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Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia

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Zambia Medicines Regulatory Authority

**GUIDELINES FOR AUTHORISATION OF CLINICAL TRIALS OF MEDICINES
AND ALLIED SUBSTANCES IN ZAMBIA**

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**i. Abbreviations**

ADR	Adverse Drug Reaction (Adverse Device Reaction)
AE	Adverse Event
CoA	Certificate of Analysis
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Application
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
MA	Marketing Authorisation
NHRA	National Health Research Authority
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
ZAMRA	Zambia Medicines Regulatory Authority



ii. Definitions

The definitions below apply specifically to the terms used in this guideline:

“Act” means the Medicines and Allied Substances Act no. 3 of 2013;

“adult” means a person who is eighteen (18) years of age or above;

“adverse event” means:

- (a) any untoward medical occurrence that may be present during use or treatment with a medicine or allied substance whether or not related to the use or treatment, including any unfavorable and unintended sign, symptom, abnormal laboratory finding or disease temporarily associated with the use of the medicine or allied substance; or
- (b) in the case of blood and blood products, any undesirable or unintended occurrence associated with transfusion or donation including incidents, near misses, errors, deviations from standard operating procedures and accidents;

“adverse reaction” means a response to a medicine or allied substance which is noxious and unintended including a response arising from:

- (a) the use of a medicine or allied substance within the terms of the marketing authorisation;
- (b) the use of a medicine or allied substance outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- (c) occupational exposure to a medicine or allied substance; and
- (d) in the case of blood and blood products, unintended response in a –
 - (i) donor during collection of blood; or
 - (ii) patient during transfusion of blood or blood components;

“adverse Events of Special Interest” means an adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could



be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted (Based on CIOMS VII);

“accountability record” means a log of investigational medicines or allied substances kept by an investigator conducting a clinical trial;

“allied substances” has the meaning assigned to it in the Medicines and Allied Substances Act No. 3 of 2013 and include acaricides, cosmetics, disinfectants, food supplements, feed additives and supplements, medical and surgical sundries, medical devices and condoms;

“amendment” means a written description of a change(s) to or formal clarification of a protocol or investigational product dossier;

“applicable regulatory requirement(s)” means any law(s) and regulation(s) addressing the conduct of clinical trials of an investigational medicine or allied substance;

“applicant” means an individual, company, institution or organisation that acts on behalf of the Sponsor to initiate and manage the trial as its local representative.

“approval(s)” means the affirmative decision in writing by the by The Authority or other regulatory agencies or Research Ethics Committee or National Health Research Ethics Board that the clinical trial application has been reviewed and the clinical trial may be conducted within the constraints set forth by an Ethics Review Body, Good Clinical Practice (GCP), and the applicable regulatory requirements;

“assent” means a process by which a child, who is capable of understanding, voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the child's decision to participate. Assent is documented by means of a written, signed and dated assent form from the child. As part of the assent process, parents and guardians must give informed consent;



“audit” means a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)

“auditor” means a person who carries out an audit;

“audit Certificate” means a declaration of confirmation by the auditor that an audit has taken place;

“audit Report” means a written evaluation by the sponsor's auditor of the results of the audit;

“audit Trail” means documentation that allows reconstruction of the course of clinical trial processes;

“Authority” means the Zambia Medicines Regulatory Authority;

“auxiliary product(s)” include background therapy, rescue medication, challenge agents, and/or medical products to assess endpoints;

“blinding/masking” means a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware; and double-blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s);

“case report form” means a data acquisition tool designed to record clinical trial protocol-required information to be reported by the investigator to the sponsor on each clinical trial participant;

“certificate of analysis (COA)” means an authenticated document issued by an appropriate Authority that certifies the quality and purity of pharmaceuticals, animal and plant products;



“challenge agent/organism/product” means an agent administered to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed;

“child” means a person who is below the age of eighteen (18) years, whether a marital or non-marital child;

“clinical trial site(s)” means the location(s) where trial-related activities are actually conducted;

“clinical trial” means any interventional study or investigation in or involving human participants intended to:

- (a) discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational medicine or allied substance; and/or to identify any adverse events or reactions to an investigational medicine or allied substance; and/or to study absorption, distribution, metabolism and excretion of an investigational medicine or allied substance with the objective of ascertaining its safety and/or efficacy; or
- (b) test new procedures that may prevent, detect, or diagnose, treat or manage diseases or conditions to determine if the procedure is safe or effective;

“clinical trial protocol” means a document that describes the background, rationale, objective, design, methodology, statistical considerations, and how a clinical trial shall be conducted. The term “clinical trial protocol” refers to clinical trial protocol and clinical trial protocol amendments;

clinical trial/study report means a documented description of a trial of any investigational product conducted in human participants, in which the clinical and statistical description, presentations and analyses are fully integrated into a single report (see ICH E3 Structure and Content of Clinical Study Reports);

“comparator (product)” means an investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial;



“compliance” means adherence to all the clinical trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements;

“confidentiality” means prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a participant's identity;

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

“contract research organisation (CRO)” means a person or organisation (commercial, academic or other) providing a service used by either the sponsor or the investigator to fulfil trial-related activities;

“coordinating investigator” means an investigator assigned the responsibility for the coordination or oversight of investigators at different clinical trial sites participating in a multi-centre trial;

“data and safety monitoring board (DSMB) or independent data-monitoring committee (IDMC) or monitoring committee or data monitoring committee” means an independent data-monitoring committee established by the Sponsor to assess, at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints and to recommend to the Sponsor whether to continue, modify, or stop a trial;

“date of commencement of clinical trial” means the date when the clinical trial starts to screen participants for the purpose of enrolment into the clinical trial;

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



“drug/medicine” means:

- a. human medicine, veterinary medicine, medicinal product, herbal medicine or any substance or mixture of substances for human or veterinary use intended to be used or manufactured for use for its therapeutic efficacy or for its pharmacological purpose in the diagnosis, treatment, alleviation, modification or prevention of disease or abnormal physical or mental state or the symptoms of disease in a person or animal;
- b. a substance or mixture of substances prepared, sold or represented for use in:
 - i. Restoring, correcting or modifying organic functions in man, and
 - ii. The diagnosis, treatment, mitigation or prevention of disease, disorder or abnormal physical state or the symptoms of it, in man, or
- c. nutritional supplements;

“epidemic” means the occurrence in a community or a region of cases of an illness, specific health related behavior or other health-related events clearly in excess of normal expectancy;

“essential records” means records that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see appendix VI);

“food/dietary or nutritional supplement” means concentrated sources of nutrients or other substances produced in a pharmaceutical dosage form such as tablets, gelatine capsules (soft or hard), sachets, syrups and powders. Dietary components include herbs, vitamins and minerals (with concentration less than the recommended daily allowance), natural oils, royal jelly, pollen and bee propolis. All these ingredients can be included in dietary supplements on the condition that their sole function is supplementation and improvement of body function;

“good clinical practice (GCP)” means a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected;



“good clinical practice (GCP) inspection” means the act by the Authority of conducting an official review of documents, facilities, records and any other resources that are deemed to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organisations (CRO’s) facilities, or at other establishments deemed appropriate by the Authority;

“good manufacturing practice (GMP)” means a system for ensuring that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorisation;

“impartial witness” means a person who is independent of the trial who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant’s legally acceptable representative cannot read, and who reads the informed consent form and any other documented information supplied or read to the participant and/or their legally acceptable representative;

“independent ethics committee (IEC)” means an independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants;

“infectious human challenge trial” means a trial that involve the deliberate exposure of human volunteers to infectious agents. Trial participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner;



“informed consent” means a process by which a participant or their legally acceptable representative voluntarily confirms their willingness to participate in a clinical trial after having been informed and been provided with the opportunity to discuss all aspects of the clinical trial that are relevant to the participant’s decision to participate. Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form. Obtaining consent remotely may be considered when appropriate;

“institution (medical)” means any public or private entity or agency or medical or dental facility where clinical trials are conducted;

“interim clinical trial/study report” means a report of intermediate results and their evaluation based on analyses performed during the course of a trial;

“investigational medicine or allied substance (also referred to as investigational product)” means a medicine or allied substance (including a placebo) being tested or used as a reference in a clinical trial, including a medicine or allied substance with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use;

“investigational medicine or allied substance dossier (also referred to as investigational medicinal product dossier or investigational product dossier)” means the compilation of quality, safety and efficacy (manufacturing, clinical and non-clinical) information on an investigational medicine or allied substance, in a format prescribed by the Authority;

“investigator’s brochure” means a compilation of the clinical and non-clinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants;

“investigator” means a person, regardless of title or position, who is responsible for the design, conduct, or reporting of a clinical trial;



“legally acceptable representative” means an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant to the participant’s participation in the clinical trial;

“lot release certificate (LRC)” means an official document that authorises the manufacturer to release a specific lot of a product;

“medical device” means an instrument, apparatus, implement, a medical equipment, machine, contrivance, implant, in vitro reagent or any other similar or related article, including a component, part or an accessory which is:

- a. recognised in the official national formulary or pharmacopoeia or a supplement to them, or
- b. intended for use in the diagnosis of a disease or any other condition, or in the cure, mitigation, treatment or prevention of disease in humans and animals, or
- c. intended to affect the structure or a function of the body of the human being or other animal and which does not achieve any of its principal intended purposes through chemical action within the body of the human being or any other animal and which is not dependent on being metabolized for the achievement of any of its principal intended purposes;

“medical expert” means an appropriately qualified medical personnel designated by the Sponsor who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose;

“monitor” means a person appointed by the Sponsor or CRO to oversee the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the Protocol, SOPs, GCP and the applicable regulatory requirements;

“monitoring” means an act of overseeing the progress of a Clinical Trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s);



“monitoring report” means a written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs;

“multicentre trial” means a clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator;

“pandemic” means an emergency occurring worldwide or over a wide area crossing international boundaries and affecting a large number of people;

“participant identification number” means a unique identifier assigned by the investigator to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial related data;

“participant or trial participant” means an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control;

“pharmacy” means a drugstore, druggist, chemist or any business or premises registered as such under section sixteen of the Medicines and Allied Substances Act No. 3 of 2013;

“placebo” means an inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure;

“principal investigator” means the lead person responsible for providing oversight and is legally liable for the conduct of a clinical trial and who is a researcher or a qualified health professional, resident in Zambia;

“protocol” means a document that describes the objective(s), design, methodology, statistical considerations and the organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout this Guideline, the term “protocol” refers to protocol and protocol amendments;



“protocol deviation” means an accidental or unintentional change to, or non-compliance with the clinical trial protocol that does not increase risk or decrease benefit or does not have a significant effect on the participants’ rights, safety or well-being; and/or the reliability of the study data;

“protocol violation” means any change, divergence, or departure from the study design or procedures defined in the protocol that might significantly affect participants’ rights, safety or welfare and/or the reliability/integrity of the study data;

“public health emergency” has the meaning assigned to the words in the Zambia National Public Health Institute Act, 2020;

“quality assurance (QA)” means all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s);

“Quality Control (QC)” means the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled;

“randomisation” The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias;

“register” means as per the Medicines and Allied Substances Act No. 3 of 2013;

“registered product or a product with marketing authorisation” means the authorisation granted, under section thirty-nine of the Medicines and Allied Substances Act, for the placement of a medicine or allied substance on the market;

“regulatory authorities” Bodies having the power to regulate. The expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities;



“reliance” implies that the work done (e.g inspection of a site or assessment of protocol) is shared by the trusted authority while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities;

“serious adverse event (SAE)” means any untoward medical occurrence during a clinical trial that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect;

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

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

“sponsor” means an individual, company, institution or organisation that takes responsibility for the initiation, management and arrangement of the financing of a clinical trial. A clinical trial may have one or several sponsors where permitted under regulatory requirements. All sponsors have the responsibilities of a sponsor set out in this guideline. In accordance with applicable regulatory requirements, sponsors may decide in a documented agreement setting out their respective responsibilities. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors;



“sponsor-investigator” means an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator;

“standard operating procedures (SOPs)” Detailed, written instructions to achieve uniformity of the performance of a specific function;

“sub- or co-investigator” Any individual member of the Clinical Trial team designated and supervised by the Principal Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows);

“study pharmacist (pharmacist of record)” means a registered pharmacist appointed by the Sponsor/Principal Investigator to ensure the proper management of pharmaceutical investigational products to be used in the study;

“The Authority” means Zambia Medicines Regulatory Authority;

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

“vaccine” means a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters;



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

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

“well-being (of the trial participants)” means the physical and mental integrity of the participants participating in a clinical trial; and

“who listed level three or four authorities” implies the competence level of a national medicines regulatory agency based on the WHO global benchmarking.



1. Introduction

This guideline is issued by the Authority pursuant to Section 68 of the Act and prescribes the information to be incorporated in the applications for Authorisation of Clinical Trials in Human Participants by an applicant who intends to conduct a Clinical Trial in Zambia.

This Guideline seeks to ensure that clinical trials conducted in Zambia are designed and conducted according to sound scientific principles and ethical standards within the framework of Good Clinical Practice. Compliance with this guideline provides the assurance that the rights, safety and wellbeing of clinical trial participants are protected and that the information obtained from the clinical trial can be relied upon by the Authority and other stakeholders. The information obtained from clinical trials contributes to the assessment of safety, efficacy or performance of a medicine or an allied substance and informs decisions regarding the marketing authorisation of a medicine or an allied substance. The Authority may from time to time amend any part of this guideline.

Objective

This guideline sets out the procedures that should be followed by applicants who wish to conduct clinical trials in human participants involving the use of registered and unregistered medicines or allied substances in Zambia, and the steps that the Authority takes to review, evaluate, authorise and monitor the conduct of clinical trials.

Scope

This guideline is addressed to investigators, the pharmaceutical industry, Clinical Research Organisations and Sponsors of clinical trials, whether for academic purposes or for generation of data intended for inclusion in the regulatory submissions for medicinal products. This guideline is intended to be applied during all clinical stages of product development prior to and after marketing authorisation. This guideline applies to clinical trials of medicines and allied substances for human use.



2. Requirements

2.1. When an application is required

2.1.1. An application for approval to conduct a clinical trial is required for the following categories of medicines and allied substances:

2.1.1.1. Unregistered medicines and allied substances

2.1.1.2. Registered medicines and allied substances:

- i. Registered medicines and allied substances where the use in the proposed clinical trial is outside the conditions of approval. These may include changes to indication(s) and clinical use, target patient population(s), route(s) of administration, dosage regimen(s) and standard treatment.
- ii. A Clinical Trial application is also required when a medicines or allied substance is used to gain further information about the authorised form, i.e within the conditions of approval.

2.1.1.3. Challenge agents in Human Infectious Studies shall be regulated in the same manner as vaccines (biological products), and are expected to be studied with authorisation in accordance with clinical trial regulations, whether or not an investigational vaccine (biological product) is to be used in the same clinical investigation protocol.

2.1.1.4. Research on a drug/device combination product when the combination product, or a new constituent part, lacks sufficient safety/efficacy data, changes the approved drug's formulation, route, or dosage, or involves a new or high-risk indication. For more details, refer to



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Appendix XII: Clinical Investigations and Performance Evaluation of Medical Devices.



2.1.1.5. Appendix X

2.1.2. Applicants are advised to engage the Authority for clarification on whether a study is to be classified as a clinical trial, when in doubt.

2.1.3. Applicants are required to submit their applications online via the Clinical Trials portal found on www.zamra.co.zm.

2.2. Categories of clinical trials

2.2.1. Clinical trials shall be categorised as follows:

2.2.1.1. Clinical Trials involving a Locally Manufactured Investigational Product

- i. An Investigational Product with Marketing Authorisation
- ii. An Investigational Product without Marketing Authorisation

2.2.1.2. Clinical Trials involving an Imported Investigational Product

- i. An Investigational Product with Marketing Authorisation
- ii. An Investigational Product without Marketing Authorisation

2.3. Consultative Meetings with the Authority

2.3.1. An applicant for a clinical trial may meet with officers of the Authority for consultation prior to applying or during the conduct of a clinical trial.

2.3.2. An applicant may request a pre-submission meeting or submit pre-submission enquiries before submission of clinical trial applications. These consultations may be useful for applications that include complex issues of new active substances or pharmaceutical products, new or complicated study designs, and for new researchers.

2.3.3. An applicant who intends to apply for a clinical trial addressing a public health emergency or through an expedited review model is advised to request a pre-submission meeting.



- 2.3.4. Written requests for pre-submission meetings should be submitted to the Authority along with a brief synopsis/study summary of the proposed study, a list of preliminary questions to be addressed by the Authority's representatives during the meeting, and a summary of significant quality aspects of the investigational product, and any other documents pertinent to the discussions or enquiry.

2.4. Clinical Trials Review Process

- 2.4.1. The review and approval process by the Authority is expected to take up to 60 working days from the time a complete and validated application package is received by the responsible Unit to approval. This timeline excludes the time taken by the applicant to address the queries raised. Applicants are encouraged to work in coordination with the Authority to enable the achievement of these timelines.
- 2.4.2. For clinical trials addressing a public health emergency, the expedited timeline for review and approval may be reduced to 10-15 working days, subject to early submission of a complete application.
- 2.4.3. The Authority reviews the documents submitted to assess the protocol and quality of the investigational products and determine whether the use of the investigational product for the clinical trial does not cause any harm or pose undue risk to the health of clinical trial participants or other persons i.e the clinical trial is not contrary to the best interests of a clinical trial participants, and the objectives of the clinical trial may be achieved.
- 2.4.4. The application is reviewed by internal and/or external experts. A confidentiality agreement is signed by reviewers to ensure that the content of the application remains confidential. The initial review may result in queries that need to be addressed by the



applicant. It is recommended that the reviewers do not have direct contact with the applicant and that all correspondence is directed through the Authority's Director General.

- 2.4.5. The Authority may, during evaluation, request clarification, additional documents and/or samples. Once a query has been raised and issued to the applicant, the evaluation process or clock shall stop. Queries are to be addressed within the timelines specified in Appendix I: Timelines, after which the application shall be considered to have elapsed. To facilitate the review process, all queries issued must be addressed in a single submission.
- 2.4.6. The Authority may rely on and use relevant Clinical Trial decisions, reports or information from well-resourced regulatory authorities (or WHO Listed, WHO Maturity level 3 or 4 Authorities) or from relevant regional and international bodies.
- 2.4.7. Non-compliance and non-conformity to the requirements prescribed in this guideline shall lead to rejection of the Clinical Trial Application.
- 2.4.8. A decision to defer, approve or reject an application shall be made within sixty (60) working days (



2.4.9. Figure 1).

2.4.10. Following approval of the clinical trial, a clinical trial certificate shall be valid for the duration of the clinical trial as per the approved protocol, but not more than 5 years from the date of approval. The approval may be renewed on submission of an application for renewal of the clinical trial certificate.

2.4.11. In the event of a rejection of an application, an applicant may appeal to the Minister of Health within thirty (30) calendar days in writing. The applicant shall give grounds for review for each reason given for the rejection of the clinical trial based on the information submitted in the application. Where an appeal is not submitted by the applicant within the thirty (30) calendar days, the decision of the Authority in respect of the application shall stand.

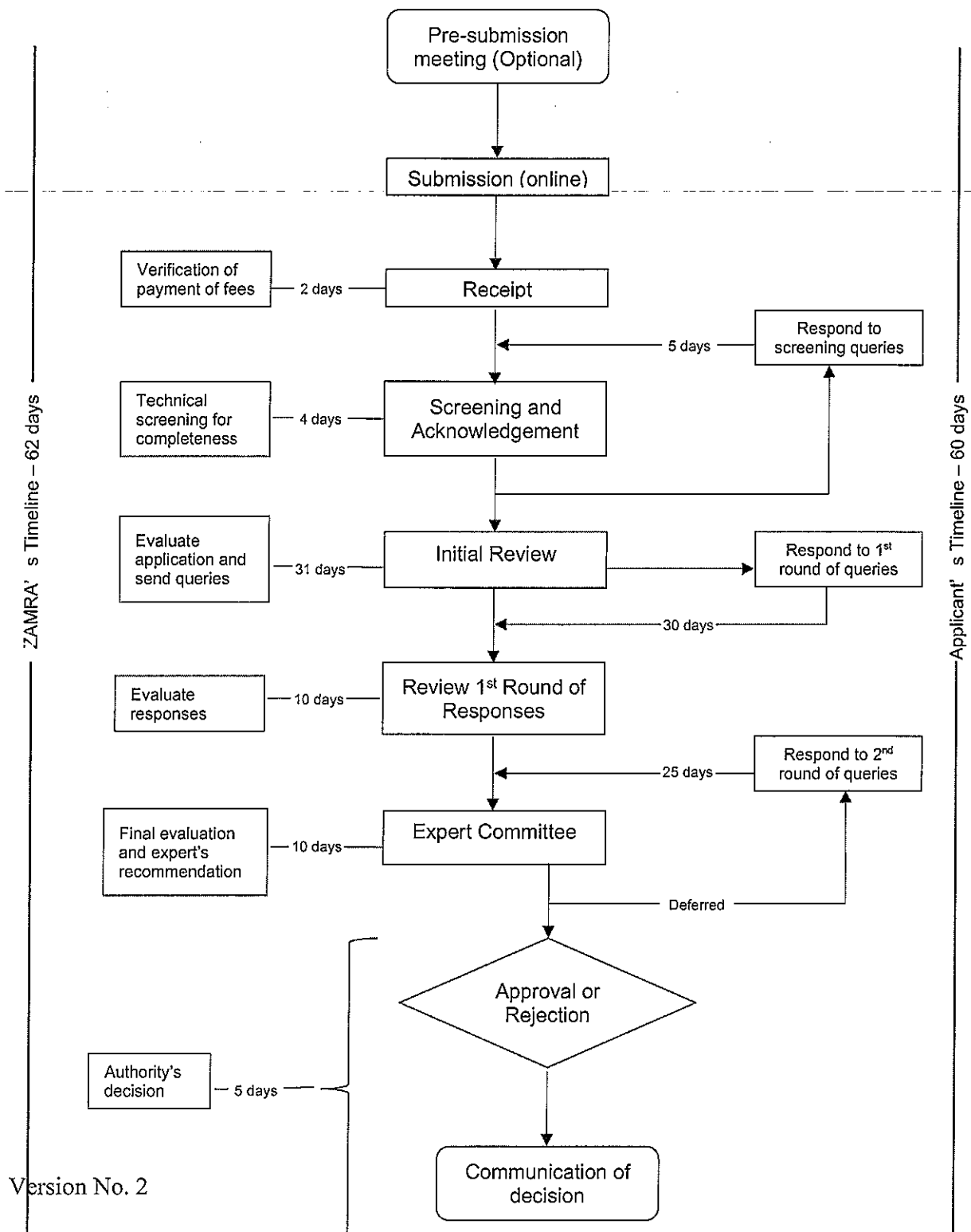
2.4.12. The Authority reserves the right to request information or material, or define conditions not specifically described in this guideline, to allow the Authority to adequately ensure safety and well-being of Clinical Trial participants and credibility of the Clinical Trial data.

