Ethiopian Food and Drug Authority

Guidelines for Authorization of Medical Device Clinical Investigation

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Abbreviation/Acronyms

AE	Adverse Events
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
DMC	Data Monitoring Committee
EFDA	Ethiopian Food and Drug Authority
DoC	Declaration of Conformity
EC	Ethical Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IRB	Institutional Review Board
IVD	Invitro Diagnostic Device
MD	Medical Device
NRA	National Regulatory Authority
NRERC	National Research Ethics Review Committee
PI	Principal Investigator
QMS	Quality Management System
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

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1. Introduction

Clinical investigation of medical interventions are conducted to provide information that can ultimately improve access to safe and good performing medical device with meaningful impact on patients or users, while protecting those participating in the studies.

Ethiopian Food and Drug Authority is mandated by the Food and Medicine Administration Proclamation No 1112/2019 to authorize the conduct of clinical investigation, monitor and inspect the process as to its conduct in accordance with good medical practice, evaluate the results and authorize the use of the result in such a way that benefit the public; order the clinical trial to be suspended or stopped.

To carry out this mandate, the Authority has issued this guideline to detail the requirements for the authorization of the clinical investigation. In addition, to facilitate the application process, forms and formats are included in the annex of the guideline. Considering the diversity of clinical investigation designs and data sources used to support regulatory and other health policy decisions, this guideline focuses on designing quality into clinical investigation.

For the clinical investigation of medical device, applicants are advised to consult the Authority's Guideline for Medical Device Good Clinical Practice and international recognized standards such as Clinical investigation of medical devices for human subjects' Good clinical practice (latest version of ISO 14155).

2. Definition

Authority is Ethiopian Food and Drug Authority

Adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Clinical investigation is systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device. The clinical investigation is synonym with the clinical trial.

Clinical investigation plan (CIP) is document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Comparator is medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a clinical investigation.

Contract research organization (CRO) is person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.

Coordinating investigator is investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation.

Data monitoring committee (DMC) is independent committee that may be established by the sponsor to assess at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation.

Deviation is instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP.

Ethics committee (EC) is independent body whose responsibility is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation.

Investigation site is institution or site where the clinical investigation is carried out.

Investigational medical device is medical device being assessed for safety or performance in a clinical investigation.

Investigator's brochure is compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.

Principal investigator is qualified person responsible for conducting the clinical investigation at an investigation site.

Serious adverse device effect (SADE) is adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

serious adverse event (SAE) is adverse event that

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization. Or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c) led to foetal distress. foetal death or a congenital abnormality or birth defect

Sponsor is individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation.

Subject is individual who participates in a clinical investigation.

3. Scope

This Guideline applies for the conduct of clinical investigation on human beings in Ethiopia to assess the safety and/or performance of medical devices for regulatory purposes. It is applicable for investigational devices that fulfil the definition of medical device indicated in the Food and Medicine Administration Proclamation No. 1112/2019.

It does not apply to in vitro diagnostic medical device.

4. Objectives

The objectives of this Guideline are:

- To guide sponsor and/or investigator (s) on the documents and process required for the application and conduct of clinical investigations using investigational medical device in Ethiopia.
- To set requirements for sponsor and/or investigator (s) for amendments of medical device clinical investigation plans or other clinical investigation related documents that are made after approval.
- To guide the period and the content of the (progress & final) report and adverse events reporting in relation to clinical investigation conducted in Ethiopia.

5. Determination of the Need for Clinical Investigation

5.1. General Principles

A manufacturer of a medical device is expected to design and manufacture a product that is safe and performs as intended throughout its life cycle. To ensure this outcome, the Authority has issued the marketing authorization guidelines for IVDs and Non-IVD medical devices in which the fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance' are described. The Essential Principles require that a medical device achieves its intended performance during use according to its labelling and that the known, and foreseeable risks, and any undesirable side-effects, are minimised and acceptable when weighed against the benefits of the intended performance. Chapter four of both guidelines for marketing authorization require clinical evidence for both categories of the devices that is generated from the clinical evaluation which is the assessment and analysis of data generated from the clinical intended use of the product in order to verify the clinical safety and performance of the device.

Given the complexity of the medical device milieu, the Authority undertakes the assessment of what is acceptable clinical evidence for the purpose of demonstrating compliance with the Essential Principles on a case-by-case basis. However, it is still important to give guiding principles to the developers and manufacturers of medical devices for determination of the need of clinical investigation. It is crucial to also have an understanding of how medical devices are brought to market in the country and of the role that clinical data and its evaluation plays in this process.

The diversity of medical devices and the technologies on which they are based pose special challenges for developers and manufacturers when trying to identify what should constitute evidence sufficient to demonstrate compliance with the Essential Principles. Clinical evidence is an important component of the technical documentation of a medical device, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation.

Clinical evidence is the evidence generated by clinical evaluation of clinical data. The inputs for clinical evaluation are primarily clinical data in the form of clinical investigation reports, literature reports/reviews and clinical experience. The data required to establish the evidence

of compliance with the Essential Principles may vary according to the characteristics of the medical device, its intended use, the claims made by the manufacturer, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.

5.2. Determination of the need for clinical investigation

Clinical investigations are necessary to provide data not available through other sources (such as literature or nonclinical testing) required to demonstrate compliance with the relevant Essential Principles (including safety, clinical performance and acceptability of benefit/risk associated with its use). When a clinical investigation is conducted, the data obtained is used in the clinical evaluation process and is part of the clinical evidence for the medical device.

When considering the need for a clinical investigation, the developers and manufacturers should consider whether there are new questions of safety, clinical performance and/or effectiveness for a particular medical device and intended use that need to be addressed in a clinical investigation.

For long established technologies, the clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of, for example, published literature, reports of clinical experience, post-market reports and adverse event data may, in principle, be adequate to establish the safety, clinical performance, and/or effectiveness of the medical device, provided that new risks have not been identified, and that the intended use(s)/purpose(s) has/have not changed.

