Medicines Control Authority of Zimbabwe

MCAZ/PVCT/GL-04

GUIDELINES FOR CLINICAL TRIAL APPLICATION AND AUTHORIZATION IN ZIMBABWE

EFFECTIVE DATE: 04/03/2022

Medicines Control Authority of Zimbabwe

106 Baines Avenue

P O Box 10559

Harare

Email: mcaz@mcaz.co.zw

Website: www.mcaz.co.zw

Reviewed by:	..... Signature	1/3/2022 ..... Date
Checked by HoD/HoU:	..... Signature	1/03/2022 ..... Date
Approved by QM:	..... Signature	1/03/2022 ..... Date
Authorised for use by: Director-General	..... Signature	4/3/2022 ..... Date

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1.0 APPLICATION

This is an application guideline for all those who wish to conduct clinical trials of a medicine in human participants in Zimbabwe in line with Section 17(1) of the Medicines and Allied Substances Control Act (MASCA) Chapter 15:03. When assessing if a study falls under the definition of a clinical trial requiring written authorization from MCAZ, the following questions should be considered:

1.1. Is your study a clinical trial of medicinal products?
1.2. Is the study objective to study the therapeutic, diagnostic or preventive effect of one or more medicinal products?
1.3. Is the study objective to identify or investigate adverse reactions from one or more medicinal products?
1.4. Is the study objective to study the pharmacological effect (pharmacodynamics) of one or more medicinal products?
1.5. Is the study objective to study the absorption, distribution, metabolism or excretion (pharmacokinetics) of one or more medicinal products?

If the answer is yes to either of the questions above, then the study falls under the definition of a clinical trial requiring written authorization by MCAZ**.**

2.0 PURPOSE

The Medicines Control Authority of Zimbabwe has updated the application guidelines for clinical trials authorization in Zimbabwe in line with the Medicines Allied Substance Control Act (MASCA) Chapter 15:03 and Statutory Instrument (SI 150) and other local and international requirements. To achieve compliance, this guideline should be used in conjunction with the current Guidelines for Good Clinical Practice in Zimbabwe.

3.0 BACKGROUND AND INTRODUCTION

According to the Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03], a clinical trial is defined as a systematic study done in human beings or animals in order to establish the efficacy of, or to discover or verify the effects or adverse reactions of medicines or medical products, and includes a study of the absorption, distribution, metabolism and excretion of medical products. The Act also states that no person shall conduct a clinical trial of any medical product without the prior written authorization of the Authority, granted with the approval of the Secretary for Health and Child Care.

This guideline sets out the procedures that should be followed by applicants who wish to conduct clinical studies involving the use of registered and unregistered medical products in Zimbabwe, and the steps that the Authority will take to review, evaluate and authorize the conduct of clinical trials. Applicants are recommended to approach the MCAZ Pharmacovigilance and Clinical Trial (PVCT) Division for clarification on whether their study is to be classified as a clinical trial if in doubt. For guidance on the phase of the study to be applied for, please refer to the GCP Guidelines.

The review and approval process in Zimbabwe is expected to take up to 60 working days from the time the completed application is received by the Medicines Control Authority of Zimbabwe's PVCT Division to approval. This timeline **excludes** the time when the applicant is addressing the queries raised. We encourage all applicants to work in coordination with the MCAZ to enable the achievement of these timelines. For clinical trials for emergency preparedness, the expedited timeline for review and approval may be reduced to 15-30 working days subject to early submission of a complete application.

Applicants are required to submit their applications via the Electronic Clinical Trials Registry System portal found at https://e-ctr.mcaz.co.zw/**.** After approval of the clinical trial application, the principal investigator is required to submit to MCAZ all Adverse Events (AEs), Adverse Events Following Immunization (AEFIs) and Serious Adverse Events (SAEs) safety reporting via the Electronic Pharmacovigilance (E-PV) system portal found at https://e-pv.mcaz.co.zw/

For further information refer to the MASCA [Chapter 15:03], MASCA Statutory Instrument SI 150, MASCA Fee schedule, Good Clinical Trial Practice (GCP) Guidelines for Zimbabwe, Guidelines for Conducting Good Clinical Practice (GCP) Inspections in Zimbabwe and Pharmacy Guidelines for Investigational Medical Products available on MCAZ website www.mcaz.co.zw

4.0 DEFINITIONS

4.1 **Amendment (to clinical trial protocol):** A written description of a change(s) to or formal clarification of a protocol.

4.2 **Applicable Regulatory Requirements:** Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

4.3 **Assisted Review**: An approach, which may be used on a case-by-case basis to assist a single country in the review of a Clinical Trial Application, or to assist a country in the processing of a Clinical Trial Application undergoing joint review, in the in-country level steps. The request for assistance comes from the country to WHO, and in an AVAREF Assisted Emergency Review, the request for assistance comes from the country to AVAREF.

