ETHIOPIAN FOOD AND DRUG AUTHORITY

GUIDELINE FOR GOOD CLINICAL PRACTICE

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Document History

Version No.	Reason for amendment	Effective Date
001	New version	25/01/2010
002	To separate the CT authorization guideline and CT inspection to harmonize with international standards and practice	01/04/2018
003	To separately develop good clinical practice and good clinical practice inspection guidelines with alignment of the current legal document of EFDA and reflection of the current practice in the field of clinical trial	25/09/2024
004	To correct the approval and issue dates in alignment with the new EFDA Document Control SOP.	30/06/2025

Asnakech Alemu,

Pharmacovigilance and Clinical Trial Lead Executive Office

Signature

FORWORD

Good Clinical Practice is an international ethical and scientific standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. Clinical trials conducted in accordance with this standard will help to assure that the rights, safety and well-being of trial participants are protected and the clinical trial results are reliable. The compliance of all stakeholders to the principles of GCP should be ensured throughout the conduct of the clinical trials.

According to Proclamation No. 1112/2019, Article 4 and Sub-article 11, indicates that the authority has the mandate to authorize the conduct of clinical trial, monitor and inspect the process as to its conduct in accordance with good clinical practice. Similarly, as per Article 27 and sub article 7 states that "It shall be the responsibility of the primary investigator and sponsor of the clinical trial to ensure the safety of the participant, provide adequate information to prospective participants about the risks, medical benefits, and treatment alternatives available to the participant" which is the purpose of GCP compliance. The clinical trial directive also requires that all stakeholders including sponsor and investigators shall ensure the conduct of clinical trials as per the GCP principles and shall be handled by GCP trained staff. More specifically article 15, sub article 3 dictates clinical trials shall be conducted in compliance with good clinical practice principles.

I am confident that through steadfast governmental guidance, the dedication of the scientific community to adhere to principles of GCP, the strong resolve of our personnel for our people, and the backing of our collaborative allies, we will prevail to meet the implementation of the guideline.

I would like to extend my heartfelt gratitude to the U. S. Pharmacopeial Convention Promoting the Quality of Medicines Program (USP/PQM) for its invaluable financial and technical support. My sincere appreciation also goes out to all experts including clinical trial researchers and ethics committee members who have directly or indirectly contributed their expertise to the revision of this guideline. I invite all interested parties to continue showing their support by sharing their feedback and suggestions with the EFDA at P.O.Box 5681 Addis Ababa, Ethiopia, or by reaching out via telephone at 251-115524122 or email at contactefda@efda.gov.et.

HERAN GERBA, Director General, Ethiopian Food and Drug Authority

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ABBREVIATIONS AND ACRONYMS

AE	Adverse Events
CPP	Certificate of Pharmaceutical Product
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
EFDA	Ethiopian Food and Drug Authority
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethical committee
IRB	Institutional Review Board
NRA	National Regulatory Authority
NRERB	National Research Ethical Review Board
PQM	Promoting the Quality of Medicines Program
SOP	Standard Operation Procedure
SAE	Serious adverse event
USAID	United States Agency for International Development
USP	U. S. Pharmacopeial Convention
WHO	World Health Organization

DEFINITIONS

The following definitions are provided to facilitate interpretation of the Guideline; they apply only to the words and phrases used in this Guideline. Although every effort has been made to use standard definitions used by ICH, the words and phrases used in this Guideline may have different meanings in other contexts and other documents.

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Applicable Regulatory Requirement(s)

Any law (s) and regulation(s) addressing the conduct of clinical trials of investigational products

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements

Blinding/Masking

It is a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-

blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

A printed, optical or electronic document designed to record all the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and /or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. It also includes investigation in human participants with invasive diagnostic procedures. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance to trials

Adherence to all the trial–related requirements, Good Clinical Practice (GCP) requirements and the applicable regulatory requirements

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicenter trial

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original

Direct Access

Permission to examine, analyzes, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g. Domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data are credible and accurate, and that the rights, integrity and confidentiality of trial participants are protected. Any reference to GCP in this Guideline should be understood as a reference to the current WHO/ICH GCP guidelines.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

Independent data-monitoring committees may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

National Research Ethics Review Board (NRERB)

An independent body is established under the Ministry of Education (MoE) whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, the methods and materials to be used in obtaining and documenting informed consent of the trial subjects.

Informed Consent

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 through a written, signed, and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (ies).

Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinical trial at a right site and for the rights, health and welfare of the participants in the trial. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

The investigator should have qualifications and competence which could be evidenced by an up-to date curriculum vitae and other credentials. The medical/dental care and decisions must always be the responsibility of a clinically competent person legally allowed and registered to practice health care in Ethiopia.

Investigator's Brochure

A collection of data consisting of all the information known prior to the clinical trial concerning the clinical and non-clinical data on the investigational product(s). There should be adequate data to justify the nature, scale and duration of the proposed trial.

Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial

Multicenter Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical Study

Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities

Bodies having the power to regulate. In the guideline the expression of Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections and these bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reactions (Serious ADR)

Any untoward medical occurrence at any dose:

- Results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not

include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function

Sub investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

Participant /Trial participant

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control

Participant Identification Code A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site

The location(s) where trial-related activities are actually conducted

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, children, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial

1. INTRODUCTION

Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for designing, conducting, recording and reporting trials that involve human participant. Clinical trials conducted in accordance with this standard will help to assure that the rights, safety and well-being of trial participants are protected; that the conduct is consistent with the principles that have their origin in the Declaration of Helsinki; and that the clinical trial results are reliable.

According to article 4(11) of Food and Medicine Administration (Proclamation No. 1112/2019); The Ethiopian Food and Drug Authority is responsible to authorize the conduct of clinical trials, monitor and inspect the process as to its conduct in accordance with good clinical practice, evaluate the results and authorize the use of the result in such a way that benefits the public; and order the clinical trial to be suspended or stopped where necessary. Article 27 (sub-article 1- 11) of this proclamation also provides detail requirements for the clinical trial.

Similarly, article 5(16) of the definition of organization, power and duties of the Ethiopian Food and Drug Authority issued by the council of Ministers Regulation (No. 531/2023), the Authority shall have the powers and duties to evaluate clinical trial request and authorize; monitor and inspect to ensure the trial performed by the authorization and good clinical trial practice; evaluate and authorize the use of the result in such a way it benefits the public; when necessary, order at any time, the clinical trial to be suspended or terminated.

Furthermore, the essences of the above high-level legal statements are more clarified under the Clinical Trial Directive (Directive No. 964/2023) including clinical trial (CT) application; CT protocol review & Authorization; conduct & amendment of CT, independent ethical committee & CT team; monitoring & GCP inspection; and others.

Accordingly, clinical trial studies must undergo review by the Authority for use of the investigational product or intervention in human participants, to ensure that the study is appropriately designed to meet its stated objectives, according to all applicable laws and regulation and procedures of the country. The conduct of the trial is subject for inspection at initiation time, during the conduct and at the end of trial and based on different conditions at different times by the authority.

The purpose of this guideline is to provide with clearly articulated standards of good clinical practice in research that are also relevant to local realities and contexts and to ensure that clinical trials conducted on human participants are designed and conducted according to sound scientific and ethical standards within the framework of good clinical practice. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The guideline was developed with consideration of the current good clinical practices of the World Health Organization (WHO) and the International Council for Harmonization (ICH).

2. SCOPE

This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to EFDA. This guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorization applications in accordance with national laws and regulations requirements and Systems that need to be in place, and within these, the roles and responsibilities of various stakeholders (notably sponsors, investigators, ethics committees, and regulatory authorities) involved in the conduct of health and clinical trial studies are considered.

3. GUIDELINE STRUCTURE

This EFDA GCP Guideline is composed of principles and annexes that expand on the principles, with specific details for different types of clinical trials. The principles are intended to apply across clinical trial types and settings and to remain relevant as technological and methodological advances occur. The principles outlined in this guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial. This guideline should be read in conjunction with other EFDA guidelines relevant to the design and conduct of clinical trials.

4. PRINCIPLES OF GCP

Clinical trials are a fundamental part of clinical research that supports the development of new medicines or uses of existing medicines. Well-designed and conducted clinical trials help answer key questions in healthcare and drug development. Their results are essential for evidence-based

healthcare decisions. Trials with inadequate design and/or poorly conducted trials may place participant safety at risk and yield inadequate or unreliable evidence and are unethical. They waste resources and the efforts and time of investigators and participants.

The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials. This guideline encourages thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial. This includes evaluation of trial characteristics, such as the design elements, the investigational product being evaluated, the medical condition being addressed, the characteristics of the participants, the setting in which the clinical trial is being conducted, and the type of data being collected. Careful consideration of factors relevant to ensuring trial quality is needed for each clinical trial.

The principles are intended to support efficient approaches to trial design and conduct. For example, innovative digital health technologies, such as wearables and sensors, may expand the possible approaches to trial conduct. Such technologies can be incorporated into existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials. This will aid in keeping clinical trial conduct in line with advancing science and technological developments. The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design. This guideline is intended to be media neutral to enable the use of different technologies for the purposes of documentation.

The use of innovative clinical trial designs and technologies may help include diverse patient populations, as appropriate, and enable wider participation. The design of the trial, to ensure appropriate quality and meaningful trial outcomes, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers. Their input can increase the likelihood of meaningful trial outcomes, which are relevant to both trial participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participation in the trial does not become unduly burdensome for those involved.

Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results. Quality by design should be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results. Clinical trial processes

and risk mitigation strategies implemented to support the conduct of the trial should be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability. Trial designs should be operationally feasible and avoid unnecessary complexities.