The key considerations in clarifying the need for clinical investigations

1. Identifying relevant clinical essential principles (for example, specifics of safety, clinical performance, acceptability of benefit/risk) for the medical device and its intended use/purpose(s).
2. Performing risk management activities such as a risk analysis will help in identifying the clinical data necessary to address residual risks and aspects of clinical performance not completely resolved by available information (e.g. design solutions, nonclinical and material/technical evaluation, conformity with relevant standards, labelling).

Risk control measures include inherent safety by design, protective measures in the medical device itself or in the manufacturing process, and information for safety. The decision to use a medical device in the context of a clinical procedure requires the residual risk to be balanced

against the anticipated benefits of the procedure. A clinical investigation may be required to further elucidate the benefit/risk in a defined patient population;

3. Conducting a proper clinical evaluation will demonstrate which clinical data are necessary, and can be adequately contributed to by sources such as literature searching, prior clinical investigations (including clinical data generated in other jurisdictions), clinical experience, or clinical data available from comparable devices, and which clinical data should be generated from clinical investigation(s) when data are unavailable or insufficient to demonstrate conformity to the Essential Principles. Available clinical data from comparable devices should be carefully examined for comparability and adequacy.

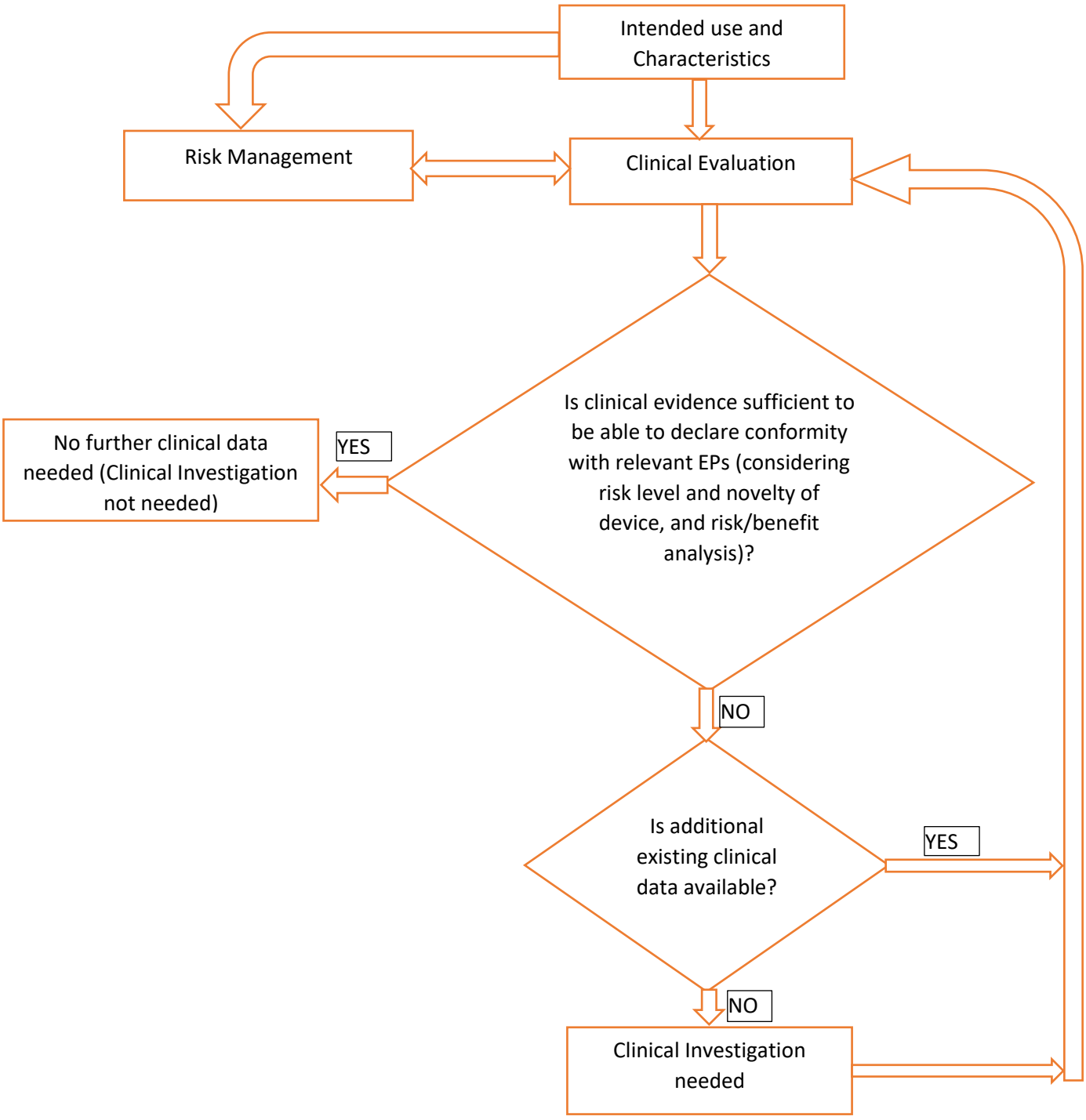

Figure 1: Key considerations for determining the need for clinical investigations

When it is determined that the clinical investigation is needed, then it should be planned, conducted, monitored and reported as per the medical devices good clinical practices described in this guideline and other relevant regulatory requirements of the Authority.

6. Application Requirements for Authorization of Clinical Investigation

The applicants need to submit information as per the outline indicated.

6.1. Application Form

The application form attached as Annex I of this guideline shall be completed, signed and submitted to the Authority.

6.2. Service Fee

The applicant shall pay the required payment in accordance with the recent Rate of Service Fees of Ethiopian Food and Drug Authority (EFDA). The Authority will not conduct assessment of application unless applicable fees have been paid in full.

6.3. Agreement between Sponsor and Investigators

Prior to the commencement of the clinical investigation, the investigator(s) and the sponsor must establish written agreement on the clinical investigation plan, the monitoring, the auditing, and on standard operating procedures (SOP), and the allocation of investigation-related responsibilities. An agreement made on the basis of this principle between the investigator(s) and the sponsor as Annex II and a joint declaration by the sponsor and principal investigator concerning sufficient funds to complete a study should be submitted as Annex III. Template for declarations of investigator(s) is included in Annex IV.