2.4.13. To ensure transparency, summarised review comments on Clinical Trial Applications shall be published by the Authority in a format and/or content provided in 2.21. Critical information regarding the trial shall be treated with strict confidentiality.

2.4.14. The Authority shall apply the same internal procedures, review process and criteria described in this guideline to all applications regardless of the applicant.



Figure 1. Clinical Trial Application Processing Workflows



**2.5. Clinical Trial Application (CTA) – General Requirements**

2.5.1. A person who intends to conduct a clinical trial shall apply for authorisation to conduct a clinical trial in a manner described in this section (section 2.5). An application shall be submitted by an Applicant, who can be an individual, company, institution, or organisation that acts on behalf of the Sponsor to initiate and manage the trial as its local representative. In the case of an international Sponsor, a local Applicant designated by the Sponsor is responsible for initiation and management of the trial in the local context.

2.5.2. A Clinical Trial Application made to the Authority shall be accompanied by the following:

- i. Covering Letter
- ii. Non-refundable Application and GCP Inspection Fee as per the prescribed ZAMRA Fee Schedule.
- iii. Completed ZAMRA Clinical Trial Application Form signed by authorised persons (PI and Sponsor's authorised representative)
- iv. A Clinical Trial Protocol
- v. A proof of registration with Pan African Clinical Trials Registry (PACTR)
- vi. Investigator's Brochure (IB), Summary of Product Characteristics or package leaflet, where applicable
- vii. Investigational Product (IP) Dossier (if applicable)
- viii. Good Manufacturing Practice (GMP) Certificate or equivalent (for medical devices, nutritional supplements and cosmetics)
- ix. Ethical Approval or proof of submission for Ethical Approval
- x. Approval or proof of submission of an application to the National Biosafety Authority for a clinical trial involving a genetically modified organism or product of a genetically modified organism.
- xi. Insurance Cover for Trial Participants
- xii. Financial Declaration
- xiii. DSMB Membership (including CVs) and signed Charter



- xiv. Sponsor/PI Contractual Agreement
- xv. Sponsor and Monitor/Contract Research Organization (CRO) Contractual Agreement
- xvi. Informed Consent and Assent Forms (if applicable)
- xvii. Statistical Analysis Plan (SAP)
- xviii. Evidence of accreditation/competence of designated laboratory(ies) and other clinical facilities
- xix. Financial disclosure
- xx. Monitoring Plan
- xxi. Samples of investigational medicine or allied substance and/or comparator, where applicable

2.5.3. In the case of multi-centre Clinical Trials, the site-specific (if applicable) and Global Protocols should be submitted.

2.5.4. All clinical trial application documents shall be in English language, in electronic format (Microsoft Word or selectable/searchable PDF), and submitted online via the Clinical Trials portal on the website www.zamra.co.zm.

2.5.5. A Clinical Trial Application shall not be assessed if, upon preliminary screening at the time of submission, the minimum required documents are not submitted as per **Section 2.5**.

2.5.6. Failure of the applicant to address all outstanding issues related to an application within specified timelines (period from issuance of the query(ies)) renders an application elapsed.

2.5.7. The application shall indicate the phase of clinical trial that is intended; see **Table 1** and



Appendix VIII: Phases of Clinical Trials.

2.6. Clinical Trial Application (CTA) – Documents

2.6.1. Cover Letter

The cover letter shall be addressed to:

The Director-General.

Zambia Medicines Regulatory Authority,

Plot No. 2350/M, Off KK International Airport Road,

P. O Box 31890,

Lusaka, Zambia.

2.6.2. Application Fees and Good Clinical Practice (GCP) Inspection Fees

An application shall be accompanied by a non-refundable application fee and GCP Inspection Fee as specified in the Zambia Medicines Regulatory Authority Fee Schedule. GCP inspection fee shall apply to each Clinical Trial Site.

2.6.3. ZAMRA Clinical Trial Application Form

The application forms (Appendix XIV: Clinical Trial Application Form) shall be filled in and signed by the Sponsor, Principal Investigator, Co- or Sub-Investigator and monitor (where applicable).

2.6.4. Clinical Trial Protocol

2.6.4.1. General Information

This shall include:

- i. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- ii. Name and address of the Sponsor and Monitor



- iii. Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the Sponsor.
- iv. Name, title, address, and telephone number(s) of the Sponsor's medical expert (or dentist when appropriate) for the trial.
- v. Name and title of the Principal Investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- vi. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial site related medical (or dental) decisions (if other than principal investigator).
- vii. Name, title, address, and telephone number(s) of the other investigators designated by the PI to be responsible for some aspects of the study.
- viii. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.
- ix. Contractual agreement between the investigator and Sponsor.
- x. A clear statement on compensation and benefits package for clinical trial participants.
- xi. Publication policy.

2.6.4.2. Background Information

This shall include:

- i. Justification for the study.
- ii. Name and description of the investigational medicine(s) or allied substance(s) including:
 - a. A summary of findings from non-clinical studies that potentially have significance to the clinical trial.
 - b. Summary of findings from clinical studies/trials that are relevant to the clinical trial and provide background to the trial.



- iii. Summary of the known and potential risks and benefits, if any, to human participants (Benefit-risk assessment).
- iv. Summary of the local background rates with respect to the condition for which the intervention is proposed.
- v. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- vi. Description of the population to be studied. Adequate justification is required in cases where the study is to be conducted in vulnerable participants.
- vii. A statement that the trial shall be conducted in compliance with the protocol, Good Clinical Practice (GCP), ZAMRA requirements, and other applicable regulatory requirement(s).
- viii. References to literature and data that are relevant to the clinical trial and that provide background for the clinical trial.
- ix. Signed declaration by the applicant and all investigators that, they are familiar with and understand the protocol and shall comply with principles of Good Clinical Practice (GCP) as determined by the Authority in the conduct of the trial.
- x. Justification why the clinical trial is being conducted in Zambia (if not covered above).

2.6.4.3. Trial Purpose and Objectives

- i. Aim of the trial and reason for its execution.
- ii. A detailed description of the objectives and the purpose of the trial.

2.6.4.4. Trial Design

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

- i. The phase of the clinical trial to be conducted,



- ii. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.
- iii. Number of participants to be involved in the trial and the statistical justification.
- iv. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- v. Justification (or validation where applicable) if markers are being used as endpoints.
- vi. A description of the measures taken to minimise/avoid bias, including: Randomisation and Blinding.
- vii. The expected duration of participant participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- viii. A detailed description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of the clinical trial, and the entire clinical trial.
- ix. Maintenance of trial treatment randomisation codes and procedures for breaking the codes/blinding (for safety reasons).
- x. Description of source documents and any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.
- xi. Description of procedures for handling protocol deviations.

2.6.4.5. Selection of participants

- i. Participant inclusion criteria
- ii. Participant exclusion criteria
- iii. Mechanism for pre-screening, where appropriate, and screening of participants.

**2.6.4.6. Discontinuation of Trial Intervention and Participant Withdrawal from Trial**

Participant withdrawal criteria (i.e. terminating treatment with an investigational medicine or allied substance or trial treatment) and procedures specifying:

- i. When and how to withdraw participants from the clinical trial or treatment with an investigational medicine or allied substance;
- ii. The type and timing of the data to be collected for withdrawn participants, including the process by which the data are handled, in accordance with applicable regulatory requirements;
- iii. Whether and how participants are to be replaced; and
- iv. The follow-up for participants withdrawn from trial treatment or treatment with an investigational medicine or allied substance.

2.6.4.7. Treatment and interventions of study participants

- i. The treatment(s) to be administered, including the name(s) of all the medicine(s) or allied substance(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational medicine or allied substance treatment / clinical trial treatment group / arm of the clinical trial.
- ii. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the clinical trial.
- iii. A description of the clinical trial treatment(s) and the dosage and dosage regimen of the investigational medicine(s) or allied substance(s).
- iv. Description of the dosage form, packaging, and labeling of the investigational product(s) and sample of label to be used for investigational medicine or allied substance.
- v. Quantities and sources of all investigational products and/or comparators (whether to be imported or purchased locally).



- vi. Accountability procedures for the investigational medicine(s) or allied substance(s), including the placebo(s) and/or comparator(s), if any.
- vii. Procedures for monitoring participant adherence.
- viii. Description of treatment applied to control group(s) or control period(s), placebo, and other therapy and any other treatment that may be given concomitantly including measures to be implemented to ensure the safe handling of the medicines or allied substances.
- ix. Description of diagnostic devices or kits to be used in the clinical trial.
- x. Description of special analyses and/or tests or procedure to be carried out.
- xi. Procedures put in place to ensure post-trial access for research participants. The principal investigator is required to describe in the protocol the procedures put in place to ensure post-trial access for research participants who still need an intervention identified as beneficial in the trial. Only those participants who derive benefit from the investigational product will be considered. Benefit must be objective as well as significant to be clinically justifiable and be based on study endpoints and not only investigator opinion. Post-trial access is not applicable for Phase I and II studies. However, it may be necessary for particular diseases such as cancer and or rare diseases for which no other medicines or other standard of care is available. Follow up studies or rollover studies may be proposed by the investigators to allow continued access to the medicines by participants until the product is registered or is available through the national program or any other approved means and these follow up studies and rollover studies are considered as clinical trials and need to be approved and monitored by ZAMRA and Ethics Committee. Any other scenario is handled on a case-by-case basis by the Authority.

**2.6.4.8. Assessment of Efficacy**

- i. Specification of the efficacy parameters.
- ii. Methods and timing for assessing, recording, and analysing efficacy parameters.
- iii. Where any trial-related committees (e.g., independent data monitoring committee (IDMC)/adjudication committees) are utilised for the purpose of assessing efficacy data, the committees' procedures, timing and activities should be described in the protocol or a separate document.

2.6.4.9. Assessment of Safety

- i. Specification of safety parameters.
- ii. The methods, extent and timing for recording and assessing safety parameters. Where any trial-related committees (e.g., IDMC) are utilised for the purpose of assessing safety data, procedures, timing and activities should be described in the protocol or a separate document.
- iii. The methods, extent and timing for assessing, recording, and analysing safety parameters.
- iv. Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.
- v. List of adverse events of special interest (AESI) and/or expected adverse events – information shall include;
 - a. Whether event is related to the intervention or not.
 - b. Rationale for listing each event
 - c. Expected rate or frequency of each event
 - d. Laboratory limits (if applicable)
- vi. The type and duration of the follow-up of participants after adverse events.
- vii. Provision for dealing with all adverse events.
- viii. A clear description of study procedures and quantities of any body fluids to be collected for study analysis.

**2.6.4.10. Statistical considerations**

This includes:

- i. Frequency of (DSMB) or (SMC) meetings, if applicable.
- ii. A description of the statistical methods to be employed, including timing of any planned interim analysis(es) and the statistical criteria for the stopping of the trial.
- iii. The number of participants planned to be enrolled. In multi-centre trials, the numbers of enrolled participants projected for each clinical trial site should be specified.
- iv. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- v. The level of significance to be used or the threshold for success on the posterior probability in a Bayesian design.
- vi. Criteria for the termination of the trial.
- vii. The selection of participants to be included in the planned analyses, a description of the statistical methods to be employed and procedures for handling intercurrent events and accounting for missing, unused and spurious data. These should be aligned with the target estimands, when defined (see ICH E9(R1)) Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- viii. Procedures for reporting any protocol violations.
- ix. The selection of participants to be included in the analyses (e.g. all randomised participants, all dosed participants, all eligible participants, evaluable participants).
- x. A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).
- xi. The number of participants to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified.



- xii. Methods for data analyses and evaluation of results.
- xiii. Procedure for accounting for missing, unused, and spurious data.

2.6.4.11. Direct Access to Source Data/Documents/Records

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit clinical trial-related monitoring, audits, IRB/IEC review, inspections from the Authority and provide direct access to source data/documents.

2.6.4.12. Quality Control and Quality Assurance

- i. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted and data is generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- ii. The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/monitor, and inspection by the Authority.
- iii. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements, made by the sponsor with the principal investigator and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.
- iv. The protocol should contain a description on how to maintain quality control and quality assurance of the study such as: criteria for selection of investigators, monitors and the monitoring plan.

**2.6.4.13. Investigational Medicine or Allied Substance Accountability**

Description of procedures relating to sourcing, transportation, receipt, storage, preparation, dispensing, use, and disposal of investigational medicines or allied substances.

2.6.4.14. Definition of the end-of-trial

- i. The end of a clinical trial is usually considered as the last visit of the last participant (LPLV). Safety monitoring or diagnostic intervention is completed for the final remaining participant. This milestone transitions the study from its active clinical phase into the trial close-out, data analysis, and reporting phases.
- ii. A later date of the end-of-trial may be explicitly specified and justified in the clinical trial protocol. A sponsor can define a later endpoint in the protocol (e.g., the completion of specific long-term global pharmacovigilance follow-ups or the final secondary endpoint laboratory analysis).
- iii. If a trial is halted prematurely due to safety concerns, a lack of efficacy (futility), or sponsor decision, the date of the formal decision to stop the study acts as the operational end of the trial.
- iv. The Authority shall be notified of the end-of-trial within 30 calendar days after reaching the end-of-trial.

2.6.4.15. Biological Samples

- i. The handling of biological specimen: plans for collection, laboratory evaluation, and storage of biological specimens for analysis in the current trial and for future use in ancillary studies, if applicable should be described in the protocol.



- ii. Studies in which biological samples are being stored for future use shall be described in the protocol.

Note: Authorisation to transfer or to store (for future use) samples must be obtained from NHRA.

2.6.4.16. Ethics

- i. General ethical considerations relating to the clinical trial and the informed consent sheet or form or otherwise to be given to patients or volunteers, should be described.
- ii. A clear statement on composition and benefit package for clinical trial participants.
- iii. A statement that the trial shall be conducted in compliance with the protocol, GCP, ZAMRA requirements, and other applicable regulatory requirement(s).

2.6.4.17. Data Handling and Record Keeping

- i. Procedure for keeping a list of participating volunteer/patients and detailed records indicated on the case report form (CRF) for each individual taking part in the trial.
- ii. All clinical and experimental data (electronic or paper) shall be kept in a secured place, locally, for a period of not less than 10 years and not less than 20 years for New Drug Application (NDA) after completion of the clinical trial and be made readily available for review upon request by The Authority.

2.6.4.18. Publication of Clinical Trial report

- i. Publication policy, if not addressed in a separate agreement.



- ii. Publication policy, including a plan for the dissemination of the results (publishing plan).
- iii. The Authority shall be informed of any results to be publicly released at least 14 days before this information is released.

2.6.4.19. Clinical Trial Monitoring

- i. Description of the management team and Data Safety Monitoring Board (DSMB), data monitoring committee (DMC) or Safety Monitoring Committee (SMC), where applicable.
- ii. Statement of whether the DSMB, DMC or SMC is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.
- iii. Where the DSMB, DMC or SMC is applicable, the names, composition, and qualifications of the members, including the Chairperson, must be stated in the protocol or a separate document.
- iv. Where the DSMB, DMC or SMC is not applicable, a justification shall be provided in the clinical trial protocol.

2.6.5. Proof of Registration of the Clinical Trial

- 2.6.5.1. As part of a Clinical Trial application, proof of registration of the clinical trial with a Clinical Trial Registry, which is WHO-recognised and publicly accessible, shall be submitted.
- 2.6.5.2. It is mandatory for all trials to be registered with the Pan African Clinical Trials Registry (PACTR).

**2.6.6. Investigator's Brochure (IB)**

2.6.6.1. Investigator's Brochure (IB) containing information on the following but not limited to:

- i. Physical, chemical, and pharmaceutical properties and formulations;
- ii. The pharmacological aspects including its metabolites in all animal species tested;
- iii. The pharmacokinetics and metabolism including its biological transformation in all animal species tested;
- iv. Toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study etc;
- v. Results of clinical pharmacokinetic studies;
- vi. Information regarding safety, pharmacodynamics, efficacy and dose responses that were obtained from previous clinical trials in humans;
- vii. Human pharmacological and clinical data with the substance concerned and any other supporting documentation sufficient to establish quality, safety and efficacy where applicable;
- viii. Marketing experience in countries where the investigational product is being marketed or approved. Where appropriate, there should be discussions of published reports;
- ix. Clear instructions on storage and handling of investigational products.

2.6.6.2. The IB should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the IP in the trial and be presented in the form of summaries.

2.6.6.3. An updated IB should be submitted whenever it is updated. Additional information and any changes that have been incorporated in the updated IB should be highlighted for ease of review and evaluation.



- 2.6.6.4. For the contents of an IB, refer to Section 7.0 of the current version of ICH E6 Guidelines for more details.
- 2.6.6.5. Stability data for initial batches, certificates of analysis for three batches or batch analysis data for three batches;
- 2.6.6.6. Name and address of the manufacturer(s) or manufacturing licenses;
-
- 2.6.6.7. The sample label to be used for the Investigational products shall be incorporated into the investigator's brochure or submitted as a separate document.
- 2.6.6.8. Good Manufacturing Practice (GMP) certificate or equivalent from the country of manufacture of the Investigational Product (IP) (including placebo) issued by the competent, recognised Authority shall be incorporated into the IB or submitted as a separate document.
- 2.6.6.9. For trial medicines and allied substances included in the study, registered by ZAMRA, the following documentation only should be provided:
- i. Generic and Brand name (if any) of the product, registration number of the product and a current Package Insert or Summary of Product Characteristics (SmPC) of the product. The Certificate of Analysis will only be required for the application to import the study medicine or allied substance.
 - ii. The approved SmPC may be used in place of the IB if the IP has Marketing Authorisation (MA) in Zambia and is used according to the terms of the marketing authorisation. If the conditions of use in the Clinical Trial differ from those authorised, the SmPC should be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IP in the clinical trial. Where the IP is identified in the protocol only by its active substance, the sponsor should select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any Clinical Trial Site.



Note: For products that are approved by other reference agencies such as USFDA, EMA, TGA, WHO Listed Authorities etc. and products that are WHO prequalified, proof of such approval should be submitted including cGMP certificates. Certification of GMP compliance of manufacturing sites of the Investigational Medicinal Products, adjuvants, comparators and placebos shall be provided.

2.6.7. Investigational Product Dossier (IPD)

- 2.6.7.1. The Investigational Product Dossier (IPD) gives information related to the quality of the IP (i.e. including reference product and placebo), manufacture and control of the IP, and data from non-clinical studies and from its clinical use. However, in many cases where the IP has a Marketing Authorisation (MA) issued by the Authority, an IPD is not required.
- 2.6.7.2. The IPD is required for a pharmaceutical form of an active substance or placebo or comparator being tested or used as a reference in a Clinical Trial, including products already with MA but used or assembled (formulated or packaged) in a way different from the authorised form.
- 2.6.7.3. Data from non-clinical studies and clinical studies/use will be required for products already with MA when used for an unauthorised indication or to gain further information on the authorised form.

Note: For the format of the IPDs, Refer to appropriate ZAMRA guidelines for application for marketing authorisation, eg:

- For Medicinal Products: *Guidelines on Common Technical Document Format;*
- For Nutritional Supplements: *Guidelines on Nutritional Supplements; and*
- For Medical Devices: *Applicable guidelines on medical devices.*



- For placebo: *Appendix X: Dossier for a Placebo product to be used in a clinical trial.*

2.6.7.4. Manufactures or Marketing Authorisation Holders may submit an IPD directly to the Authority.

2.6.8. Good Manufacturing Practices (GMP) Certificate

2.6.8.1. A GMP certificate or equivalent document (for Medical Devices, Nutritional Supplements or Cosmetics) issued by the national Regulatory Authority or relevant Authority of the country of origin; or a GMP statement or equivalent issued by WHO or a WHO-listed, WHO Maturity level 3 or 4 Regulatory Authority or other regulatory agency recognised by the Authority, for the inspection conducted within the last three (3) years shall be required when the IP has no Marketing Authorisation in Zambia.

2.6.9. Ethics approval and approval from other relevant regulators

2.6.9.1. Parallel clinical trial applications for Ethical approval and/or other regulators and in Zambia are encouraged to minimise the timelines for clinical trial approvals.

2.6.9.2. Research involving humans should satisfy the ethical standards and any other applicable internationally recognised ethics guidelines. Ethical approval to conduct a clinical trial in humans issued under section 18 (3) or (4) of the National Health Research Act No. 2 of 2013 is required before a clinical trial certificate can be issued. Ethical approval, or proof of submission of an application for ethical approval in case of parallel submission should be submitted.

2.6.9.3. For clinical trials involving a genetically modified organism or a product of a genetically modified organism, approval from the National Biosafety Authority (NBA) is required. The National Biosafety Authority is responsible for the issuance of permits



for the use of genetically modified organisms or product of a genetically modified organism in clinical trials and certify facilities where clinical trials involving a genetically modified organism or product of a genetically modified organism are conducted.

2.6.10. Insurance Cover

- 2.6.10.1. Sponsors and Principal Investigators shall ensure appropriate insurance cover for Clinical Trial participants and shall submit as evidence a Certificate of insurance cover for participants. The insurance policy shall grant specific cover associated with the reimbursement of damages and death caused to participants by the Clinical Trial activities throughout the entire study period, thus covering any civil liability of the investigator and sponsor of the Clinical Trial, without excluding any damage which may be unintentionally caused by accident and/or be attributed to negligence, imprudence or inexperience. The level of risk that participants will be exposed to will differ across phase I-IV trials; therefore, the sponsor is required to provide insurance cover adequate to match the risk involved in the clinical trial. A person conducting a clinical trial shall insure the persons participating in such trial for an amount proportionate to the risk of participating in the clinical trial or as the Authority may direct.
- 2.6.10.2. The clinical trial insurance cover shall be obtained from a local insurance company.
- 2.6.10.3. A clinical trial insurance certificate shall contain at least:
- i. Insurance company name
 - ii. Policy number
 - iii. Initial Date
 - iv. Expiry Date
 - v. Insured (Policy Holder/Sponsor)



- vi. Description of activity (purpose of the policy)
- vii. Information concerning the clinical trial
 - Title of insured protocol and protocol number (if available)
 - Number of trial centres covered
 - Number of participants (planned number of participants who are expected to take part in the Clinical Trial)
 - Insured (list all events that are covered by the insurance policy e.g. deaths, permanent and temporary impairment of health conditions, relevant financial consequential losses which are the direct consequence of the trial and which can be traced to the liability of all people operating for the performance of the trial).
 - Exclusions (if provided for that specific protocol, please list all exclusions).

2.6.10.4. Update of Insurance Cover

- i. An updated insurance cover for the study shall be submitted to the Authority once the insurance cover/certificate expires or exceeds the validity period of the insurance.
- ii. In the event that the sample size for a clinical trial increases due to an amendment, an updated insurance cover should be submitted to the Authority to include coverage for the additional participants to be recruited.

2.6.10.5. For details on the clinical trial insurance, refer to Appendix XI: Guidance on Liability Insurance for Clinical Trials

2.6.10.6. The indemnification of investigators and trial sites for liabilities arising from trial conduct (except where investigator negligence is proven) is mandatory and should be indicated in the clinical trial agreement with the investigator.



