



Zambia Medicines Regulatory Authority

**Guidelines for Authorisation of Clinical Investigations Involving Medical
Devices in Humans**

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Table of Contents

i.	Abbreviation	3
ii.	Definition	4
1.	Introduction.....	8
2.	General Requirements.....	9
3.	Documents Required for Application for a Clinical Investigation Certificate	10
3.1.	General Documents.....	11
3.2.	Scientific Documents	12
4.	Conduct of Clinical Investigation	27
5.	Reporting and End of the Clinical Investigation.....	28
5.1.	Safety Reporting	28
5.2.	Major and Minor Protocol Deviations	28
5.3.	Periodic Update (progress) Report.....	28
5.4.	End/Termination of clinical investigation	29
5.5.	End of Clinical Investigation	29
5.6.	Early or Premature Termination	29
5.7.	Clinical Investigation Report.....	29
6.	Labelling of Medical Devices.....	30
7.	Application for Clinical Investigation Amendments	30
	Annex I: Agreement between Investigator & Sponsor.....	31
	Annex II: Declaration of Sponsor and Principal Investigator	32
	Annex III: Declaration by Investigator(s).....	33
	Annex IV: Recommended Format for CVs of Investigators in Clinical Investigation	35
	Annex V: Clinical Investigation Report	36
	Annex VI: Abridged product dossier requirements.....	39
8.	References.....	41
9.	Amendment Sheet.....	42

**i. Abbreviation**

AE	Adverse Events
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CTA	Clinical Trial Application
DMC	Data Monitoring Committee
DoC	Declaration of Conformity
GCP	Good Clinical Practice
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Information For Use
IRB	Institutional Review Board
ISO	International Organisation for Standardization
IPD	Investigational Product Dossier
IVD	Invitro Diagnostic Device
MA	Marketing Authorisation
MD	Medical Device
NHRA	National Health Research Authority
PACTR	Pan African Clinical Trials Registry
PI	Principal Investigator
QMS	Quality Management System
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
SUSAR	Suspected Unexpected Serious Adverse Reaction
ToC	Table of Content
WHO	World Health Organisation
ZAMRA	Zambia Medicines Regulatory Authority

**ii. Definition**

In this guideline unless the context otherwise specifies:

Authority means the Zambia Medicines Regulatory Authority

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

Analytical Performance Study evaluates an in vitro diagnostic (IVD) device's technical ability to correctly detect or measure a target analyte under defined conditions

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

Clinical Investigation Plan (CIP) (Protocol) is a document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation

Comparator is a 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 a 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 an investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation



Data monitoring committee (DMC) is an 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 to the sponsor whether to continue, suspend, modify, or stop the clinical investigation

Device Label is a display of written, printed, or graphic information that appears on a device or its packaging and provides important information about the device

Deviation is an instance of failure to follow, intentionally or unintentionally, the requirements of the CIP

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

Information for Use (IFU) provides instructions for the safe and effective use of a medical device

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

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

Investigational Product Dossier (IPD) is a regulatory document submitted to regulatory authorities to authorise clinical trials involving a test product, detailing its quality, safety, and effectiveness or performance.

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



Medical Device means any instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- providing information by means of *in vitro* examination of specimens derived from the human body;
- and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means;

Principal Investigator is a qualified person responsible for conducting the clinical investigation at an investigation site

Serious adverse device effect (SADE) is an SAE that is related, with a causal or reasonably possible relationship, to the use of: The MD under investigation (IMD)

Serious adverse event (SAE) that led to:

- death,
- serious deterioration in the health of the subject, that either resulted in, or
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalisation, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.



- foetal distress, foetal death or a congenital abnormality or birth defect

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

Participant is an individual who participates in a clinical investigation



1. Introduction

The Zambia Medicines Regulatory Authority (ZAMRA) is a statutory body established pursuant to the Medicines and Allied Substances Act, No.3 of 2013 of the Laws of Zambia (“the Act”). One of the mandates of the Authority is to regulate, control and monitor the conduct of clinical trials involving medicines and allied substances in humans. To carry out this mandate, the Authority has issued this guideline, pursuant to Sections 49 and 50 of the Act, to provide for information to be incorporated in the applications for grant of Clinical Trial Certificate by an applicant who intends to conduct a clinical trial involving an investigational medical device in Zambia.

The guideline aims to set requirements for the application, conduct and reporting of clinical investigations involving investigational medical devices, and to guide the sponsor and/or investigators on the documents and processes required for the application, conduct and reporting of clinical investigations using an investigational medical device. In addition, to facilitate the application process, forms and formats have been included as annexes to the guideline.