6.4. Research ethics committee approval

For all clinical investigations of devices falling within the scope of the medical devices, a relevant ethics committee approval is required. Therefore, device clinical investigation application must be reviewed and receive written recommendation and written approval from Institutional Review Board (IRB) and National Research Ethics Review Committee (NRERC) of the Federal Democratic Republic of Ethiopia respectively. A copy of such approval letter from NRERC shall be provided to the Authority.

This approval should be sought either before or in parallel with the application for authorization of device clinical investigation by the Authority. However, the authorization of clinical

investigation by the Authority shall only be issued after the approval of the clinical investigation by NRERC.

Clinical investigators should be aware that under the provisions of article 27 of Food and Medicine Administration Proclamation (No. 1112/2019), a clinical investigation may not proceed if grounds for objection have been raised by the Authority, even if approval has been granted by a research ethics committee. Hence, authorization of the device clinical investigation studies by the authority is required prior initiation of the study.

6.5. Clinical investigation plan (CIP)

The applicant shall submit the latest version of the clinical investigation plan both in hard copy and soft copy to the Authority at a time of application for authorization of the clinical investigation. The content of a CIP and any subsequent amendments together with justification shall include all the topics listed in this section of the dossier.

6.5.1. General

A) Identification of the clinical investigation plan

a) Title of the clinical investigation.
b) The phase of the clinical investigation
c) Reference number identifying the specific clinical investigation.
d) Version and issue date of the CIP with the page number and the total number of pages on each page of the CIP
e) Summary of the revision history in the case of amendments.

B) Sponsor

Name and address of the sponsor of the clinical investigation. If the sponsor is not resident in Ethiopia, the name and address of coordinator or agent representing the sponsor shall also be required.

C) Principal investigator, coordinating investigator and investigation site(s)

a) Name, address, and professional position of
    i. principal investigator(s),
    ii. coordinating investigator, if appointed
b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.
c) Name(s) and address(es) of other institutions involved in the clinical investigation.

The sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list can be kept separately from the CIP. The definitive list shall be provided with the clinical investigation report.

D) Overall synopsis of the clinical investigation

A summary or overview of the clinical investigation shall include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s).
lt may be useful to include a flow chart showing the key stages of the clinical investigation or any other information that can be of value for the conduct of the clinical investigation.

6.5.2. Identification and description of the investigational device

a) Summary description of the investigational device and its intended purpose.
b) Details concerning the manufacturer of the investigational device.
c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.
d) History of development of the investigational device, if applicable
e) Description as to how traceability shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers.
f) Intended purpose of the investigational device in the proposed clinical investigation.
g) The populations and indications for which the investigational device is intended.
h) Description of the investigational device including any materials that will be in contact with tissues or body fluids. (This shall include details of any medicinal products, human or animal tissues or their derivatives, or other biologically active substances.)
i) Summary of the necessary training and experience needed to use the investigational device.
j) Description of the specific medical or surgical procedures involved in the use of the investigational device.

6.5.3. Justification for the design of the clinical investigation

Justification for the design of the clinical investigation, which shall be based on the conclusions of the evaluation and shall comprise

a) an evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the investigational device in human subjects, and
b) an evaluation of clinical data that are relevant to the proposed clinical investigation.

6.5.4. Risks and benefits of the investigational device and clinical investigation

a) Anticipated clinical benefits.
b) Anticipated adverse device effects.
c) Residual risks associated with the investigational device, as identified in the risk analysis report.
d) Risks associated with participation in the clinical investigation.
e) Possible interactions with concomitant medical treatments.
f) Steps that will be taken to control or mitigate the risks.
g) Risk-to-benefit rationale.

The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control is described in ISO 14971.

6.5.5. Objectives and hypotheses of the clinical investigation

a) Objectives, primary and secondary.
b) Hypotheses to be accepted or rejected by statistical data from the clinical investigation.
c) Claims and intended performance of the investigational device that are to be verified.
d) Risks and anticipated adverse device effects that are to be assessed.

6.5.6. Design of the clinical investigation

A) General

a) Description of the type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice.
b) Description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking.
c) Primary and secondary endpoints, with rationale for their selection and measurement.
d) Methods and timing for assessing, recording, and analysing variables.
e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.
f) Any procedures for the replacement of subjects.

B) Investigational device(s) and comparator(s)

a) Description of the exposure to the investigational device{s) or comparator(s). if used.
b) Justification of the choice of comparator(s).

c) List of any other medical device or medication to be used during the clinical investigation.
d) Number of investigational devices to be used, together with a justification.

C) Subjects

a) Inclusion criteria for subject selection.
b) Exclusion criteria for subject selection.
c) Criteria and procedures for subject withdrawal or discontinuation.
d) Point of enrolment.
e) Total expected duration of the clinical investigation.
f) Expected duration of each subject's participation.
g) Number of subjects required to be included in the clinical investigation.
h) Estimated time needed to select this number (i.e. enrolment period).

D) Procedures

a) Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation.
b) Description of those activities performed by sponsor representatives (excluding monitoring).
c) Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.

Example: Factors include subject baseline characteristics, concomitant medication, the use of other medical devices and subject-related factors such as age, gender or lifestyle. The methods for addressing these factors in the clinical investigation, for example by subject selection, clinical investigation design (such as stratified randomization) or by statistical analysis shall be described.

The follow-up period during the clinical investigation shall permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the investigational device and allow any risks associated with adverse device effects over that period to be identified and assessed.

The CIP shall specifically address what medical care, if any, will be provided for the subjects after the clinical investigation has been completed or withdraw before the clinical investigation is completed.

E) Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.

lt is possible to provide a detailed plan for monitoring arrangements separately from the CIP.

