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A Review of Essential Documents in Clinical Research

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ABSTRACT

A clinical research study is any investigation that includes clinical trials, which entail the prospective assignment of individuals or groups of individuals to one or more health-related interventions in order to assess the effects on health outcomes. The process of developing new drugs must include clinical trials. To ensure that the trial data was authentically collected and the results of the data were verified, conducting a clinical trial necessitates the preparation and maintenance of a wide range of critical documentation. The current article aims to get an overview of the clinical trial process and various types of documentation. This clinical trial documentation helps to guarantee that it is carried out rigorously, ethically, in accordance with legal standards, and in a way that demonstrates the effectiveness and safety of novel therapies. The fundamentals of clinical research, clinical trials, and the crucial paperwork needed to carry out clinical trials will all be covered in this article. The Informed Consent Form (ICF), Case Report Form (CRF), study monitoring plan, and clinical study report are among the crucial documents. These papers should be gathered, arranged, and preserved in a regulatory binder that is kept during the trial. Modern medications for the treatment of diseases must be developed using the most up-to-date diagnostic techniques, which can only be found through clinical research.

INTRODUCTION

Clinical research is the key to the discovery of the latest diagnostic methods and the development of modern drugs for the treatment of diseases. [1] Clinical trials are an essential part of the drug development process. Conducting a clinical trial requires the production and maintenance of a wide range of essential documents to ensure the authenticity of the trial data collected and verify the results of the data. Documentation in clinical trials also ensures that the trial is conducted in a rigorous and ethical manner, meets regulatory requirements, and provides evidence of the safety and efficacy of new treatments. In this review, we will discuss the basics of clinical research, clinical trials, and the essential documents required for the conduct of clinical trials. **[2]**

Definition: Clinical Research

Clinical research is a branch of healthcare science that determines the safety and efficacy of medications, devices, diagnostic products, and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis, or relieving the symptoms of a disease. It involves the study of health and illness in people. The goal of clinical research is to develop knowledge that improves human health. [3]

Reasons for Conducting Clinical Research

Clinical research is undertaken to collect data on usual and unusual events, conditions, and population groups to allow us to

- Observe treatment and health management practices.
- Test interventions to develop new drugs and vaccines and to find new uses for existing therapies.
- Specific disease management, treatment, and prevention
- Evaluating ways in which genetics are related to diseases. [4]

Clinical Trials: Definition

- A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate their effects on health outcomes.
- It may also be referred to as an interventional trial.
- Interventions include, but are not limited to, drugs, cells, and other biological products; surgical procedures; radiologic procedures; devices; behavioral treatments; process of care changes; prevention care; etc. [6]

Purpose of Clinical Trials

Clinical trials can be used to study, determine, and establish many things, including:

- New drugs are not yet approved by the regulatory agency. (U.S. FDA in the USA, CDSCO in India).
- New uses of drugs that are already approved by the regulatory agencies.
- New forms to administer drugs. (Pill form)
- Use of alternative medicines. (herbs and vitamins)
- New tests to find and track diseases.
- Drugs or procedures that relieve symptoms
- A new drug or device is safe and effective for people to use. [6]

Phases of the clinical trial

Phase 0

- **Pre-phase 1 trial, also known as a proof of concept trial**
- **Study participants:** 10 to 15 healthy volunteers
- **Length of study:** less than 7 days

- **Purpose of study:** pharmacokinetics, particularly oral bioavailability and half-life of drugs.
- **Dose:** A very small dose or a level below the therapeutic level
- **Patient monitor:** clinical investigator [7]

Phase 1

- **Name:** First in human studies
- **Study participants:** 20 to 100 healthy volunteers or people with the disease or condition.
- **Length of study:** several months
- **Purpose of study:** safety and dosage
- **Dose:** Sub-therapeutic but with ascending doses
- **Patient monitor:** clinical investigator [7]

Phase 2

- **Name:** Therapeutic exploratory trials
- **Study participants:** 100 to 300 people with disease
- **Length of study:** several months to 2 years
- **Purpose of study:** efficacy and side effects
- **Dose:** Therapeutic dose
- **Patient monitor:** clinical investigator [7]

Phase 3

- **Name:** Therapeutic confirmatory, comparative efficacy, or pivotal trial
- **Study participants:** 300 to 3000 people with disease
- **Length of study:** 1 to 4 years
- **Purpose of study: safety** and efficacy

- **Dose:** Therapeutic dose
- **Patient monitor:** clinical investigator and clinical physician [7]

Phase 4

- **Name:** Post-marketing surveillance
- **Study participants:** Several thousand people with the disease
- **Purpose of study:** safety, efficacy, later side effects, and other uses of that drug.
- **Dose:** Therapeutic dose
- **Patient monitor:** clinical physician [7]

DOCUMENTATION IN CLINICAL RESEARCH

All records, in any form, including written, electronic, magnetic, and optical records, scans, x-rays, and electrocardiograms, that describe or record the methods, conduct, and results of a trial, the factors affecting a trial, and the actions taken Such a record are known as a "document," and the process is known as "documentation." Trial documents are both a resource and an outcome. They are the outcome of the study and a resource for the regulators. Documentation plays a vital role in clinical research. It validates how authentic the research data was collected and verifies the result of the data. [8]

Purpose of Documentation in Clinical Research

Documentation in clinical research is important for:

- Evaluation of the conduct of a trial and the quality of the data produced
- Successful management of the trial by the investigator, sponsor, and monitor
- Validation by regulatory authorities and sponsors' audits
- Reconstruct the trial as it happened.
- It should enable an independent observer to reconfirm the data.
- It is the tool that confirms the eligibility criteria of the subject in the given trial.