The overarching principles provide a flexible framework for clinical trial conduct. They are structured to provide guidance throughout the life cycle of the clinical trial. These principles are applicable to trials involving human participants.

The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results.

4.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.

4. 1.1 The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.

4. 1.2 The safety of the participants should be reviewed periodically as new safety information becomes available, which could have an impact on the participant or the conduct of the trial.

4. 1.3 Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the known and anticipated risks.

4.1.4 When designing a clinical trial, the scientific goal and purpose should carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow for generalizing the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population.

4.1.5 A qualified physician or, when appropriate, a qualified dentist should have the overall responsibility for the trial-related medical care given to, and medical decisions made on behalf of, participants; however, the practical interactions and the delivery of medical care and

decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements.

4.1.6 The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection requirements.

4.2. Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed.

4.2.1 Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For potential participants unable to provide informed consent, their legally acceptable representative should provide consent prior to clinical trial participation.

4.2.2 The process and information provided should be designed to achieve the primary objective of enabling potential trial participants to evaluate the benefits and risks of participating in the trial and to make an informed decision on whether or not to participate in the trial. The information provided during the informed consent process should be clear and concise so as to be understandable by potential participants or legally acceptable representatives.

4.2.3 The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefit and risk of medical intervention(s), the setting and context in which the trial will be conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants (or their legally acceptable representatives) and obtain informed consent.

4. 3. Clinical trials should be subject to an independent review by an institutional review board/National Research Ethics Review Board (IRB/NRERB).

4.3.1 A trial should always be conducted in compliance with the protocol that receives prior IRB/NRERB approval/favorable opinion.

4.3.2 Periodic review of the trial by the IRB/NRERB should also be conducted in accordance with applicable regulatory requirements.

4.4. Clinical trials should be scientifically sound for their intended purpose and based on robust and current scientific knowledge and approaches.

4.4.1 The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.

4.4.2 Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s), including, if applicable, the condition to be treated, diagnosed or prevented; the current understanding of the underlying biological mechanism (of both the condition and the treatment); and the population for which the investigational product is intended.

4.4.3 There should be periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.

4.5. Clinical trials should be designed and conducted by qualified individuals.

4.5.1 Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and statisticians. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s).

4.6. Quality should be built into the scientific and operational design and conduct of clinical trials.

4.6.1 Quality of a clinical trial is considered in this guideline as fit for purpose. The quality and amount of the information generated during a clinical trial should support good decision making.

4.6.2 Factors critical to the quality of the trial should be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Quality by design involves focusing on the design of all components of the trial in order to maximize the likelihood of trial success (i.e., the trial will answer the research question).

4.6.3 Strategies should be implemented to avoid, detect and address serious non compliance with GCP, the trial protocol and applicable regulatory requirements to prevent recurrence.

4.7. Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected.

4.7.1 Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results.

4.7.2 The focus should be on the risks to participants beyond those associated with standard medical care. The risks relating to investigational products that have a marketing authorization

when used in the clinical trial context may differ from the routine care of patients and should be taken into consideration.

4.7.3 Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun.

4.8. Clinical trials should be described in a clear, concise and operationally feasible protocol.

4.8.1 A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results.

4.8.2 The scientific objectives of any trial should be clear and explicitly stated in the protocol.

4.8.3 The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data management plan, monitoring plan) should be clear, concise and operationally feasible.

4.9. Clinical trials should generate reliable and valid results.

4.9.1 The quality and amount of the information generated in a clinical trial should be sufficient to provide confidence in the trial's results and support good decision making.

4.9.2 Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data.

4.9.3 Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection. Trial processes should support the key trial objectives.

4.9.4 Computerized systems used in clinical trials should be fit for purpose, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes.

4.9.5 Clinical trials should incorporate efficient and well-controlled processes for managing records through appropriate management of data integrity, traceability and protection of personal information, thereby allowing the accurate reporting, interpretation and verification of the clinical trial-related information.

4.9.6 Clinical trial-related records should be retained securely by sponsors and investigators for the required period of time and should be available to regulatory authorities upon request to enable reconstruction of the trial conduct and results in order to ensure the reliability of trial results.

4.9.7 The transparency of clinical trials in drug development includes registration on publicly accessible and recognized databases and the public posting of clinical trial results.

4.10. Roles and responsibilities in clinical trials should be clear and documented appropriately.

4.10.1 The sponsor may transfer or the investigator may delegate some or all their tasks, duties or functions (hereafter referred to as activities), but they retain overall responsibility for their respective activities.

4.10.2 Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively.

4.10.3 The sponsor or investigator should maintain appropriate oversight or supervision of the aforementioned activities, respectively.

4.11. Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, handled and disposed of in accordance with the product specifications and the trial protocol.

4.11.1 Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP standards.

4.11.2 Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.

4.11.3 Investigational products should be used in accordance with the protocol and relevant trial documents.

4.11.4 Manufacturing, handling and labeling of investigational products should be undertaken in a manner that aligns with treatment assignment and maintains blinding, where applicable.

4.11.5 Investigational product labeling should follow applicable regulatory requirements.

4.11.6 Adequate measures to ensure that the investigational product is handled and shipped appropriately should be implemented.

4.12. Equitable Research Partnerships should be established by applying the Global Code of Conduct that opposes double standards in research and supports long-term equitable research relationships between partners in low-income and high-income settings based on fairness, respect, care, and honesty.

4.12.1. Local relevance of the clinical trial is essential and should be determined in collaboration with local partners. Clinical trial that is not relevant in the location where it is undertaken imposes burdens without benefits.

4.12.2 Local researchers should be included, wherever possible, throughout the trial process, including in study design, study implementation, data ownership, intellectual property and authorship of publications.

4.12.3 Any research that uses biological materials and associated information such as traditional knowledge or genetic sequence data should clarify to participants the potential monetary and non-monetary benefits that might arise. A culturally appropriate plan to share benefits should be agreed to by all relevant stakeholders, and reviewed regularly as the research evolves.

4.12.4 Double standards: A clinical trial that would be severely restricted or prohibited in a high-income setting should not be carried out in a lower-income setting. Exceptions might be permissible in the context of specific local conditions (e.g. diseases not prevalent in high-income countries).

5. STAKEHOLDER IN CLINICAL TRIAL

5.1. NATIONAL RESEARCH ETHICS REVIEW BOARD AND INSTITUTIONAL REVIEW BOARD (NRERB/ IRB)

5.1.1. The NRERB and IRB's objective is to protect the rights and welfare of human participants in biomedical and behavioral research. The IRB reviews and oversees human participant research to ensure that it meets the ethical principles cited in this guideline, national regulatory authority regulations, and that it complies with legal requirements and other pertinent regulations, guidance, and local laws.

5.1.2. The NRERB and IRB's duty is to inform and assist the investigators and advisors on ethical and procedural standards related to the use of human participants in research, to facilitate compliance with this guideline, Ethiopian law, and international regulations.

5.1.3. The NRERB has the authority to approve, require modification in, or disapprove all research activities. Regularly follow and terminate clinical trials that fall within its jurisdiction.

5.1.4. The NRERB and IRB have the responsibility to ensure that research studies conducted under its jurisdiction are designed and conducted in a manner that protects the rights, welfare and privacy of research participants.

5.1.5. The protocol should be submitted for comment, guidance, and where appropriate, approval to NRERB, which is independent of the investigator, the sponsor, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country

5.1.6. The principal focus of the NRERB/IRB is ethical review of the protocol. However, scientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects' and researchers' time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out or arrange for a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound.

5.1.7. Review by the NRERB/IRB also helps ensure that the research is evaluated by a party that is independent of the trial. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.

5.1.8. The applicants need to consider submission of their protocol to NRERB prior to national regulatory authority. The comments given and approval by the independent national ethics board is considered as prerequisite to review and get approval from national regulatory authority. For detail information and requirements needed, the national research ethics review guideline need to be followed, reviewed and considered by all applicants.

5.1.9. IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with country regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

5.1.10. The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

5.2 PRINCIPAL INVESTIGATOR (PI)

5.2.1. Principal Investigator's Qualifications and Agreements

5.2.1.1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the NRERB/IRB, and/or the Authority.

5.2.1.2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's brochure, in the product information and in other information sources provided by the sponsor.

5.2.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements

5.2.1.4. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority (ies).

5.2.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

5.2.2. Adequate Resources

5.2.2.1. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period.

5.2.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

5.2.2.3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

5.2.2.4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5.2.2.5. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

5.2.2.6. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or

party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

5.2.3. Medical Care of Trial participants

5.2.3.1 A qualified physician or appropriate health professional, who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

5.2.3.2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for inter current illness (es) of which the investigator becomes aware.

5.2.3.3. It is recommended that the investigator inform the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

5.2.3.4.Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

5.2.4. Communication with NRERB/ IRB

5.2.4.1. Submission to the NRERB/ IRB shall be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements.

5.2.4.2. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the NRERB/IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to participants.

5.2.4.3 As part of the investigator's/institution’s written application to the NRERB/IRB/ the investigator/institution should provide the NRERB/ IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator’s Brochure to the IRB/NRERB.

5.2.4.4. During the trial the investigator/institution should provide to the IRB/NRERB all documents subject to review.

5.2.5. Compliance with Protocol

5.2.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor which was given approval/favorable opinion by the NRERB/IRB and authorized by the Authority. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm the agreement.

5.2.5.2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the NRERB/IRB as an amendment, except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

5.2.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

5.2.5.4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants without prior regulatory authority approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a) To the IRB/NRERB for review and approval/favorable opinion,
b) To the sponsor for agreement and, if required,
c) To the Authority

5.2.6. Investigational Product(s)

5.2.6.1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

5.2.6.2. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution’s duties for investigational product(s) accountability at the trial site(s) to registered and GCP trained pharmacist or another appropriate health professional who is GCP trained.