6.5.7. Statistical considerations

With reference to 6.6.5 and 6.6.6, the description of and justification for

a) statistical design, method and analytical procedures,
b) sample size,
c) the level of significance and the power of the clinical investigation,
d) expected drop-out rates,
e) pass/fail criteria to be applied to the results of the clinical investigation,
f) the provision for an interim analysis, where applicable,
g) criteria for the termination of the clinical investigation on statistical grounds,
h) procedures for reporting any deviation(s) from the original statistical plan,
i) the specification of subgroups for analysis,
j) procedures that take into account all the data,
k) the treatment of missing, unused or spurious data, including drop-outs and withdrawals,
l) the exclusion of particular information from the testing of the hypothesis, if relevant, and
m) in multicentre clinical investigations, the minimum and maximum number of subjects to be included for each centre.

Special reasoning and sample size(s) may apply for the early clinical investigation(s), e.g. feasibility clinical investigation (s).

6.5.8. Data management

a) Procedures used for data review, database cleaning, and issuing and resolving data queries.
b) Procedures for verification, validation and securing of clinical data systems.
c) Procedures for data retention.
d) Specified retention period.
e) Other aspects of clinical quality assurance, as appropriate.

6.5.9. Amendments to the CIP

Description of the procedures to amend the CIP.

6.5.10. Deviations from clinical investigation plan

a) Statement specifying that the investigator is not allowed to deviate from the CIP, exception may apply.
b) Procedures for recording, reporting and analysing CIP deviations.
c) Notification requirements and time frames.
d) Corrective and preventive actions and principal investigator disqualification criteria.

6.5.11. Investigational device(s): Quality, Handling & Accountability

a) Description of the procedures for the accountability (amount received, distributed, returned, unused etc) of investigational devices.
b) Quality management system or medical device good manufacturing practice implemented by the manufacturing facility during design, manufacturing, shipment, handling, storing and distribution of the devices.
c) Responsible person for investigational product accountability

GCP also requires investigators to control receipt, administration, and disposition of the investigational product. After approval of the clinical trial by the Authority, investigator/sponsor can request order permit to import investigational device (s) and comparator device (if applicable) using the requirements indicated on Annex V.

Procedure for receiving, handling and storing, issuing and investigational products and comparator devices (if applicable) should be provided by the sponsor.

6.5.12. Statements of compliance

a) Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
b) Statement specifying compliance with this guideline and other relevant national and international Standard.
c) Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC or regulatory authority have been obtained.

d) Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed.
e) Statement specifying the type of insurance that shall be provided for subjects.

6.5.13. Informed consent process

a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information, as needed.
b) Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, illiterate subjects, shall be included.

6.5.14. Safety Monitoring and Management; device deficiencies and Reporting

a) Definitions of adverse events and adverse device effects.
b) Definition of device deficiencies.
c) Definitions of serious adverse events and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.
d) Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority.
e) Details of the process for reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device).
f) Details of the process for reporting device deficiencies.
g) List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment.
h) Emergency contact details for reporting serious adverse events and serious adverse device effects.
i) Information regarding the DMC, if established.

Any adverse incident involving a medical device undergoing clinical investigation should be reported to the sponsor, and the Ethiopian Food and Drug Authority.

The sponsor has primary responsibility for reporting of study safety data to EFDA and other investigators and for the ongoing global safety assessment of the investigational product. A

Data Monitoring Committee (DMC) may be constituted by the sponsor to assist the overall safety management. Even though reporting of safety data is the primary responsibility of the sponsor, the principal investigator must report serious adverse event (SAE) and the measures taken to manage the AE to the Authority, in writing, within 48 hours of occurrence of the event (with the format indicated in Annex VI), even if the AE is considered not to be related to the research procedures. Summary of other non-serious adverse events should be reported every six months together with the progress in tabulated form.

Applicant may consult internationally recognized documents such annex-F of ISO 14155 for categorization of Adverse Events categorization.

6.5.15. Monitoring the Clinical investigation

The sponsor shall assess the extent and nature of monitoring appropriate for the clinical investigation, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation. Results of this assessment shall be used to develop a monitoring plan.

Sponsors generally perform site monitoring of a clinical investigation to ensure quality of investigation and well-being of the subject. The sponsor may perform such monitoring directly or may utilize the services of an outside individual or organization e.g., contract research organization (CRO) through the monitor.

6.5.16. Vulnerable population

a) Description of the vulnerable population.
b) Description of the specific informed consent process.
c) Description of the specific care that should be provided for those group of subjects
d) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed or participant withdrawal before the investigation is completed.

6.5.17. Suspension or premature termination of the clinical investigation

a) Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.

b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation if the clinical investigation involves a blinding/masking technique.
c) Requirements for subject follow-up.

6.5.18. Publication policy

a) Statement indicating the results of the clinical investigation will be submitted and approved by the Authority before publication (if the result is to be published).
b) Statement indicating the conditions under which the results of the clinical investigation will be offered for publication.

6.5.19. Investigational Site(s) and Investigator (s)

The complete address of the clinical investigation site(s) showing the activities performed at the site(s) should be described.

There should be adequate number of qualified investigators to conduct the proposed clinical investigation. The investigator's curriculum vitae or other statement of education, training and experience may provide initial information about the investigator's qualifications to provide medical care and to conduct clinical research as per the recommended format indicated in the Annex VII.

6.5.20. Responsibility of Sponsor and Monitor

The sponsor is generally responsible for ensuring that the applicable regulatory review is performed by the Authority and to obtain any authorizations for the conduct of the clinical investigation before the commencement of the investigation. Details of the sponsor including the name and complete addresses should be provided.

Information on the selection of investigation site (s) and the selection of properly qualified, trained, and experienced investigators and study personnel should be provided.

The sponsor is also responsible for the quality of investigational device(s) including handling of the investigational device(s) during shipment and updating supporting data on investigational devices. Hence such information should be provided in the respective section of this Guideline.

Monitors are responsible for protecting the rights and well-being of human participants, confirming the reported investigation data are accurate, complete, and verifiable from source

documents, the conduct of the investigation in compliance with currently approved clinical investigation plan, with medical device GCP, and with the applicable regulatory requirement(s).