- It documents the progress of the subject from consenting until the subject completes the study.
- It records the accountability of the investigational product dispensed, consumed, and returned by the subject.
- It serves as the complete medical record of the subject and a reference to the treating physician at any point in time. [8]

Good Documentation Practice in Clinical Research

The Department of Medicine Clinical Research Unit has prepared this document to provide guidance to all faculty and staff involved in the conduct of research on the best practices related to documentation.

Good study documentation will allow an individual with basic knowledge of the particular project to recreate the events of the study. Key attributes for good documentation were first described by the US FDA in the form of ALCOA: Attributable, Legitimate, Contemporaneous, Original, and Accurate. These are also adapted by the World Health Organisation (WHO). These criteria evolved with time.

- Attributable: obvious who created a document and when
- Legislative: The records should be easily read.
- Contemporaneous: results recorded as they are observed; signatures attached to a date when it occurred.
- Original: The study record should be original. Not a photocopy.
- Accurate: high level of honesty and accuracy in reporting. double-checked for accuracy.[9]

TRIAL MASTER FILE

The Trial Master File (TMF) contains those essential documents that individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced. A trial master file (TMF) is a compilation of documents that prove that the clinical trial has been conducted following regulatory requirements (including good clinical practice).

Guideline E6 states that a trial master file should be established at the beginning of the trial, both at the investigator's or institution's site and at the sponsor's office. The TMF needs to be maintained throughout the trial, with some documents being prepared before the trial, some during the trial, and others after the trial has been completed. The documents included in the TMF should confirm compliance with the clinical trial protocol, good clinical practice, and the integrity of the data collected without any additional explanation from the sponsor, investigator, or institution. The TMF should be available and accessible upon request. There needs to be one TMF for each clinical trial. There are two types of trial master files available.

- Sponsor trial master file.
- Investigator trial master file or investigator site file.

The ICH Guideline for Good Clinical Practice Section 8 outlines the documents that are considered 'essential' and the other documents that need to be filed in the TMF. [10]

ESSENTIAL DOCUMENTS

Essential documents are those documents that, individually and collectively, permit evaluation of the conduct of a trial and the quality of the data produced. Collectively, these documents are known as the "Regulatory Binders". These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of good clinical practice and all applicable regulatory requirements.

Trial master files should be established at the beginning of the trial, both at the investigator's or institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both the investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. The minimum list of essential documents that have been developed follows: [11]

INVESTIGATOR'S BROCHURE

- The investigator brochure is a collection of clinical and non-clinical data on the investigational product that is relevant to the study of the product in human subjects.

- IB is a comprehensive document summarising the information about the investigational product obtained during a clinical trial.
- The information should be presented in a short, simple, and objective way.
- IB is prepared by the sponsor, who also controls the distribution of the document.
- The sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator, and investigators are responsible for providing the up-to-date IB to the responsible IRB or IEC. [2] [8]

Purpose of the Investigator Brochure

- To provide information to investigators and others involved in the trial, such as the dose, dose frequency, methods of administration, and safety monitoring procedures.
- The IB also provides insight to support the study's subjects in clinical management during the course of the clinical trial.
- For the assessment of an appropriate proposed clinical trial, a medically qualified person should participate in the editing of IB. [2] [8][11]. A statement that reminds investigators and other recipients to treat the investigator's brochure as a confidential document and an important resource for the investigator's team, the Institutional Review Boards (IRBs), and the Independent Ethics Committee (IEC). [2]

INFORMED CONSENT FORM

- A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.
- Informed consent is documented by means of a written, signed, and dated informed consent form.
- It must be obtained prior to any study procedure being performed.
- Informed consent is a communication process between a researcher and a participant.
- It is a basic right. [2] [8]

Elements in the Informed Consent Form

- Protocol number or name of the study
- Purpose of the study.
- Duration of the study and subject involvement
- A statement that the protocol and informed consent were reviewed with the participant, including the risks and benefits of the study.
- Alternative treatment options were discussed.
- Confidentiality record
- Number of subjects
- Compensation for injury
- Time for questions to be asked and answered
- Description of the participant's decision
- Contact details
- Subject responsibilities
- Subject satisfaction
- Use understandable language.
- A copy of consent was given to the participant.
- Sign a copy of the informed consent form. [2][8]

CASE REPORT FORM

- The case report form is one of the essential documents, which are documents that individually and collectively permit evaluation of the conduct and quality of the trial. E.g., CRF, Protocol, IB, and ICF.