5.2.6.3.The investigator/institution and/or a pharmacist or other appropriate GCP trained individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators

should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

5.2.6.4. The investigational product(s) should be stored as specified by the sponsor

5.2.6.5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

5.2.6.6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

5.2.7. Randomization Procedures and Un-blinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor and report to regulatory authority any premature un-blinding (e.g., accidental un-blinding, un-blinding due to a serious adverse event) of the investigational product(s).

5.2.8. Informed Consent of Trial participants

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form should be translated to local language. The informed consent process should include the following:

a) Prior to consenting and enrolling participants, the investigator should have the IRB/NRERB's documented approval/ favourable opinion of the informed consent materials and process;
b) The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity. This is to ensure that the trial participants or their legally acceptable representatives have an adequate understanding of the objectives of the trial, alternative treatments, the potential benefits and risks, burdens and their rights and obligations to be able to make an informed decision as to their participation in the trial;
c) Varied approaches (e.g., text, images, videos and other interactive methods) may be used in the informed consent process including for providing information to the participant.

5.2.8.1. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented.

5.2.8.2. New information that could impact a participant's willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB/NRERB's approval/favorable opinion in advance of use.

5.2.8.3. Neither the investigator, nor the trial staff, should coerce or unduly influence a participant to participate or to continue to participate in a trial.

5.2.8.4. None of the information provided to the participant during the informed consent process should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor or their service providers from liability for negligence.

5.2.8.5. The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves, the participant's legally acceptable representative should provide their consent on behalf of the participant.

5.2.8.6. The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.

5.2.8.7. Before informed consent may be obtained, the investigator or investigator site staff the participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented.

5.2.8.8 New information that could impact a participant's willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB/NRERB's approval/favourable opinion in advance of1 use.

5.2.8.9. Neither the investigator, nor the trial staff, should coerce or unduly influence a participant to participate or to continue to participate in a trial.

5.2.8.10. None of the information provided to the participant during the informed consent process should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor or their service providers from liability for negligence.

5.2.8.11. The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves, the participant's legally acceptable representative should provide their consent on behalf of the participant.

5.2.8.12. The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.

5.2.8.13. Before informed consent may be obtained, the investigator or investigator site staff the informed consent discussion and the informed consent materials to be provided to participants should explain the following as applicable:

5.2.8.14.Prior to participation, the participant or the participant's legally acceptable representative should receive a copy paper of the signed informed consent form and any other informed consent materials provided to the participants, or in accordance with applicable regulatory requirements. During trial participation, the participant or the participant's legally acceptable representative should receive a copy of the consent form updates and any other updated informed consent materials provided to participants.

(a) The purpose of the trial;

(b) That the trial involves research and summary of the experimental aspects of the trial;

(c) The trial's investigational product(s) and the probability for random assignment to the investigational product, if applicable;

(d) The trial procedures to be followed including all invasive procedures;

(e) The participant's obligations;

(f) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, the participant's partner, to an embryo, foetus or nursing infant;

(g) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this;

(h) The alternative procedure(s) or course(s) of treatment that may be available to the participant and their important potential benefits and risks;

(i) The compensation and/or treatment available to the participant in the event of trial-related injury;

(j) Any anticipated prorated compensation to the participant for trial participation;

(k) Any anticipated expenses to the participant for trial participation;

(l) That the participant's trial participation is voluntary, and the participant may refuse to participate or may withdraw, at any time, without penalty or loss of benefits to which the participant is otherwise entitled;

(m) The process by which the participant's data will be handled, including in the event of the withdrawal of participation in accordance with regulatory requirements;

(n) That by agreeing to participate in the trial, the participant or their legally acceptable representative allows direct access to original medical records, per applicable regulatory requirements, while safeguarding the confidentiality of the participant. This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the IRB/NRERB(s), regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s);

(o) That records identifying the participant will be kept confidential and, to the extent permitted by the applicable regulatory requirements, will not be made publicly available. If the trial results are published, the participant's identity will remain confidential. The trial may be registered on publicly accessible and recognised databases, per applicable regulatory requirements;

(p) That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue trial participation;

(q) The person(s) to contact for further trial information and the trial participant's rights, and whom to contact in the event of suspected trial-related injury;

(r) The foreseeable circumstances and/or reasons under which the participant's trial participation may be terminated;

(s) The expected duration of the participant's trial participation;

(t) The approximate number of participants involved in the trial;

(u) That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it.

5.2.8.15. Where a minor is to be included as participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process, and assent from the minor to enroll in the trial should be obtained as appropriate. A process for re-consent should be considered if, during the course of the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

5.2.8.16. When a clinical trial includes participants who may only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g., minors, patients with severe impaired decision-making capacity), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant should sign and personally date the informed consent form or assent form as appropriate.

5.2.8.17. In exceptional circumstances (e.g., public health emergencies), when the usual methods to obtain and document informed consent are not possible, the use of alternative measures and technologies in accordance with local IRBs/NRERB and applicable regulatory requirements should be considered

5.2.9. Records and Reports

5.2.9.1. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

5.2.9.2. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

5.2.9.3. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

5.2.9.4.Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

5.2.9.5. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

5.2.9.6. Essential documents should be retained in the site of trial after the last approval of a marketing application for appropriate time based on the requirement and proposed time of specific trail. It is the responsibility of the sponsor to inform the investigator/institution about overall retention of the documents and period required for retention in writing.

5.2.9.7. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.2.9.8. Upon request of the monitor, auditor, IRB/NRERB, or the regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

5.2.10. Progress Reports

5.2.10.1. The investigator should submit progress reports of the trial status to Authority biannually for trials having a study period of more than one year. For those trials with a study period of less than one year, the final report should be submitted at the end of period.

5.2.10.2. The investigator should promptly provide written reports to the sponsor, the NRERB/IRB and, the Authority on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

5.2.11. Safety Reporting

5.2.11.1. All serious adverse events (SAEs) should be reported within 24 hours to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also report all serious adverse drug events to the Authority within 48 hours of the occurrence of the SAE.

5.2.11.2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol. These types of adverse events must be reported to the Authority as per regulatory requirements.

5.2.11.3. For reported deaths, the investigator should supply the sponsor and the Authority with any additional requested information (e.g., autopsy reports and terminal medical reports).

5.2.12. Premature Termination or Suspension of a Trial

5.2.12.1 If the trial is prematurely terminated or suspended for any reason, the investigator/ institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and should inform the regulatory authority (ies).

5.2.12.2. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the Authority, and should provide the sponsor and the Authority a detailed written explanation of the termination or suspension.

5.2.12.3. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the Authority and provide the authority a detailed written explanation of the termination or suspension.

5.2.12.4. If the NRERB/IRB terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and the Authority. The investigator/institution provides the sponsor /the Authority with a detailed written explanation of the termination or suspension.

5.2.13. Final Report(s) by Investigator

Upon completion of a clinical trial, it is important to follow specific protocols and reporting procedures to ensure transparency, accountability, and adherence to regulatory requirements. The investigator should notify the institution where the trial was conducted about the trial's completion. This notification should include a summary of the trial's outcome, detailing the results and any significant findings. The investigator and/or the institution should submit a final report NRERB or IRB and the Authority. This report should include a comprehensive summary of the trial's outcome, highlighting the key results, any deviations from the original protocol, and the overall conduct of the study.

5.3. THE ETHIOPIAN FOOD AND DRUG AUTHORITY (EFDA)

The Ethiopian Food and Drug Authority (EFDA) have specific roles and responsibilities regarding the conduct of clinical trials within Ethiopia. These responsibilities ensure that clinical trials are conducted ethically, safely, and in compliance with national and international standards. The EFDA has specific roles related to:

- Regulatory Oversight: Ensuring that all clinical trials conducted within the country adhere to ethical guidelines and regulatory requirements.
- Protection of Human Subjects: Safeguarding the rights, safety, and well-being of participants involved in clinical trials.
- Quality Assurance: Ensuring the scientific validity and integrity of clinical trial data.

5.3.1. Has responsibility to Reviewing and approving clinical trial protocols to ensure they are scientifically sound and ethically justified. EFDA is entitled to Evaluating the risk-benefit ratio of the proposed clinical trials.

5.3.2. Shall ensure that all clinical trials are reviewed and approved by an accredited IRB or NRERB. As well as Monitoring the performance and compliance of IRBs.

5.3.3. Will provide guidance to sponsors, investigators, and IRBs on regulatory requirements and best practices.

5.3.4. Conduct inspections of clinical trial sites to ensure compliance with approved protocols, Good Clinical Practice (GCP) guidelines, and regulatory requirements.

5.3.5. Monitor the conduct of clinical trials to ensure ongoing compliance and integrity of the trials.

5.3.6. Will manage a registry of all clinical trials conducted in Ethiopia and ensure that clinical trial information is publicly accessible to promote transparency and accountability.

5.3.7. Monitor and evaluate reports of adverse events and serious adverse events occurring during clinical trials.

5.3.8. Ensure that appropriate actions are taken to protect participants when adverse events occur

5.3.9. Will take enforcement actions against non-compliance, including suspension or termination of clinical trials.

5.3.10. Imposing penalties or sanctions on sponsors or investigators who violate regulatory requirements.

5.3.11. Preparing and disseminating reports on the status and outcomes of clinical trials conducted in Ethiopia.

5.4. SPONSOR

Throughout the clinical trial life cycle, the sponsor is accountable for putting in place risk-proportionate procedures that guarantee participant safety and trial results' dependability.