- 2.6.10.7. Investigators may obtain medical malpractice insurance to cover legal claims arising from allegations of medical negligence and malpractice for study staff.

2.6.11. Financial Declaration

- 2.6.11.1. The financial aspects of the trial should be documented in an agreement between the Sponsor and the Principal Investigator/Contracted Research Organisation/Institution.

- 2.6.11.2. A declaration must be signed by both the Sponsor and the Principal Investigator which states that there are sufficient funds available to complete the Trial.

2.6.12. Data Safety Monitoring Board (DSMB)

- 2.6.12.1. The Data Safety Monitoring Board (DSMB) is sometimes called Data Safety Monitoring Committee (DSMC); Independent Data Monitoring Committee (IDMC); Data Monitoring Committee (DMC) or Safety Monitoring Committee.

- 2.6.12.2. A DSMB may be established by the Sponsor to assess at intervals the progress of a Clinical Trial, the safety data, and the critical efficacy endpoints and to recommend to the Sponsor whether to continue, modify or stop a trial. All clinical studies require safety monitoring throughout the duration of the research, but not all studies require monitoring by a DSMB. DSMBs may be critical for studies intended to save lives, prevent serious disease progression, or reduce the risk of a major adverse health outcome. DSMBs are particularly important in studies where interim data analysis is required to ensure the safety of research participants.

- 2.6.12.3. Where the Sponsor considers that a DSMB may not be relevant to the study, a justification shall be provided in the clinical trial protocol.

- 2.6.12.4. The Authority may direct the Sponsor to establish a DSMB.



2.6.12.5. A DSMB shall be considered relevant in the following kinds of studies:

- i. Controlled studies with mortality and/or severe morbidity as a primary or secondary end-point.
- ii. Randomised controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality.
- iii. Early studies of a high-risk intervention (risk of nonpreventable, potentially life-threatening, complications; or risk of common, preventable adverse events of interest [especially type A drug reactions]), whether or not randomised.
- iv. Studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes.
- v. Studies where the design or expected data accrual is complex, or where there may be ongoing questions concerning the impact of accrued data on the study design and participants' safety, particularly in studies with a long duration.
- vi. Studies where the data justify their early termination, such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality.
- vii. Studies carried out in emergency situations.
- viii. Studies which involve vulnerable populations.

2.6.12.6. The Sponsor shall include the charter of work, membership, and curriculum vitae of all the DSMB members.

2.6.12.7. All members of the DSMB shall sign the charter

2.6.12.8. A DSMB Charter shall include:

- i. Terms of Reference
- ii. Membership and their CVs



- iii. Proof of Independence of the Committee
- iv. Scope of work for Members/responsibilities of the Committee which is to assess the progress of a Clinical Trial including safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial.
- v. Meeting scheduled covering the following aspects:
 - a. Initial meeting to review and discuss the DSMB charter, including the role and responsibilities of the DSMB, the protocol safety monitoring plan, and the statistical methodology
 - b. An early safety review meeting during the early stages of implementation of a study to review early safety information and factors relating to quality of conduct of the study.
 - c. Periodic review meetings to review the efficacy and safety data generated during this period and the progress of the study. The expected frequency of these meetings should be specified.
 - d. Final study closeout meeting at the termination or conclusion of a study may be held to consider the efficacy and safety data generated from the study and provide any final recommendation to the sponsor.
 - e. The DSMB charter should indicate whether the meetings are to be held in person or by teleconference.
- vi. Standard Operating Procedures of the Committee

2.6.12.9. For local trials, at least one member must be Zambian. For multicenter trials, it is recommended that at least one member of the DSMB is Zambian.

2.6.13. Sponsor/PI Contractual Agreement

The Sponsor/PI Contractual Agreement shall indicate:

- i. The study title



- ii. Protocol version and date
- iii. Trial site
- iv. Investigational Product
- v. Definitions of all terms
- vi. Effective date of agreement
- vii. Outline of the Sponsor's responsibilities which shall include
 - a. General management of the trial
 - b. Provision of adequate funding, resources/logistics and Investigational Products for the study
 - c. Insurance for the study participants
- viii. Outline of the PI's responsibilities which shall include:
 - a. Conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC and The Authority
 - b. Comply with procedures for data recording/reporting
 - c. Permit monitoring, auditing and inspection
 - d. Retain all trial related essential records until the sponsor informs the PI these documents are no longer needed
 - e. PI's time committed to the study
- ix. Term (period of study duration) and Termination of agreement (conditions for this)
- x. Confidentiality
- xi. The Sponsor and the PI shall sign this agreement and the protocol

2.6.14. Sponsor and Monitor/Contract Research Organization (CRO) Contractual Agreement

- i. An Agreement duly signed and dated by Sponsor and the Local Monitor or representative of the CRO shall be provided.



- ii. The agreement shall outline the specific delegated tasks/duties to the CRO or Local Monitor.
- iii. A copy of the signed monitoring plan for the study shall be included in the submission

2.6.15. Informed Consent and Assent

2.6.15.1. The consenting age shall be 18 years or in line with the definition of “child” in the Constitution of Zambia.

2.6.15.2. Version-controlled and dated Informed Consent Forms and age-appropriate Assent Forms (where applicable) in the English language and appropriate Local Language Translations should be provided with the clinical trial application.

2.6.15.3. As a minimum, the consenting procedures should meet the requirements provided in Section 2.8 of the ICH E6 (R3) guideline.

2.6.15.4. The informed consent discussion and the written informed consent form and any other written information to be provided to participants shall include explanations of the following, but not limited to:

- i. All the elements listed in section 2.8.10 of the ICH E6 (R3) guideline.
- ii. The clinical trial insurance available for participants in case of clinical trial-related injuries resulting from participation in the clinical trial, and instructions on how to claim compensation.
- iii. The Informed Consent Forms should be in line with NHRA guidelines and templates.

2.6.16. Statistical Analysis Plan (SAP)

The proposed SAP for the study shall be submitted initially at the Clinical Trial Application, and the final SAP shall be submitted before data lock.



Note: Refer to the current version of ICH E9 for further guidance on the development of the SAP.

2.6.17. Financial Disclosure

- 2.6.17.1. Principal Investigators shall provide copies of Financial Disclosure forms provided to Study Sponsors regarding their financial interests for the period of their participation in a study, that is, from the date the Investigator entered into an agreement with the Sponsor, and for one year following the end of his or her participation in the study.
- 2.6.17.2. The Authority shall be provided with updates if any relevant information changes during the study and for one year following its completion.

2.6.18. Evidence of Accreditation/Competence of Designated Laboratory(ies) and Other Clinical Facilities

- 2.6.18.1. An applicant shall provide documented evidence demonstrating that all laboratories and specialised facilities participating in the clinical trial meet the required regulatory, quality, and operational standards. This documentation ensures the integrity, accuracy, and reproducibility of the data generated during the study.
- 2.6.18.2. Core documentation required for laboratories for each designated local, central, or reference laboratory, include:
- Valid accreditation certificates from recognised national or international accrediting bodies (e.g., ISO 15189, or national equivalents).
 - Official statements, certifications, or recent audit summaries confirming adherence to Good Laboratory Practice standards.



- iii. A comprehensive, up-to-date list of reference intervals and laboratory normal ranges for all protocol-specified analytes, including the effective dates and the signatures of the laboratory director/manager.
- iv. Recent performance reports from external quality assessment (EQA) or proficiency testing programs.

2.6.18.3. Core documentation required for competence of other specialised facilities such as imaging centers (MRI, CT, PET), cardiology units (ECG/ECHO core labs), pharmacy units, etc:

- i. Evidence of regular calibration, maintenance logs, and validation records for critical equipment used to capture primary efficacy or safety endpoints.
- ii. Valid institutional or licenses required to operate specialised medical and diagnostic equipment.
- iii. Summaries or indices of Standard Operating Procedures (SOPs) governing sample handling, data storage, and technical quality control measures.
- iv. Certification of clinical trial sites issued by NHRA and pharmacy license issued by ZAMRA.

2.6.18.4. Core documentation required to establish technical competence; append the professional credentials of key laboratory and facility staff:

- i. Current, signed, and dated Curriculum Vitae (CVs) for the Laboratory Manager, Chief Pathologist, or lead facility investigators.
- ii. Evidence of specialist or other registrations or practicing licenses with the relevant professional bodies.
- iii. Documented evidence of relevant training in specified areas.

2.6.19. Monitoring Plan

2.6.19.1. Monitoring shall be submitted with the clinical trial application.



2.6.19.2. The sponsor shall develop a monitoring plan that is tailored to the specific human participant protection and data integrity risks of the trial.

2.6.19.3. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasise the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

2.6.20. Samples of investigational medicine or allied substance and/or comparator

2.6.20.1. Where the investigational product or comparator is not registered with the Authority, at least two samples, packed and labeled in the container in which they will be supplied to the clinical trial site, shall be submitted to the Authority for assessment or quality testing.

2.6.20.2. The Authority may waive the requirement to submit the samples on a case-by-case basis.

2.7. Inclusion of Pregnant Women, Breastfeeding Women and Children in Clinical Trials

2.7.1. Inclusion of Pregnant and Breastfeeding Women in Clinical Trials

2.7.1.1. The inclusion of pregnant and breastfeeding women in clinical trials must be based on sound ethical and scientific rationale. Their inclusion is recommended when:



- i. The investigational product is intended for use during pregnancy or lactation (e.g., obstetric indications).
- ii. There is an unmet medical need for pregnant or breastfeeding women (e.g., HIV, cancer, life-threatening infections).
- iii. Preclinical and clinical data, including reproductive toxicology and PK studies in pregnant animals and non-pregnant humans, support trial inclusion.
- iv. The product is likely to be used by pregnant or breastfeeding women in clinical practice.
- v. Potential benefits to the woman and foetus/infant justify the potential risks.

2.7.1.2. Considerations for Pregnant Women:

- i. Risk-benefit assessment must include disease severity, existing therapies, stage of pregnancy, and potential harm to mother or foetus.
- ii. Pharmacokinetic studies may be needed where pregnancy alters drug metabolism, or the risk of under/overdosing is high.
- iii. Long-term follow-up of pregnancy and child outcomes should be considered where feasible.

2.7.1.3. Women who become pregnant during research

- i. In cases where a drug or biological product is known to be mutagenic or teratogenic, pregnant women must be removed from the study, and followed up and provided care through the duration of their pregnancy and delivery.
- ii. Access to diagnostic tests must be provided to reveal any fetal anomalies. If anomalies are detected, women who wish may be referred for appropriate care.
- iii. When there is no evidence based on which a potential harm to the fetus can be assumed, women who become pregnant should not automatically be removed from the study, but must be offered the option to continue or end their participation. For instance, in some cases it may be appropriate for a woman to



stay in the study for safety monitoring but be removed from the investigational product. If the woman opts for continued participation, investigators and sponsors must offer adequate monitoring and support.

2.7.1.4. Considerations for Breastfeeding Women

- i. Studies should assess drug transfer into breast milk and its impact on infant health and development.
- ii. Inclusion is encouraged if real-world use is likely or if data are needed to inform safe dosing during lactation.
- iii. Research must pose no greater risk than routine clinical procedures used during breastfeeding.
- iv. Participants must be fully informed about potential risks and benefits.

2.7.2. Inclusion of children/minors in clinical trials

2.7.2.1. The inclusion of children (minors under the age of 18) in clinical trials must be justified by a strong ethical and scientific rationale. Children should only be enrolled in clinical trials when:

- i. The investigational product is intended for use in paediatric populations.
- ii. There is an unmet medical need in children that cannot be addressed adequately by existing therapies.
- iii. Preclinical and adult clinical data support acceptable safety and pharmacokinetic profiles to justify paediatric studies.
- iv. The disease or condition being investigated occurs primarily or exclusively in children.
- v. The potential direct benefit to the child participant outweighs the foreseeable risks.

2.7.2.2. Ethical Considerations:



- i. Informed consent must be obtained from the parent(s) or legal guardian(s), and assent should be sought from the child in accordance with their age, maturity, and psychological state.
- ii. The protocol must include age-appropriate information materials for both parents/guardians and children.
- iii. The trial must comply with local laws and international ethical guidelines on research involving minors, including the Declaration of Helsinki and CIOMS guidelines.

2.7.2.3. Scientific and Safety Considerations:

- i. Age stratification should be clearly defined, with appropriate dosing and safety monitoring plans for each age group (e.g., neonates, infants, children, adolescents).
- ii. Pharmacokinetic and pharmacodynamic studies should be included, where relevant, to account for developmental differences in drug metabolism.
- iii. Long-term follow-up should be considered, especially for interventions with potential delayed effects on growth, development, or organ function.
- iv. The protocol must include procedures for monitoring and reporting adverse events, with special attention to age-specific safety concerns.

2.7.2.4. Study design considerations:

- i. Use formulations suitable for paediatric administration, considering palatability, dosage flexibility, and ease of use.
- ii. Dosing regimens should be scientifically justified and age-appropriate.



2.8. Requirements for Non-Clinical Safety Studies for the Conduct of Human Clinical Trials

- 2.8.1. The clinical development of a medicine follows a sequential series of steps, from drug discovery through non-clinical testing to clinical trials and eventual marketing authorisation. Results from each stage must support progression to the next stage.

Table 1. Stages of drug development

Pre-clinical		Phase-I		Phase-II	Phase-III	Phase-IV
In-vitro <i>/in-silico</i>	In-vivo	1 st in human Dose Finding and Safety	Special groups including healthy volunteers	Proof of concept, Safety & preliminary efficacy	Safety & Efficacy (sufficient powering and randomisation)	Post- approval safety in use, especially long-term AEs/SAEs

- 2.8.2. Non-clinical testing is required to establish the safety profile, pharmacology, toxicology, and pharmacokinetics of the IP before clinical testing can be initiated.
- 2.8.3. Non-clinical safety studies characterise toxic effects, including target organ impact, dose dependence, exposure relationships, and reversibility, to establish safe starting doses and monitoring parameters for clinical trials. Although initial non-clinical data may be limited, these studies must thoroughly identify and simulate potential adverse effects under the specific conditions of the proposed human testing.
- 2.8.4. Clinical trials should be extended based on the demonstration of adequate safety in the previous clinical trial(s), as well as on additional non-clinical safety information that becomes available as clinical development proceeds.
- 2.8.5. Serious adverse clinical or non-clinical findings can influence the continuation of clinical trials. Within the overall clinical context, these findings should be evaluated to determine the appropriateness and design of additional non-clinical and/or clinical studies.



- 2.8.6. Tests of the functionality and metabolism of the candidate molecule (primary pharmacodynamics and pharmacokinetics) can be explored in vitro and in animal models. These characteristics can be confirmed for experimental formulations of the candidate medicine in the same systems.
- 2.8.7. The following non-clinical studies should be reported (based on ICH M3) to support first-in-human clinical trials:
- 2.8.7.1. Pharmacology studies
- Safety pharmacology core studies: assessment of effects on the cardiovascular, respiratory, renal, gastrointestinal, haematological and central nervous systems.
 - Primary pharmacodynamics studies: In vivo and/or in vitro studies, assessing the mode of action/effects of the candidate compound on the target.
- 2.8.7.2. Toxicokinetic and pharmacokinetic studies
- Data gathered during in vitro studies on metabolic and blood protein binding data for animals and humans.
 - Systemic exposure data from toxicology studies. Biodistribution and elimination.
 - These studies are not usually required for biological medicines apart from immunotherapeutic medicines, blood products, live vaccines, or gene products.
- 2.8.7.3. Acute toxicity studies:
- Single-dose toxicity studies in more than one mammalian species can be completed during studies that define dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) in the species used for toxicity testing. The NOAEL relevant to the intended use of the IP can be accepted as a guide to estimating the maximum dose to be used in clinical trials.
- 2.8.7.4. Repeated-dose toxicity studies
- Vary in length according to duration, therapeutic indication, and scope of the proposed clinical program.



- Minimum duration for two weeks in two mammalian species (one of which is not a rodent) but may need to be extended to be relevant for the proposed trial duration.
- Repeat-dose toxicity studies can be designed to collect data supporting single-dose acute toxicity studies.

2.8.7.5. Reversibility of toxicity

- Animal studies can indicate the potential for reversibility of adverse events that are detected.

2.8.8. Further non-clinical studies will be conducted on a case-by-case basis and at any clinical trial phase, including:**2.8.8.1. Assessments of carcinogenic potential****2.8.8.2. Photosafety testing, immunotoxicity, juvenile animal toxicity, additional toxicity studies, non-clinical abuse liability, etc.****2.8.8.3. For biotechnology-derived products, appropriate non-clinical safety studies should be determined in accordance with the ICH S6 guideline.****2.8.8.4. For life-threatening or serious diseases – such as resistant infections, cancer, etc., that do not have a current adequately effective therapy.****2.8.8.5. Teratogenicity**

- i. Teratogenicity, Developmental and reproductive toxicity studies will be required before exposure of women of child-bearing potential to the investigational drug or comparators.
- ii. Pregnant women must be excluded in all first-in-human studies.
- iii. In the extremely rare case that the participant falls pregnant while in a first-in-human or phase I study, the participant should be terminated immediately from study treatment and the pregnancy and the baby be carefully followed up.

2.8.8.6. Clinical trials in paediatric populations: Results from repeated-dose toxicity studies of appropriate duration in adult animals, the core safety pharmacology package, and the



standard battery of genotoxicity tests should be available before initiation of trials in paediatric populations. Safety data from previous adult animal and human exposures, juvenile animal studies, carcinogenicity testing and reproduction toxicity studies relevant to the age and gender of the paediatric patient populations under study may be required on a case-by-case basis.

2.8.8.7. Platform technologies: Where a medicine or vaccine is of the same or similar class and is based on a well-accepted formulation with minor modifications to the active ingredient, then the applicant can request that the pre-clinical program be reduced. This is particularly relevant in biosimilar studies.

2.8.9. Where animal testing is required, examinations for adverse effects and toxicity need to be conducted in suitable animal models and in more than one family of animals (not all rodents or non-human primates), at least one of which is considered relevant to the human condition. Conduct of research in animals in Zambia requires approval from a health research ethics committee and NHRA.

2.8.10. Key points for evaluation of non-clinical data to support phase I clinical trial

- 2.8.10.1. Have the relevant non-clinical tests as required by ICH and other guidelines been conducted and reported in this application? Is there an acceptable justification for any omissions?
- 2.8.10.2. Is there adequate evidence of safety and evidence supporting efficacy from non-clinical studies to proceed with clinical studies, particularly for early phase or first-in-human clinical trials? Is there an acceptable justification for any omissions?
- 2.8.10.3. For the first-in-human clinical study, are the proposed starting dose, dose escalation, and maximum exposure justified based on the non-clinical data for this application?
- 2.8.10.4. Has the current formulation been included in the reported non-clinical test results? Are the non-clinical data relevant to the proposed formulation and route of administration in the clinical study application?



- 2.8.10.5. Where medicines are used in combination, special consideration needs to be given to the potential adverse effects and the dosages used of both the IP and the registered medicine(s).
- 2.8.10.6. Are there additional surveillance activities for participants that should be conducted during the proposed clinical trial, based on the reported results from the non-clinical studies (or potential adverse effects reported from medicines in the same class)?
- 2.8.10.7. Development and Reproductive Toxicity and teratogenicity studies are not usually required for first-in-human studies, as the safety of the candidate IP given to non-pregnant women must be established before trials in pregnant or breastfeeding women can be undertaken.

2.9. Considerations for First-in-Human / Phase-I Clinical Trials

- 2.9.1. Dose selection for First-in-Human and early clinical trials
 - 2.9.1.1. The starting dose and maximum exposure, as well as dose escalation steps during the clinical trial, should be justified and outlined in the protocol.
 - 2.9.1.2. The methods used and calculations on how doses and estimated exposure levels were determined, including modelling methods (e.g., PK/PD and physiologically based pharmacokinetic (PBPK)), should be summarised in the Clinical Trial Application Form and Clinical Trial Protocol and the details included in the investigational brochure (IB).
 - 2.9.1.3. Deviations from the prespecified dose escalation and decision-making criteria would warrant the submission of major amendment(s). Decision making criteria for adapting dosage based on clinical data based on emerging clinical data should be described.
 - 2.9.1.4. Sentinel dosing of two participants (one active, one placebo) is required at a minimum for the first single ascending dose (SAD) and multiple ascending dose (MAD) cohorts.
 - 2.9.1.5. Moving from single and multiple dosing



- i. The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should consider the specific PK and PD characteristics of the IP, the available non-clinical safety data, and all data from participants in previous single-dose cohorts.
 - ii. A maximum duration of dosing should be stated in the protocol for every cohort. The expected exposure after multiple dosing (C_{max} and $AUC_{0-\tau}$) should have been covered during preceding SAD parts/trials.
- 2.9.1.6. The choice of route of administration for dosing in humans should be based on the non-clinical data, the characteristics of the IP, and the intended therapeutic use.
- 2.9.1.7. Integrated protocol
- i. The practice of conducting first-in-Human/early clinical trials with integrated protocols means that the information generated in previous parts needs to be analysed and integrated into an assessment in a limited timeframe before deciding on proceeding to the next part.
 - ii. All parts, and the criteria to move from one part to another, should be predefined within an integrated protocol, as should possible modifications, based on the totality of available information and the related uncertainty.
 - iii. Recommendations for time sequence for the conduct of different parts:
 - Overlapping of SAD and MAD parts may be acceptable. The proposed overlap, however, should be scientifically justified and supported by decision points and a review of available data before starting the MAD part.
 - Other single-dose parts (e.g., food interaction) could be conducted in parallel to the SAD part, provided the dose chosen and the expected exposure are equal to or lower than that which was reached in a concluded preceding SAD cohort where all relevant data have been reviewed and no dose escalation stopping criteria were met.



- Other study parts that involve multiple dosing (e.g., drug-drug interaction) should generally not overlap with earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed before starting these parts. Deviation from this should be justified in the protocol.
- 2.9.1.8. The protocol should define unambiguous stopping rules that result in an immediate stop to dosing.
- 2.9.1.9. To prioritise participant safety and data integrity, First-in-Human clinical trials should be undertaken in appropriate clinical facilities and conducted by investigators and medical staff with the appropriate levels of training and experience in early-phase clinical trials. Clinical facilities should have appropriate physical layout and participant accommodation, emergency and resuscitation capability.
- 2.9.1.10. Sites must have access to emergency supplies, and staff must be prepared for medical emergencies.
- 2.9.1.11. Procedures should be established between the clinical research unit and its nearby intensive care unit (ICU) regarding the responsibilities and undertakings of each in the transfer and care of patients.
- 2.9.1.12. The research site / PI must have prior arrangements with the appropriate specialist(s) at the nearby hospital to enable rapid admission and avoid long ER/casualty waiting. The Sponsor/Applicant must cover the costs of such admissions and facilitate immediate payments to the applicable hospital.
- 2.9.1.13. Monitoring and communication of adverse events
- i. For all clinical trials, adverse events of special interest (AESI) should be defined, based on non-clinical findings and observations from experience with other similar active ingredients. Suitable monitoring activities for these AESIs should be described.