- CRF extracts the most important data from the source documents for data entry or analysis. Source documents are original documents, data, and records. E.g., hospital records, X-rays, subject diaries, laboratory notes, and ECG.
- Generally supplied by the sponsor.
- Captures all data specified in the protocol.
- It is prepared by a team including an investigator, data manager, clinical investigation site staff, medical person, barcode readers, and a specialty role related to a particular organ or disease, i.e., the consulting team.
- It is reviewed by the project clinician, lead CRA, lead statistician, lead programmer, and lead data manager.
- It is approved by CRO, Sponsor, IRB, or IEC, and FDA. [12]

Purpose of the Case Report Form

- Capturing all protocol-required information
- Facilitates the data collection and entry
- Benefits of data management
- Benefits of statistical analysis
- Simplifies database design and data validation processes as well as manipulation of data during statistical analysis. [12]

ELEMENTS OF CASE REPORT FORM

➢ Header

- Center number
- Study number
- Participant number
- Visit date

- Footer
- Safety modules
- Efficacy modules

It includes

- Screening status
- Lab specimen tracking forms
- Inclusion criteria
- Exclusion criteria
- Enrollment physical examination
- Enrollment History
- Enrollment laboratory
- Daily assessment
- Daily laboratory report
- Clinical failure
- Study drug status
- Death
- Adverse vents
- Concomitant medications
- Final status[12]

STUDY MONITORING PLAN

- A study monitoring plan in a clinical trial is a document that outlines the procedures for monitoring the conduct of the trial to ensure that it is being conducted in compliance with the

study protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. [2] [8]

Purpose of the Study Monitoring Plan

- The purpose of a study monitoring plan is to ensure the safety of the study participants and the quality of the data generated by the study.
- A well-designed study monitoring plan is essential for ensuring that a clinical trial is conducted in compliance with all applicable regulations and guidelines and that the safety and well-being of the study participants are protected.
- Regular monitoring of the study can help to identify and address any issues that may arise, and it can ensure that the data generated by the study is accurate and reliable. [2] [8] [11]

Elements of the Study Monitoring Plan

The Study Monitoring Plan typically includes the following components:

- Monitoring objectives: The objectives of the monitoring activities are outlined, which can include assessing the conduct of the study, identifying and addressing any issues that may arise, and ensuring the accuracy and completeness of the data.
- Monitoring activities: The specific monitoring activities that will be conducted are described, such as site visits, review of study documents, and data monitoring.
- Monitoring frequency: The frequency of the monitoring activities is determined based on the risk level of the study and the number of participants involved. High-risk studies with many participants may require more frequent monitoring activities.
- Monitoring responsibilities: The individuals responsible for conducting the monitoring activities are identified, including the sponsor, the study monitor, and the investigator.
- Data management: The procedures for data management and data monitoring are described, including the methods for verifying the accuracy and completeness of the data.
- Reporting: The reporting procedures for monitoring activities are outlined, including the requirements for reporting any issues or discrepancies that are identified during the monitoring process. [2]

CLINICAL STUDY REPORT

- A case report form is an integrated report of a clinical study of any therapeutic, prophylactic, or diagnostic agent in which clinical and statistical descriptions, presentations, and analyses are provided in a single report, incorporating tables and figures into the main text of the report and in appendices.

- It provides an explanation of how the critical design features of the study were chosen and information on the plan, methods, and conduct of the study.

- Includes efficacy and safety data.

- Represents the most complete synthesis of the planning, execution, and results of a clinical study. [13]

Purpose of the Clinical Study Report

- The main purpose of a CSR is to communicate the results of a clinical study with all regulatory authorities in the ICH region, such as Europe, the USA, Japan, and other similar regulatory agencies around the world.

- CSRs are the key means by which regulators can assess the outcomes of clinical studies. [13]

Elements of a Clinical Study Report

The format and content of a CSR are defined by ICH including Study objectives, Investigational plans, A detailed description of the study design, Selection of the study population (inclusion or exclusion criteria), Treatments, Efficacy and safety variables, Statistical methods, Study patients, Patient disposition, Protocol deviations, Efficacy and safety evaluations, Statistical or analytical methods, Tables, figures, and listings, Efficacy conclusions, Safety conclusions, Discussion and overall conclusions, Tables, figures, and listings referred to but not included in the text of the above sections, Reference list and Appendices.[13]

CONCLUSION

A clinical trial is compulsory for a drug or device to ensure its safety and efficacy in humans before its usage. Clinical trials can provide answers regarding the use or not of a therapeutic agent that can benefit millions of patients worldwide. A clinical trial requires the production and maintenance of a wide range of essential documents to ensure that the trial is conducted in a rigorous and ethical manner, meets regulatory requirements, and provides evidence of the safety and efficacy of new treatments. The essential documents include the investigator brochure, informed consent form, case report form, study monitoring plan, and clinical study report. These documents should be collected, organized, and maintained in a regulatory binder, which should be kept up-to-date throughout the trial. Compliance with these requirements ensures the integrity of the trial participants and contributes to the development of safe and effective new treatments. Let us conclude with a quote saying the importance of documentation as well as GCP: “Incorrect documentation is often worse than no documentation”.

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