5.4.1. Trial Design

5.4.1.1. The sponsor must make sure that there is enough safety and efficacy information from nonclinical research, clinical trials, and/or real-world data to justify human exposure via the designated route, at the prescribed dosages, for the intended duration, and in the trial population before beginning any trials

5.4.1.2. By identifying and controlling the risks to the aspects that are essential to the trial's quality, sponsors can include quality into the clinical trial's design.

5.4.1.3 To support the development plan and clinical trial protocols, sponsors should take into account input from a wide range of stakeholders, including patients and healthcare professionals. They should also take this into account when developing any other participant-facing information, such as informed consent materials.

5.4.1.4. The sponsors should make sure that every component is operationally doable and should steer clear of needless complication in terms of procedures and data gathering. When appropriate, protocols, data collection instruments, and other operational documentation should be clear, succinct, and consistent with their intended use.

5.4.2. Resources

The sponsor should make sure there are enough resources available to carry it out properly.

5.4 .3 Allocation of Activities

The sponsor should decide who will play what responsibilities before starting clinical trial operations and allocating trial-related tasks appropriately.

5.4.4. Qualification and Training

Throughout the trial process, the sponsor should assign adequately qualified persons (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors, and monitors) to the tasks to which they are assigned.

5.4.5. Medical Expertise

The sponsor must to have medical staff on hand who may offer guidance on any particular medical issues or queries pertaining to the trial.

5.4.6. Financing

An agreement between the sponsor and the investigator/institution should detail the trial's financial details.

5.4.7. Agreements

5.4.7.1. Prior to starting any operations, agreements signed by the sponsor with the investigator/institution, service providers, and other parties (such as the adjudication committee and independent data monitoring committee) involved in the clinical trial should be recorded.

5.4.7.2. Agreements should be revised as needed to take into account material modifications to the tasks assigned.

5.4.7.3. The agreement of the investigator/institution and, if relevant, the service provider should be obtained by the sponsor:

a) To carry out the experiment in conformity with the authorized protocol, GCP, and any applicable regulatory requirements;
b) To abide by the protocols for reporting and recording data;
c) Should keep the trial's important records for as long as necessary to comply with any regulatory requirements, or longer if the sponsor notifies the investigator/institution or the service provider that the records are no longer required;
d) To allow sponsors, NRERB, and regulatory bodies to monitor, audit, and examine, including to grant direct access to source data and facilities, including those of service providers.

5.4.7.4. Before the trial begins, the roles and responsibilities of the coordinating investigator(s) and the other participating investigators should be recorded.

5.4.7.5. Any trial-related actions carried out by the sponsor that are transferred to and taken on by a service provider ought to be recorded in a contract. Sponsor retains all trial-related activities that are not expressly passed to and taken on by a service provider.

5.4.7.6. Any service provider that the sponsor designates to carry out any tasks that fall under the investigator's review should be disclosed to the investigator. The investigator is still in charge of these kinds of tasks.

5.4.7.7. A sponsor may assign some or all of the sponsor's trial-related responsibilities to a service provider, but the sponsor retains final say over all trial-related matters, including participant rights protection, trial participant safety and well-being, and trial data reliability. Any service provider engaged in clinical trial operations must put in place suitable quality control and notify the sponsor of any events that could compromise trial participants' safety or the study's outcomes.

5.4.7.8. In order to make sure the service provider is capable of doing the tasks that have been transferred to them; the sponsor must evaluate the provider's suitability and make their choice. Where necessary, the sponsor should give the service providers the protocol and any other paperwork needed for them to carry out their duties.

5.4.7.9. Access to pertinent data (such as SOPs and performance metrics) is necessary for the sponsor to choose and supervise service providers.

5.4.7.10. When significant trial-related tasks are delegated to service providers and then further subcontracted, the sponsor should make sure that proper oversight is in place.

5.4.7.11. Trial-related Service providers should carry out their trial operations in compliance with the national GCP regulations, which may be satisfied by using their current procedures.

5.4.7.12. Sponsorship of a clinical trial can be one or many, depending on the relevant regulatory criteria. When conducting trials with several sponsors, it is imperative that the sponsors possess a formal agreement that outlines their individual duties, taking into account the national regulatory requirements and/or customs. When a responsibility is not assigned to a specific sponsor in the recorded agreement, all sponsors are responsible for it.

5.4.8. Selection

5.4.8.1 Although the choice of the investigator(s) and/or institution(s) belongs to the sponsor, it should be in line with the national directive. Each investigator must demonstrate that they have the necessary facilities and resources to carry out the trial in a way that is appropriate, and they must also be qualified by education, training, and experience. In multicenter studies, the sponsor bears the obligation for organizing a coordinating committee and/or selecting coordinating investigator(s). Their tasks should be well defined before they get involved in the trial.

5.4.8.2. The protocol and an updated Investigator's Brochure should be given by the sponsor to the investigator(s) or institution(s), along with enough time to examine the information and protocol.

5.4.9. Communication with IRB/IEC and Regulatory Authority

5.4.9.1 Notification/Submission to Regulatory Authority

Before starting the clinical trial(s), the sponsor (or the sponsor and the investigator) should submit any necessary application(s) to the relevant regulatory authority for review, acceptance, and/or approval to start the trial(s), in compliance with any applicable regulatory requirement(s). Any submission or notification must be dated and provide enough details to identify the protocol.

5.4.9.2. Confirmation of Review by NRERB

a) Where a submission to the IRB or NRERB is mentioned, the sponsor, the investigator, or the institution may do so in compliance with any applicable regulatory requirements. (See section on communication with IRB/IEC and regulatory authorities).
b) The following should be achieved, as the sponsor should make sure of:

(i) The necessary NRERB's name and address, in addition to:

(aa) a declaration stating that it is set up and runs in compliance with GCP and all relevant regulations;

(bb) Record the trial's termination, the suspension of approval or favorable opinion, and any prior and subsequent NRERB approval or favorable opinion.

5.4.10. Sponsor Oversight.

5.4.10.1. In order to guarantee accurate trial results, trial participant safety, and appropriate decision making, the sponsor must make sure that the trial's design, conduct, procedures, and information and data generation are of a high enough calibers.

5.4.10.2. The sponsor is responsible for making sure that the trial procedures are carried out in accordance with the trial protocol and any associated paperwork, as well as with any applicable legal and ethical requirements.

5.4.10.3. For protocol violations to be categorized as significant, the sponsor must establish trial-specific criteria (i.e., those that affect the participants' rights, safety, and well-being as well as the validity of the results).

5.4.10.4. The effects of trial decisions on participant rights, safety and well-being, and the validity of trial findings should be suitably evaluated. Risks associated with these choices should be appropriately addressed during the trial's preparation, execution, and reporting.

5.4.10.5. The scope and variety of oversight procedures have to be appropriate for the task at hand, taking into account the trial's complexity and potential hazards. An essential component of the oversight process is the selection and supervision of investigators and service providers. Quality assurance and quality control procedures pertaining to the trial-related operations of investigators and service providers are under the sponsor's supervision.

5.4.10.6. To enable the prompt implementation of necessary steps, the sponsor must guarantee appropriate and fast issue escalation and follow-up.

5.4.10.7. In order to periodically evaluate the safety and efficacy endpoints of a clinical study and advise the sponsor on whether to proceed, make modifications, or terminate the trial, the sponsor may want to think about setting up an independent data-monitoring committe**e (**IDMC).

5.4.10.8. In some studies, sponsors may additionally, if appropriate, set up an endpoint assessment/adjudication committee to examine significant endpoints that investigators submit and decide whether the endpoints satisfy protocol-specified requirements. Regardless of whether the trial is blindfolded, these committees should usually be blinded to the assigned treatments when conducting their assessments in order to guarantee that the data they analyze are as free of bias as feasible.

5.4.10.9. Members of a committee that is formed to address matters that may affect trial participant safety or the validity of the results should possess the necessary experience and be able to manage conflicts of interest. The committee should also have formal working rules, such as charters, and record its decisions.

5.4.11. Quality Management

The sponsor must put in place a suitable framework to oversee quality at every turn during the trial. In order to support participant rights, safety and well-being, and the validity of trial results, quality management involves the design and implementation of effective clinical trial protocols, including tools and processes for trial conduct (including for data collecting and management).

The approach to quality management that the sponsor should take is proportionate and risk-based. It entails integrating quality into the clinical trial's design, or quality by design, and determining the factors that are most likely to have a significant impact on participant rights, safety and well-being, and the reliability of the results. In the clinical trial report, the sponsor is required to provide details about the quality management strategy used during the trial.

5.4.11.1. Risk Management

The following describes a proportionate approach to risk identification and management:

5.4.11.1.1. Risk Identification

The Sponsors ought to recognize risks/hazards that could significantly affect variables that are essential to quality. Every step of the clinical trial's procedures, including patient selection, informed consent, randomization, administration of experimental products, data handling, and service provider activities, should take risks into account.

5.4.11.1.2. Risk Evaluation

The sponsor should evaluate potential risks by considering:

a) the likelihood of harm/hazard occurring;
b) the extent to which such harm/hazard would be detectable;
c) The impact of such harm/hazard on trial participant protection and the reliability of trial results.

5.4.11.1.3. Risk Control

a) Risk control should be commensurate with the significance of the risk to the rights, health, and safety of participants as well as the validity of trial findings. Protocol design and execution, monitoring plans, agreements between parties outlining roles and duties, systematic measures to guarantee SOP adherence, and process and procedure training are all examples of risk mitigation activities.
b) The sponsor should establish acceptable boundaries for variance within which this procedure can be supported. If a deviation is found that is outside of these ranges, an

assessment should be done to see if there may be a systemic problem and whether any action is required.

5.4.11.1.4. Risk Communication

The sponsor should communicate the identified risks and mitigating activities, if applicable, to those who are involved in taking action or are affected by such activities. Communication also facilitates risk review and continual improvement during clinical trial conduct.