Considering the diversity of clinical investigation and performance study designs, and data sources used to support regulatory and other health policy decisions, this guideline focuses on designing quality into clinical investigations and performance studies. Analytical performance studies (involving stored samples) are out of the scope of this guideline, except in situations where specimens are collected from human participants specifically for the analytical performance study, which may result in risk for participants.

In addition to this guidance document, the applicant is advised to consult the Authority’s Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia and Guidelines for In Vitro Diagnostic Medical Device Market Authorisation Table of Contents (IVD MA ToC) on the format of submission of the quality information, and internationally recognized standards such as Clinical investigation of medical devices for human participant - Good Clinical Practice (latest version of ISO 14155), and In vitro diagnostic medical devices - Clinical performance studies using specimens from human participant - Good study practice (latest version of ISO 20916).



The Authority may amend any part of this Guideline from time to time.

1.1. Scope

This Guideline applies to the conduct of clinical investigation and performance studies involving medical devices (including in vitro medical devices) in humans or on biological samples from human participants in Zambia. It is applicable to investigational devices that fulfil the definition of medical device under the Act. The guideline provides for a procedure for application for authorisation to conduct a clinical investigation and performance study involving a medical device.

2. General Requirements

- 2.1. A person who intends to conduct a clinical investigation involving a medical device shall apply to the Authority as provided in this guideline.
- 2.2. An application shall be accompanied by supporting information as provided under **Section 3**. These shall be in an electronic text-selectable pdf, or Microsoft Word, submitted via the Authority's online portal. The application documents shall be in English language.
- 2.3. An application for authorisation of a device clinical investigation shall be accompanied by the proof of payment of fees as set out in the fee schedule of the Authority.
- 2.4. The Authority may, during evaluation, request additional information or samples through a letter indicating the queries.
- 2.5. The Authority shall, within 60 working days of receipt of an application, issue a Clinical Trial (Investigation) Certificate if the application meets all the requirements. The **60 working days** is regulatory time and excludes the time taken by the applicant to respond to queries.



2.6. The Clinical Trial (Investigation) Certificate shall be valid for a period as shall be specified in the Certificate.

2.7. All staff involved in clinical investigation shall be qualified by education, training and experience.

2.8. The Authority shall inspect clinical trial sites during the trial and at such intervals as it may determine.

2.9. Any amendment to the trial protocol, trial arrangements and investigational product shall be submitted to the IRB/IEC that originally approved the protocol and to the Authority for approval before such amendments are implemented.

2.10. Serious and non-serious adverse events (AEs) and device deficiencies that could lead to serious adverse event including serious health threats occurring during clinical investigations shall be reported to the Authority regardless of the causality.

3. Documents Required for Application for a Clinical Investigation Certificate

A Clinical Investigation Application made to the Authority shall be accompanied by the following:

- Cover letter
- Application Form via online portal (www.zamra.co.zm)
- Proof of Payment of prescribed fees
- Clinical Investigation Plan (protocol)
- Informed Consent and/Assent Form
- Investigator's Brochure (without MA in Zambia, as applicable)
- Ethical Committee approval letter or proof of submission for Ethical clearance
- Clinical Investigation insurance for participants
- Investigational Medical Device Dossier (without MA in Zambia, as applicable)
- Copy of valid ISO 13485 certificate from Manufacturer
- Labelling of Device



- Information for Use (IFU)
- Statistical Analysis Plan
- Clinical investigation agreement between sponsor and clinical investigation site(s)/principal investigator(s)
- Clinical investigation agreement between sponsor and Clinical Research Organization (CRO), if applicable
- Curriculum Vitae of the Principal investigator(s) and investigator(s)
- Disclosure of Principal Investigator Conflict of interest

3.1. General Documents

- Cover letter addressed to the Director General
- Application Form – completed via online portal (www.zamra.co.zm)
- Proof of payment of prescribed fees
- Proof that the clinical investigation is registered with the Pan African Clinical Trials Registry (PACTR) or a Clinical Trial Registry which is WHO recognised and publicly accessible shall be submitted either as a certificate of registration or registration number indicated on the CIP and application form.
- Informed Consent and/or Assent Form
- Ethics Committee approval letter or proof of submission for ethical clearance.