The monitor acts as the main line of communication between the sponsor and the investigator.

Monitor should be appointed by the sponsor. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge and professional qualifications needed to monitor the clinical investigation adequately. A monitor's qualifications should be documented and checked by sponsors.

6.5.21. Bibliography

List of bibliographic references pertaining to clinical investigation.

6.6. Investigator's brochure (IB)

The content of the IB shall contain, as a minimum, all topics listed in this guideline

6.6.1. General

A) Identification of the IB

a) Name of the investigational device.
b) Document reference number
c) Version and date of the IB with the page number and the total number of pages on each page of the IB.
d) Confidentiality statement, if appropriate.
e) Summary of the revision history in the case of amendments, if appropriate.

B) Sponsor and manufacturer

Name and address of the sponsor and manufacturer of the investigational device.

6.6.2. Investigational device information

a) General description of the investigational device and its components including materials used.
b) Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.
c) Regulatory classification of the investigational device.
d) Summary of relevant manufacturing processes and related validation processes.

e) Description of the mechanism of action of the investigational device, along with supporting scientific literature.

f) Manufacturer's instructions for installation and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant.

g) Description of the intended clinical performance.

6.6.3. Results from preclinical testing

Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing justifying its use in human subjects. The summary shall include or, where applicable, refer to the results of

a) design calculations,
b) in vitro tests,
c) mechanical and electrical tests,
d) duty cycle or reliability tests,
e) validation of software relating to the function of the device,
f) any performance tests,
g) ex vivo tests, and
h) an evaluation of biological safety.

NB: Guidance on the biological evaluation of medical devices is given in ISO 10993.

6.6.4. Existing clinical data

a) Summary of relevant previous clinical experience with the investigational device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device.

b) Analysis of adverse device effects and any history of modification or recall.

6.6.5. Risk management

a) Summary of the risk analysis, including identification of residual risks.

b) Result of the risk assessment.

c) Anticipated risks, contra-indications, warnings, etc. for the investigational device.

6.6.6. Regulatory and other references

a) List of International Standards, if any, complied with in full or in part.
b) Statement of conformity with national regulations, where appropriate.
c) List of references, if relevant.

6.7. Conduct of a clinical investigation

The clinical investigation shall be conducted in accordance with the principles set in the Authority's Guideline for Medical Devices Good Clinical Practice.

Sponsors and investigators must ensure that the investigation is conducted in full accordance with the approved clinical investigation plan (CIP) and the requirements of this guideline.

There must be adequate monitoring in place to ensure that the rights, safety and well-being of subjects are protected.

All information relating to the clinical investigation must be recorded, processed and stored by the sponsor or investigator in such a way that it can be interpreted and reported, and not impact upon the confidentiality of the records and personal data of the subjects. The personal data of the subjects must be protected in line with General Data Protection Regulations.

Study records documenting each trial - related activity provide critical verification that the study has been carried out in compliance with the clinical investigation plan.

Case report forms (CRFs) for each scheduled study visit to capture all the necessary data collected from and reported for each participant should be developed and a copy of this CRF/eCRF should be provided for review during application of clinical trial authorization.

There must be an emergency procedure to enable immediate identification of the devices within the investigation – this may be required in the event of an immediate recall of the devices.

6.8. Reporting and End of the Clinical Investigation

6.8.1. Periodic Update (progress) Report

Formats for periodic progress reports of the clinical trial study should be provided. The specified reporting period should be supported by justification. Abbreviated or less detailed reports may be acceptable. Format for periodic report should consider points such as:

- CIP deviation
- CIP amendment

- SAE report (in multicentre study overall safety report (if applicable)
- Clinical investigation status summary including recruitment status
- A discussion of any interim analyses

6.8.2. End/Termination of clinical investigation

The Authority should be informed with an official letter of the sponsor when discontinuation/termination of the clinical investigation occurs either prematurely, or upon suspension or upon the end including completion of the objectives of the clinical investigation. The investigator/sponsor should provide written commitment letter indicating that the Authority will be informed when any such discontinuation/termination of the investigation occurs and upon completion of the investigation, to provide the findings of the study (for review) before dissemination. This commitment letter must be submitted during application for clinical investigation authorization. The official letter of the sponsor must be provided to the Authority within 90 days of the end of a clinical investigation by the sponsor.

If the investigation is prematurely ended or terminated or suspended for any reason, the investigator should promptly inform the subjects, should ensure appropriate therapy and follow-up for the participants.

The definition of the end of the investigation should be provided in the CIP by the sponsor. An earlier end of the clinical investigation, which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as ‘early termination’.

In the case of early termination of any clinical investigation, the sponsor must notify the end of the investigation to the Authority immediately within 15 days after the investigation is halted, with clear reasons and justification, and describe follow- up measures, if any, taken for safety reasons.

6.8.3. Clinical investigation Report

The sponsor shall provide clinical investigation report to the Authority within one year of the end of the completion of the investigation. The content of the report should contain all information provided in Annex VIII of this guideline.

Sponsor/investigator should notify and obtain prior written approval from the Authority before dissemination and use of the results of the investigation in accordance with article 4(11) of Food and Medicine Administration Proclamation No. 1112/2019. Hence, publication and

dissemination of results of the investigation should be conducted after submission of the final clinical investigation report and written approval from the Authority.

7. Labelling of Medical Devices

All devices intended for clinical investigation must bear the wording ‘exclusively for clinical investigation’ or “for clinical investigation use only”. To avoid misunderstandings as to the nature of the clinical investigation, i.e., that it is the device under investigation and not the patient, all clinical investigators should ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the device and that it is segregated, where possible, from devices in routine use. In some cases, the clinical investigator may consider it necessary to attach appropriate warning signs to the device under investigation.

8. Application for Clinical Investigation Amendments

Amendments to be made to the conduct of a clinical investigation after its commencement may be allowed. All proposed changes to the clinical investigation whether relating to the device, aspects of the clinical investigation plan, investigators or investigating institutions must be notified to the Authority.