5.4.11.1.5. Risk Review

In order to determine if the quality management activities that have been implemented are still relevant and effective, the sponsor should review risk control measures on a regular basis, taking into account new information and experience.

5.4.11.1.6. Risk Reporting

The sponsor is required to provide in the clinical trial report a summary of the risks and the corrective measures implemented in response to significant departures from the permissible ranges.

5.4.12. Quality Assurance and Quality Control

The sponsor bears the responsibility of devising, executing, and upholding suitable processes for quality assurance and control, as well as documented procedures, to guarantee that trials are carried out and data is generated, recorded, and reported in accordance with the protocol, GCP, and any relevant regulatory requirements.

5.4.12.1. Quality Assurance

Throughout the clinical trial, quality assurance should be implemented. This involves putting procedures in place to identify possible or actual reasons of substantial noncompliance with the protocol, GCP, and/or any regulatory requirements so that remedial and/or preventive actions can be taken.

5.4.12.2. Audit

Audits must to be carried out in a way that is commensurate with the risks involved in running the trial. An independent and distinct audit from regular monitoring or quality control duties, a sponsor's audit aims to assess the efficacy and compliance of the procedures implemented to oversee and carry out the trial.

5.4.12.2.1. Selection and Qualification of Auditors

a. It is recommended that the sponsor designate personnel who are not affiliated with the clinical research under audit.
b. The sponsor is responsible for making sure the auditors have the necessary training and expertise to carry out audits correctly.

5.4.12.2.2. Auditing Procedures

a. The sponsor is responsible for making sure that the auditing of clinical trials and processes is carried out in compliance with the sponsor's defined policies for what has to be audited, how it should be done (remote or on-site), how often it should be done, and the format and content of audit reports.
b. The trial's significance for submissions to regulatory bodies, the number of participants, the trial's type and complexity, the degree of risk to the trial participants, and any problems found should all be taken into consideration by the sponsor when creating its audit plan, program, and procedures for a trial audit.
c. The observations and findings of the auditor(s) should be documented.
d. The regulatory authority (ies) shouldn't regularly seek the audit reports in order to maintain the independence and value of the audit function. On a case-by-case basis, regulatory authority (ies) may request access to an audit report in the event that there is evidence of substantial GCP non-compliance or during legal proceedings.
e. When required by applicable regulatory requirements, the sponsor should provide an audit certificate.

5.4.12.3. Quality Control

Every step of the data handling process should include quality control to guarantee that the data are accurate and have been processed correctly. The primary quality control tasks in clinical trials are data management and monitoring procedures. A risk-based approach may be used to carry out and report on the quality control of sites (apart from investigator sites, like centralized image reading facilities), including on-site and/or centralized operations.

5.4.12.4. Monitoring

As the study moves forward, monitoring aims to protect the rights, safety, and well-being of participants as well as the validity of the trial's findings. One of the main methods of quality

control is monitoring. Monitoring entails a wide range of tasks, such as speaking with investigator sites, confirming the credentials of the investigator and investigator site staff as well as the resources on the site, providing training, and reviewing trial documents and data using a variety of techniques, such as source data verification, source data review, data analytics, and visits to institutional facilities carrying out trial-related activities. Certain monitoring tasks might be carried out by individuals in different roles and using different techniques.

Nonetheless, those who are not involved in the clinical conduct of the experiment under observation should carry out the monitoring. The monitoring strategy should be part of the monitoring plan and take into account the services and activities that are involved, including decentralized settings. In compliance with applicable statutory requirements, institution policy, and established data security standards, monitors and other trial staff members must uphold the confidentiality and data protection obligations.

Depending on the monitoring method and the clinical trial design, monitoring operations may involve centralized monitoring and site monitoring (conducted remotely or on-site). Considering the risks that have been recognized, the sponsor should decide what kind and how much monitoring is necessary. A variety of factors should be taken into account, including the trial's objective, purpose, design, complexity, blinding, number of participants, investigational product, and current understanding of the safety profile and endpoints.

5.4.12.4.1. Investigator Site Monitoring

a. The activities of the clinical trials at the investigator locations (e.g., including their pharmacies and local laboratories, as applicable) may be monitored. Based on recognized risks, the frequency of monitoring activities should also be decided. With the knowledge acquired, monitoring operations and their frequency should be adjusted as necessary.
b. This monitoring activity may be performed on-site or remotely depending on the nature of the activity and its objectives.
c. Monitoring may include secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems.

5.4.12.4.2. Centralized Monitoring

a. Centralized monitoring is the timely examination of collected data by qualified and trained individuals employed by the sponsor (e.g., medical monitor, data scientist/data manager, and biostatistician).
b. Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Use of centralized data analytics can help identify systemic or site-specific issues, including protocol non-compliance and potentially unreliable data.
c. Centralized monitoring may support the selection of sites and/or processes for targeted site monitoring

5.4.12.4.3. Monitoring Plan

A monitoring plan specific to the identified potential safety concerns, risks to the quality of the data, and/or other risks to the validity of the trial results should be developed by the sponsor. Procedures pertaining to participant safety and trial endpoints should receive special attention. The monitoring strategy, the parties' respective monitoring activities, the different instruments and methodologies to be utilized for monitoring and the justification for their usage should all be covered in the plan. In addition to taking site capabilities and potential burden into account, the monitoring approach should guarantee proper oversight of trial conduct. The plan ought to concentrate on elements that are essential to quality. The applicable policies and procedures of the sponsor should be cited in the monitoring plan. The monitoring strategy should cover the main data and activities (such as those pertaining to primary endpoints, key secondary endpoints, and processes meant to ensure patient safety) that are monitored outside the investigator site (such as central laboratories, central reading facilities, etc.).

5.4.12.4.4. Monitoring Procedures

Persons performing monitoring should follow the sponsor’s monitoring plan and applicable monitoring procedures.

5.4.12.4.5. Monitoring Activities

Monitoring in accordance with the sponsor’s requirements and monitoring plan should generally include the following activities across the clinical trial life cycle, as applicable.

5.4.12.4.5.1. Communication with Parties Conducting the Trial

a. Creating and keeping a channel of communication open between the sponsor, the investigator, and any other participants in the conduct of the study (such as centrally

performed activities). Generally speaking, every site needs a designated monitor who serves as their point of contact.

b. Notifying the investigator or other relevant parties of any deviations from the protocol, GCP, or relevant regulatory requirements that have been found, and taking the necessary steps to stop the deviations from happening again. Remedial actions should, where appropriate, center on highlighting significant deviations.
c. Notifying the investigator or any other parties or individuals involved in the trial's conduct of any source records, data entry errors, or omissions in data acquisition tools, and making sure that any necessary corrections, additions, or deletions are dated, appropriately documented, and approved.
d. Actions taken in relation to the deviations, errors or omissions should be proportionate to their importance

5.4.12.4.5.2. Investigator Site Selection, Initiation, Management and Close-out

a. Choosing the location and verifying that the investigator, the participants, and the resource are sufficiently qualified, equipped, and have access to facilities (such as laboratories, equipment, and investigator site staff) to carry out the trial in a safe and appropriate manner.
b. Verifying that the trial's participants, investigator, investigator site personnel, and other relevant parties are well-informed about the trial and adhere to the protocol's current approved version as well as any related documents, including the current Investigator's Brochure, pertinent data about the investigational product, and guidelines for their assigned tasks.
c. Confirming that the investigator is maintaining the essential records (see essential records for the conduct of a clinical trial).
d. Confirming that informed consent was obtained before participation in the trial (see section on informed Consent of Trial Participants) for all enrolled participants at the site.
e. Determining whether adverse events are appropriately reported within the time periods required by the protocol, GCP and the applicable regulatory requirement(s).
f. Clarifying the sponsor’s protocol requirements for source records and the site’s location of such data. (g) Verifying that the blinding is maintained, where applicable.
g. Reviewing and reporting the participant recruitment and retention rates.

h. Confirming that the investigator provides the required reports, notifications or other information in accordance with the protocol and trial procedures.
i. Confirming the arrangement for the retention of the essential records and the final accountability of the investigational product (e.g., return and destruction or alternative disposition, if appropriate) during site close out activity.

5.4.12.4.5.3 Monitoring of Investigational Product Management

Confirming, for the investigational product(s):

i. that storage conditions are acceptable and in accordance with the storage requirement specified in the protocol;
ii. that supplies are sufficient throughout the trial and are used within their shelf-life;
iii. that the correct investigational product(s) are supplied only to participants who are eligible to receive it at the protocol specified dose(s) and, where appropriate, in accordance with the randomization procedures;
iv. ensure the necessary instructions regarding the appropriate use, handling, storage, return and destruction, or alternative disposal of the investigational product(s) are given to the participants, investigator, investigator site staff, and other pertinent parties and individuals involved in the trial conduct;
v. that the receipt, use, return and destruction, or alternative disposition of the investigational product(s) are controlled and documented adequately;
vi. that the disposition of unused investigational product(s) complies with applicable regulatory requirement(s) and is in accordance with the sponsor requirements;
vii. where product available on the market is dispensed and used in accordance with applicable regulatory requirements, some of the previously outlined considerations may not be applicable.

5.4.12.4.5.4 Monitoring of Clinical Trial Data

a) Verifying that the investigator is enrolling only eligible trial participants.
b) Verifying if trial-related records were reported on time and comparing the reported trial data's accuracy, completeness, and consistency to the source records and other trial-related records. When necessary, data analytics can be used to help this work and it can be conducted utilizing samples. Insufficient data quality may be indicated by other factors or by past monitoring findings that call for adjusting the sample size.