For all clinical investigations of devices falling within the scope of the medical devices, relevant ethics committee approval is required. Therefore, device clinical investigation application must be reviewed and receive written approval from relevant ethics body. This approval should be sought either before or in parallel with the application for authorisation of device clinical investigation by the Authority

- Clinical investigation insurance for participant
- Copy of valid ISO 13485 certificate from Manufacturer
- Clinical investigation agreement between sponsor and clinical investigation site(s)/principal investigator(s)
- Clinical investigation agreement between sponsor and Clinical Research Organization (CRO), if applicable



- 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 and a joint declaration by the sponsor and principal investigator concerning sufficient funds to complete a study should be submitted in the format provided in **Annex II** and **III** respectively. Additionally, a declaration by the investigator(s), in the format included in **Annex IV**, should be submitted.

- Curriculum Vitae of the Principal investigator(s) and investigator(s)
- Disclosure of Principal Investigator Conflict of Interests

3.2. Scientific Documents

3.2.1. Clinical investigation plan (CIP)/Protocol

The applicant shall submit the latest version of the clinical investigation plan to the Authority at the time of application for authorisation of the clinical investigation. The content of a CIP and any subsequent amendments together with justification shall include all the topics listed below.

3.2.1.1. General

a) Identification of the clinical investigation plan

- i. Title of the clinical investigation
- ii. The phase of the clinical investigation
- iii. Reference number identifying the specific clinical investigation.
- iv. Version and issue date of the CIP with the page number and the total number of pages on each page of the CIP
- v. Summary of the revision history in the case of amendments.

**b) Sponsor**

Name and address of the sponsor of the clinical investigation.

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

- i. Name, address, and professional position of
 - a. Principal Investigator(s); and
 - b. Coordinating Investigator, if appointed
- ii. Name and address of the investigation site(s) in which the clinical investigation will be conducted.
- iii. 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 participants, duration of the clinical investigation, follow-up, objective(s) and endpoint(s).

It 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.

3.2.1.2. 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) Description as to how traceability of the device shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers.
- e) Intended purpose of the investigational device in the proposed clinical investigation.
- f) The populations and indications for which the investigational device is intended.
- g) 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.)
- h) Summary of the necessary training and experience needed to use the investigational device.
- i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

3.2.1.3. 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 participant, and
- b) an evaluation of clinical data that are relevant to the proposed clinical investigation.

3.2.1.4. 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.

This risk management process should include risk analysis, risk-to-benefit assessment and risk control as is described in ISO 14971.

3.2.1.5. Objectives and hypotheses of the clinical investigation

- h) Objectives i.e primary and secondary.
- i) Hypotheses to be accepted or rejected by statistical data from the clinical investigation.
- j) Claims regarding the intended performance of the investigational device that are to be verified.
- k) Risks and anticipated adverse device effects that are to be assessed.

3.2.1.6. Design of the clinical investigation

a) General

- i. 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.
- ii. Description of the measures to be taken to minimise or avoid bias, including randomisation and blinding/masking.



- iii. Primary and secondary endpoints, with rationale for their selection and measurement.
- iv. Methods and timing for assessing, recording, and analysing variables.
- v. Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring, maintenance and calibration.
- vi. Any procedures for the replacement of participants.

b) Investigational device(s) and comparator(s)

- i. Description of the exposure to the investigational device(s) or comparator(s).
- ii. Justification of the choice of comparator(s) if used.
- iii. List of any other medical device or medication to be used during the clinical investigation that may have a bearing on participant safety and/or outcome measures (study endpoints).

c) Participant

- i. Inclusion criteria for subject selection.
- ii. Exclusion criteria for subject selection.
- iii. Criteria and procedures for subject withdrawal or discontinuation.
- iv. Point of enrolment.
- v. Total expected duration of the clinical investigation.
- vi. Expected duration of each subject's participation.
- vii. Number of participants required to be included in the clinical investigation.
- viii. Estimated time needed to select this number (i.e. enrolment period).

d) Procedures

- i. Description of all the clinical-investigation-related procedures that participant undergo during the clinical investigation.
- ii. Description of those activities performed by sponsor representatives (excluding monitoring).



- iii. 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 clinical investigation, for example by subject selection, clinical investigation design (such as stratified randomisation) or by statistical analysis shall be described.

The follow-up period during the clinical investigation shall permit the demonstration of performance over a period 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 participant after the clinical investigation has been completed or withdrawn before the clinical investigation is completed.

3.2.1.7. Statistical considerations

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 consider 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 participants 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).

3.2.1.8. 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.

3.2.1.9. Amendments to the CIP

Description of the procedures to amend the CIP.

3.2.1.10. Deviations from clinical investigation plan

- a) Statement specifying that the investigator is not allowed to deviate from the CIP, exceptions may apply.
- b) Procedures for recording, reporting and analysing CIP deviations.