- ii. Due to the high risk of First-in-Human / Phase 1 trials, four-weekly progress reports on a ZAMRA template should be submitted (Appendix VI: Clinical Trials Four-Weekly Progress Report Form).

2.9.1.14. The indemnification of investigators and trial sites for liabilities arising from trial conduct (except where investigator negligence is proven) is mandatory and should be indicated in the clinical trial agreement with the investigator.

2.10. Human Challenge Trials

Refer to Annex 10 of the WHO Expert Committee on Biological Standardization, sixty-seventh report. Geneva: World Health Organization; 2017 (WHO technical report series; no. 1004).
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2.11. Sub-studies

- 2.11.1. A sub-study is a discrete separate study, which is part of a Clinical Trial and should be described in the application form and in the protocol. Examples include pharmacokinetic or pharmacogenetic sub-studies.
- 2.11.2. Participation of Clinical Trial participants in a sub-study either involves the entire trial population or a specified subgroup of participants receiving the Investigational Products (IPs) as specified in the protocol. Sub-studies should not include a trial population that is different from that of the main trial. For a sub-study, an additional informed consent is required. It should be clear to participants participating in a Clinical Trial if the decision to take part in a sub-study is optional and separate from that of the main trial. An optional sub-study should be mentioned in the main Informed Consent Form (ICF) and a more detailed ICF for the sub-study should be provided and signed.
- 2.11.3. Sub-studies involving products that are not part of the IPs or auxiliary products in the main study shall require separate CTA.

**2.12. Requirements for Key Study Personnel****2.12.1. Requirements for the Principal Investigators and the Co- or Sub-Investigators**

2.12.1.1. The Principal Investigator (PI) is a person responsible for the conduct of the Clinical Trial at a trial site who is a suitably qualified person, resident in Zambia and a member of, and in good standing with, the relevant professional body in Zambia. If a trial is conducted by a team of individuals at a trial site, the PI is the responsible leader of the study team. The PI must be able to provide sufficient supervision and oversight of the conduct of the trial. The PI has sole or joint responsibility for the conduct of the trial and delegation of responsibilities of the trial.

2.12.1.2. Principal Investigator(s) directly in charge of a trial at each site must:

- i. Be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial.
- ii. Possess at least a degree in a relevant professional field.
- iii. Be thoroughly familiar with the appropriate use of the Investigational Product(s), as described in the protocol.
- iv. Be aware of, and should comply with, GCP and the applicable regulatory requirements.
- v. Have evidence of Good Clinical Practice training within the last 3 years.
- vi. Be a Zambian who resides in Zambia.
- vii. Provide evidence of registration with the relevant professional bodies in Zambia.
- viii. Provide evidence of registration with NHRA.
- ix. The Co- or Sub-Investigator shall meet the requirements above.
- x. The PI must have actively participated in at least two clinical trials as a Co- or Sub-Investigator.
- xi. The Authority shall review and ascertain the Investigator's compliance to regulatory requirements.

**2.12.2. Requirements for the Clinical Trial Medical officer (Study Physician) or Dentist****2.12.2.1. The Clinical Trial Medical officer must:**

- i. Be qualified by education, training, and experience.
- ii. Be a medical officer or dentist, as applicable, and where necessary or as directed by the Authority, with specialisation relevant to the study population and clinical trial protocol.
- iii. Be thoroughly familiar with the appropriate use of the Investigational Product(s), as described in the protocol.
- iv. Be aware of, and should comply with, GCP and the applicable regulatory requirements.
- v. Have evidence of Good Clinical Practice training within the last 3 years.
- vi. Be resident in Zambia and available at the clinical trial site to attend to the medical needs of the clinical trial participants.
- vii. Provide evidence of registration with the relevant professional bodies in Zambia.

2.12.3. Requirements for the (Study) Pharmacist**2.12.3.1. The study Pharmacist must:**

- i. Be qualified by education, training and experience.
- ii. Have full registration with the relevant professional bodies.
- iii. Have a valid practicing license from the relevant professional bodies in Zambia.
- iv. Be knowledgeable in the use and management of the Investigational Product(s).
- v. Knowledgeable on import/export regulations, Good Distribution Practices and disposal guidelines in Zambia.
- vi. Be knowledgeable of, and should comply with, GCP and the applicable regulatory requirements.
- vii. Have evidence of Good Clinical Practice Training within the last 3 years.
- viii. Be resident in Zambia and available at the clinical trial site to handle and manage investigational products.



Note: For trials that do not involve medicines or biological products, an appropriately qualified individual may be delegated to handle the investigational products.

2.12.4. Requirements for Study Coordinator, Laboratory Manager, Data Manager, Local Monitor, and Quality Assurance Officer

- i. Must be qualified by education, training and experience.
- ii. Where applicable, must have a valid practicing license from the relevant professional bodies in Zambia.
- iii. Knowledgeable and in compliance with applicable regulatory requirements, and GCP.
- iv. Must have evidence of Good Clinical Practice training within the last 3 years.
- v. Must be resident in Zambia.

Note: For responsibilities in Clinical Trials, refer to Guidelines for Good Clinical Practice in Zambia

2.13. Importation and Management of Investigational Products for Clinical Trial

2.13.1. Importation of Investigational Products

2.13.1.1. On approval of the Clinical Trial, an application for an import permit must be submitted to the Authority for importation of the Investigational Product through approved ports of entry.

2.13.1.2. An application for importation of Investigational Products and trial products shall receive prior approval from the Authority.

2.13.1.3. Approval to import products for Clinical Trials shall only be granted to recognised clinical research entities whose protocol has been approved by the Authority.



- 2.13.1.4. Application to import Investigational Products shall be made to the Authority via the online application portal (www.zamra.co.zm) and attach supporting documents:
- Completed ZAMRA *Application for Importation/Exportation Permit for Medicine or Allied Substance* on the portal.
 - Proof of approval of the Clinical Trial by the Authority.
 - Proforma Invoice stating the quantities and source of each Investigational Product and trial-related product to be imported.
 - Certificate of Analysis (CoA) of Investigational Products for all batches to be imported.
 - Lot Release certificate(s) (where applicable) for all batches to be imported.
- 2.13.1.5. The IPs being imported should have more than six months of shelf life (before expiry) upon arrival.
- 2.13.1.6. The Principal Investigator shall notify The Authority within 48 hours through clinicaltrials@zamra.co.zm or alternative means of each consignment of Investigational Product batches received on site. The notification shall include the following details: Name of product(s), quantities and batches received.
- 2.13.1.7. The Proforma Invoice shall bear the full name and address of the manufacturer and the recognised Clinical Research entity, the name/description of the Investigational Product and placebo, and quantity to be imported.
- 2.13.1.8. The Investigational Product shall be appropriately labeled with the approved labels to indicate that they are samples for the conduct of Clinical Trials only. The label shall bear the following basic information:
- For Clinical Trial purposes **ONLY**
 - Trial name or protocol code or identification
 - The name, number or identifying mark of the IP
 - The batch / lot number
 - Expiry date (if applicable)
 - Dosage (if applicable)



- vii. The name and address of the sponsor
- viii. Storage conditions / instructions
- ix. The name and address of the premises where the clinical trial is to be carried out.

Registered products that are used in a clinical trial must also be labelled as above.

- 2.13.1.9. Products imported may be inspected by officials of the Authority at the port of entry before they are released to the recognised clinical research entity or agent.
- 2.13.1.10. The above notwithstanding, all other statutes governing importation procedures in Zambia shall apply to imported Investigational Products.
- 2.13.1.11. For Investigational Products purchased locally, the Principal Investigator shall document the source, proof of purchase, quantities purchased and Certificate of Analysis (CoA) for each batch of Investigational Products.
- 2.13.1.12. Copies of all documents on Investigational Products, whether purchased locally or imported, shall be kept on site for verification and accountability during GCP inspections.

2.13.2. Disposal of Investigational Products

- 2.13.2.1. Used, destroyed/broken, and expired Investigational Products may be destroyed upon authorisation by the Sponsor.
- 2.13.2.2. Reconciliation of all Investigational Products shall be performed and verified by or on behalf of the Sponsor, explaining any discrepancies satisfactorily.
- 2.13.2.3. An official request to dispose of the Investigational Products, indicating the type and quantity of each product to be destroyed, shall be made to ZAMRA as stipulated in the applicable guideline on disposal.
- 2.13.2.4. The destruction process shall be supervised by officers of the Authority and representatives of other relevant agencies, where applicable, and a disposal certificate issued.



2.13.2.5. Where the Sponsor/Investigator wishes to donate Investigational Products, an official request to donate the Investigational Products, indicating the type and quantity of each product to be donated, shall be made to the Authority as stipulated in the guidelines for donation.

2.13.3. Storage of Investigational Products (IPs)

2.13.3.1. All Investigational Products must be stored in a Pharmacy or, where applicable, appropriate storage facilities.

2.13.3.2. All requirements for a Pharmacy shall apply, i.e. temperature control and temperature monitoring, access control, etc.

2.13.3.3. Storage facilities must be according to the storage requirements for the IP(s).

2.14. Reporting and Management of Adverse Events

2.14.1. The Principal Investigator is responsible for submitting safety reports to the Authority.

2.14.2. The Sponsor should ensure that all Adverse Events (AEs) that are both serious and unexpected are reported to the Authority.

2.14.3. Reporting should occur within the timeframe specified in Appendix I: Timelines and format or template specified in Appendix III: Serious Adverse Event Report Form.

2.14.4. Any participant who experiences a Serious Adverse Event following use of an Investigational Product shall receive immediate medical attention and the event reported to the Authority within specified timelines.

2.14.5. Reports of serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reaction (SUSARs) during the trial must be reported promptly to ZAMRA as soon as possible, but no later than 7 calendar days of occurrence is known by the principal investigator/investigators. Where the initial report did not include all the information or an assessment of the event, a complete report with an assessment of the event shall be submitted within 8 calendar days following an initial report. A follow-up report should



also be submitted when there is a change in the severity or new development on an SAE initially reported or when the SAE resolves.

- 2.14.6. Non-Serious AEs should be submitted as part of the Six-monthly Progress Report.
- 2.14.7. Medication errors, pregnancies (where applicable) and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as AEs.
- 2.14.8. All fatal cases shall be accompanied by a formal autopsy report.
- 2.14.9. In exceptional cases where a formal autopsy is not practicable or permitted by the next of kin, a verbal autopsy report may be provided.
- 2.14.10. The verbal autopsy conducted, and the report submitted shall be in accordance with current version of the W.H.O Standard Verbal Autopsy Instrument for investigating causes of death.
- 2.14.11. Any adverse event to the investigational product shall receive immediate medical attention and be reported to the Authority within specified timelines.
- 2.14.12. The Principal Investigator is required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes to enable Causality Assessment by the Technical Committee. All additional information should be clearly marked as follow-up information and should include the Protocol Number and Participant Number.

2.15. Clinical Trial Amendments

- 2.15.1. Any amendment to the clinical trial protocol, clinical trial arrangements and investigational medicine or allied substance shall be submitted to the research ethics committee that originally approved the protocol and to the Authority for approval before such amendments are implemented.



2.15.2. Changes that constitute an amendment include but are not limited to following:

- i. Changes that affect patient selection and monitoring
- ii. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
- iii. Changes that affect patient discontinuation
- iv. Changes that result in the extension of the duration of the clinical trial
- v. Changes that result in change to the chemistry and manufacturing information that may affect drug safety and quality (For example: specifications for the drug where the limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and, the addition of new raw materials, solvents, reagents, catalysts or any other material used in the manufacture of the drug substance).

2.15.3. All applications for amendments shall attract a fee which shall be determined as per ZAMRA Fee Schedule.

2.15.4. The sponsor may make amendments to the protocol after the commencement of the clinical trial. If those amendments are substantial and are likely to have an impact on the safety of the clinical trial participants or to change the interpretation of the scientific documents in support of the conduct of the clinical trial, the sponsor shall notify The Authority of the reasons for, and content of, these amendments.

2.15.5. The following changes do not count as an 'amendment':

- i. Safety Report (SR) is not per se an amendment and thus does not have to be notified as an amendment to the Authority. However, the sponsor must verify whether the data presented in the SR requires a change to the documentation submitted with the request for authorisation of a clinical trial. If this change amounts to an amendment, the applicant should apply for an amendment.



- ii. A change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as an amendment, if the sponsor and legal representative remain identical. However, the sponsor should ensure that the Authority is aware of this change as soon as possible, in order to allow the Authority to exercise its supervisory function.

2.15.6. Major amendments

- i. Amendments to the clinical trial are regarded as 'major' where:
 - a. The amendment is likely to have a significant impact on:
 - The safety or physical or mental integrity of the clinical trial participants, or
 - The scientific value of the clinical trial.
 - b. The amendment affects the quality of the investigational medicine or allied substance.
- ii. In all cases, an amendment is only to be regarded as 'major' when one or both above criteria are met.
- iii. The following are examples of changes regarded as major amendments:
 - a. Study Design & Methodology: Adding or eliminating a study arm or IP, changing primary or secondary endpoints, or altering the statistical analysis plan in a way that impacts the trial's validity.
 - b. Participant Safety & Risk/Benefit:
 - Changes affecting drug dosage, frequency, or the duration of exposure for participants.
 - Significant changes to inclusion/exclusion criteria, such as opening the trial to a more at-risk population (e.g., including pregnant women or children for the first time).
 - Updating study documents with knowledge of new, serious, or life-threatening risks discovered mid-trial.



c. Procedures & Monitoring:

- Adding or removing tests or procedures that change the risk level for participants (e.g., adding invasive biopsies or additional radiation exposure).
- Changes to participant safety monitoring visits, especially in Phase I or II trials.

d. Trial Management:

- Appointment of a new Principal Investigator, Contract Research Organisation or a change in the Sponsor.
 - Addition of a Clinical Trial Site
 - A temporary halt of the study to protect participants from harm or the subsequent planned restart.
 - A Change in the total number of participants
- e. Changes to the formulation and composition of the investigational product, such as changing the concentration of the active substance or using a different salt form.
- f. Change in the method of synthesis of the active substance or the manufacturing process of the finished investigational product.
- g. Widening the acceptance criteria in the specifications.
- h. Changes to test procedures for the active substance or finished investigational product.
- i. Significant changes to storage conditions (e.g., changing from room temperature to refrigeration).
- j. Changes to the primary packaging material that might affect the drug's stability.
- k. Changing the manufacturer of the active substance or the finished product.
- l. Changes to the shelf-life of the finished investigational product. However, extension of shelf-life based on supplementary stability data where the



original specifications remain unchanged and the intention to extend shelf-life was made known to the Authority at the time of initial approval of the clinical trial application will be regarded as a minor amendment.

- iv. The responsibility of assessing whether an amendment is regarded as major or not lies with the sponsor.
- v. The Authority shall, however, recommend a reclassification of a Sponsor's classification of an amendment when necessary.
- vi. The annual update of the IB is not per se a major amendment. However, the sponsor must verify whether the update relates to changes which are to be considered as major. In that case, the rules for notification of major amendments apply to the change.
- vii. The sponsor should also assess whether the combination of major amendments leads to changes of the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would then be subject to a new authorisation procedure.
- viii. All other amendments that do not meet the above criteria for major amendments will be considered as minor amendments.
- ix. Without prejudice to the above points, the Authority reserves the right to direct an amendment to the protocol.

2.15.7. Format and content of amendment application - The notification of an amendment should include the following:

- i. A signed cover letter, including a highlighted indication of any special issues related to the amendment and indication where the relevant information or text is in the original application dossier.
- ii. A description of the amendment:
 - a. An extract from the amended documents showing previous and new wording in track changes, as well as the extract only showing the new wording;



- b. Notwithstanding the previous point, if the changes are so widespread or far-reaching that they justify an entire new version of the document, a new version of the entire document should be submitted. In this case, an additional table should list the amendments to the document. In this list, identical changes can be grouped;
 - c. The new version of the amended document(s) should be identified with the date and an updated version number.
 - iii. Supporting information including, where applicable:
 - a. summaries of data;
 - b. an updated overall risk/benefit assessment;
 - c. possible consequences for participants already included in the trial;
 - d. possible consequences for the evaluation of the results.

2.16. Clinical Trial Records

- 2.16.1. The sponsor/investigator must record, handle and store all information in respect of a clinical trial to ensure that the clinical trial is conducted in accordance with good clinical practices and in a way that allows its complete and accurate reporting as well as its interpretation and verification.
- 2.16.2. The sponsor/investigator must keep all records related to the conduct of a clinical trial in a format that facilitates verification for the purpose of an inspection.
- 2.16.3. The sponsor/investigator must submit requested records within 48 hours if safety concerns arise. Additionally, the Regulatory Authority can request the submission of additional information within seven days to facilitate an inspection of a site.
- 2.16.4. The investigator must maintain complete and accurate records in respect of the use of an investigational product in a clinical trial, including:
 - 2.16.4.1. A copy of all versions of the Investigator's Brochure for the drug;
 - 2.16.4.2. Records respecting each change made to the investigator's brochure, including the



- rationale for each change and documentation that supports each change;
- 2.16.4.3. Records respecting all adverse events in respect of the drug that have occurred locally or internationally, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
- 2.16.4.4. Records in respect of the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the use of the drug may endanger the health of the clinical trial subjects or other persons;
- 2.16.4.5. Records in respect of the shipment, receipt, disposition, return and destruction of the drug.
- 2.16.5. For each clinical trial site, an undertaking from the principal investigator that is signed and dated by the principal investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that the principal investigator will conduct the clinical trial in accordance with good clinical practices.
- 2.16.6. For each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Committee and Regulatory Authority for that clinical trial site.

2.17. Clinical Trial Reports

2.17.1. Notification of commencement of the clinical trial

- 2.17.1.1. The Sponsor, Applicant, or PI shall notify the Authority of the exact date of commencement of the clinical trial within 15 working days of the trial initiation.
- 2.17.1.2. If the trial does not begin or is delayed past six months from the date of approval, the Sponsor, Applicant, or PI shall submit a six-monthly progress report stating the reasons for the delay.

2.17.2. Six-Monthly Progress Report



- 2.17.2.1. Six-Monthly reports of the progress of a Clinical Trial starting from the date of the Authority's approval of the Clinical Trial shall be submitted to the Authority in the format or template provided in Appendix V: Clinical Trials Six-Monthly Progress Report Form. The reports must be submitted to the Authority within 15 working days after the end of the reporting period. A reporting period shall be considered as six months beginning from the date ZAMRA approved the Clinical Trial.
- 2.17.2.2. If the trial does not begin or is delayed, the Authority shall be informed of the actual date of commencement within three months of issuance of the Clinical Trial Certificate.
- 2.17.2.3. If the study has not commenced recruitment, reasons should be given as to why the recruitment has not commenced. Failure to inform the Authority of the commencement of the study, within this period shall have regulatory implications (e.g. notice of concern, suspension or revocation of Clinical Trial Certificate).
- 2.17.2.4. If the trial is terminated before the Sponsor achieves its purpose, the reason shall be conveyed in writing to the Authority within fifteen (15) calendar days. This shall include:
- i. Justification for the premature ending or temporary halt of the trial;
 - ii. Number of patients receiving intervention at the time of the study termination;
 - iii. Proposed management of patients receiving intervention at the time of halt or study termination; and
 - iv. Implications of the discontinuation on the evaluation of the final results.
- 2.17.3. Data and Safety Monitoring Board (DSMB) Report
- 2.17.3.1. Duly signed and authenticated DSMB reports and/or minutes shall be submitted to the Authority.
- 2.17.3.2. The DSMB reports shall be submitted within 10 working days from the date of the report.



2.17.4. Protocol Violation and Protocol Deviation Reports

2.17.4.1. The Principal Investigator shall notify the Authority in writing of all Protocol Violations and Protocol Deviations that occur at the site and CAPAs implemented to avoid future occurrence, in the format or template provided in Appendix IV: Clinical Trial Protocol Deviation/Violation Report Form.

2.17.4.2. The Protocol Violation and Protocol Deviation reports shall be submitted within 10 working days from the date the site becomes aware.

2.17.5. Interim Analysis Reports

2.17.5.1. If the approved protocol includes provisions for interim analysis, a comprehensive report on the interim results shall be submitted to the Authority within thirty (30) calendar days of obtaining these results.

2.17.6. Close-out Report

2.17.6.1. The Principal Investigator/Sponsor shall notify the Authority in writing, not later than 30 calendar days after the conclusion of the clinical trial.

2.17.6.2. The clinical trial site can be closed when the following activities are completed:

- i. The study has reached the last participant's last visit - all participants have finished their final protocol interventions and follow-ups;
- ii. All data queries have been resolved, case report forms finalised, and the database locked (certain sites in a multicentre study may be exempted from the database-lock requirement); and
- iii. Investigational products are fully reconciled and accounted for.

2.17.6.3. In the case of early termination of the clinical trial, where the clinical trial is stopped prematurely, the closeout report shall be submitted within 30 calendar days of termination of the clinical trial.



- 2.17.6.4. A Close-Out report on the study shall be submitted to the Authority after study conclusion or termination in the recommended format (Appendix VII: Close-out Report Form).
- 2.17.6.5. A copy of the disposal certificate of the IP(s) issued by the Authority, or other applicable documentation, shall be attached to this report.
- 2.17.7. Final Report
- 2.17.7.1. In addition to the report referred to above, the PI/Sponsor shall, not later than 12 months after the completion of the study, compile and submit to The Authority a comprehensive formal report conforming to the ICH E3 Guideline for the Structure and Content of Clinical Study Reports.
- 2.17.7.2. The report shall include a short but comprehensive summary of the essential findings of the trial and of its methodology and course.
- 2.17.7.3. The Final report shall be submitted in hard and electronic copies.
- 2.17.7.4. Publication of manuscript(s) from the trial in a scientific journal or other medium shall require a no-objection opinion from the Authority. Publication of trial data shall be 30 calendar days after submission of the intended publication to the Authority.
- 2.17.8. Temporary Halt of a Trial
- 2.17.8.1. A temporary halt of a trial is a stoppage of the trial which is not envisaged in the approved protocol and where there is an intention to resume it. A temporary halt may be, but not limited to:
- i. due to a major amendment, or
 - ii. part of an urgent safety measure. In this case, the notification of the temporary halt of a trial shall be made immediately and, at the latest, within 15 calendar days from when the trial is temporarily halted.
- 2.17.8.2. The reasons and scope, e.g. stopping recruitment or interrupting treatment of participants already included, should be clearly explained.



- 2.17.8.3. The restart of the trial is subject to the PI/Sponsor providing evidence that it is safe to restart the trial of which the Authority must approve.

2.18. Post-Trial Access to Investigational Products

- 2.18.1. Where provision is made for post-trial access to study IPs, the study shall request for approval from the Authority for the initiation of post-trial access to study IPs for study participants.
- 2.18.2. The request for approval for the initiation of post-trial access to study IPs shall be supported by adequate safety and efficacy data. The efficacy data must provide evidence of continued clinical benefit to study participants.