Monitoring should:

i. Verify that the data required by the protocol and identified as critical in the monitoring plan are consistent with the source;
ii. Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations;
iii. Examine data trends, such as the range, consistency and variability of data within and across sites;

c) Identifying significant errors in data collection and reporting at a site or across sites, potential data manipulation and data integrity problems.

5.4.12.4.6. Monitoring Report-start here

a. Reports on monitoring operations must to contain an overview of the material that was examined, an explanation of noteworthy discoveries, conclusions, and the steps necessary to address them, along with a follow-up on the resolution of any issues that weren't addressed in earlier reports. The protocols of the sponsor should specify the requirements for monitoring reports, including their frequency and content.
b. Reports of investigator site and/or centralized monitoring should be provided to the appropriate sponsor staff as described in the sponsor's procedures in a timely manner for review and follow-up.
c. When needed, the report should describe findings requiring escalation for action and resolution. The sponsor should decide on the appropriate action to be taken, and these decisions and the resolution of the actions involved, where needed, should be recorded.

5.4.13. Noncompliance

5.4.13.1. When an investigator, institution, or member of the sponsor's staff violates the protocol, SOPs, GCP, or any applicable regulatory requirement(s), the sponsor should take appropriate and proportionate measures to ensure compliance.

5.4.13.2. The sponsor shall conduct a root cause analysis, implement appropriate corrective and preventive actions, and, unless otherwise justified, confirm the adequacy of such actions in the event that noncompliance is discovered that materially affects or has the potential to materially affect the rights, safety, or well-being of trial participants or the reliability of trial results. The sponsor shall, in accordance with applicable regulatory requirements, notify the regulatory

authority and/or NRERB of any issues that could materially affect the rights, safety, and well-being of trial participants or the validity of trial results.

5.4.13.3. The sponsor should stop the investigator's or institution's involvement in the study if the monitoring and/or audits reveal significant noncompliance on their part that endures despite attempts at correction. If noncompliance results in the termination of an investigator's or institution's participation, the sponsor shall quickly notify the relevant regulatory authority (ies), NRERB

5.4.14. Safety Assessment and Reporting

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s). The Investigator's Brochure or, where applicable, the current scientific information such as a basic product information brochure, forms the basis of safety assessment and reporting for the clinical trial. For further information, (see investigator's brochure section)

5.4.14.1. Sponsor Review of Safety Information

Relevant safety information should be compiled, if needed, and reviewed by the sponsor on a regular basis. The protocol, investigator's brochure, informed consent papers, and related documentation may need to be updated as a result. In order to determine whether new information could influence a participant's decision to continue in the trial, have an impact on how the trial is conducted, or change the approval or favorable opinion of the NRERB, and/or regulatory authority(ies), as appropriate, the sponsor should review the emerging safety information that is currently available. This kind of information should be promptly shared with the participants, investigator, NRERB, and regulatory agencies, if appropriate.

5.4.14.2. Safety Reporting

a. The sponsor should submit to the regulatory authority (ies) safety updates and periodic reports, including changes to the Investigator's Brochure, as required by applicable regulatory requirements.
b. The sponsor should, in accordance with the applicable regulatory requirement(s) and with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, expedite the reporting to the regulatory authority(ies) of all adverse drug reactions (ADRs) that meet three criteria: suspected, unexpected and serious (i.e., SUSARs).
c. In compliance with applicable regulatory requirements, safety reporting to regulatory authorities should be carried out by evaluating the expectedness of the reaction in relation to

the applicable product information (e.g., the reference safety information (RSI) contained within the Investigator's Brochure or alternative documents).

d. Reporting SUSARs to the appropriate investigator(s), institution(s)**,** NRERB should be done in a way that emphasizes the need for prompt action and takes into account the product's safety profile's changing body of knowledge. It is important to follow regulatory guidelines when reporting SUSARs to investigators or organizations. Periodic reporting of line listings together with an overall safety assessment may be appropriate in some places.
e. Urgent safety issues requiring immediate attention or action should be reported to the NRERB and/or regulatory authority (ies) and investigators without undue delay and as specified in regulatory requirements.
f. Alternative arrangements for safety reporting to regulatory authorities, NRERB, and investigators and for reporting by investigators to the sponsor should be prospectively agreed upon with the regulatory authority (ies) and the NRERB if applicable, and described in the clinical trial protocol, (e.g., SAEs considered efficacy or safety endpoints, which would not be subject to unblinding and expedited reporting).

5.4.14.3 Managing an Immediate Hazard

In order to address participation hazards immediately, the sponsor should act quickly. The sponsor must identify the sources of the hazard and then implement the necessary corrective measures. In the event of an imminent hazard, the sponsor ought to think about whether the protocol has to be changed. The investigator/institution or sponsor shall, in compliance with applicable regulatory requirements, report the information on the immediate hazard and any subsequent protocol revision to the NRERB and/or regulatory authorities.

5.4.15. Insurance/Indemnification/Compensation to Participants and Investigators

5.4.15.1. Except for claims resulting from malpractice and/or carelessness, the sponsor shall, if required by the applicable regulatory requirement(s), offer insurance or indemnify (legal and financial covering) the investigator and the institution against claims originating from the trial.

5.4.15.2. The sponsor’s policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.4.15.3. The approach to compensating trial participants should comply with applicable regulatory requirement(s).

5.4.16. Investigational Product(s)

5.4.16.1. Information on Investigational Product(s)

The sponsor should ensure that an Investigator's Brochure is developed and updated as significant new information on the investigational product becomes available. Alternatively, for authorized medicinal products, the sponsor should identify the basic product information to be used in the trial (see section on investigator's brochure).

5.4.16.2. Manufacturing, Packaging, Labeling and Coding Investigational Product(s)

a. The investigational product(s) (including active control(s) and placebo, if applicable) should be manufactured in compliance with any applicable GMP, coded and labeled to protect the blinding, if applicable, and characterized as appropriate for the stage of development of the product(s). The labeling should also adhere to any applicable regulatory requirement(s).
b. The sponsor is responsible for identifying suitable reconstitution fluids and processes, devices for product infusion, if applicable, and acceptable storage temperatures and other storage conditions (e.g., protection from light) for the investigational product(s). The sponsor is responsible for disclosing these conclusions to all relevant stakeholders, including monitors, investigators, pharmacists, and storage managers.
c. The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.
d. In blinded trials, the sponsor should implement:
    i. a process to blind the sponsor staff, trial participant and/or investigator as appropriate to the investigational product identity and assignment to prevent and detect inappropriate unblinding;
    ii. a procedure and mechanism that permits the investigator to rapidly identify the product(s) in case of a medical emergency where unblinding is considered necessary, while protecting the identity of the treatment assignment of the other trial participants;
    iii. a mechanism that protects the blinding of the trial where a participant's treatment assignment is unblinded for the purpose of safety reporting to regulatory authorities and/or NRERB, where appropriate.
e. Before the new formulation is used in clinical trials, the results of any additional studies of the formulated product (e.g., stability, dissolution rate, bioavailability) that are necessary to determine whether these changes would significantly alter the pharmacokinetic profile of the

product should be available. This is especially true if significant formulation changes are made in the investigational product(s) (including active control(s) and placebo, if applicable) during the course of clinical development.

5.4.16.3. Supplying and Handling Investigational Product(s)

a. The investigational product(s) or, where appropriate, trial participants must be provided by the sponsor in compliance with all applicable regulatory requirements and after receiving the necessary approval/favorable opinion from the NRERB and the regulatory authority(ies) for the trial.
b. The sponsor is responsible for making sure that guidelines on the handling and storage of investigational product(s) are accessible to the investigator, institution, or trial participants. The protocols ought to take into account proper and secure receiving, handling, storing, dispensing, recovering unused product from participants, and returning unused investigational product(s) to the sponsor (or, in the event that the sponsor permits and in accordance with relevant regulatory requirement(s), finding an alternate disposal method).
c. The following actions by the sponsor are necessary to prevent any disruption to the trial and to enable participants to continue receiving treatment:
    i. Make sure that the investigational product(s) are delivered on time to the investigator(s) or, if applicable, to trial participants in compliance with applicable regulatory regulations.
    ii. Maintain records that document the identity, shipment, receipt, return and destruction, or alternative disposition of the investigational product(s) (see section on essential records for the conduct of a clinical trial);
    iii. Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, return and destruction, or alternative disposition after trial completion, or expired product reclaim);
    iv. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition;
    v. Take steps to ensure that the investigational product(s) are stable over the period of use and only used within the current shelf-life;
    vi. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications should this become necessary and maintain records of batch sample analyses and characteristics.

The samples should be kept for as long as necessary to comply with any regulatory requirements or until the trial data analysis is finished, whichever comes first. Since the manufacturer keeps the samples, the sponsor is not required to keep them in trials where an approved medication is utilized as an exploratory product without being altered from its approved status.