- c) Notification requirements and time frames in line with local requirements
- d) Corrective and preventive actions and principal investigator disqualification criteria.

3.2.1.11. 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 shall apply to the Authority in the prescribed manner, for importation of investigational device (s) and comparator device (if applicable).

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

3.2.1.12. 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 regulatory requirements.
- c) Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the Ethics Committee (EC) and other relevant regulatory authorities have been obtained.
- d) Statement specifying that any additional requirements imposed by the EC or



regulatory authorities shall be followed.

- e) Statement specifying the type of insurance that shall be provided for participant.

3.2.1.13. Informed consent process

- a) Description of the general process for obtaining informed consent and/or assent, including the process for providing participants with new information, as needed.
- b) Description of the informed consent process in circumstances where the participant is unable to give it, for example, under-age, in the case of emergency treatment, illiterate participant, shall be included.

3.2.1.14. Safety Monitoring and Management: device deficiencies and reporting

- a) Definitions of adverse events, adverse device effects, serious adverse events, serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.
- b) Definition of device deficiencies.
- c) 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 authorities.
- d) 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).
- e) Details of the process for reporting device deficiencies.
- f) List of foreseeable adverse events and anticipated adverse device effects,



together with their likely incidence, mitigation or treatment.

- g) Emergency contact details for reporting serious adverse events and serious adverse device effects.
- h) Information regarding the Independent Data Monitoring Committee (IDMC), if established.

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

The sponsor has primary responsibility for reporting of study safety data, to the Authority and participating investigators, and for the ongoing global safety assessment of the investigational product. An IDMC 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 the site becoming aware of the event, even if the AE is considered not to be related to the research procedures. Summary of other non-serious adverse events should be reported as a line list every six months with the progress report.

Applicants may consult internationally recognized documents such ISO 14155 annex-F, for categorisation of Adverse Events.

3.2.1.15. 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 participants. The sponsor may perform such monitoring directly or may utilize the services of an outside individual or organisation e.g., contract research organisation (CRO) through the monitor.

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

3.2.1.16. Vulnerable populations

- 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 these groups of participants.
- d) Description of how these groups will be protected.
- e) Description of what medical care, if any, will be provided for participant after the clinical investigation has been completed or participant withdrawal before the investigation is completed.

3.2.1.17. 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 participant follow-up.

**3.2.1.18. Criteria for withdrawal of participant**

A description of the criteria of how participants may withdraw or be withdrawn from the study.

3.2.1.19. Publication policy

- a) A statement indicating that the Authority will be notified prior to publication of findings of the clinical investigation (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.

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

The complete address of the clinical investigation site(s) describing the activities performed at the site(s).

There should be adequate number of qualified investigators to conduct the proposed clinical investigation.

3.2.1.21. Responsibilities of Sponsor

The sponsor is generally responsible for obtaining any authorisations 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 the CIP.

3.2.1.22. Responsibilities of Monitor

Monitors are responsible for protecting the rights and well-being of human participant, 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.

Monitors 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.

3.2.1.23. Bibliography

List of bibliographic references pertaining to clinical investigation.

3.2.2. Investigational Medical Device Dossier

Information on the device relating to the safety, quality and performance should be submitted in the format attached as **Annex VII**.

3.2.3. Investigator's brochure (IB)

The Investigator's Brochure shall contain, as a minimum, all topics listed below:

3.2.3.1. General



a) Identification of the IB

- i. Name of the investigational device.
- ii. Document reference number
- iii. Version and date of the IB with the page number and the total number of pages on each page of the IB.
- iv. Confidentiality statement, if appropriate.
- v. 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.

3.2.3.2. 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.



3.2.3.3. 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 participant.

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.

3.2.3.4. 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.

**3.2.3.5. 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.

3.2.3.6. 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.

4. Conduct of Clinical Investigation

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

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

There must be adequate monitoring in place to ensure that the rights, safety and well-being of participant 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 participant. The personal data of the participant must be protected in line with applicable local data protection laws.

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.

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.

5. Reporting and End of the Clinical Investigation

5.1. Safety Reporting

Investigators have a responsibility to report all safety-related events to the Authority. Serious Adverse Events including Suspected Unexpected Serious Adverse Events (SUSARs) shall be reported within 48 hours of the site becoming aware. Non-serious AEs shall be reported as a line list attachment to the six-monthly progress report. Device deficiencies that could have led to a serious adverse device effect, including serious health threat should be reported within 15 working days.