2.19. Clinical Trials during Public Health Emergencies

- 2.19.1. In cases of a public health emergency, expedited regulatory review pathway for Clinical Trials shall be employed in line with approved guidelines. Without unnecessarily compromising patient safety, the maximum advantage of the shortest, realistic timelines will be made a priority, because in emergencies, time is of vital essence.
- 2.19.2. The emergency procedure may involve joint reviews/inspections, data sharing, and communication with the Authority to speed up approval of the Clinical Trial. Parallel/simultaneous ethical and regulatory review is encouraged. A timeline of 10-15 working days is recommended for the processing of Clinical Trial Applications. These timelines are for the entire process from receipt of a complete Clinical Trial Application package to the final decision, except for clock stops. A shorter timeline may be considered where the product is already registered with the Authority for other indication(s). (See Appendix Ig: Clinical Trial Application Review Process Flowchart - Public Health Emergencies)



2.19.3. The documentation to be submitted will be the same as outlined in section 2.5, however, this will be dealt with on a case-by-case basis. Researchers are encouraged to have pre-submission meetings with the Authority to discuss their protocol and any anticipated problems so that the approval process will be shortened. The Authority will also coordinate with relevant stakeholders such as NHRA, NBA, AMA, WHO and others when necessary to achieve the desired result.

2.19.4. General considerations

2.19.4.1. All the necessary ethical approvals shall be obtained for the study. Additionally, all ethical principles shall apply.

2.19.4.2. Requirements for filing a Clinical Trial Application during an emergency shall be the same as required under Section 2.0.

2.19.4.3. The format and content of an application for the conduct of a Clinical Trial in emergencies shall be as described in Section 2.0.

2.19.4.4. The timelines for processing such applications shall, however, be shortened (refer to Appendix Ig: Clinical Trial Application Review Process Flowchart - Public Health Emergencies).

2.19.4.5. The timelines for submitting reports from Clinical Trials may be shortened.

2.19.4.6. The Authority shall, however, prescribe other relevant information to be provided considering the phase and nature of the intended trial.

2.20. Clinical Trials Register

2.20.1. All clinical trial applications, either approved or rejected, shall be listed on the Authority's clinical trial register. The information to be listed on the Authority's clinical trial register shall include the protocol number, public title, scientific title, date submitted and date of approval or rejection of the clinical trial application.

**2.21. Publication of Summarised Public Assessment and Public Inspection Reports**

2.21.1. In line with the WHO Global Benchmarking Maturity Level 4 requirements and international good regulatory practices to promote transparency, accountability and communication and to and gain public trust in clinical trial research oversight, the Authority shall publish Summarised Public Assessment Reports (PAR) for Clinical Trial Applications and Public Inspection Reports (PIR), including Good Clinical Trial Practice (GCP) Inspections.

2.21.2. Clinical Trial Application Public Assessment Report

- 2.21.2.1. When an application for a clinical trial has been authorized or rejected by the Authority and the authorization or rejection communication have been sent to the principal investigator, a summarized public assessment report for the clinical trial shall be prepared and published.
- 2.21.2.2. Publication of summarised PAR for clinical trial applications shall be included as conditions of authorisation for all the clinical trials that will be authorised by ZAMRA.
- 2.21.2.3. The public assessment report should be prepared and published within 30 calendar days after sending the clinical trial authorisation or rejection to the investigator.
- 2.21.2.4. The PAR shall contain non- confidential information. Any confidential and intellectual property will be redacted prior to publication of the reports.
- 2.21.2.5. Where possible the public assessment report shall be written in simple language which is understood by the public.
- 2.21.2.6. The clinical trial public assessment report shall contain summarized information of the following information:
- i. Title of Study and Protocol version and ZAMRA reference
 - ii. Date of receipt of application
 - iii. Clinical trial phase
 - iv. Study sites.



- v. Applicant/Principal Investigator name and address
- vi. Sponsor Name and Address
- vii. Study Duration
- viii. Proposed date or actual date of commencement of the clinical trial
- ix. Clinical Trial Authorisation Validity Period
- x. Study Design
- xi. Study Population
- xii. Study Objectives
- xiii. Eligibility Criteria
- xiv. Information on vulnerable populations
- xv. Information on consent, decision making confidentiality and participant insurance.
- xvi. Scientific and Technical Issues
- xvii. Recruitment Materials, Questionnaires and Other Study Instruments
- xviii. Information on study medicines and comparators (name and manufacturer and justification for the study medicines and comparators)
- xix. Summary review of the quality, safety and efficacy (Only non-confidential information shall be provided)
- xx. Application review process taken e.g. expedited, normal or emergency.
- xxi. Status after review (Approved or rejected)
- xxii. Final conclusion of the review

2.21.2.7. The public assessment reports shall be published on the Authority's website and/or online Clinical Trial Registry Platform and shall be in pdf format.

2.21.3. **Good Clinical Practice Inspection Public Inspection Reports**

2.21.3.1. Following the conclusion of a GCP inspection and issuance of a GCP inspection closure letter, a summarised GCP inspection public assessment report for the clinical trial and site inspected shall be prepared and published within 60 calendar days.



- 2.21.3.2. The public GCP inspection report shall remain valid until the next inspection, following which the most recent inspection report will be published.
- 2.21.3.3. The public GCP inspection report shall remain valid until the next inspection, following which the most recent inspection report will be published.
- 2.21.3.4. Publication of summarised PIR for GCP inspections shall be included as conditions of authorisation for all the clinical trials that will be authorised by the ZAMRA.
- 2.21.3.5. The PIR shall contain non- confidential information. Any confidential and intellectual property will be redacted prior to publication of the report.
- 2.21.3.6. Where possible the public assessment report shall be written in simple language which is understood by the public.
- 2.21.3.7. The GCP public inspection report shall contain summarized information of the following information:
- i. ZAMRA Clinical Trial Reference Number
 - ii. Inspection Reference Number
 - iii. Title of Clinical Trial
 - iv. Protocol Number
 - v. Final Approved Protocol Version used for the Inspection.
 - vi. Name of Principal Investigator(s)
 - vii. Clinical Trial Site and Address
 - viii. Sponsor
 - ix. Date of Contact
 - x. Date of Report
 - xi. Name of ZAMRA gazetted inspectors
 - xii. Scope
 - xiii. Objective
 - xiv. Background
 - xv. Documents inspected (Confidentiality to be maintained)
 - xvi. Personnel interviewed (Do not mention names only designations)



- xvii. Facilities inspected.
- xviii. Summary of the findings maintaining confidential e.g. 5 major findings and 2 minor findings were noted.
- xix. Summary of regulatory actions taken during and after the inspection
- xx. Conclusion of the inspection after the Corrective and Preventative Actions (CAPA)

2.21.3.8. The public inspection reports shall be published on the Authority's website and/or e-Clinical Trial Registry Platform and shall be in pdf format.

2.22. Reliance Approach

- 2.22.1 ZAMRA employs the reliance approach for clinical trial investigational products. The Authority employs the reliance approach where the safety and efficacy of the investigational product have already been confirmed through WHO prequalification or when the investigational product has been approved in WHO-listed, WHO ML3 or ML4 countries and countries considered to be trustworthy by the Authority.
- 2.22.2 The approach facilitates conducting regulatory reviews and evaluations in a timely manner and, at the same time, accelerates the evaluation process without compromising the quality, safety, and efficacy/performance of investigational products, as well as the design of clinical trials.
- 2.22.3 The Authority will, however, maintain its regulatory responsibilities for decision-making. For more information, refer to the Authority's guidelines for reliance and recognition for regulatory decision making.



3. References

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7. ICH E11 (R1): clinical investigation of medicinal products in the pediatric population.
8. ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 2016.
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11. Medicines and Allied Substances Act No. 3 of 2013, Parliament of Zambia, 2013.
12. Medicines Control Authority of Zimbabwe. (2026). Guidelines for Clinical Trials Applications and Authorisation in Zimbabwe (4 ed.).
13. Metrology Act No. 6 of 2017, 2017.
14. National Health Research Act No 2 of 2013, 2013.
15. Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical Trials and Medicinal products for human use.
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18. Structure and content of clinical study reports - ICH Harmonised Tripartite Guideline, E3.
19. Tanzania Medicines and Medical Devices Authority, Guidelines for Application to Conduct Clinical Trials in Tanzania, 2020
20. WHO Expert Committee on Biological Standardization Sixty-seventh report; Annex 10: Human challenge trials for vaccine development: regulatory considerations, WHO, 2017.



4. Appendices

Appendix I: Timelines

Unless otherwise specified, timelines are working days.

Appendix Ia: Serious Adverse Events (SAE) Reporting Timelines

Type of Safety Report	Time Frame For Reporting	Format
REPORTS FROM SITES IN ZAMBIA		
- Serious Adverse Events (SAEs). and - Suspected Unexpected Serious Adverse Reactions (SUSARs)	- Within 7 calendar days. - Follow-up information/report within 8 calendar days after the initial report or change in the event.	- Authority's Adverse Event reporting form (Appendix III: Serious Adverse Event Report Form) - Electronic submissions must be E2B compliant.
Non-Serious Adverse Events	Submitted as part of a six-monthly progress report and on request	- Line listing, or - Individual reporting in accordance with the data elements specified in the ICH guidance Document E2A
REPORTS FROM FOREIGN SITES		
(For multi-centre studies with Zambia as a participating country)		
Serious Adverse Events	Within 7 calendar days of becoming aware of the information.	Line listing Reports should include an assessment of the importance and implications of any findings.
Non-serious Adverse Events	6 months	Line listing
Foreign regulatory decisions that affect the safety or use of the product	Within 7 calendar days	Detailed report Records with respect to all adverse events in respect of the IP that have occurred inside or outside the country, including



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Type of Safety Report	Time Frame For Reporting	Format
		information that specifies the indication for use and the form of the IP at the time of the adverse event may be added
OTHER REQUIREMENTS		
Literature reports that affect the safety of the product	Within 15 calendar days	Detailed report and/or copy of the publication Records with respect to the enrolment of Clinical Trial participants, including information sufficient to enable all Clinical Trial participants to be identified and contacted if the sale of the drug may endanger the health of the Clinical Trial participants or other persons, may be added.
Notification of change in nature, severity or frequency of risk factors	Within 15 calendar days	Complete and accurate records with respect to each change made to the Investigator's Brochure, including the rationale for each change and documentation that supports each change
New information impacting on risk benefit profile of product or conduct of trial	Within 7 calendar days	Communicate with appropriate scientific and medical judgments being applied to each situation. Additional information may include copies of diagnostic test results, laboratory reports or medical record progress notes
Development/Periodic Safety Update Reports (DSURs/PSURs)	• Six-monthly for New Chemical Entities or as per Safety Monitoring Guidelines • On request by the Authority, within the period stipulated in the request.	As a follow-up report including copies of diagnostic test results, laboratory reports or medical record progress notes


Appendix Ib: Other Timelines

ACTION	REFERENCE	TIMELINE
Notification for the implementation of an urgent intervention (not as per protocol) necessary to protect the life of participants	2.17.8.1	Immediate notification via email (clinicaltrials@zamra.co.zm and pharmacy@zamra.co.zm), followed by a written report, within 7 calendar days
Submission of Six-monthly progress reports	2.17.2	Within 15 working days after the end of the reporting period. The reporting period in this instance is considered as six months beginning from the date ZAMRA approved the specific Clinical Trial.
Notification of Trial Commencement	2.17.1	• 15 working days from the date of clinical trial initiation • Six-monthly progress report if trial is delayed
Notification of Protocol violation/deviation report	2.17.4	Within 10 working days of the site becoming aware of the deviation/violation.
Submission of Data Safety and Monitoring Board Report	2.17.3	Within 10 days of the date of report.
Notification of temporary halt, interruption, or termination of an approved trial before achievement of its purpose.	2.17.4 2.17.6.3 2.17.8	Within fifteen (15) calendar days
Notification of end-of-trial	2.6.4.14	Within 30 calendar days after reaching end-of-trial
Submission of Close-out report	2.17.6	Not later than 30 calendar days after the completion of a Clinical Trial
Notification of Interim Analysis Report	2.17.5	Within 30 calendar days of obtaining such report.



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ACTION	REFERENCE	TIMELINE
Submission of Final Report of Clinical Trial as per ICH E3 Guideline (unless otherwise specified on Clinical Trial Certificate)	2.17.7	Not later than 12 Months after the completion of the trial



Appendix Ic: Special Reporting Timelines for Clinical Trials in Phase I and Public Health Emergencies

Type of Safety Report	Time Frame For Reporting	Format
REPORTS FROM SITES IN ZAMBIA		
- Serious Adverse Events (SAEs). and - Suspected Unexpected Serious Adverse Reactions (SUSARs)	Within 48 hours of becoming aware of the information.	- Authority's Adverse Event form - Electronic submissions must be E2B compliant.
Non-Serious Adverse Events	Submitted as part of a four-weekly progress report and on request	- Line listing, or - Individual reporting in accordance with the data elements specified in the ICH guidance Document E2A
REPORTS FROM FOREIGN SITES		
(For multi-centre studies with Zambia as a participating country)		
Serious Adverse Events	Within 48 hours of becoming aware of the information.	Line listing Reports should include an assessment of the importance and implications of any findings.
Non-serious Adverse Events	Submitted as part of a four-weekly progress report and on request.	Line listing
Foreign regulatory decisions that affect the safety or use of the product	Within 48 hours of becoming aware of the information.	Detailed report Records with respect to all adverse events in respect of the IP that have occurred inside or outside the country, including information that specifies the indication for use and the form of the IP at the time of the adverse event may be added



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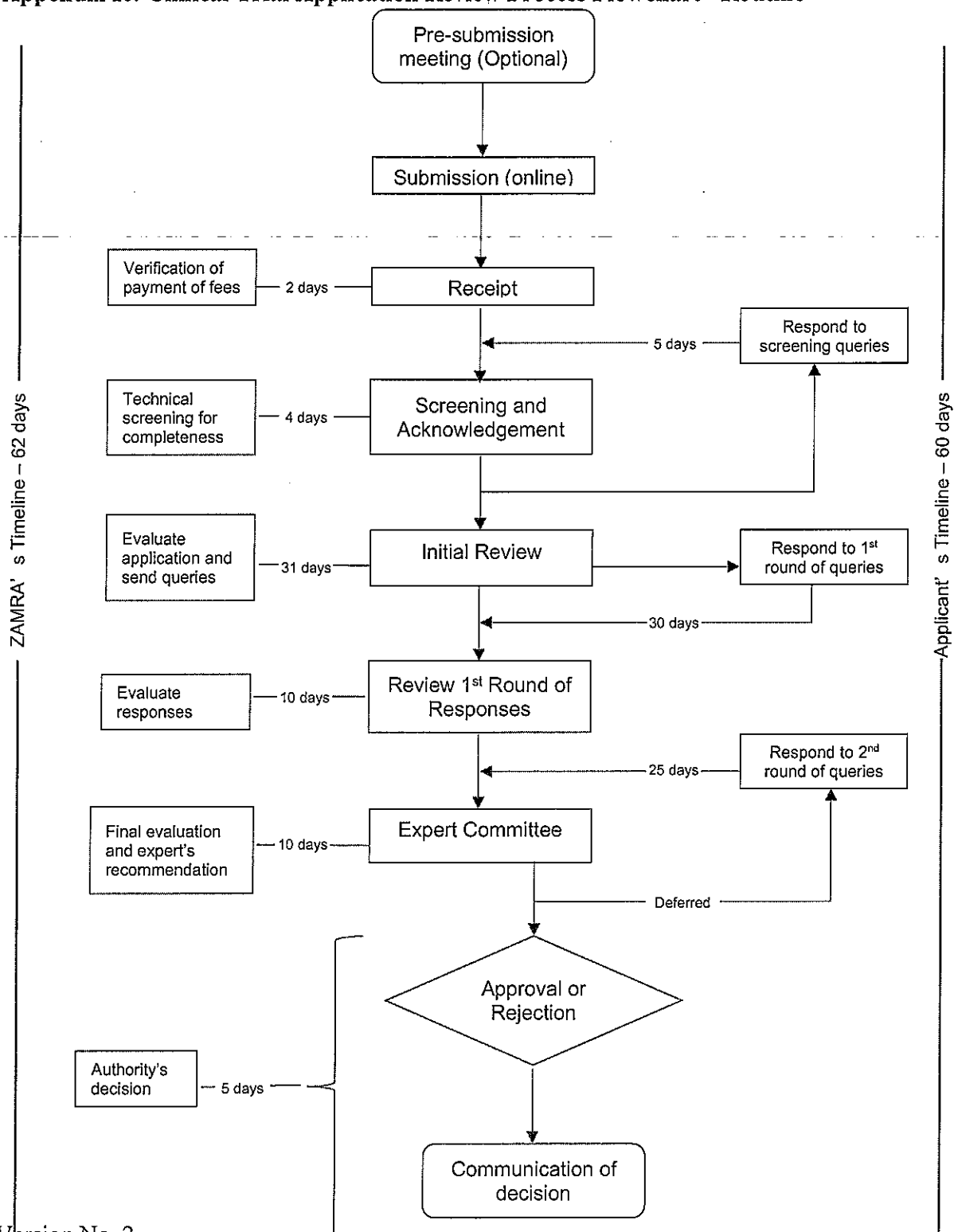
Appendix Id: Processing of Submitted Documents by ZAMRA

ACTIVITY	TIMELINE****
Processing of Clinical Trial Applications – routine pathway	62 working days
Processing of Clinical Trial Application – expedited review pathway	30 working days
Processing of Clinical Trial Application – Public Health Emergency	10-15 working days
Processing of import permits for Investigational Products	05 working days
Processing of Six-monthly progress and safety reports	15 working days
Notification of receipt of submissions including SAE, DSMB reports	10 working days
Communicating GCP Inspection findings	20 working days
Processing of applications for minor protocol amendment	21 working days
Processing of applications for major protocol amendment	41 working days
Processing of final Clinical Trial reports	30 working days

****Timelines specified are working days and exclude clock stop time

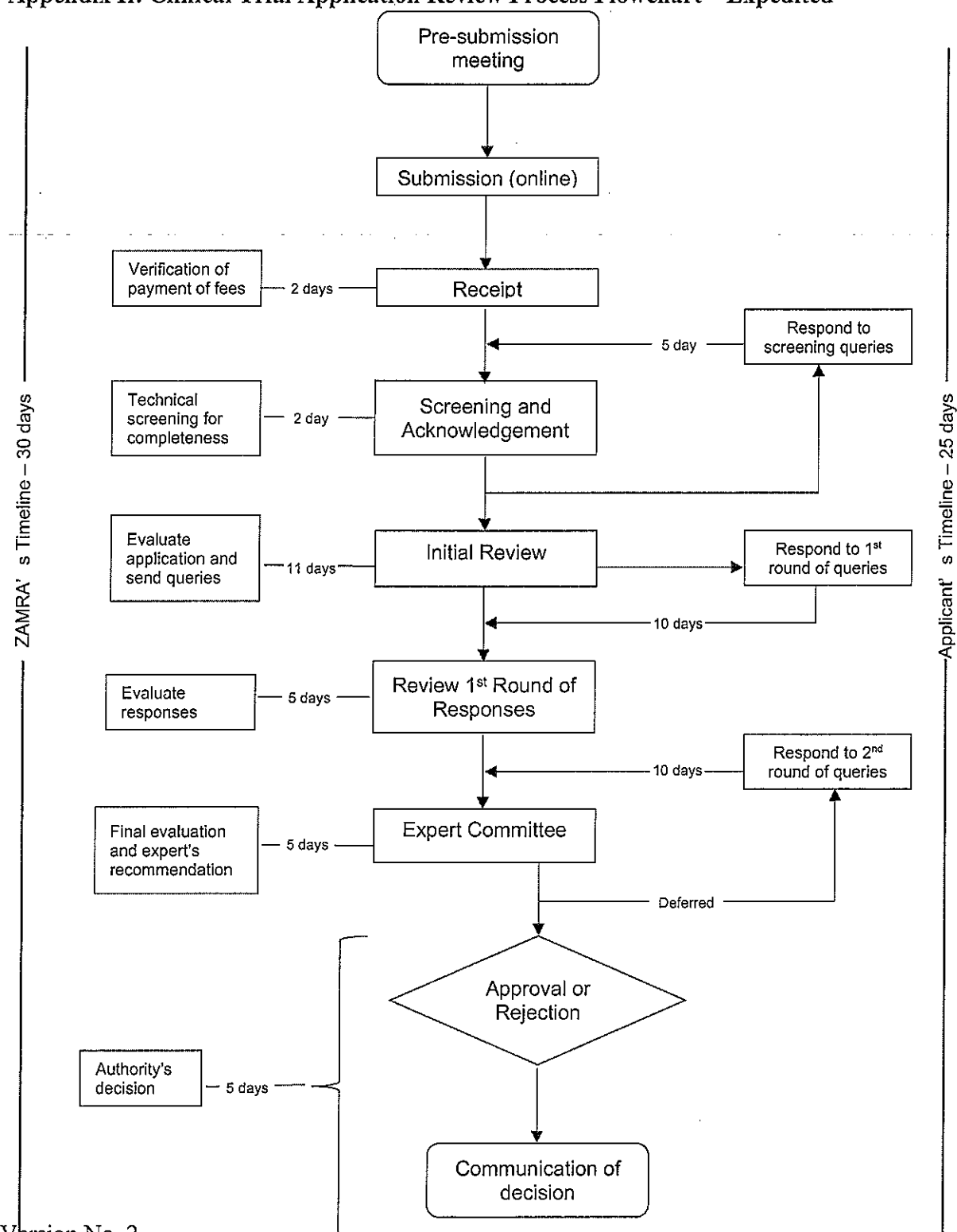


Appendix Ie: Clinical Trial Application Review Process Flowchart - Routine



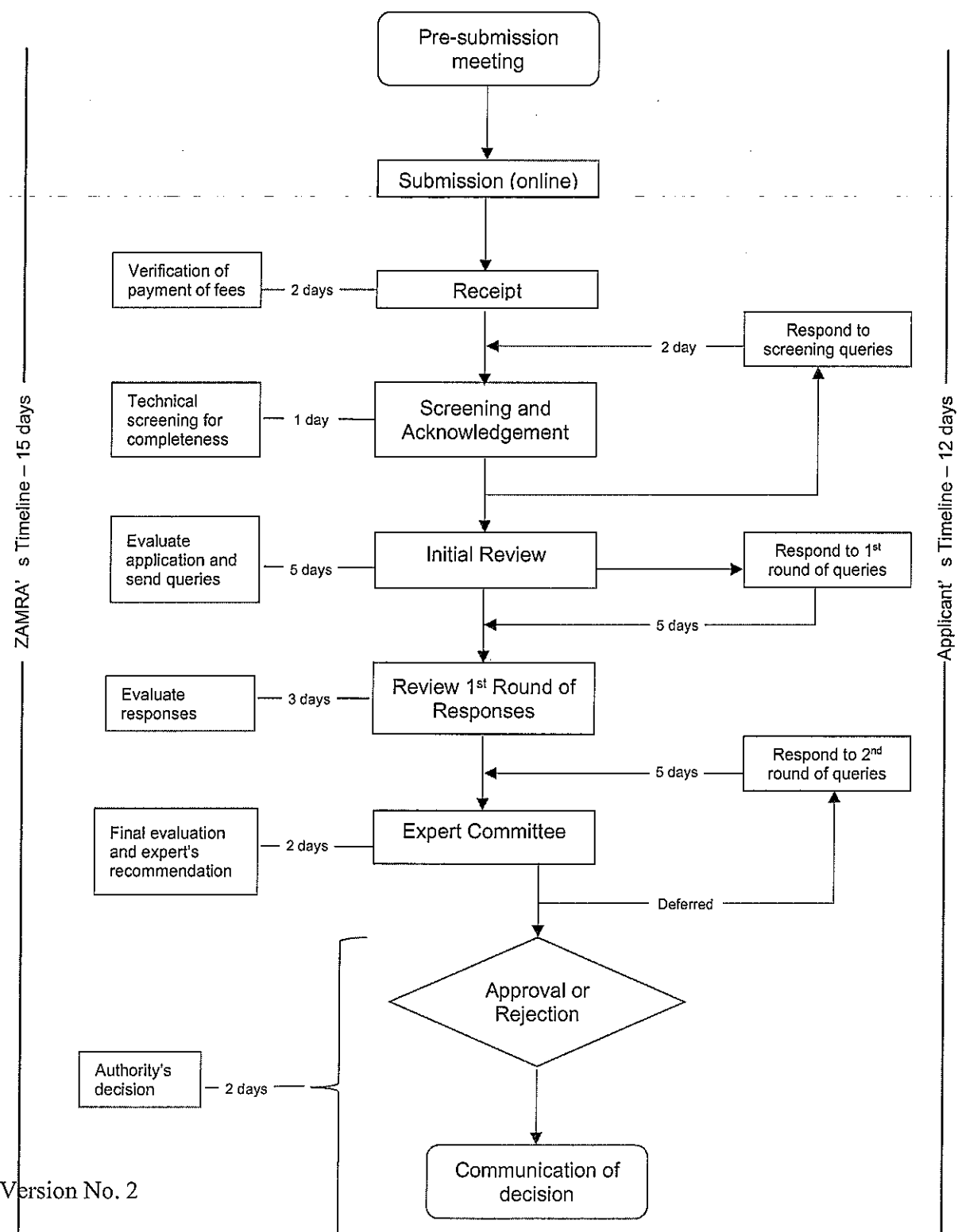


Appendix If: Clinical Trial Application Review Process Flowchart – Expedited





Appendix Ig: Clinical Trial Application Review Process Flowchart - Public Health Emergencies