5.4.17. Data and Records

5.4.17.1 Data Handling

a. The sponsor should ensure the integrity and confidentiality of data generated and managed.
b. The sponsor should apply quality control to the relevant stages of data handling to ensure that the data are of sufficient quality to generate reliable results. The sponsor should focus their quality assurance and quality control activities and data review on critical data, including its relevant metadata.
c. The sponsor should pre-specify data to be collected and the method of its collection in the protocol (section on Clinical Trial Protocol and Protocol Amendment(s)). Where necessary, additional details, including a data flow diagram, should be contained in a protocol-related document (e.g., a data management plan).
d. The sponsor should ensure that data acquisition tools are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial.
e. The sponsor should ensure that documented processes are implemented to ensure the data integrity for the full data life cycle.
f. The sponsor should implement measures to ensure the safeguarding of the blinding, if any (e.g., maintain the blinding during data entry and processing).
g. The sponsor should provide guidance to investigators/institutions, service providers and trial participants, where relevant, on the expectations for data capture, data changes, data retention and data disposal.
h. The sponsor should not make changes to data entered by the investigator or trial participants unless justified and documented by the sponsor and agreed upon by the investigator.

i. The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry.

j. The sponsor should ensure that the investigator has access to data collected in accordance with the protocol during the course of the trial including relevant data from external sources, for example, central laboratory data, centrally read imaging data and, if appropriate, ePRO data that are necessary to enable the investigators to make decisions (e.g., on eligibility, treatment, continuing participation in the trial and care for the safety of the individual trial participants). The sponsor should pay special attention to data that may unblind the investigator and include the appropriate provisions in the protocol.

k. The sponsor should not have exclusive control of data captured in data acquisition tools.

l. The sponsor should ensure that the investigator has access to the required data for retention purposes.

m. The sponsor should ensure that the investigator receives instructions on how to navigate systems, data and relevant metadata for the trial participants under their responsibility.

n. The sponsor should seek investigator endorsement of their data at predetermined milestones.

o. The sponsor should document the data management steps to be undertaken prior to data analysis. These steps may vary depending on the purpose of the analysis to be conducted (e.g., data for IDMC, for interim analysis or the final analysis).

p. Prior to provision of the data for analysis, edit access to the data acquisition tools should be restricted as appropriate to the purpose of the analysis; for example, for interim analysis, the restriction may only be temporary or managed differently compared to the final analysis.

q. Changes to the data analysis set after the trial has been unblinded (if applicable) or deviations from the planned statistical analysis should only happen in extraordinary situations (e.g., data discrepancies that must be resolved for the reliability of the trial results) and should be well-documented and justified. Any modifications to the data must be approved by the investigator and recorded in an audit trail. Any modifications to the post-unblinding data and any departures from the intended statistical analyses must be documented in the clinical trial report.

r. The sponsor should use an unambiguous trial participant identification code (see glossary term) that allows identification of all the data reported for each participant.

s. The sponsor should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants, in accordance with applicable regulatory requirements on personal data protection.

t. In accordance with applicable regulatory requirements, the sponsor should document what happens to data when a participant withdraws or discontinues from the trial.

u. The sponsor should ensure that trial data are protected from unauthorized access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.

v. The sponsor should have processes and procedures in place for reporting incidents (including security breaches) that have a significant impact on the trial data to relevant parties, including regulatory authorities, where relevant.

w. When using computerized systems in a clinical trial, the sponsor should:

    i. Have a record of the computerized systems used in a clinical trial. This should include the use, functionality, interfaces and validation status of each computerized system, and who is responsible for its management should be described. The record should also include a description of implemented access controls and internal and external security measures;

    ii. Ensure that the requirements for computerized systems deployed by the sponsor (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerized systems in clinical trials. These requirements should be proportionate to the importance of the computerized system and the data or activities they are expected to process;

    iii. Maintain a record of the individual users who are authorized to access the system, their roles and their access privileges:

    iv. Ensure that access rights granted to investigator site staff are in accordance with delegations by the investigator and visible to the investigator;

v. In the case of systems used by the investigator or institution, determine whether they are suitable for their intended use or whether any known issues can be appropriately addressed. Examples of such systems include electronic health records, other record-keeping systems for the collection of source data, and investigator site files. This evaluation ought to take place and be recorded during the clinical trial site selection procedure;

vi. Ensure that there is a process in place for service providers and investigators to inform the sponsor of system defects identified or incidents that could potentially constitute a serious non-compliance with the clinical trial protocol, trial procedures or GCP.

5.4.17.2. Statistical Programming and Data Analysis

This section concerning documentation of operational aspects of clinical trial statistical activities should be read in conjunction with ICH E9 Statistical Principles for Clinical Trials, which provides detailed guidance on statistical principles for clinical development, trial design, conduct, analysis and reporting.

a. The sponsor should ensure that appropriate and documented quality control of statistical programming and data analysis is implemented (e.g., for sample size calculations, results for IDMC, outputs for clinical trial report, statistical or centralized monitoring).
b. The sponsor should ensure the traceability of data transformations and derivations during data processing and analysis.
c. The sponsor should ensure that the allocation to or exclusion of each trial participant from any analysis set is predefined (e.g., in the protocol or the statistical analysis plan). The rationale for inclusion or exclusion for any participant (or particular data point) should be clearly described and documented. Procedures should be in place to describe unblinding; these descriptions should include:
    i. who was unblinded, at what time point and for what purpose they were unblinded;
    ii. who should remain blinded;
    iii. the safeguards in place to preserve the blinding.
d. The sponsor should retain the statistical programming records that relate to the output contained or used in reports of the trial results, including quality control/validation

activities performed. Outputs should be traceable to the statistical software programs, and they should be dated and time stamped and protected against any changes.

5.4.17.3. Record Keeping and Retention

a. The sponsor (or subsequent owners of the data) should retain all of the sponsor-specific essential records pertaining to the trial in conformance with the applicable regulatory requirement(s).
b. The sponsor should inform the investigator(s)/institution(s) and service providers, when appropriate, in writing of the need for essential records retention and should notify the investigator(s)/institution(s) and service providers, when appropriate, in writing when the trial-related records are no longer needed.
c. The sponsor should report any transfer of ownership of the essential records to the appropriate authority as required by the applicable regulatory requirement(s).

5.4.17.4 Record Access

a. The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s) provide direct access to source records for trial-related monitoring, audits, NRERB review and regulatory inspection.
b. The sponsor should ensure that trial participants have consented to direct access to their original medical records and other participant-related trial documents for trial-related monitoring, audit, NRERB review and regulatory inspection as part of the informed consent.

5.4.18. Reports

5.4.18.1 Premature Termination or Suspension of a Trial

When a trial is abruptly stopped or terminated, the sponsor is required to notify the regulatory authority, the investigators/institutions, and the trial's sponsor of the reason(s) behind the stoppage or termination. In line with any applicable regulatory requirement(s), the sponsor, investigator, or institution should also promptly notify the NRERB and give the reason(s) for the termination or suspension.

5.4.18.2 Clinical Trial/Study Reports

a. The sponsor shall make sure that the clinical trial reports, including interim reports, are prepared and provided to the regulatory agency (ies) as required by the applicable

regulatory requirement(s), regardless of whether the trial is completed, terminated prematurely, or an interim analysis is conducted for regulatory submission.

b. Investigators should be provided with a summary of the trial results.
c. For blinded trials, it should be taken into account to provide the investigator with a concise summary of the trial's overall results as well as information regarding the participants' final course of therapy. When participants are given this information, the language used should be non-technical, intelligible to laypeople, and non-promotional. Only when the trial has been unblended and all pertinent analysis and findings have been finished and approved may the sponsor provide this information.

5.5. CLINICAL MONITOR

5.5.1. Responsibilities

5.5.1.1 Clinical monitors serve as vigilant guardians of trial integrity, data quality, and participant safety. The clinical monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

5.5.1.2 The main responsibility of the monitor is to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements.

5.5.1.3 The monitor is responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly to the sponsor and the relevant ethics committee(s).

5.5.1.4 The clinical monitor should follow a predetermined written set of standard operating procedures (SOP). A written record should be kept of all visits, telephone calls and letters to the investigator.

5.5.2. Qualifications

The role of a clinical monitor is critical in ensuring the successful execution of clinical trials. The clinical monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical, and/or scientific qualifications, and clinical trial experience. The qualifications most appropriate for a monitor will depend on the type of trial and nature of the product under investigation.

5.5.3 Assessment of the trial site, Conducting Site Visits, Developing and Implementing Study-Specific Monitoring Plans:

5.5.3.1 The clinical monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an adequate number of trial subjects are likely to be available for the duration of the trial.

5.5.3.2 Clinical monitors create customized monitoring plans for each clinical study. These plans outline how they will oversee the trial, including site visits, data review, and compliance checks.

5.5.3.3 The clinical monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of standard operating procedures (SOP).

5.5.3.4 Clinical monitors visit study sites regularly. During these visits, they assess trial progress, review documentation, and interact with site staff.

5.5.3.5 They verify that informed consent processes are followed, study procedures are correctly executed, and adverse events are appropriately documented.

5.5.3.6 The clinical monitors proactively identify any deviations, discrepancies, or challenges during site visits. These could relate to data quality, protocol adherence, or safety reporting. When issues arise, they collaborate with site personnel to address them promptly. Corrective actions may involve additional training, process adjustments, or protocol clarifications.

5.5.4 Staff education and compliance

The clinical monitor should ensure that all staff assisting the investigator in the trial have been adequately informed about and will comply with the details of the trial protocol. They capacitate and collaborate with the study team to align monitoring activities with the study protocol and regulatory requirements.

5.5.5 Data management-Verifying Data Accuracy, Completeness, and Compliance

The clinical monitor should assist the investigator in reporting the data and results of the trial to the sponsor, e.g. by providing guidance on correct procedures for completion of case-report forms (CRFs), and by verifying the accuracy of data obtained. Clinical monitors meticulously review study data to ensure accuracy and completeness. They compare data against the trial protocol, case report forms (CRFs), and source documents. Compliance checks involve confirming that the study procedures adhere to ethical guidelines, regulatory standards, and good clinical practice (GCP) principles.(see also Section on record keeping and handling of data).

5.5.6 Case Report Forms-Documenting Monitoring Activities

The clinical monitor is responsible for ensuring that all case-report forms (CRFs) are correctly filled out in accordance with original observations. Any errors or omissions should be clarified with the investigator, corrected, and explained on the CRF. Procedures should be established for the investigator's certification of the accuracy of CRFs by a signature, initials or similar method. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the clinical trial.