In addition, when a sponsor and/or investigator must take urgent safety measures to protect the subjects from immediate hazard allows them to do so before notifying the Authority, but they must notify the participants and the authority in writing as soon as possible.

Major amendments to the conduct of the clinical investigation which may arise from changes to the clinical investigation plan or from new information relating to the scientific documents in support of the investigation should be submitted for approval. However, investigator/sponsor can implement minor amendments immediately after submission and proper categorization of amendments are confirmed in writing by the Authority.

The sponsor or sponsor representative (principal investigator in some case, if appointed by the sponsor) are responsible for the submission of major amendments to the Authority prior to the implementation of such amendments in the conduct of the clinical investigation.

The application should include the application form set out in Annex IX and the proposed version of the clinical investigation plan and/or other documents affected by the proposed change, with an explanatory cover letter of the sponsor to the Authority. The applicant must submit the original wording, revised wording, and rationale for the change including a copy of a complete clinical investigation plan incorporating all amendments.

Annex I: Application Form for submission of Medical device Clinical investigation

A. Medical Device Clinical Investigation Identification:

1. Name of scientific working group ……
2. Title of medical device clinical investigation …….
3. Phase of the medical device clinical Investigation……
4. State the objective of the investigation and the reasons thereof…….
   ……
   ……..……..……
   ……..……
   ……
5. Duration of (time period for) the Investigations ……

B. Sponsor Identification

1. The name of the sponsor of the investigation……
2. Full address of the sponsor……
   ……

C. Details of investigator (s)

State the name(s), telephone number(s) and qualification of the person (s) who will conduct the investigation

Name	Qualification	Address & telephone No.	Email address

D. Details of CRO and/or medical device clinical investigation sites

1. State the name(s), physical address and telephone number of the institution (s) or places where the medical device clinical investigation will be conducted. Detail name and address of CRO, Clinical investigation sites, statistical analysis sites etc. should be provided

   ……
   ……

……

……

…….

2. Statement on the capacity of the institutions /investigation site to carry out the clinical trial……
   ……
   …….

E. Information on the Investigational medical device, comparator

1. The name of the investigational medical device: ……
   ……
   ……..
2. Intended use of investigation medical device and medical device being used as a control
   …….
   ……
   ……
   ……..
3. State the name and address of the manufacturing site……..
4. Medical device used as comparator …….

F. Population of the investigation participant

1. Description of the participants (e.g. age group of the subjects, type of study participant, sex)……
   ……..……..
2. Number of participants expected to take part and Justification thereof (based on statistical consideration)……

…..……..……
…….

G. Ethical committee

1. Is this clinical investigation plan approved by National Research Ethics Review Committee (NRERC)? Yes/No
   If No, Please provide the reasons thereof.……
   ……
   ……
2. Is this clinical investigation plan approved (has got favorable opinion) by Institutional Review Board (IRB), Level A? Yes/No
   If No, Please provide the reasons thereof.……
   ……
   ……
3. If any, Please specify the name and address of other Ethical clearance certificate related to this clinical trial. ……

H. Insurance

1. Description of the name and address of the company who will insure all the subjects in the proposed investigation ……
2. State the amount of insurance in respect of each participant……

   …..……..……

Signature of principal investigator …… Signature of sponsor ……..

Name and address of principal investigator
Date…… Name and address of the sponsor
Date:…….

Stamps

FOR OFFICIAL USE ONLY

Date of Approval……

Signature of the person to sign on the behalf of the Authority

Name……

Position……..

Signature ……..

Date of Rejection and the reasons (if)……..

……

Medical device clinical investigation information documents attached:

- Clinical Investigation plan
- Investigator’s brochure
- Principal investigator's CV: current, signed and dated
- CV of key members of the Investigation team: current, signed and dated
- Investigational supplies accountability
- Signature logs of principal investigator and key members of investigation site team
- Ethics committee (EC) notification correspondence and opinion/approval
- case report forms (CRFs)
- Signed agreement between principal investigator(s)/investigation site(s) and Sponsor
- Shipping records for investigational device
- informed consent documents
- Randomization list for randomized clinical Investigation
- adverse event reporting forms;
- Disclosures of conflicts of interest
- administrative forms to track research funds and expenses;
- formats for reports of monitoring visits;
- Insurance certificate
- Formats for progress reports, annual reports, and final study reports etc.

Annex II: Agreement between Investigator & Sponsor

Name of scientific working group (study team):

1. The Sponsor: ……..

2. The Investigator(s): ……

3. Other (if any): ……

4. Name of the clinical investigation: ……..

We hereby agree, in the capacity of principal investigator, the sponsor, and the site of the clinical investigation in the above-named project to conduct the investigation in accordance with the statements and procedures stipulated in the clinical investigation plan agreed up on by the Food and Drug Authority of Ethiopia and ourselves.

We also agree to submit a copy of our findings to the Authority prior to its being published elsewhere in any manner or form.

Signature of principal investigator: _____ Date: _____

Signature of the sponsor: _____ Date: _____

Annex III: Declaration of Sponsor and Principal Investigator concerning sufficient funds to complete the investigation

Title of Clinical Investigation:

…….

Clinical Investigation Plan No:……

I, <full name>, representing <sponsor >

And

I, <full name>, Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified clinical trial study.

Sponsor:

Signature _____ Date: _____-

Name

Address

Contact details

Principal Investigator :

Signature of Principal Investigator: _____ Date: _____

Name

Address

Contact details

Annex IV: Declaration by Investigator(s)

Name: _____

Title of Clinical Investigation: _____

Name Clinical Investigation: _____

Clinical Investigation Site: _____

I/We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

I/We, the undersigned, hereby declare that all information contained in, or referenced by, this application is complete and accurate and is not false or misleading.

I/we am (are) familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the principal investigator within the context of this study.

I/we have thoroughly read, understood, and critically analysed the CIP and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).

To the best of my/our knowledge, I/we have the potential at the site(s) I/we am (are) responsible for, to recruit the required number of suitable participants within the stipulated time period.

I/we will not commence with the investigation before written authorizations from the relevant Research Ethics Committee(s) as well as the Authority have been obtained.