Appendix II: Clinical Trials Regulatory Framework – Key Legislative Functions

Clinical Trials Regulatory Framework (Key Legislative Functions)

Applicant/Sponsor/Investigator

- Initiates, manages and finances Clinical Trial
- Submits Clinical Trial Application
- Conducts Clinical Trial
- Submit Clinical Trial Reports and Amendments

National Health Research Act

National Health Research Authority

- Regulate and monitor the conduct of research
- Grant authority to conduct health research
- Set research ethical standards and guidelines
- Register and accredit research institutions and health researchers
- Maintain a central health research repository
- Conduct inspections and enforcement

National Health Research Ethics Board

- Regulate health research ethics
- Register and accredit health researchers
- Regulate and monitor the conduct of health research
- Regulate health research ethics committees
- Review research protocols
- Give ethical approval
- May delegate any of its functions to a research ethics committee

Health Research Ethics Committee

- Review and approve research protocols
- Monitor the conduct of research

Medicines and Allied Substances Act

Zambia Medicines Regulatory Authority

- Regulate and monitor the conduct of clinical trials
- Evaluates Clinical Trial Applications
- Evaluates quality, clinical & safety of Investigational Product
- Issues Clinical Trial Certificate
- Receives and assesses Clinical Trial Reports and Amendments
- Conducts GCP and Compliance Inspections
- Maintains Clinical Trial Register
- Publishes Public Assessment and Inspection Reports

Biosafety Act

National Biosafety Authority (If product contains GMOs)

- Biosafety risk & scientific evaluation of Investigational Product
- Assesses public perception
- Certifies facilities
- Issues permit for use of GMO product
- Conducts compliance inspections

**Appendix III: Serious Adverse Event Report Form****SERIOUS ADVERSE EVENT REPORTING FORM FOR CLINICAL TRIALS IN HUMAN PARTICIPANTS**

This is intended for all Investigators/Sponsor/Applicants conducting clinical trials in Zambia. This has been prepared to serve as a form for those reporting serious adverse events occurring during the use of registered or unregistered medicines or allied substances in approved clinical trials.

INSTRUCTIONS

1. Complete all parts of this form, sign and date the form.
2. This form should be used for reporting both initial and follow-up safety reports.
3. This form should be typed.

SERIOUS ADVERSE EVENT REPORT

PART 1: ADMINISTRATIVE INFORMATION	
1.1 Reference, Certificate or Permit Number	
(a) REC Reference Number:	NA ☐
(b) NHRA Reference Number:	NA ☐
(c) NBA Reference Number:	NA ☐
(d) ZAMRA Reference Number:	NA ☐
1.2 Study Title:	
1.3 Protocol Number:	
1.4 Study Sponsor:	
1.5 Principal Investigator:	
1.6 Clinical Trial Site:	
1.7 Contact Person:	Name: Email: Phone:
1.8 Type of Report:	Initial ☐ Follow-up ☐ Resolution ☐



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1.9 Date of Report:	(Day - Month - Year)
1.10 Date Site Awareness:	(Day - Month - Year)
PART 2: DETAILS OF THE PARTICIPANT	
2.1 Participant ID:	
2.2 Participant Date of Birth:	
2.3 Participant Sex:	Male ☐ Female ☐
2.4 Participant's medical and drug history relevant to the current adverse event:	
PART 3: DETAILS OF THE ADVERSE EVENT	
3.1 Date of onset of adverse event (dd/mm/yyyy):	
3.2 Description of the adverse event:	
3.3 Reason for Seriousness:	
☐ Results in Death;	
☐ Is Life-threatening (an actual risk of death at the time of the event);	
☐ Requires inpatient hospitalisation or prolongation of existing hospitalisation;	
☐ Results in persistent or significant disability/ incapacity;	
☐ Is a congenital anomaly/birth defect; or	
☐ Other important medical event that may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed above (specify)	
.....	
3.4 Outcome of the event at the time of this report:	
☐ Recovered/Resolved — Date of Resolution: _____	



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☐ Recovering/Resolving☐ Recovered/Resolved with sequelae (specify): _____☐ Not recovered/Not resolved☐ Fatal — Date of Death: _____ — Autopsy performed? ☐ Yes ☐ No ☐ Pending☐ Unknown

3.5 Relevant investigations conducted to diagnose or treat the adverse event (attach results):

3.6 Working diagnosis:

3.7 How was the adverse event managed?

PART 4: DETAILS OF THE MEDICINES OR ALLIED SUBSTANCES

4.1 Investigational Medicines or Allied Substances

Name	Dosage	Route of admin.	Start date	Stop date

4.2 Concomitant Medicines or Allied Substances

Name	Dosage	Route of admin.	Start date	Stop date	Indication

PART 5: INVESTIGATOR'S ASSESSMENT OF THE ADVERSE EVENT

5.1 Suspected medicine or allied substance:

5.2 Did the event abate after withdrawing the suspected product?

☐ Yes ☐ No ☐ NA



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5.3 Did the event reappear after reinitiating the suspected product?

☐ Yes ☐ No ☐ NA

5.4 Relationship (causality classification) of adverse event to suspected medicine or allied substance

☐ Certain/Definite

☐ Probable

☐ Possible

☐ Unlikely/Not related

☐ Awaiting further information

☐ Unassessable

☐ Other Classification (Specify):

5.5 Other remarks

Name of Reporter:

Designation in the study:

Signature:

Date:



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Appendix IV: Clinical Trial Protocol Deviation/Violation Report Form**PROTOCOL VIOLATION/DEVIATION REPORTING FORM**

This is intended for all Investigators/Sponsor/Applicants conducting clinical trials in Zambia. This has been prepared to serve as a form for those reporting deviations or violations of approved clinical trial protocols.

INSTRUCTIONS

1. Complete all parts of this form, sign and date the form.
2. This form should be typed.

PROTOCOL DEVIATION/VIOLATION REPORT

SECTION A: ADMINISTRATIVE INFORMATION		
1. Reference, Certificate or Permit Number		
(e) REC Reference Number:		NA ☐
(f) NHRA Reference Number:		NA ☐
(g) NBA Reference Number:		NA ☐
(h) ZAMRA Reference Number:		NA ☐
2. Study Title:		
3. Protocol Number:		
4. Study Sponsor:		
5. Principal Investigator:		
6. Contact Person:		
7. Study Site:		
8. Date of Report:	(Day - Month - Year)	



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SECTION B: PROTOCOL DEVIATION/VIOLATION

9. *Date of Occurrence:*

10. *Date Site Awareness:*

11. *Participant ID (if applicable):*

12. *Description of the Protocol Deviation or Violation:*

13. *Explain the reasons for deviation/violation:*

14. *Classification of the Protocol Deviation or Violation:*

- ☐ *Minor Protocol deviation - does not increase risk or decrease benefit or does not have a significant effect on the participants, rights, safety or well-being; and/or the reliability of the study data*
- ☐ *Major Protocol violation - might significantly affect participants' rights, safety or welfare and/or the reliability of the study data*
- ☐ *Critical Protocol violation – has significantly affected participants' rights, safety or welfare and/or the reliability of the study data*

15. *Describe the impact of the deviation/violation on the participants' rights, safety or well-being; and/or the reliability of the study data:*

16. *Describe any steps taken to address this deviation/violation:*

17. *Describe what corrective actions you have taken to prevent recurrence:*

18. *Other remarks:*

19. <i>Name of Reporter</i>	<i>Designation in the study</i>	<i>Signature</i>	<i>Date</i>



Appendix V: Clinical Trials Six-Monthly Progress Report Form

SIX-MONTHLY PROGRESS REPORTING FORM FOR CLINICAL TRIALS

INSTRUCTIONS

3. This form is to be completed six-monthly from the date of approval of the clinical trial by the Zambia Medicines Regulatory Authority (ZAMRA).
4. The applicant/sponsor must complete Parts A and B.
5. Part A is specifically for the study participants in Zambia. The Applicant must include the reporting period and the number of the progress report submission (e.g., 1 or 2).
6. Part B is an overall safety line listing for the study in Zambia (and any other issues of special concern outside Zambia). It includes all Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS) for all participants in this study.

CLINICAL TRIAL SIX-MONTHLY PROGRESS REPORT

PART A: STUDY OVERVIEW - ZAMBIA		
Progress Report No:		
Reporting Period:		
1 Reference, Certificate or Permit Number		
(a) REC Reference Number:		NA ☐
(b) NHRA Reference Number:		NA ☐
(c) NBA Reference Number:		NA ☐
(d) ZAMRA Reference Number:		NA ☐
2 Study Title		
3 Protocol number		
4 Name of Sponsor		
5 Principal Investigator		
6 Contact Person:	Name: Email:	



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	<i>Phone:</i>
7 List of all active trial sites, addresses, and Principal Investigators (PIs)	
8 Trial Information:	
8.1 Date of approval of study	
8.2 Date of study initiation	
8.3 Current status of the study	
8.4 Treatment hold (if applicable) with reasons (start date and stop date of hold should be included)	
8.5 Expected date of completion	
9 Number of participants in the trial (per site), (this section should be cumulative):	
9.1 Screened (signed consent)	
9.2 Randomised	
9.3 Withdrawn from treatment (continue in follow-up), with reasons	
9.4 Withdrawn from study (early termination), with reasons	
9.5 Study completed	
9.6 Lost to follow-up	
9.7 Deaths	
10 PI/Sponsor comment on progress to date	
11 Summary Data Safety Monitoring Board or Safety Committee recommendations	



PART B: OVERALL SAFETY LINE LISTING

12 Safety Line Listing of all Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS) for all participants per site in this study in Zambia

Note: Detailed Site-specific Line listing of all adverse events may be submitted as an attachment as per the Clinical Trials guideline

SAEs and SUSARS	Relationship to study medicine (investigator's opinion)	Outcome(s)
Site 1: (name of site)		
e.g. Pneumonitis (7 patients)	Possible (2) Probable (1) Definite (2) Unrelated (2) unknown (0)	7 patients recovered 2 still treated
Site 2: (name of site)		
Any safety issues of special concern outside Zambia		



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13 Line Listing of protocol deviations/violations at the site: <i>NOTE: Zambia Site-specific Line Listing of all protocol deviations/violations may be submitted as an attachment</i>		
Protocol Deviations/Violations	Resolution/Action taken	
Site 1: (name of site)		
Site 2: (name of site)		
14 National Principal Investigator comment on other major safety concerns (this should include information impacting on the risk-benefit profile, including changes in nature, severity or frequency of risk factors, etc.)	(Provide detailed text here)	
15 For Material Transfer Agreement (MTA), how much of the quantity stipulated in the protocol have been transferred. (attach fraction form)		
16 Provide the summary of investigational product (End of Study Progress Report):		



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▪ <i>Authorized for importation</i> ▪ <i>Imported</i> ▪ <i>Used during the Clinical Trial</i> ▪ <i>Destroyed (include the destruction certificate(s)) and</i> ▪ <i>Quantity to be exported</i>	
15.1 <i>Overall comment on Investigational Product Reconciliation</i>	
17 <i>Planned date for provision of trial results to ZAMRA and NHRA (applicable to final progress report)</i>	
18 <i>Attachments</i>	☐ <i>AEs Line listing</i> ☐ <i>Protocol Deviation/violation log</i> ☐ <i>Protocol amendment log</i> ☐ <i>Biological sample (international) shipment log</i> ☐ <i>Other (Specify):</i>
We, the undersigned, agree that we have reviewed the above-mentioned report and is accurate. The trial is conducted according to the approved protocol and Zambian legal, ethical and regulatory requirements. In case of deviation or violation, those are reported accordingly.	
Signature of National Principal Investigator	Date
Signature of Applicant/Sponsor	Date

**Appendix VI: Clinical Trials Four-Weekly Progress Report Form****FOUR WEEKLY ABRIDGED PUBLIC HEALTH EMERGENCY / FIH INTERIM PROGRESS
REPORT FORM FOR CLINICAL TRIALS**

1. Due to the rapidly changing dynamics of the condition/disease, it has become necessary for the Zambia Medicines Regulatory Authority (ZAMRA) to introduce a four-weekly public health emergency (PHE) Abridged Interim Safety and Futility Monitoring Report Form for clinical trials.
2. This form is to be completed four-weekly from the date of approval of the clinical trial by ZAMRA. Fill in reports even if enrolment has not yet started.
3. This form does not replace the required six-monthly Progress Report Form for clinical trials.
4. The applicant/sponsor must complete Parts A, B and C.
5. Part A specifically applies to the study participants in Zambia.
6. Part B focuses on Suspected Unexpected Serious Adverse Reactions (SUSARS) for all sites and all participants in this study.
7. Part C enables the Sponsor/Applicant to raise any other areas of concern with regard to futility and safety.

CLINICAL TRIAL FOUR-WEEKLY ABRIDGED PROGRESS REPORT**PART A: STUDY OVERVIEW (ZAMBIA)**

19	ZAMRA Reference number	
20	Study Title	
21	Protocol number	
22	Details of Sponsor / Applicant:	
22.1	Name of Sponsor	
22.2	Name of Applicant	
22.3	Contact Person	
22.3.1	Telephone number	



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22.3.2 Cell-phone number	
22.3.3 E-mail address	
23 Trial Information:	
23.1 Date of ZAMRA approval of study	
23.2 List of Local Ethics Committees Review and date of their approval / non-approval of study	
23.3 Treatment hold (if applicable) with reasons (start date and stop date of hold should be included)	
24 Number of participants in the trial (per site), (this section should be accumulative):	
24.1 Screened (signed consent)	
24.2 Screening failure (with reasons)	
24.3 Randomised	
24.4 Withdrawn from treatment (continue in follow-up) with reasons	
24.5 Withdrawn from study (early termination) with reasons	
24.6 Study completed	
24.7 Lost to follow-up	
24.8 Deaths	
25 Summary of any new Data Safety Monitoring Board or Safety Committee recommendations since last report	

PART B: OVERALL SAFETY LINE LISTING

SUSARS AND/OR SERIOUS ADR	Indicate whether Local/International	Outcome(s)
e.g. Pneumonitis (7 patients)		7 patients recovered 2 still treated



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PART C: OTHER AREAS OF CONCERN WITH REGARDS TO FUTILITY, EFFICACY AND/OR SAFETY

<i>Signature of National Principal Investigator</i>	<i>Date:</i>
<i>Signature of Applicant/Sponsor</i>	<i>Date:</i>



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Appendix VII: Close-out Report Form**CLINICAL TRIAL SITE CLOSE-OUT REPORT FORM****INSTRUCTIONS**

1. This form is to be completed following the conclusion or termination of the clinical trial.
2. The clinical trial site can be closed when the following activities are completed:
 - a. The study has reached the last participant's last visit - all participants have finished their final protocol interventions and follow-ups;
 - b. All data queries have been resolved, case report forms finalised, and the database locked (certain sites in a multicentre study may be exempted from the database-lock requirement); and
 - c. Investigational products are fully reconciled and accounted for.

CLINICAL TRIAL SITE CLOSE-OUT REPORT

PART 1. SITE INFORMATION		
1. Reference, Certificate or Permit Number		
(a) REC Reference Number:		NA ☐
(b) NHRA Reference Number:		NA ☐
(c) NBA Reference Number:		NA ☐
(d) ZAMRA Reference Number:		NA ☐
2. Study Title:		
3. Protocol number:		
4. Name of Sponsor:		
5. Principal Investigator:		
6. Contact Person:	Name: Email: Phone:	
7. Name and address of clinical site(s):		
8. Date of last participant's last visit:		



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9. Reason for closure: (Termination or end of study)	
10. Date of study completion or termination:	
11. Date of this Report:	
12. Clinical Site Personnel Involved with the Study: (attach delegation log)	

PART 2. CLINICAL SITE CLOSE-OUT CHECKLIST

Instructions: Please provide comment(s) for each of the items listed below. Additional sheets may be attached if necessary.

OBJECTIVE	COMMENTS
13. All regulatory and other essential records are up-to-date and on file (Refer to Guidelines for the Conduct of Clinical Trials):	Provide a list of documents on file at the site
14. Notification of all relevant oversight bodies of the closure of the study site:	☐ REC ☐ NHRA ☐ NBA ☐ ZAMRA ☐ Other (specify):
15. Signed, informed consent is on file for each study participant:	Provide a list of participants (use codes/study IDs)
16. Documentation of all protocol violations/ deviations and/ or appropriate "note- to- file" in the relevant essential document file:	Provide list
17. Appropriate follow- up and reporting of all SAEs to sponsor, ethics committee and regulatory authorities:	Provide number of SAEs reported. Summary of outcome for SAEs listed is relevant
18. Completion of all Case Report forms for each participant	☐ No ☐ Yes
19. Entry/submission of all relevant data into database / to sponsor/coordination center (If not complete, indicate the timeline for accomplishing this and document in the comments section):	☐ Completed ☐ Not Completed (Give reasons):



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20. Status of all outstanding data edits, queries or delinquent forms and timeline for their resolution	
21. Tentative date for submission of full Clinical Study Report (note the timelines in the Clinical Trials guidelines):	
22. Requirements for retention of study records. (Indicate if each requirement has been fulfilled):	
23. Investigational Product accountability a. Quantity of IPs received: b. Quantity of IPs utilised in the study : c. Quantity of IPs disposed of (attach copy of destruction certificate (s)): d. Quantity of IPs onsite/returned to sponsor:	
24. Status/shipment/analyses of all participant specimens according to protocol requirements (including plans for future shipments or period of time they will be stored on- site):	
25. If blinded study IP was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding:	

PART 3: STATUS OF PAST OBSERVATIONS/RECOMMENDATIONS MADE DURING MONITORING, AUDITS OR INSPECTIONS

OBJECTIVE	COMMENTS
26. Have corrective measures been implemented for all observations and recommendations?	Provide a summary of measures implemented for each point:
27. Are there any outstanding issues or activities to be implemented?	Include problems identified, if any, and recommendations/ action items for corrections:



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28. Additional comments:

Signature of National Principal Investigator

Date

Signature of Applicant/Sponsor

Date

**Appendix VIII: Phases of Clinical Trials****Phase I**

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans. These trials are tested in a small group of people (20 -100).

Phase II

These trials are performed in a limited number of participants and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose response relationships in order to provide an optimal background for the design of extensive therapeutic trials latter in a larger group of people (100 - 300).

Phase III

Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated, and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use. 300 to 3,000 volunteers who have the disease or condition.



Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorisation was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, Clinical Trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.



Appendix VIX: Essential records for the conduct of a Clinical Trial

- 1.0 Essential records are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements and the reliability of the results produced.
- 2.0 Essential records also serve several other important purposes. Filing essential records at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory Authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected. Certain essential records may also be reviewed by the institutional review board or the Research Ethics Committee.
- 3.0 Determining which records are essential will be based on consideration of the guidance in Appendix C of the ICH E6(R3) Guideline.
- 4.0 The investigator/institution should have access to and the ability to maintain the essential records generated by the investigator/institution before and during the conduct of the trial and retain them in accordance with this guideline.
- 5.0 Records should be identifiable and version controlled (when appropriate) and should include authors, reviewers and approvers as appropriate, along with date and signature (electronic or physical), where necessary.
- 6.0 These essential records should be maintained in or referred to from repositories held by the sponsor and by the investigator/institution for their respective records. These repositories may be referred to



as a Trial Master File (TMF). The repository held by the investigator/institution may also be referred to as the Investigator Site File (ISF).

- 7.0 The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.
- 8.0 When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.
- 9.0 The investigator/institution should have control of all essential records and records generated by the investigator/institution before, during, and after the trial.
- 10.0 Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory Authority(ies).
- 11.0 Refer to the guidance on essential records in Appendix C of the ICH E6(R3) Guideline for more details.
- 12.0 Applying the criteria in section C.3.1 of Appendix C of the ICH E6(R3) Guideline, the trial records that are considered essential are listed in the Essential Records Table, and these should be retained when produced. This table is not an exhaustive list, and other trial records may also be considered essential by the sponsor or the investigator.
- 13.0 For some trial records listed in the Essential Record Table, their presence and nature are dependent on the trial design, trial conduct and risk proportionate management of the trial and may not be produced.