5.5.7 Investigational product-Identifying Issues and Implementing Corrective Actions:

The clinical monitor should confirm that procedures for the storage, dispensing, and return of investigational product(s) are safe, adequate, and properly documented in accordance with local regulations and the trial protocol (see also Section on Responsibilities of the sponsor).

5.5.8 Communication-Collaborating with Investigators and Site Staff

The clinical monitor should facilitate communication between the investigator and sponsor. The clinical monitor (or some other responsible person designated by the sponsor and known to the investigator) should be available to the investigator at all times for reporting of adverse events or consultation on other trial-related matters. Clinical monitors build strong relationships with investigators, study coordinators, and other site personnel. Effective communication fosters trust and facilitates problem-solving. They provide guidance on GCP compliance, data collection, and study procedures.

5.5.9 Notification of the trial or submission to the drug regulatory authority

The monitor should assist the investigator in notifying the drug regulatory authority of the clinical trial and submitting any necessary documentation.

5.5.10 Reports

The clinical monitor should submit a written monitor report to the sponsor after each site visit and after all relevant telephone calls, letters and other contacts with the investigator. The report should include details of the findings and any actions taken. Clinical monitors prioritize participant safety. They review adverse events, serious adverse events (SAEs), and safety reporting. If safety concerns emerge, they escalate them to the study team, ensuring timely intervention. Detailed documentation is crucial. Clinical monitors maintain monitoring visit reports, tracking findings, actions taken, and follow-up plans. These records contribute to the overall trial documentation and regulatory submissions.

5.6 DATA SAFETY MONITORING BOARD (DSMB)

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises trial sponsor. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations.

The primary responsibilities of the DSMB are to

1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and
2) make recommendations to sponsor concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

Prior to initiating any data review, the DSMB is responsible for defining its deliberative processes, including: event triggers that would call for an unscheduled review, stopping procedures that are consistent with the protocol, unmasking (unblinding), and voting procedures. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

5.6.1 Roles of the DSMB

5.6.1.1 Participant Safety Monitoring

- The DSMB continuously monitors participant safety throughout the trial. This includes reviewing adverse events and ensuring that risks are minimized.
- The board has the authority to recommend modifications to the study protocol if participant safety is compromised.

5.6.1.2 Data Integrity Oversight

- Ensuring the accuracy and completeness of data is a key role. The DSMB evaluates data quality and addresses any issues related to data collection and management.
- The board ensures that data handling procedures adhere to regulatory standards and best practices.

5.6.1.3 Interim Data Analysis

- The DSMB conducts interim analyses to assess the efficacy and safety of the intervention. This involves analyzing data at predefined points during the trial.
- Based on interim findings, the DSMB can recommend continuing, modifying, or terminating the trial.

5.6.1.4 Protocol Review and Approval

- Before the trial begins, the DSMB reviews the study protocol to ensure it is scientifically sound and ethically appropriate.
- The board ensures that the protocol includes adequate provisions for monitoring participant safety and data integrity.

5.6.1.5 Unblinded Data Access

- In blinded studies, the DSMB has access to unblinded data to make informed decisions about participant safety and trial continuation.
- The board ensures that unblinded data is kept confidential and is only used for decision-making purposes.

5.6.2 Responsibilities of DSMB

5.6.2.1 Regular Meetings

- The DSMB holds regular meetings to review accumulated data, discuss safety issues, and make decisions regarding the trial's progress.
- Meeting frequency is determined by the trial's risk level, complexity, and phase.

5.6.2.2 Adverse Event Reporting

- The DSMB reviews all serious adverse events (SAEs) and unexpected adverse events (UAEs) to determine their impact on participant safety.
- The board ensures that appropriate measures are taken to address any safety concerns.

5.6.2.3 Risk-Benefit Assessment

- The DSMB continuously evaluates the risk-benefit ratio of the intervention. This involves balancing the potential benefits of the intervention against the risks to participants.
- The board makes recommendations to investigators and sponsors based on these assessments.

5.6.2.4 Communication with Stakeholders

- The DSMB communicates its findings and recommendations to trial sponsors, investigators, and regulatory authorities.
- The board ensures that communication is clear, timely, and maintains the confidentiality of sensitive information.

5.6.2.5 Documentation and Reporting

- The DSMB maintains comprehensive records of its activities, including meeting minutes, interim analyses, and recommendations.
- The board prepares regular reports summarizing its findings and actions taken to ensure participant safety and data integrity.

RELATIONSHIP BETWEEN DSMBS AND IRBS

The DSMB should provide feedback at regular and defined intervals to the IRBs. After each meeting of the DSMB, the DSMB's Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to his/her local IRB.

The responsibility to establish a DSMB for a clinical trial typically falls on the trial sponsor. The sponsor can be a pharmaceutical company, a government agency, a non-profit organization, or an academic institution conducting the research. In some cases, especially in large-scale or multi-center trials, the establishment of the DSMB may involve collaboration between multiple stakeholders, including co-sponsors, contract research organizations (CROs), and funding agencies. However, the primary responsibility typically remains with the trial sponsor

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s)

6.1.2. Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7. Name(s) and address (es) of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2. Background Information

6.2.1. Name and description of the investigational product(s).

6.2.2. A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials those are relevant to the trial.

6.2.3. Summary of the known and potential risks and benefits, if any, to human participants.

6.2.4. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6. Description of the population to be studied.

6.2.7. References to literature and data that are relevant to the trial and that provide background for the trial.

6.3. Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial

6.4. Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3. A description of the measures taken to minimize/avoid bias, including: (a) Randomization. (b) Blinding.

6.4.4. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

6.4.5. The expected duration of participants participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6. A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

6.4.7. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8. Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5. Selection and Withdrawal of Participants

6.5.1. Participant’s inclusion criteria.

6.5.2. Participant’s exclusion criteria.

6.5.3. Participants withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

a) When and how to withdraw participants from the trial/investigational product treatment.
b) The type and timing of the data to be collected for withdrawn participants.
c) Whether and how participants are to be replaced.
d) The follow-up for participants withdrawn from investigational product treatment/trial treatment.

6.6. Treatment of Participants

6.6.1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3. Procedures for monitoring participants' compliance.

6.7. Assessment of Efficacy

6.7.1. Specification of the efficacy parameters.

6.7.2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.

6.8. Assessment of Safety

6.8.1. Specification of safety parameters.

6.8.2. The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3. Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.

6.8.4. The type and duration of the follow-up of participants after adverse events.

6.9. Statistics

6.9.1. A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).

6.9.2. The number of participants planned to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification

6.9.3. The level of significance to be used.

6.9.4. Criteria for the termination of the trial.

6.9.5. Procedure for accounting for missing, unused, and spurious data.

6.9.6. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7. The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

6.10. Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, NRERC/IRB review, and regulatory inspection(s), providing direct access to source data/documents.

6.11. Quality Control and Quality Assurance

6.11.1. Description of identified quality factors and associated risks in the trial unless documented elsewhere.

6.11.2. Description of the monitoring approaches that are part of the quality control process for the clinical trial.

6.11.3. Description of the process for the handling of non-compliance with the protocol or GCP

6.12. Ethics

Description of ethical considerations relating to the trial.

6.13. Data Handling and Record Keeping

6.13.1. Specification of data to be collected and the method of its collection. Where necessary, additional details should be contained in a clinical trial-related document.

6.13.2. The identification of records to be recorded directly into the data acquisition tools (i.e., no prior written or electronic record of data) and considered to be source data.

6.13.3. A statement that records should be retained in accordance with applicable regulatory requirements.

6.14. Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15. Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16. Supplements

If any, supplements to the protocol may be included.

7. INVESTIGATOR'S BROCHURE

7.1. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitors procedures. The IB also provides insight to support the clinical management of the study participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (NRERC) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/NRERC. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor- investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2. General Considerations

The IB should include:

7.2.1. Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

7.2.2. Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team, the IRB/NRERC and the Authority.

7.3. Contents of the Investigator’s Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1. Table of Contents

7.3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3. Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the

investigational product(s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4. Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

7.3.5. Nonclinical Studies

Introduction:

The results of all relevant pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

− Nature and frequency of pharmacological or toxic effects

−Severity or intensity of pharmacological or toxic effects

− Time to onset of effects

− Reversibility of effects

− Duration of effects

− Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose

- Carcinogenicity
- Special studies (e.g. irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6. Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

a) Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b) Safety and Efficacy

A summary of information should be provided about the investigational product's/ products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications)

would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7. Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

8. 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. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit

function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/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 investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guideline may be participants to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial. The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

List of Workshop Participants

Name of Participants	Position	Institution
Dr. Solomon Mequanente (PhD)	Associate Professor of Pharmacology	AAU
Dr. Abule Takele	Secretary of NRERB	MoE
Dr. Shemsu Umer (PhD)	National Clinical Trial Ethics committee Deputy chairperson	AAU
Mr. Solomon Shiferaw	Technical Advisor	EFDA
Dr. Adamu Bayisa	Research Coordinator	AHRI
Dr. Worku Bedada	National Clinical Trial Advisory member	ACMC
Mrs. Haregewoin Mulugeta	Drug Information and RDU expert	EFDA
Mr. Dawit Dikaso	Policy Advisor	EFDA
Mrs. Demekech Damte	AHRI, Alert, Institution Ethics Committee Secretary	AHRI
Mr. Ajema Bekele	Medicine Registration Expert	EFDA
Mr. Gemmechu Hasen	Researcher	AHRI
Mrs. Adanech Birhanu	Analyst and Safety Expert	EFDA
Mr. Debalke Fantaw	Biological Medicine Dossier Evaluator	EFDA
Mr.Abebe Alemneh	Medicine Registration, Clinical Data Assessor	EFDA

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2. HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP) GUIDANCE FOR IMPLEMENTATION
3. ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3) Draft version Endorsed on 19 May 2023 Currently under public consultation
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