5.2. Major and Minor Protocol Deviations

Major deviations from the investigational plan (protocol) that have a substantial impact on the safety or rights of participant or on the robustness or reliability of the clinical data generated by the investigation shall be submitted without delay but not later than 5 working days. Minor deviations shall be reported as a line list attachment to the 6-monthly report.

5.3. Periodic Update (progress) Report

The applicant conducting the clinical trial must submit progress reports to the Regulatory Authority on a six-monthly basis from the date of initiation of the clinical trial and within 30 days of the completion or termination of the clinical trial. Periodic Update (progress) Reports should be submitted using the format provided in the *Guidelines for Authorisation of Clinical Trials in Medicines and Allied Substance in Zambia*.

**5.4. End/Termination of clinical investigation**

The Authority should be informed in writing by the investigator 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.

5.5. End of Clinical Investigation

The investigator must inform the Authority within 30 days of the end of a clinical investigation by the sponsor. The definition of the end of the investigation should be provided in the CIP.

5.6. Early or Premature Termination

Where the investigation is prematurely ended or terminated or suspended for any reason, the Investigator must notify the Authority immediately within 10 working days after the investigation is halted, with clear reasons and justification, and a description of follow-up measures, if any, taken for safety reasons.

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

The Investigator should further promptly inform the participant and ensure appropriate therapy and follow-up for the participants.

5.7. 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 VI** of this guideline.

The Sponsor/investigator should notify the Authority before dissemination and use of the results of the investigation.

**6. Labelling of Medical Devices**

All devices intended for clinical investigation (Investigational Devices) 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.

7. Application for Clinical Investigation Amendments

Amendments to be made to the conduct of a clinical investigation after its commencement may be authorised. 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, where a sponsor and/or investigator must take urgent safety measures to protect the participant from immediate hazard, they may do so before notifying the Authority, however, they must notify the participants and the Authority in writing as soon as possible.

Major and minor 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.

The Investigator is 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, proof of payment of the prescribed fee 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: 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 upon by the Zambia Medicines Regulatory Authority 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 II: Declaration of Sponsor and Principal Investigator

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 III: 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 IV: 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 V: Clinical Investigation Report**

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 participant 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 participant with a description of how missing data or deviation(s) were dealt with in the analysis, including participant
 - ✓ 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 participant 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 VI: Abridged product dossier requirements**

Abridged product dossier content requirements
1. ADMINISTRATIVE
1.1 Cover letter (if applicable)
1.2 Submission table of contents
1.3 List of terms/Acronyms
1.4 Application form/Administrative information
1.5 Listing of device(s)
1.6 QMS (valid ISO 13485 certificate) or other regulatory certificates
1.7 Free sale certificate/Certificate of marketing authorisation
1.12 Statements, Certifications, Declarations of conformity
2. SUBMISSION CONTEXT (Product Information)
2.4 Device description
2.4.1 <i>Comprehensive device description and principle of operation</i>
2.5 Indications for use and/or intended use
2.5.1 <i>Intended use; Intended purpose; Intended user; Indications for use</i>
2.5.2 <i>Intended environment/setting for use</i>
2.6 Global market history/(Commercial History)
2.6.1 <i>Global market history</i>
2.6.4 <i>Evaluation/inspection reports issued by the Recognized SRA, if available</i>
2.7 Other submission context information
2.7.1 <i>Global prices</i>
3. Analytical performance and other evidence
3.2 Risk management
3.5 Analytical performance
3.5.4.2 Precision of measurement (repeatability and reproducibility) - <i>If applicable, studies to establish repeatability undertaken by non-laboratory personnel are provided (Note: Precision in the hands of end users may be appraised by the manufacturer in the clinical studies, and thus may not be included in the analytical studies).</i>
3.6 Other studies
3.6.4 <i>Usability/Human factors</i>
3.6.5 <i>Stability of the IVD</i>
3.6.5.1 <i>Claimed shelf life</i>
3.6.5.2 <i>In-use stability</i>
3.6.5.3 <i>Shipping stability</i>
5 LABELLING AND PROMOTIONAL MATERIAL
5.2 Product/package labels



5.3 Package insert/Instructions for use

5.6 Technical/operators manual

5.8 Other labelling and promotional materials

Adapted from Abridged prequalification assessment: prequalification of in vitro diagnostics, PQDx_173 version 5. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.



8. References

1. Medicines and Allied Substances Act No 3 of 2013.
2. Guidelines for Authorization of Medical Device Clinical Investigation, 1st 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 participant - Good clinical practice.
5. BSI Standards Publication, BS EN ISO 14155:2011.

**9. Amendment Sheet**

Date identified	Amendment identified by	Short description of the changes proposed to the document	Review of proposed amendment