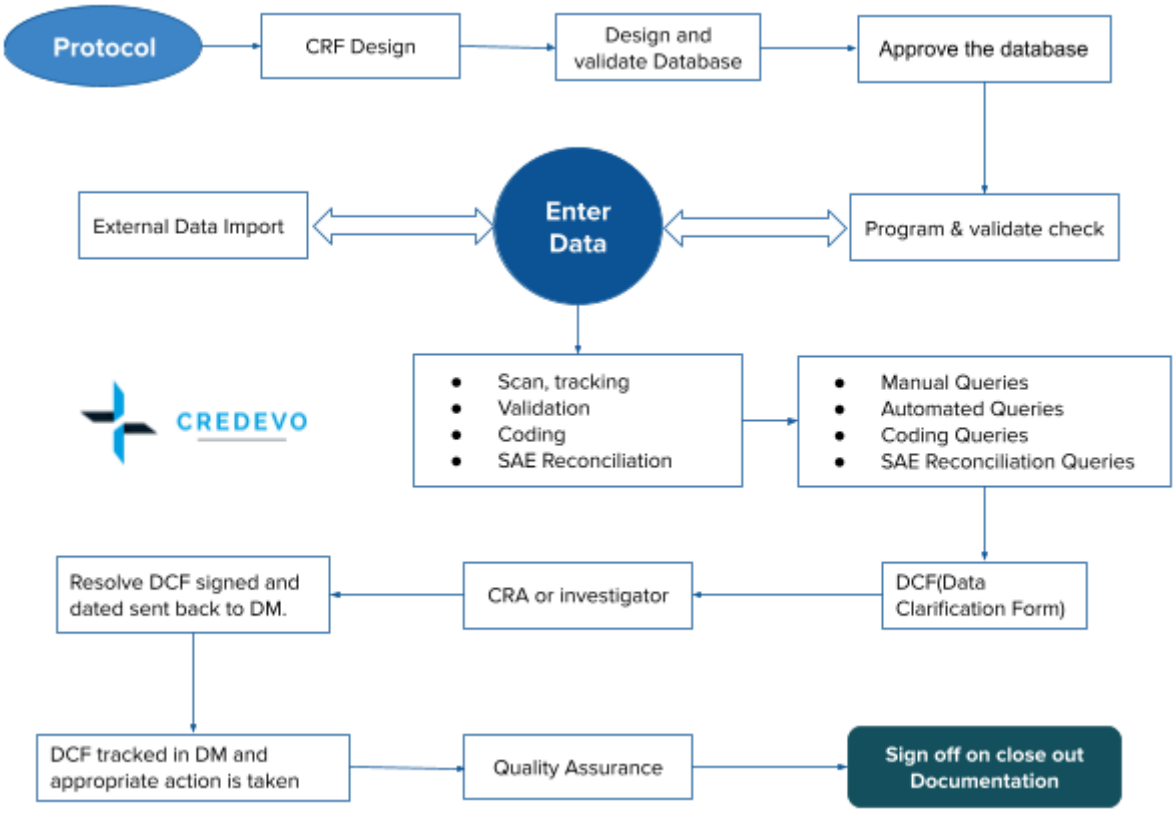
The common type of SOPs in clinical trials include

- Form Design (Paper-based CRF)
- Database Design (Paper-based CRF)
- Form and Database Testing
- Data Validation Plan
- Writing CRF Completion Guidelines
- Double Data Entry Application Development
- CRF/DCF Tracking
- Double Data Entry Application
- Entry and verification of data

- Data Validation and Cleaning
- Data Management Report
- Backup Schedules and Policies
- Disaster Recovery Plan
- Database Lock & unlock
- Project Change Request
- Archiving

Process for data management in clinical trials

- The clinical data management process generally starts with a plan to create a protocol, approve and sign the relevant document.
- Now moving forward with the next step, design/development is the second and most crucial step, as it incorporates setup of the database, form design, edit checks, validation, etc.
- Then comes the next step, the data management, and review. This step involves analysis, statistical planning, programming, and medical writing.
- The final step of CDM consists of filing, submission coordination, QA, review, and create a submission for the regulatory authority.



Data validation

- If the data from clinical trials is entered wrongly into the system, it creates a big downstream while reporting. And, the unstructured data, even if entered correctly, will incur costs to clean, transform, and store.
- Therefore, it is necessary to ensure that the data which enters the system is correct and meets the desired quality standards. Hence, to avoid such data inconsistencies, data validation becomes necessary.
- Data validation refers to the process which ensures the accuracy and quality of data. It is implemented by building several checks into a system or report to ensure the logical consistency of input and stored data.

Discrepancy management

Discrepancy management (DM) is also known as query resolution. DM is the process that systematically addresses discrepancies generated within a study.

The DM includes

- Review discrepancies,
- Investigate the reason, and
- Resolve them with documentary proof or declare them as unresolvable.

DM helps to clean the data and gather enough evidence for the deviations seen in the data. All Clinical Data Management Systems (CDMS) will have a discrepancy database in order to record and store all the discrepancies with an audit trail.