4.4 **Clinical Trial [MASCA]:** Is defined in the Medicines and Allied Substances Control Act [Chapter 15:03] as follows: "A systematic study in human beings or animals in order to establish the efficacy of, or to discover or verify the effects or adverse reactions of medicines, and includes a study of the absorption, distribution, metabolism and excretion of medicines". This also includes any trial for vaccines/biologics or well-known established indication or registered product, and academic medicines studies in human by undergraduate and postgraduate students in partial fulfilment of academic requirements, and 'off label use'. If in doubt please consult MCAZ on whether a study constitutes a clinical trial or not in terms of MASCA Chapter 15:03.

4.5 Clinical Trial [ICH: E6 (R2)]: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

4.6 Compliance (in relation to clinical trials): Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

4.7 Co-ordinating Investigator: An investigator assigned the responsibility for the co-ordination of investigators at different centres participating in a multicentre trial.

4.8 Contract Research Organisation (CRO): A scientific body (commercial or academic) contracted by a sponsor to perform some of the sponsors trial-related duties and function

4.9 Documentation: All records in any form (written, electronic, magnetic optical records, scans, x-rays and electrocardiograms and others) that describe or records the methods, conduct, and/or results of a trial, the factors affecting a trial and the actions taken. These include the protocol, copies of submissions and approval from MCAZ, investigators Curriculum Vitae, consent forms, monitor reports, audit certificates, reference ranges, raw data, laboratory results, completed CRF and the final report.

4.10 Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of data produced.

4.11 Ethics Committee: An independent body consisting of medical, scientific, legal, religious and consumer group representatives whose responsibility is to verify that the rights, safety, and well-being of human participants involved in a trial are protected. An Ethics Committee provides public assurance of that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigators, facilities and the methods and material to be used in obtaining and documenting informed consent of the trial participants. The Committee is independent of the investigator, sponsor and relevant authorities. Ethical Committee may also be referred to as Institutional Review Board (IRB).

4.12 Fast-track: Fast track is a process designed to facilitate the development, and expedite the review of clinical trial applications for the conduct of clinical trials during public health emergencies.

4.13 Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of

clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial participants are protected.

4.14 Good Manufacturing Practice (GMP): That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use and as required by the product specification.

4.15 Independent Data-Monitoring Committee (IDMC) / Data and Safety Monitoring Board (DSMB) / Safety Monitoring Committee (SMC) or Data Monitoring Committee (DMC): An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

4.16 Informed Consent: A process by which a participant voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate and includes the objectives, potential benefits, risks and inconveniences, and the participant's rights and responsibilities. Informed consent is documented by means of a written, signed and dated informed consent form.

4.17 Inspection (GCP inspection): The act by the MCAZ 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 organizations (CRO's) facilities, or at other establishments deemed appropriate by the MCAZ.

4.18 Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

4.19 Investigator: An individual responsible for the conduct of the clinical trial at a trial site. If it is conducted by a team of investigators at a trial site, the leader of the team may be called principal investigator (see definition below).

4.20 Investigators Brochure: A collection of data consisting of all the information known prior to the clinical trial concerning the clinical and non-clinical data on the investigational product(s). There should be adequate data to justify the nature, scale and duration of the proposed trial. *Please note that for investigational new medical products that have not been approved for use, an investigator's brochure and all supporting development and safety information available at the time of application must be submitted.*

4.21 Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial including a product with a marketing authorisation when used or assembled 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.

4.22 **Joint review:** This process involves a joint assessment of the application by the Authority with the relevant IRBs and other receiving national drug regulatory agencies (NRAs).

4.23 **Medical product:** These include medicines, vaccines, diagnostics or medical devices and their accessories.

4.24 **Monitor:** 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 SOP's, GCP and the applicable regulatory requirements.

4.25 **Monitoring Plan:** A description of the methods, responsibilities and requirements for monitoring the trial.

4.26 **Multicentre Trial:** A clinical trial conducted according to one single protocol but at more than one site. It is carried out by more than one investigator.

4.27 **Pandemic:** an emergency occurring worldwide or over a wide area crossing international boundaries and affecting a large number of people.

4.28 **Participant /Trial participant:** An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

4.29 **Principal Investigator:** A person responsible for the conduct of the clinical trial at a trial site who is a medical practitioner, or dentist or other qualified person, resident in the country and a member of good standing of a professional medical association. If a trial is conducted by a team of investigators at a trial site, the principal investigator is the responsible leader of the team.

4.30 **Protocol:** 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.

4.31 **Public health emergency definition:** An occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin, that poses a substantial risk of a significant number of human facilities or incidents or permanent or long-term disability.

4.32 **Quality Assurance (QA):** Systems and processes established to ensure the trial is performed and the data generated, documented and reported in compliance with GCP and appropriate regulatory requirements.

4.33 **Quality Control (QC):** The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

4.34 **Reliance:** The act whereby the NRA in one jurisdiction may take into account and give significant weight to – i.e., totally or partially rely upon – evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others. Reliance may also form part of a stepwise confidence-building approach towards possible recognition.