	Essential Records Table If these trial records are produced, they are considered essential and should be retained. <i>Note: An asterisk (*) identifies those essential records that should generally be in place prior to the start of the trial.</i>
1.	Investigator's Brochure or basic product information brochure (e.g., summary of product characteristics, package leaflet or labelling)*
2.	Signed protocol* and subsequent amendments during the trial
3.	Dated, documented approval/favourable opinion of the Research Ethics Committee (REC) of information provided to the REC*
4.	REC composition*
5.	Clinical Trial Certificate and other regulatory authority(ies) authorisation, approval and/or notification of the protocol* and of subsequent amendments during the trial (where required)
6.	Completed signed and dated informed consent forms
7.	Completed participant identification code list, screening log and enrolment log
8.	– Notification by originating investigator to sponsor of serious adverse events (SAEs) and related reports – Notification by investigator (or sponsor) to the Authority and REC of SAEs and SUSAR) and of other safety information – Notification by sponsor to investigators of safety information
9.	Progress reports to the Authority
10.	Source records



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11.	Data and relevant metadata (including documentation of data corrections) in the data acquisition tools
12.	Interim report and submission to the Authority, where applicable
13.	Final clinical trial report and submission to the Authority
14.	Sample of data acquisition tools (e.g., case report forms (CRFs), diaries, clinical outcome assessments, including patient-reported outcomes) that are provided to the investigator and/or REC*
15.	Sample of information given to trial participants* – Informed consent materials (including all applicable translations) – Any other documented information (e.g., instructions for use of an investigational product or a device) – Advertisement for participant recruitment
16.	Arrangement between parties on the financial aspects of the trial*
17.	Clinical Trial Insurance statement*
18.	Signed agreement between involved parties,* for example: • Investigator/institution and sponsor • Investigator/institution and service providers • Sponsor and service providers • Sponsor and IDMC and/or adjudication committee members
19.	Documentation of selection, assessment* and oversight of service providers conducting important clinical trial-related activities



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20.	Relevant documents evidencing qualifications of investigator(s) and sub-investigator(s) (e.g., curriculum vitae) involved in conducting the trial*
21.	Trial-specific training records* (including training materials and attendance registers)
22.	Documentation of delegation of clinical trial-related activities by the investigator*
23.	Signature sheet documenting signatures and initials, unless only electronic signatures are used (of investigator and individuals delegated by the investigator)* (can be combined with documentation of delegation above)
24.	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol*
25.	Certification or accreditation or other documentation including of validation (where required) to confirm the suitability of medical/laboratory/technical procedures/tests used during the trial conduct*
26.	Documentation of collection, processing and shipment of body fluids/tissue samples
27.	Documentation of body fluids/tissue samples storage conditions
28.	Record of retained body fluids/tissue samples at the end of the clinical trial
29.	Sample of label(s) attached to investigational product container(s)
30.	Instructions for handling of investigational product(s) and clinical trial-related materials (if not included in protocol or Investigator's Brochure), for example, pharmacy manual*
31.	Shipping records for investigational product(s) and clinical trial-related materials*
32.	Certificate(s) of analysis of investigational product(s) shipped*
33.	Investigational product(s) accountability at investigator site



34.	Documentation of investigational product storage conditions, including during shipment
35.	Records of relabelling of investigational product at the investigator site
36.	Documentation of investigational product destruction or alternative disposition
37.	Emergency decoding procedures for blinded clinical trials*
38.	Master randomisation list*
39.	Instructions for use of important clinical trial-specific systems (e.g., interactive response technologies (IRTs) user manual, electronic CRF (eCRF) manual)*
40.	Records demonstrating fitness for purpose (e.g., maintenance and calibration) for equipment used for important trial activities*
41.	Treatment allocation and decoding documentation
42.	Completed participants screening log
43.	Site monitoring reports (including site selection,* initiation,* routine and close-out)
44.	Centralised monitoring reports
45.	Records and reports of noncompliance including protocol deviations and corrective and preventative actions
46.	Documentation of relevant communications and meetings
47.	Audit certificate
48.	Documentation relating to data finalisation for analysis (e.g., query resolutions, SAE reconciliation, quality control reports, coding completion, output data sets)



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49.	Documentation of clinical trial-specific computerised system validation (e.g., specifications, testing, validation report, change control)*
50.	Documentation of the assessment of fitness for purpose for non-trial-specific computerised systems used in the trial (e.g., clinical practice computerised systems)*
51.	Documentation relating to the statistical considerations and analysis (e.g., sample size calculations,* analysis sets decisions, analysis data sets, analysis programs, quality control records and outputs)
52.	Clinical Trial-specific plans (e.g., risk management,* monitoring,* safety,* data management,* data validation* and statistical analysis) and procedures
53.	Procedures,* meeting minutes and submissions to the IDMC/adjudication committee(s)

**Appendix X: Dossier for a Placebo product to be used in a clinical trial**

The dossier for the placebo should include the following:

1. Description and composition

The complete qualitative and quantitative composition of the placebo should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form and the function of each excipient should be included.

2. Pharmaceutical development

It should be described how possible differences of the placebo preparation in relation to the investigational medicinal product regarding taste, appearance and smell are masked, where applicable.

3. Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in manufacture, packaging/assembly and testing should be provided. In case that multiple manufacturers contribute to the manufacture of the placebo, their respective responsibilities need to be clearly stated. When re-packaging and or re-labeling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation is available, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

4. Batch formula

The batch formula for the batch to be used for the clinical trial should be presented. Where relevant, an appropriate range of batch sizes may be given.

5. Description of manufacturing process and process controls

A flow chart of the successive steps, indicating the components used for each step and including in-process controls should be provided. In addition, a brief narrative description of the manufacturing process should be included.

6. Control of critical steps and intermediates

Information is not required with the exception of manufacturing processes for sterile products.

7. Process validation and/or evaluation



Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

8. Control of excipients

Specifications references to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. prefabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the aforementioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

9. Analytical procedures

In cases where reference to a pharmacopoeial monograph cannot be made, the analytical methods used should be indicated.

10. Validation of analytical procedures

Not applicable.

11. Justification of specifications

Not applicable.

12. Excipients of animal or human origin

Same information as active product is required.

13. Novel excipients

For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be provided consistent with the respective clinical phase, details are to be included on e.g. their manufacturing process, characterisation and stability. If the same novel excipient is already described in the IMPD for the respective test product, cross-reference to the relevant section will suffice.

14. Control of the placebo product: Specifications

The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. The specifications should at minimum include a test which enables to clearly differentiate between the respective investigational medicinal product and the placebo.

15. Analytical procedures

The analytical methods should be described for all tests included in the specification.



16. Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the placebo in the clinical trial, should be stated.

17. Stability

The shelf-life and storage conditions of the placebo should be defined. The shelf life of the placebo product should preferably cover the anticipated duration of the clinical trial. Stability studies are only required in cases where there is reason to suspect that the placebo product will undergo changes in physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers, hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

NB: Studies involving placebos only are considered by the Authority as clinical trials.

**Appendix XI: Guidance on Liability Insurance for Clinical Trials****GUIDANCE ON LIABILITY INSURANCE FOR CLINICAL TRIALS****1. INTRODUCTION**

In terms of the responsibilities of the sponsor/applicant as described in the current Good Clinical Practice (GCP) Guidelines, all sponsors/applicants and investigators of clinical trials must have adequate comprehensive insurance to cover any liability claim during the conduct of a clinical trial, except claims that arise from malpractice and/or negligence. This guidance seeks to clarify the requirements for such insurance for purposes of submitting for approval of a clinical trial by ZAMRA.

2. BACKGROUND

Liability insurance in clinical trials refers to the insurance or indemnity covering the liability of the sponsor/applicant and/or the investigator in respect of claims made against them by the participants with respect to injury attributable to their participation in a clinical trial.

The current GCP guidelines provide broad guidance regarding injuries (including death) for which insurance would be required. These requirements were developed with the current Association of the British Pharmaceutical Industry's (ABPI) clinical trial compensation guidelines in mind.

There is an international consensus that research participants who suffer injury as a result of their participation should be provided medical treatment at no cost to themselves or their families. Such financial or other assistance should compensate them equitably for any medical treatment for resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependents are entitled to compensation (WHO 2002 and ABPI 2014).

3. DESCRIPTION OF CLINICAL TRIALS THAT REQUIRE AN INSURANCE CERTIFICATE

Insurance is required for the conduct of interventional clinical trials involving human participants.



3.1. Responsibility for the provision of insurance in an application for the conduct of a clinical trial

- a. Evidence of comprehensive no-fault insurance for serious injury and harm and/or death should be provided by the sponsor and/or applicant.
- b. Sponsor/applicant should take responsibility of ensuring that participants are fully compensated.

3.2. Indemnification of trial sites and investigators by sponsor/applicant

- a. The sponsor/applicant must provide indemnification for all investigators and trial sites involved in their clinical studies on compliance with the protocol requirements. In cases where the investigators/site staff were negligent and/or did not comply with the protocol requirements personal malpractice insurance would apply.

4. COVERED RISK AND PROCEDURES

Notwithstanding the absence of legal commitment, the sponsor/applicant should pay compensation to all participants, including healthy volunteers suffering bodily injury, including death, in accordance with this guideline.

4.1 Payment of Compensation

The following should be considered in compensation of participants:

- a. If, on the balance of probabilities, the injury is attributable to the administration of an investigational product or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the participant in the trial.
- b. Compensation should be paid for a child injured *in-utero* through the participation of the biological parent in a clinical trial as if the child were a patient-volunteer with the full benefit of ZAMRA guidelines.
- c. Compensation should only be paid for a serious injury of an enduring or disabling nature (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious occurrences.
- d. Where there is an adverse reaction to an investigational product under trial and the injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly by the investigational product under trial.
- e. The sponsor/applicant is under strict liability in respect of injuries caused by the investigational product or procedures provided for by the protocol that would not have occurred but for the inclusion of the participant in the trial, regardless of whether the participant is able to prove negligence on the part of the sponsor/applicant or that the investigational product is defective.



5. INSURANCE AGAINST TRIAL-RELATED INJURIES

5.1 Basic Principles:

- a. Research participants should not have to bear the financial cost of rectifying harms that occur when something goes wrong during the study. It is thus essential that provision is made for comprehensive insurance against medical treatment required for trial-related bodily injury.
- b. The current Zambia GCP follows the lead of the Association of the British Pharmaceutical Industry (ABPI), which recommends that sponsors/applicant is to adopt the position of paying for treatment in the event of trial related injury, including death.
- c. If a trial-related serious bodily injury of an enduring nature occurs as a result of participation in the trial, then the insurer pays the medical costs of necessary treatment to restore the participant to his previous status as far as possible.
- d. Payment of medical expenses by the insurer is triggered when, on a balance of probabilities, bodily injury is attributable to administration of an investigational product under trial or to a clinical intervention or procedure provided for by the protocol, which (bodily injury) would not have occurred but for the participant being included in the trial. In the case of an *in utero* injury to an unborn child due to the mother's participation, payment for medical expenses proceeds as though the unborn child is a research participant.
- e. In principle, only bodily injuries of an enduring and disabling character requiring medical treatment (including exacerbation of an existing condition) and/or compensation for death are paid by the sponsor/applicant. Temporary pain or discomfort or less serious or curable complaints are generally not regarded as trial-related bodily injury. In the case of bodily injury caused by the response to an adverse reaction to an investigational product under trial, the insurance cover will apply.
- f. Payment for medical expenses is made without acknowledgement of any liability.
- g. The provision of insurance cover and payment of medical expenses does not mean that an injured participant may not pursue legal action against the sponsor/applicant to claim compensation for loss or harm not covered by the insurance.

Note:

Neither the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the participant has freely consented (whether in writing or otherwise) to participate in the trial should exclude a participant from consideration for compensation under these guidelines.



5.2 No Obligation to Pay Compensation

No obligation to pay compensation will exist:

- a. For the failure of an investigational product to have its intended effect or to provide any other benefit to the participant.
- b. To participants receiving placebo in consideration of its failure to provide a therapeutic benefit.
- c. For injury caused by other licensed medicinal products administered to the participants for the purpose of comparison with the product under trial.
- d. In the case of negligence or a serious violation of the protocol by the investigator, his/her personal malpractice insurance would apply. All healthcare professionals involved in clinical trials should have personal malpractice cover.
- e. In case of proven participant negligence, the sponsor/applicant may consider compensation on ethical grounds on a case-by-case basis.

The amount of compensation to be paid should be appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the quantum of damages commonly awarded for similar injuries by a Zambian Court in cases where legal liability is admitted.

6. INFORMED CONSENT (IC)

The informed consent discussion and the written informed consent form or any other written information to be provided to participants involved in a clinical trial must include clear instructions on reporting trial-related harms and include explanations of the compensation and/or treatment available to the participant in the event of trial-related injury. The details for submitting a claim should be explained to the participants and included in the Patient Information Sheet and informed consent discussion.

7. INSURANCE CERTIFICATE

It is unacceptable to have deductibles or co-payments for which the participant is liable.

7.1 Requirement for the Certificate:

When applying to ZAMRA for approval of a clinical trial, an insurance certificate should provide the following information and meet the following criteria:

- a. Name and local address of the insurance company, including contact name and telephone number.
- b. Title and protocol number of the clinical trial.
- c. Date of commencement and termination of coverage.



- d. Liability limit – per occurrence and total per occurrence and total for the study. Note that the limit should be adequate enough to cover extended stay in an intensive care unit or hospital.
 - e. Date of issuance of the insurance policy and expiry thereof.
 - f. Original or electronic signature of the insurer.
 - g. Special conditions if any. It is unacceptable to have special conditions which may invalidate or abate the clinical trial cover.
 - h. Any additional coverage.
 - i. Declaration of compliance with latest Zambia GCP guidelines and ABPI guidelines on the certificate and in the Patient Information Sheet.
 - j. Where the insurance is not provided by a local company, a local insurance vendor must be identified with full details.
- 7.2 A pro forma certificate would be permissible for the purposes of the application. However, a final clinical trial authorisation will only be issued once a copy of the original insurance certificate has been provided to ZAMRA which complies with all of the provisions made in the pro forma version with the exception of the date which may be modified to reflect the effective date.
- 7.3 There should be an unambiguous statement regarding the Zambian claims procedure for participants in the Patient Information Sheet.
- 7.4 The dates for insurance cover should be inclusive of the date of approval of the clinical trial, the anticipated duration of the trial procedures as well as a reasonable period for the emergence of late injuries.
- 7.5 If the sponsor ceases to exist due to it being taken over by another company, all liability must be taken over by the new company.
- 7.6 Where insurance is renewable on an annual basis, the certificate to this effect should be provided by the sponsor/applicant.
- 7.7 The insurance must be underwritten by an insurance company in accordance with the Zambian Insurance Act No. 38 of 2021.
- 7.8 Justification for the liability limits should be provided in the clinical trial application and should be specific to the nature of the health technology profile and disease process being investigated.

Please note: ZAMRA takes no responsibility for any claims for injury as a result of a clinical trial it has approved in pursuance of its statutory duties in terms of Medicines and Allied Substances Act No. 3 of 2013.

**8. PROCEDURE FOR CLAIMS**

- 8.1 Claims in pursuance to these guidelines should be made by the participant and/or immediate family to the sponsor/applicant, preferably via the investigator, setting out details of the nature and background of the claim and, subject to the participant providing on request an authority for the sponsor/applicant to review any medical records relevant to the claim, the sponsor/applicant should consider the claim expeditiously.

If there is a dispute between the participant and the investigator, claims should be made against the sponsor/applicant, unless it is proven that the occurrence is due to the investigator's negligence. In case of a claim, the participant and/or immediate family should be able to contact the broker or insurance company directly.

8.2 Arbitration in case of dispute:

In the case where the sponsor/applicant concedes that payment should be made to a participant but there exists a difference of opinion between sponsor/applicant and participant as to the appropriate level of compensation, it is recommended that the sponsor/applicant agree to seek at its own cost (and make available to the participant) the opinion of a mutually acceptable independent medico-legal expert.

The medico-legal opinion should be given substantial weight by the sponsor/applicant in reaching its decision on the appropriate payment to be made.

NOTE

- a. The provisions of this guidance do not in any way absolve the investigator of the requirement for personal malpractice insurance.
- b. The participant's medical insurance and/or state healthcare system should not be responsible for any part of treatment or compensation for trial-related injury/harm. All healthcare professionals involved in a clinical trial should have their own personal malpractice insurance to cover negligence and malpractice in the conduct of clinical trials.
- c. The fact that a sponsor/applicant has agreed to abide by these guidelines in respect of a trial does not affect the right of a participant to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation.
- d. The sponsor should provide indemnity for sites and staff taking part in the study. The following wording serve as a guide for sponsor indemnification for investigators and sites and is not an exclusive approach:



In consideration of the {PI's / Institution's / Research Unit's} participation in the study, we shall indemnify and hold harmless [Name of PI / Institution / Research Unit] and its employees from any legal liability for costs or damages for death or personal injury which may result from the administration of [Name of compound] pursuant to the said study. This indemnity does not apply to the extent that such death or personal injury arises out of any negligent act, default or omission of [Name of PI / Institution / Research Unit] or its employees. Furthermore, this indemnity is subject to the condition that the study is carried out in accordance with the Protocol approved by us in writing, that [Name of Sponsor] is notified as soon as possible on receipt of any claim, that [Name of Sponsor] shall have full control of the management and defence of any such claim and that no offer to compromise or settle any claim is made without the written agreement of [Name of Sponsor].

References

1. Association of the British Pharmaceutical Industry. 2014. Clinical Trial Compensation Guidelines.
2. National Department of Health. 2020. South African Good Clinical Practice Guidelines. 3rd Edition. South Africa.
3. World Health Organisation. 2002. Guideline 19: International Ethical Guidelines for Biomedical Research Involving Human Subjects: Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO); Geneva.
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5. ICH-E6 Good Clinical Practice Current Step 4 version dated 9 November 2016
6. Divatia, J.V., Desai A., Pramesh, C.S., Mohandas, K.M., Gupta S., & Badwe, R.A. 2012. Compensation guideline for research related injury in India. The Journal of the Associations of Physicians of India. Vol 60.
7. Council of Europe. 2005. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research. France, Strasbourg.

**Appendix XII: Clinical Investigations and Performance Evaluation of Medical Devices**

The term "clinical trial" covers both "clinical investigation" and "performance study" with a medical device.

A clinical investigation with a medical device is a systematic investigation involving one or more human participants undertaken to assess the safety or performance of the device.

A 'performance study' is a study undertaken to establish or confirm the analytical or clinical performance of an IVD.

Clinical investigations and performance studies must be approved by the Authority and the responsible research ethics committee. Parallel submission to the Authority and the research ethics committee are allowed but ZAMRA can issue an approval only if the research ethics committee has already approved the same study.

A new application to conduct a clinical trial is required for the following situations:

1. The introduction of a completely new concept of device into clinical practice where component features and/or methods of action, are previously unknown;
2. Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body, in which case compatibility and biological safety will need to be considered;
3. Where a device is proposed for a new purpose or function;
4. Where there is a new manufacturer especially of a high-risk device;
5. Studies involving additional research procedures, e.g. additional blood samples, or investigations outside those that would normally be employed in the routine management of the patient;
6. For medical devices registered with ZAMRA or a recognised regulatory agency (WHO-listed level 3 or 4 regulatory authority), where the proposed clinical trial is outside the conditions of approval. This may include changes to:
 - a. Indications and clinical use (or intended use of a device)
 - b. Target patient population



- c. Routes of administration
- d. Dosage

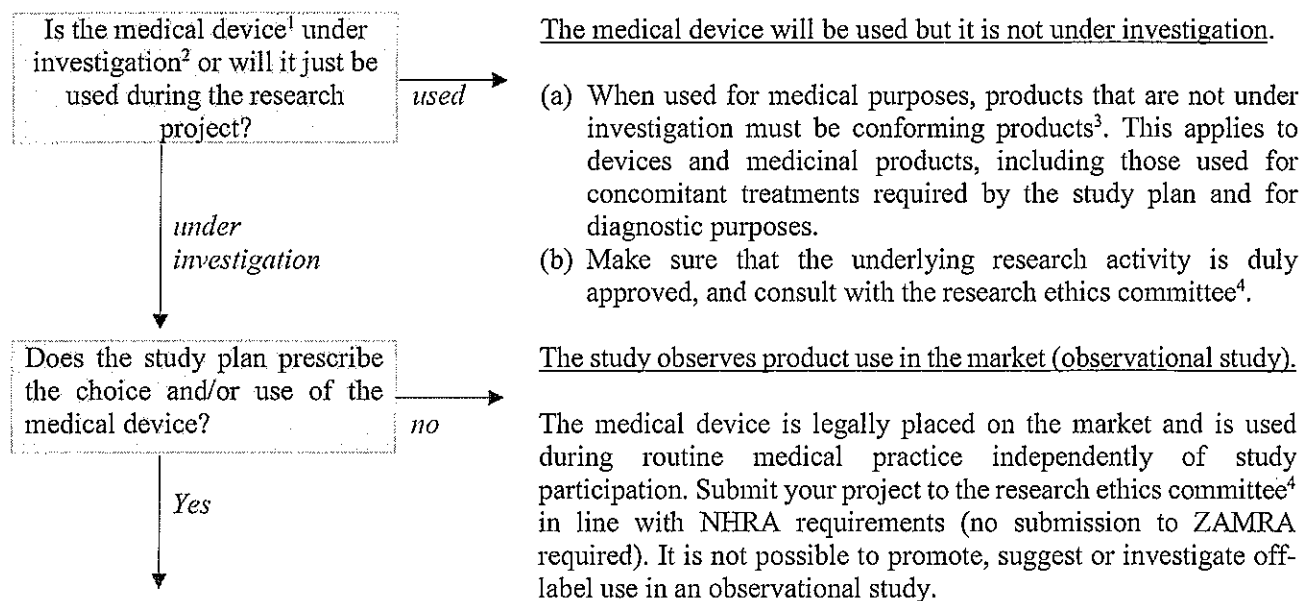
- 7. Research on a drug/device combination product if the combination is unregistered or if one of the components is unregistered.