Medical coding

- Medical coding is somewhat like translation. Here the coders obtain medical reports from clinical investigators, which may include patient condition, the doctor's diagnosis, a prescription, and whatever procedures the doctor or clinical investigators perform on the patient, and turn that into a set of codes, which make up a crucial part of the clinical trial.
- Coding helps classify reported medical terms on the Case Report Form to standard dictionary terms in order to achieve data consistency and avoid unnecessary duplication in clinical trials.
- For the classification of events, coders generally use medical dictionaries available online. Coders use Medical Dictionary for Regulatory Activities (MedDRA) for the coding of adverse events as well as other illnesses, and World Health Organization-Drug Dictionary Enhanced (WHO-DDE) for coding the medications.

Quality in clinical data management

One can maintain the quality of clinical trial data through inspection, evaluation, and standardization by using various tools and processes. The two crucial steps to manage data quality are quality assurance and quality control, known usually as QA and QC.

Quality Assurance

- Quality Assurance in data management is a continual and dynamic practice process to prevent mistakes and defects while creating data. It helps to ensure that the clinical research conducted and data generated complies with the regulatory standards.
- QA is a crucial activity required throughout the clinical research process to ensure the high quality and integrity of data. The QA process starts with examining the patient requirements and is involved in every step until the final performance qualification wherein the test results are compared to the user requirements.

The QA applies for following aspects

1. Generation, record, analysis, and reporting of the clinical data follow the protocol, Standard Operating Procedures (SOPs) and Good Clinical Practices (GCPs).
2. Identify and correct data processing errors, and provide feedback to data managers and research staff during and after completion of a study.
3. Report any special data processing situations or deviations from coding conventions.
4. Inspection of the tasks, task-execution by clinical researchers, and documents of the clinical research.
5. Determine conformity of the actual conditions with the specified requirements.
6. Ensure the protection of rights and safety of the trial subjects.
7. Examine the resultant clinical data for its correctness.
8. Determine whether the operations performed are compliant with the federal and state environmental protection laws and regulations.

Quality Assurance in CDM has numerous benefits and a few of them include

- Improves reliability of results
- Enhance accuracy and consistency through audits
- Identifies and troubleshoots the ambiguities
- Adherence to compliance

Activities in QA involves

- Computer System Validation (CSV): Computer systems validation examines all aspects of the data handling of computer systems (hardware and software) to ensure the accuracy, reliability, consistent performance, and the ability to discern invalid or altered records.
- The validation process begins with the system proposal and continues until system retirement and e-records retention based on regulatory rules.

The validation process includes the following

1. Validation planning
2. User specification
3. Detailed design & timelines
4. Configuration & coding
5. Reporting release
6. OQ – Operational Qualification
7. IQ – Intelligence Qualification

Quality Control

In clinical research, the quality control process assures internal consistency through periodic operational checks at every stage of the trial process and data handling to verify the compliance of the trial process and reliability of the data.

Data Management Plan (DMP)

The Data Management Plan is a written document, and it contains the details of the plans for the collection and management of data throughout the clinical trial lifecycle.

For productive data management, planning must begin at the time of trial design. The Data Management Plan is a part of quality control and process management in clinical trials.

- DMP should consider the collection and management of data during the trial, data sharing, and archiving at trial closure.
- The data manager ensures to carry out all tasks and procedures detailed in this plan.
- A DMP for a trial must be ready before the start of data collection. So that this will ensure that the data is in the correct format, organized, and annotated appropriately.
- A well-designed Data Management Plan will provide a road map to handle the data, establish processes to handle unforeseeable conditions, and assess potential risks.
- The ideal result is to provide a database that is accurate, reliable, secure, and ready for analysis.

Final validation of the data is carried out after entering all data into the data management plan, and this is to ensure the validity and reliability of the data.

Here are few recommendations to develop a DMP

- A draft of DMP must be available before the enrolment of the first trial participant.
- The DMP must be written in compliance with applicable regulatory requirements, oversight committees and relevant Standard Operating Procedures (SOP).

- DMP must clearly identify the roles and responsibilities of the data management group/team.
- Data management processes must be clearly defined from trial initiation to database lock.
- Data archiving and data sharing should also be documented in the DMP.

Some other aspects of clinical data management are

Electronic Data Capture

Electronic Data Capture (EDC) is a computerized system designed to collect clinical data in electronic format. EDC replaces the traditional paper-based data collection method to streamline data collection and expedite the time to market for drugs and medical devices.

The EDC system provides

- A GUI (graphical user interface) component for data entry.
- Validation component to check user data.
- Helps as a reporting tool for collected data analysis.
- Can increase data accuracy and decrease the time to collect data for studies of drug and medical devices.

Locking

- The database lock system is a complete process, but a necessary industry standard. The locking function secures the data and ensures its quality by preventing further editing prior to submission to FDA.
- After the final quality check and data validation, the formatting process leads to a delay after the lock. The EDC support partner that helps ensure data maintenance and validation throughout the study changes the outcome of database lock.
- The goal is to limit the changes made to data and keep the database clean.
- After obtaining the approval for locking from all stakeholders, the database is locked to extract the clean data for statistical analysis. Generally, modification in the database at this stage is not possible. But in case of a critical issue or other crucial operational reasons, privileged users can modify the data even after the database is locked.

Data Entry

- Data entry refers to various modes of entering information into a computer for further processing. It may be the direct computer entry that can be by a person transferring data from paper-based CRFs into a computer database.
- Understanding all these important aspects of data management in a clinical trial, you need to identify an efficient clinical data management platform.