I/we will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.

I/we will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.

Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical investigation.

[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions.]

I/we have / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice.

I/we have / have not (delete as applicable) previously been involved in a investigation which has been closed as a result of unethical practices.

I/We, the undersigned, agree to ensure that if the above-said medical device clinical investigation is approved, it will be conducted according to the submitted CIP and all applicable legal, ethical, regulatory requirements and in accordance with GCP.

Signature of principal investigator: _____ Date: _____

Name: _____

Signature of co-investigator: _____ Date: _____

Name: _____

Annex V: Required Documents for Authorizing the Importation of the Investigational device and/or Comparator device, if any

Investigational Device(s): Name/code of the devices

Importation and Release of Investigational Medical Device			
Checklist of required documentation			
Are the following documents attached and correct, as indicated:			
S. No.	**Description**	**Yes**	**No**
1	Copy of the letter of approval of medical device clinical investigation by the Authority		
2	Copy of valid GMP/QMS compliance certificate of Manufacturer issued by the competent NRA in the country of manufacture.		
3	Declaration of conformity (DoC)		
4	Sample of actual labeling materials and/or color print (Outer packaging & immediate container): Should show-the following information		
	Device name or unique code (if blinded)		
	Device label should indicate product is clinical investigation material e.g. “For use in clinical investigation only”.		
	Storage temperature, if applicable		
	Batch number, if applicable		
	Date of Manufacture and expiry date		
	Sponsor contact detail		

Annex VI: Serious Adverse Event Reporting Form

Clinical Investigation Plan (CIP) and Event Type	
Study title	
CIP No.	
EFDA Ref. No.	
Date of receipt	
Seriousness of adverse event (choose one)	Death Life-threatening Initial or prolonged hospitalization Disability Congenital Anomaly Required intervention to prevent permanent impairment Other medically important condition
Severity of the event	Minimum Moderate Sever Life-threatening Fatal
Was this event expected in terms of its severity?	Yes No
Was this event expected in terms of its specificity?	Yes No
Relationship of event to gene transfer product	Unrelated Unlikely Possible Probable Definite
Attribution of AE	Medical device Intervention Underlying disease Other suspected cause (describe)
Demographics	
PI Name	
Name of Clinical Investigation site/ Organization	
PI Telephone No.	
PI E-mail Address	
Reporter Name	
Reporter Telephone No.	
Reporter E-mail Address	
Research Participant's study identification number	
Research Participant's gender	
Research Participant's date of birth	
Research participant's date of death (if any)	
Research Participant's weight in kg	
Research participant's height in cm	
Which arm/cohort/treatment group was the participant assigned to?	
Which arm/cohort/treatment group was the subject assigned to?	

Was the device applied to the participant?	Yes No Information not available
What study product was received	Investigation medical device Placebo Comparator medical device
Is there any CIP deviations/violations/Exceptions for this participant?	Yes: (if yes, indicate in detail) …… No.
Detailed Adverse Event Information	
Adverse event date	
Description of events	
Relevant tests (e.g. X-rays) and results	
Treatment (s) of adverse events (include medications used to treat this event)	
Pre-existing conditions/relevant clinical history	
Date(s) of treatment(s) of the adverse event	
Was autopsy performed?	Yes No If yes, Date of autopsy,_____
Outcome of event	Recovered/Resolved Recovering/Resolving Not recovered/not resolved Recovered/resolved with sequelae Fatal Unknown
Documentation accompanying the report (e.g. H & P, Progress notes, discharge summary, lab or autopsy reports, other, etc)	
Product information	
Name of investigational device	
Batch/Lot Number, if any	
Manufactured date if any	
Expiry date, if any	
Name and address of the manufacturing site	
Date of first exposure of the device	
Date of most recent exposure of the device	
If course used, how many were given prior to this event?	
Was using of this product stopped because of this adverse event?	
Name of other treatment (s) (radiation, surgery) received by research participant as required by the plan	

Annex VII: Recommended Format for CVs of Investigators in Clinical Investigation

1. Study Title:
2. CIP Number:
3. Designation:
4. Personal Details
    - Name:
    - Work Address:
    - Telephone Number:
    - Fax Number:
    - Cell-phone Number:
    - e-mail address:
5. Academic and Professional Qualifications
6. Professional registration status
7. Relevant related work experience (brief) and current position
8. Participation in clinical Investigation/trials research in the last five years [Study title, CIP/protocol number, designation. If multiple trials, only list those with relevance to this application, or in the last year]
9. Peer-reviewed publications in the past five years
10. Date of last GCP training [As a participant or presenter]
11. Any additional relevant information supporting abilities to participate in conducting this trial [Briefly]

Signature:…… Date:……..

Annex VIII: Clinical Investigation Report

The content of the clinical investigation report should describe the design, execution, statistical analysis, and results of a clinical investigation. The format given here may be used in progress and final reports

1. Cover page

The title page should contain the following information:

a. title of the clinical investigation.
b. identification of the investigational devices, including names, models, etc. as relevant for complete identification.
c. if not clear from the title, a single sentence describing the design, comparison, period, usage method, and subject population.
d. name and contact details of sponsor or sponsor's representative.
e. CIP identification.
f. name and department of coordinating investigator and names of other relevant parties, e.g. experts, biostatistician, laboratory personnel;
g. statement indicating whether the clinical investigation was performed in accordance with this International Standard or any other applicable guidelines and applicable regulations;
h. date of report;
i. author(s) of report.

2. Table of contents

The table of contents should include the following information:

a. the page number or locating information of each section, including summary tables, figures, and graphs,
b. a list of appendices and their location.

3. Summary

The summary should contain the following items:

a. the title of the clinical investigation.
b. an introduction
c. the purpose of the clinical investigation

d. description of the clinical investigation population
e. the clinical investigation method used
f. the results of the clinical investigation
g. the conclusion
h. the date of the clinical investigation initiation
i. the completion date of the clinical investigation or, if the clinical investigation is discontinued, the date of
j. premature termination.