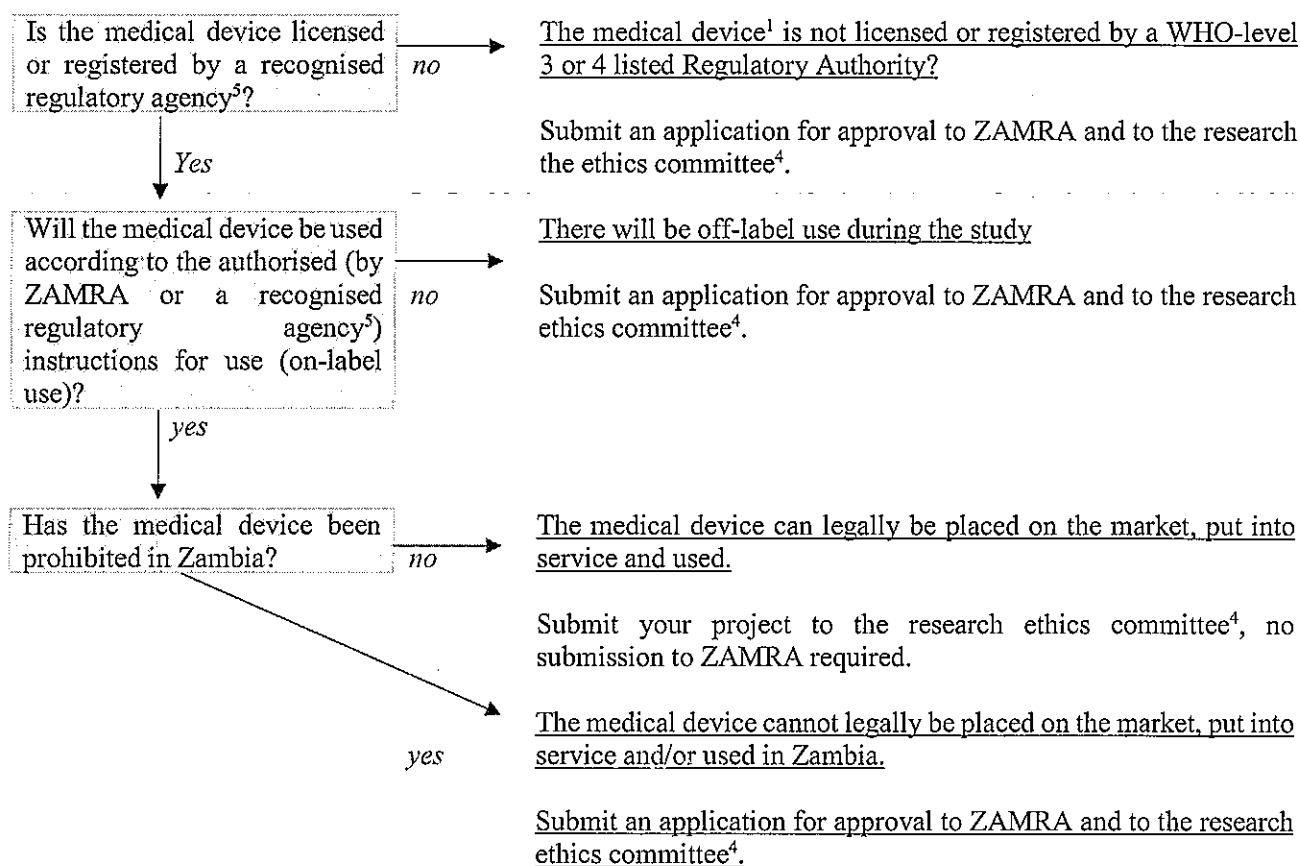
The following aspects are not relevant for the delimitation of research projects:

- Whether there will be few or many human subjects,
- High or low expected risks, prototypes or devices with a mature design,
- Patients treated with the device or volunteers without medical benefits,
- Whether the sponsor intends to place the device on the market.
- For example, a feasibility study on healthy students can be a clinical investigation of a medical device, while a retrospective study based on hospital records is not.

Below, you can find a decision tree showing the type of research which require clinical trial applications to ZAMRA. The information provided here is used for guidance only and the Authority reserves the right to require a clinical trial application for studies involving medical devices. In case of doubt, contact the Authority for guidance.

Decision tree for approval applications





¹ The medical device can be a stand-alone product, or a product that is used as part of a system, including software (e.g. an app or an MRI sequence).

² Investigation for assessment of the safety or performance of the device.

³ Authorised by ZAMRA.

⁴ The application for the clinical trial is submitted to the research ethics committee.

⁵ WHO-level 3 or 4 listed Regulatory Authority



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Appendix XIII: Clinical Trial Application Checklist

CHECK LIST FOR CLINICAL TRIAL APPLICATION

Check List: Requirements when submitting an application to conduct a Clinical Trial	
☐	1. Covering Letter
☐	2. Non-refundable Application and GCP inspection Fees as per the prescribed ZAMRA Fee Schedule. GCP inspection fee is per Clinical Trial site.
☐	3. Completed Zambia Medicines Regulatory Authority Application Forms for Conducting Clinical Trials signed by authorised persons (PI and Sponsor's authorised representative)
☐	4. Final version of the Clinical Trial Protocol (signed and dated by authorised person). For Multicenter Trials, both the global and the site-specific protocols are required.
☐	5. Proof of registration with PACTR
☐	6. Investigator's Brochure (IB) or summary of Product Characteristics/official package leaflet, where applicable
☐	7. Investigational Product (IP) Dossier (where applicable)
☐	8. Good Manufacturing Practice (GMP) Certificate or equivalent (where applicable)
☐	9. Ethical Approval or proof of submission for Ethical Approval
☐	10. Insurance Cover for Participants
☐	11. Proof of Malpractice insurance of investigators
☐	12. Financial Declaration
☐	13. DSMB Membership (including CVs) and signed Charter (where applicable)
☐	14. Sponsor/PI Contractual Agreement
☐	15. Informed Consent and Assent Forms (if applicable)
☐	16. Statistical Analysis Plan (SAP)



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☐	17. Evidence of accreditation/competence of designated laboratory(ies)
☐	18. Samples of IP/Comparator (where applicable)
☐	19. Unless otherwise specified, all Clinical Trial application documents shall be submitted in electronic copies (in Microsoft Word or searchable PDF) and in English language.

Note:

- To allow for evaluation, the following are classified as critical documents/requirement: 2, 3, 4, 6, 7, 15, and 19 (6 is required for IPs undergoing development/improvements or has no approved SmPC/ package insert. 7 is required for IPs that are not registered with the Authority)
- The following are classified as non-critical documents/requirements: 1, 5, 8, 9, 10, 11, 12, 13, 14, 16, 17 and 18

FOR ZAMRA USE ONLY

1. List of critical documents missing from the submission:

- (i)
- (ii)
- (iii)

2. List of non-critical documents missing from the submission:

- (i)
- (ii)
- (iii)

3. Screening Recommendation/Decision

- ☐ Proceed to evaluation (all the documents are submitted)
- ☐ Proceed to evaluation but send screening queries (all critical documents are submitted but some non-critical documents are missing)
- ☐ Do not proceed to evaluation. Send screening queries (At least one critical document is missing)

Screened by: **Date:**

Signature:



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Appendix XIV: Clinical Trial Application Form

Form I
(Regulation 3(1))

The Medicines and Allied Substances Act, 2013
(Act No. 3 of 2013)

The Medicines and Allied Substances (Clinical Trial) Regulations, 2025

APPLICATION FOR A CLINICAL TRIAL CERTIFICATE			
		Shaded fields for official use only	Applica tion No.
			Date/Ti me
Information Required		Information Provided	
PART I – PARTICULARS OF APPLICANT			
1.1	Name and address of applicant (Investigator) (Attach CV)		
	(a) Name:		
	(b) Academic and professional qualification:		
	(c) Physical address:		
	(d) Postal address:		
	(e) Phone:		
	(f) Fax:		
	(g) Email:		
1.2	Name and address of sponsor		
	(a) Name:		
	(b) Physical address:		
	(c) Postal address:		
	(d) Phone:		
	(e) Fax:		
	(f) Email:		
1.3	Name and address of clinical trial monitor		



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	(a) Name:	
	(b) Physical address:	
	(c) Postal address:	
	(d) Phone:	
	(e) Fax:	
	(f) Email:	
1.4	Name and address of local contact person for correspondence	
	(a) Name:	
	(b) Physical address:	
	(c) Postal address:	
	(d) Phone:	
	(e) Fax:	
	(f) Email:	
1.5	Name and address of international investigator (where applicable) (Attach CV)	
	(a) Name:	
	(b) Academic and professional qualification:	
	(c) Physical Address:	
	(d) Postal Address:	
	(e) Phone:	
	(f) Fax:	
	(g) Email:	

PART II – PARTICULARS OF THE CLINICAL TRIAL		
2.1	Title of the clinical trial	
2.2	Title – short version	
2.3	Clinical trial protocol number, version and date	
2.4	Clinical trial identification number	
2.5	Clinical trial registry number (Pan African Clinical Trial Registry)	
2.6	Phase of the clinical trial	
2.7	Clinical trial design	
2.8	Number of clinical trial sites in Zambia	
2.9	Estimated duration of the clinical trial	
2.10	Proposed date of commencement of clinical trial (dd/mm/yyyy)	
2.11	If the clinical trial is NOT to be conducted in the country of registered address of the sponsor or country of origin of the investigational medicine or allied substance, provide justification	
2.12	If any sub-studies are proposed as part of this clinical trial protocol, indicate whether these will also be conducted locally. If yes, provide details	

PART III – DETAILS OF INVESTIGATOR		
Each Investigator detailed separately		
3.1	Name, designation and address	
	(a) Name:	
	(b) Academic and professional qualification:	
	(c) Designation:	



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	(d) Role in clinical trial:		
	(e) Physical address:		
	(f) Postal address:		
	(g) Phone:		
	(h) Fax:		
	(i) Email:		
	Attach curriculum vitae		
3.2	Current work-load of Investigator(s)^a: <i>^a[Number of studies currently undertaken by investigator, and the total number of human participants or animal subjects represented by these studies. Time-commitments of researcher in relation to clinical trial work and non-trial work] In prescribed format - attach as an appendix.</i>		
PART IV – DETAILS OF LOCAL CLINICAL TRIAL SITE			
4.1	Name and address of clinical trial site (Provide detail for each clinical trial site)		
	(a) Name of clinical trial site:		
	(b) Physical address:		
	(c) Postal address:		
	(d) Phone:		
	(e) Fax:		
	(f) Email:		
4.2	Capacity of clinical trial site Number of staff, names, qualifications, experience – including, study coordinator, site facilities, emergency facilities, other relevant infrastructure [attach as an appendix if necessary] Provide details and evidence of the laboratory competences (including sub-contracted laboratory) [Attach as an appendix if necessary] Submit the Clinical Trial Site Implementation Plan (Master File)		
4.3	Detailed safety and monitoring plan for each site: [Attach as an appendix if necessary]		
PART V – HUMAN PARTICIPANT AND ANIMAL SUBJECT			
5.1	Type of human participant or animal subject <i>(State target human participant e.g. children, women, pregnant women, patients, differently abled, etc. or Target animal subject e.g. animal species, adult animals, juvenile animals, pregnant animals, etc)</i>		
5.2	Number of local human participants or animal subjects		
5.3	Total number of human participants or animal subjects <i>[in case of multicentre clinical trial sites]</i>		
5.4	Total enrolment in each local clinical trial site <i>[If competitive enrolment, state minimum and maximum number per clinical trial site.]</i>		
5.5	Volunteer base from which local human participants or animal subjects will be drawn		
5.6	Retrospective data indicating the potential of each site to recruit the required number of participants within envisaged duration of the clinical trial		



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[Attached as an appendix if necessary]

PART VI – PARTICULARS OF INVESTIGATIONAL MEDICINE OR ALLIED SUBSTANCE

6.1 Names and details of investigational medicine or allied substance to be used in clinical trial and marketing authorisation number and date of registration if applicable

[attach investigator's brochure, package insert, instructions for use or user manual, where applicable]

Name of the medicine or allied substance

Details of the manufacturer and manufacturing site

(a) Name:

(b) Physical address:

(c) Postal address:

(d) Phone:

(e) Fax:

(f) Email:

6.2 Composition of an investigational medicine to be used in a clinical trial

(Each medicine detailed separately)

Component and Quality Standard (e.g. Paracetamol USP)	Function (e.g. active ingredient, binder, etc.)	Strength (label claim)	
		XX mg	%*
		Quantity per unit	
TOTAL			

*each ingredient expressed as a percentage of the total e.g. core or coating weight.

[In addition, an investigational medicine dossier should be submitted as provided in the relevant guidelines.]

6.3 Composition of investigational allied substance to be used in a clinical trial

(Each allied substance detailed separately)

Component and Quality Standard (e.g. Vitamin C USP)	Function (e.g. active ingredient, binder, etc.)	Strength (label claim)	
		XX mg	%*
		Quantity per unit	
TOTAL			

*each ingredient expressed as a percentage of the total e.g. core or coating weight.

[In addition, an investigational allied substance dossier should be submitted as provided in the relevant guidelines.]

Particulars of an investigational allied substance that is a medical device to be used in a clinical trial

(Each device detailed separately)

Device type (In-vitro device or Non in-vitro device)

Device Class (Class A, B, C or D)



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	[In addition, an comparator allied substance dossier should be submitted as provided in the relevant guidelines.]																																											
6.4	Estimated quantity of investigational medicine or allied substance: [Each medicine, allied substance or device detailed separately]																																											
6.5	Marketing authorisation status in other countries of the investigational medicine or allied substance (a) Name of country: (b) Date applied for marketing authorisation in country in (a): (c) Date application for marketing authorisation withdrawn by applicant in country in (a): (d) Date granted marketing authorisation in country in (a): (e) Date application for marketing authorisation rejected in country in (a): (f) Date marketing authorisation suspended, revoked or cancelled by regulatory authority in country in (a): [Attach supporting documentation]																																											
6.6	Previous or on-going studies using this investigational medicine or allied substance which have been approved in another country: <table border="1"> <thead> <tr> <th></th> <th>Name of country:</th> <th>Name of country:</th> <th>Name of country:</th> </tr> <tr> <th></th> <th>.....</th> <th>.....</th> <th>.....</th> </tr> </thead> <tbody> <tr> <td>Clinical trial approval number:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Title of clinical trial:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Clinical trial protocol number:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Date of approval of clinical trial application:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Name of sponsor:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Name of investigator:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Status of clinical trial:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Date of final report:</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>					Name of country:	Name of country:	Name of country:					Clinical trial approval number:				Title of clinical trial:				Clinical trial protocol number:				Date of approval of clinical trial application:				Name of sponsor:				Name of investigator:				Status of clinical trial:				Date of final report:			
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Name of sponsor:																																												
Name of investigator:																																												
Status of clinical trial:																																												
Date of final report:																																												
	PART VII – PARTICULARS OF COMPARATOR MEDICINE OR ALLIED SUBSTANCE																																											
7.1	Name and details of the comparator medicine or allied substance and marketing authorisation number, where applicable [attach investigator's brochure, package insert, instructions for use or user manual, where applicable] (a) Name of the comparator medicine or allied substance: (b) Marketing authorisation number: Details of the manufacturer and manufacturing site (a) Name: (b) Physical and Postal Address: (c) Phone: (d) Fax: (e) Email:																																											
7.2	Composition of the comparator medicine to be used in a clinical trial (Each comparator medicine detailed separately)																																											
	Component and Quality Standard (e.g. Paracetamol USP)	Function (e.g. active ingredient, binder, etc.)	Strength (label claim) XX mg <table border="1"> <thead> <tr> <th>Quantity per unit</th> <th>%*</th> </tr> </thead> <tbody> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </tbody> </table>		Quantity per unit	%*																																						
Quantity per unit	%*																																											



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TOTAL			
*each ingredient expressed as a percentage of the total e.g. core or coating weight.			
[In addition, an comparator medicine dossier should be submitted as provided in the relevant guidelines.]			
7.3	Composition of the comparator allied substance to be used in a clinical trial		
	(Each allied substance detailed separately)		
	Component and Quality Standard (e.g. Vitamin C USP)	Function (e.g. active ingredient, binder, etc.)	Strength (label claim)
			XX mg
		Quantity per unit	%*
	TOTAL		
	*each ingredient expressed as a percentage of the total e.g. core or coating weight.		
	[In addition, an comparator allied substance dossier should be submitted as provided in the relevant guidelines.]		
	Particulars of the comparator allied substance that is a medical device to be used in a clinical trial		
	(Each device detailed separately)		
	Device type (In-vitro device or Non in-vitro device)	Device Class (Class A, B, C or D)	
	[In addition, an comparator allied substance dossier should be submitted as provided in the relevant guidelines.]		
7.4	Estimated quantity of comparator medicine or allied substance which will be required:		
	(Each comparator medicine or allied substance detailed separately)		
7.5	Marketing authorisation status in other countries of the comparator medicine or allied substance		
	(a) Name of country:		
	(b) Date applied for marketing authorisation in country in (a):		
	(c) Date application for marketing authorisation withdrawn by applicant in country in (a):		
	(d) Date granted marketing authorisation in country in (a):		
	(e) Date application for marketing authorisation rejected in country in (a):		
	(f) Date marketing authorisation suspended, revoked or cancelled by regulatory authority in country in (a):		
	[Attach supporting documentation]		
	PART VIII – OTHER DETAILS OF THE CLINICAL TRIAL		
8.1	Name and details of auxiliary medicines or allied substances which are required in the protocol, and marketing authorisation number if applicable		
8.2	Estimated quantity of auxiliary medicine or allied substance:		
	(Each medicine detailed separately)		

VIX. REGULATORY STATUS	
9.1	Regulatory status of the clinical trial in other countries (State the country in which the clinical trial has been applied for, and the current status)



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	Regulatory Status	Country	Date of Decision (e.g. Approval, etc.)
	Approved		
	Pending		
	Rejected		
	Suspended		
	Revoked		
	[In case of rejection, suspension or revocation, provide reasons]		
PART X – ETHICS COMMITTEE APPROVAL			
10.1	(a) Research Ethics Committee(s) responsible <i>for each site</i> : (b) Date of application to Ethics Committee: (c) Date of approval by Ethics Committee: (d) Details of response made by, and/or conditions required by research ethics committee, where applicable (attach response)		
PART XI – SUPPORTING DOCUMENTATION			
11.1	Attachments (supporting documents) (a) A cover letter (b) Copy of the current version of the clinical trial Protocol (c) Investigator's brochure, package insert, instructions for use or user manual, where applicable (d) Investigational medicine or allied substance dossier (where applicable) (e) Proof of insurance cover for human participants or animal subjects (f) Copy of approval from research ethics committee (g) Curriculum vitae of investigators and key study staff as determined by the Authority (h) Financial declaration by sponsor or investigator as determined by the Authority (i) Declaration by the investigator as determined by the Authority (j) Independent data monitoring committee signed charter, attach curriculum vitae for the members (where applicable) (k) Informed consent form and assent forms (where applicable) as determined by the Authority (l) Statistical analysis plan		
PART XII – DECLARATION AND SIGNATURE			
12.1	I declare that all the information I have stated is correct and truthful to the best of my knowledge and belief. a) Name: b) Designation: c) Signature: d) Date:/...../.....(dd/mm/yyyy)		



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FOR OFFICIAL USE ONLY

Date of Submission: Application No.:

Number of Binders: Payment Receipt No.:

Application Complete (Proceed for Evaluation):

Application Deficient (Refer to applicant for additional information):

OFFICIAL
STAMP



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Annexes to the application form

Annex 1: Recommended Format for CVs of Individuals Participating in Clinical Trials

1. Study Title:
2. Protocol Number:
3. Designation:
[e.g. Principal Investigator, Co-Investigator, Study Co-ordinator, Monitor, Clinical Research Associate]
4. Personal Details
Name:
Work Address:
Telephone Number:
Cell phone number:
E-mail address:
5. Academic and Professional Qualifications
6. Professional registration number
7. Current personal medical malpractice insurance details
8. Relevant related work experience (brief) and current position
9. Participation in clinical trials research in the last three years
[Study title, protocol number, designation. If multiple trials, only list those with relevance to this application, or in the last year]
10. Peer-reviewed publications in the past 3 years
11. Date of last GCP training
[As a participant or presenter]
12. Any additional relevant information supporting abilities to participate in conducting this trial
[Briefly]

Signature:

Date:



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Annex 2: Joint Declaration by Sponsor and Principal Investigator concerning sufficient funds to complete study

Title:

Protocol:

I, *<full name>*, representing *<sponsor or representative>*,
and

I, *<full name>*, Principal Investigator,

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

Signed:

Date:

SPONSOR (or alternative)

Name

Address

Contact details

Signed:

Date:

PRINCIPAL INVESTIGATOR (National PI)

Name

Address

Contact details



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Annex 3: Declaration by Principal Investigator

Name:

Title of Trial:

Protocol:

Site:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Principle Investigator within the context of this study.
2. I have notified the regulatory authority of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analysed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the Regulatory Authority have been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.
9. 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 trial.
*[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.]**
**Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)*
10. I 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. (*Attach details.)
11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
12. I will submit all required reports within the stipulated time-frames.

Investigator:

Signature:

Date:

Witness:

Signature:

Date:



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Annex 4: Declaration by Co- and Sub-Investigators

Name:

Title of Trial:

Protocol:

Principal Investigator's Name:

Site:

Designation in the study:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Investigator within the context of this study.
2. I will carry out my role in the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
3. I will not commence with my role in the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the Regulatory Authority have been obtained.
4. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.
5. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
6. 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 trial.

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

**Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)*

7. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.
8. I will submit all required reports within the stipulated time-frames.

Investigator:

Signature:

Date:

Witness:

Signature:

Date:



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Annex 5: Declaration by the Monitor

Name:

Title of Trial:

Protocol:

Site:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the clinical trial Monitor within the context of this study.
2. I have notified the regulatory authority of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I will carry out my responsibilities as specified in the trial protocol and in accordance with Good Clinical Practice (GCP)
4. 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 trial.

*[Conflict of interest exists when a monitor (or the monitor's institution), has financial or personal relationships with other persons or organisations that inappropriately influence (bias) his or her actions.]**

**Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)*

5. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
6. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
7. I will submit all required reports within the stipulated time-frames.

Monitor:

Signature:

Date:

Witness:

Signature:

Date:



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Appendix XV: Application for Amendment to a Clinical TrialForm V
(Regulation 6(1))The Medicines and Allied Substances Act, 2013
(Act No. 3 of 2013)

The Medicines and Allied Substances (Clinical Trial) Regulations, 2025

APPLICATION FOR AMENDMENT OF A CLINICAL TRIAL CERTIFICATE			
		Shaded fields for official use only	Licence Code
			Date/Time
Information Required		Information Provided	
PART I – PARTICULARS OF THE INVESTIGATIONAL MEDICINE OR ALLIED SUBSTANCE			
1.	Name of the Clinical Trial		
2.	Clinical trial certificate No.:		
3.	Name of the investigational medicine or allied substance		
PART II – PARTICULARS OF THE APPLICANT			
4.	(a) Name:		
	(b) Physical address		
	(c) Postal address		
	(d) Phone:		
	(e) Fax:		
	(f) Email:		
PART III – LIST OF AMENDMENTS			
S/No.	Description of amendment(s)		
PART IV – SUMMARY OF THE AMENDMENTS			
EXISTING ^{a, b}		PROPOSED AMENDMENT ^{a, b}	REASONS FOR AMENDMENT



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	PART V – SUPPORTING DOCUMENTATION		
	Provide relevant documentation to support the amendment.		
	PART VI – DECLARATION AND SIGNATURE		
	I declare that all the information I have stated is correct and truthful to the best of my knowledge and belief. Particulars of the person signing on behalf of the Applicant: (a) Name: (b) Designation: (c) Signature: (d) Date:/...../..... (dd/mm/yyyy)		
FOR OFFICIAL USE ONLY			
Date of Submission:			
Certificate No.:			
Payment Receipt No.:			
Application Complete (Proceed for Evaluation):			
Application Deficient (Notify applicant on deficiencies):			
OFFICIAL STAMP			



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5. Amendment Sheet

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