4. Introduction

The introduction should contain a brief statement placing the clinical investigation in the context of the development of the investigational device and relating the critical features of the clinical investigation (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development.

Any guidelines that were followed in the development of the CIP or any other agreements/meetings between the sponsor and regulatory authorities that are relevant to the particular clinical investigation should be identified or described.

5. lnvestigational device and methods

a) lnvestigational device description

The description of the investigational device should contain the following points:

a) a description of the investigational device;
b) the intended use of the investigational device(s);
c) previous intended uses or indications for use, if relevant;
d) any changes to the investigational device during the clinical investigation or any changes from the including
    - raw materials,
    - software,
    - components,
    - shelf-life,
    - storage conditions,
    - instructions for use, and
    - other changes.

b) Clinical investigation plan (CIP)

A summary of the CIP, including any subsequent amendment(s) with a rational for each amendment, should be provided. The summary should include a brief description of the following points:

a) the clinical investigation objectives;
b) the clinical investigation design including
    - the type of clinical investigation, and
    - the clinical investigation endpoints,
c) the ethical considerations;
d) the data quality assurance;
e) the subject population for the clinical investigation, with the
    - inclusion/exclusion criteria, and
    - sample size.
f) the treatment and treatment allocation schedule;
g) any concomitant medications/treatments;
h) the duration of follow-up;
i) the statistical analysis including
    - the clinical investigation hypothesis or pass/fail criteria,
    - a sample size calculation, and
    - statistical analysis methods.

c) Results

The results report should include the following points:

a) the clinical investigation initiation date;
b) the clinical investigation completion/suspension date;
c) the disposal of subjects and investigational devices;
d) the subject demographics;
e) CIP compliance;
f) an analysis, which includes
    - a performance analysis provided for in the CIP,
    - a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure,
    - a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical investigation, if any,
    - any needed subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic subgroups), as appropriate,
    - an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects
        - ✓ not passing screening tests,
        - ✓ lost to follow-up,
        - ✓ withdrawn or discontinued from the clinical investigation and the reason.

d) Discussion and overall conclusions

The conclusions should include the following points:

a) the safety or performance results and any other end points;
b) an assessment of risks and benefits;
c) a discussion of the clinical relevance and importance of the results in the light of other existing data;
d) any specific benefits or special precautions required for individual subjects or groups considered to be at risk;
e) any implications for the conduct of future clinical investigations;

f) any limitations of the clinical investigation.

e) Abbreviated terms and definitions

A list of abbreviated terms and definitions of specialized or unusual terms should be provided.

f) Ethics

The ethics report should include the following points:

a) a confirmation that the CIP and any amendments to it were reviewed by the EC (if required);
b) a list of all ECs consulted

g) Investigators and administrative structure of clinical investigation

The overview of the administrative structure should include the following points:

a) a brief description of the organization of the clinical investigation;
b) a list of investigators, including their affiliations ;
c) the names and addresses of any third parties (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation;
d) the names and addresses of the sponsor(s) or sponsors' representative(s).

h) Signature page

The signatures of the sponsor and coordinating investigator(s), indicating their agreement with the contents of the report, should be provided. If no coordinating investigator is appointed, then the signature of the principal investigators should be obtained. The signature pages may be separate from the clinical investigation report itself.

i) Annexes to the report

There can be annexes to the report which contain the following information:

a) the CIP, including amendments.
b) the instructions for use;
c) the list of principal investigators and their affiliated investigation sites, including a summary of their qualifications or a copy of their CVs;
d) the list of names and addresses of any third parties (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation;
e) the list of monitors;
f) the list of ECs;
g) the tabulation of all relevant data sets, including

- CIP deviations that can have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation,
- all adverse events, adverse device effects and device deficiencies, and
- withdrawals and discontinuations,

h) the audit certificate, if applicable.

Annex IX: Application for Amendment to Medical Device Clinical Investigation

A. **Date of Application:** _____

B. Identification of the Medical Device Clinical Investigation

1. Title of clinical investigation: _____

_____

_____

_____

2. Previous Approval number and date of approval: _____, _____
3. Previous CIP No.: _____
4. Principal Investigator: _____
5. Sponsor: _____

C. Amendment Identification

S. No.	**Description**	**Change status**	
		Yes	**No**
1	Amendment to information in the medical device clinical Investigation application form:		
2	Amendment to the Clinical Investigation Plan (CIP)		
3	Amendment to other documents appended to the initial application form		
4	Amendment to other documents or information		
5	The amendment concerns mainly urgent safety measures already implemented		
6	This amendment is to notify a temporary halt of the clinical investigation		
7	This amendment is to request the restart of the clinical investigation		
8	If other, please specify: _____ _____ _____		

D. Brief Description of the Change:

_____

_____

_____

_____

_____

_____

E. Reasons for the Amendments:

S. No.	Description	Change status	
		Yes	**No**
1	Changes in safety or integrity of clinical investigation participants		
2	Changes in interpretation of scientific documents/value of the investigation		
3	Changes in quality of investigational product(s)		
4	Changes in conduct or management of the clinical investigation		
5	Change or addition of principal investigator(s), co-coordinating investigator		
6	Change of sponsor		
7	Change/addition of site(s)		
8	Change in transfer of major investigation-related duties		
9	If other change, please specify: _____ _____ _____		

I/We, the undersigned, agree to conduct / manage the above-mentioned investigation under the conditions as stated in this application.

(The person(s) undertaking legal responsibility to sign this form).

Signature of principal Investigator: _____ Date: _____

Name of principal Investigator: _____

Signature of Sponsor: _____ Date_____

Name & Position of Sponsor: _____

Reference:

1. Food and Medicine Proclamation 1112/2019, 2019.
2. Clinical Trial Authorization Guideline, 2nd Edition, Ethiopia Food and Drug Authority, 2022.
3. Clinical investigations of medical devices – guidance for investigators, Guidance on Legislation, MHRA, May, 2021.
4. Clinical investigation of medical devices for human subjects - Good clinical practice. BSI Standards Publication, BS EN ISO 14155:2011.