4.35 **Recognition:** The routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or mutual and may in the latter case be the subject of a mutual recognition agreement

4.36 **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.

4.37 **Representative batch:** For the purpose of this guidance document, this is defined as a batch of Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Product (FPP) that is manufactured using the same formulation (for the FPP), method of manufacture and equipment, specifications and the same container closure system as the proposed clinical batch, with a similar batch size. All subsequent references in this guidance document to "representative batch" should be interpreted per this definition.

4.38 **Sponsor:** An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a trial. This excludes an individual company, institution or organisation which has been requested to provide money for a trial and does not benefit in any way from the results of the trial.

4.39 **Standard Operating Procedure (SOP):** A detailed, written instruction for the management of clinical trial. They provide a framework enabling the efficient implementation and performance of all the functions and activities for a particular trial.

4.40 **Trial Master File:** A Trial Master File (TMF) is the collection of essential documents that is used by sponsors, CROs and investigators/institutions for the management of the trial and by monitors, auditors and inspectors to review and verify whether the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the principles and standards of GCP.

4.41 **Trial Site:** The location(s) where trial-related activities are actually conducted.

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

5.0 GUIDELINES

5.1 Pre-submission Meetings/Enquiries for Clinical Trial Applications

Researchers may request a pre-submission meeting or submit a pre-submission enquiries prior to submission of clinical trial applications. These may be particularly useful for applications which will include complex issues of new active substances or pharmaceutical products, complicated study designs and for new researchers. Requests for pre-submission meetings should be submitted in writing to the Director General together with a brief synopsis/study summary of the proposed study, a list of preliminary question to be addressed by MCAZ 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. The Authority encourages and priorities these pre-submission enquiries and they are processed as matters of urgency.

5.2 Documentation for Clinical Trial Application

An application for the purpose of conducting a clinical trial of a human medicine shall be made to the Director-General on the Form MC 10 (Appendix 1) which accessible online as an application form on the Electronic Clinical Trials Application & Registry (E-CTR) platform and shall be accompanied by the appropriate fee and all the relevant documents as per the Checklist For Completeness Of An Application To Conduct A Clinical Trial (Appendix 2). For detailed guidance on how to navigate the E-CTR platform, please refer to the MCAZ Electronic Online Clinical Trial Application & Registry System External User Manual available on the MCAZ website. The following documents shall be attached:

5.2.1 Study Protocol

A Clinical Trial Protocol is a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial as defined in the ICH E6R (2) GCP guidelines. The clinical trial study protocol must be version controlled and dated and should contain the following:

5.2.1.1 General Information

i. Protocol title, protocol version 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 (if other than the sponsor).
iii. Name and title of the person(s) authorized 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 for the trial.
v. Name and title of the investigator(s) who is (are) responsible for conducting the trial, their address and telephone number(s) including updated mobile numbers.
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 investigator).

vii. 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.

5.2.1.2 Background Information

i. Justification for the study.
ii. Name and description of the investigational product(s), including:

A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

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

iii. Summary of the known and potential risks and benefits, to human participants (Benefit-risk assessment)
iv. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
v. A statement that the trial will be conducted in compliance with the protocol, GCP, RCZ and MRCZ/MCAZ requirements.
vi. Description of the population to be studied. Adequate justification is required in cases where the study is to be conducted in vulnerable participants.

5.2.1.3 Trial Objectives and Purpose

This includes a detailed description of the objectives and the purpose of the trial.

5.2.1.4 Trial Design:

i. A description of the clinical trial design should include:
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. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
iv. A description of the measures taken to minimize/avoid bias, including randomization and blinding.
v. The expected duration of participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
vi. A description of the "stopping rules" or "discontinuation criteria" for individual participants, part of/entire trial.
vii. Accountability procedures for the investigational product(s), including the placebo(s) and/or comparator(s), if any.

viii. Maintenance of trial treatment randomization codes and procedures for breaking codes/blinding (for safety reasons).

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

x. Selection and withdrawal of study participants. This will include: inclusion criteria, exclusion criteria, withdrawal criteria (i.e. terminating investigational product treatment/trial treatment); and procedures specifying when and how to withdraw participants from the trial/investigational product treatment; The type and timing of the data to be collected for withdrawn participants; whether and how participants are to be replaced; The follow-up for participants withdrawn from investigational product treatment/trial treatment.

5.2.1.5 Treatment of study participants

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

ii. Medication(s)/treatment(s) permitted (including emergency medications/antidotes) and not permitted before and/or during the trial.

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

iv. Procedures for monitoring participant's compliance.

v. Procedures put in place to ensure post-trial access for research participants.

5.2.1.6Assessment of Efficacy

This will include:

i. Specification of the efficacy parameters.

ii. Methods and timing for assessing, recording, and analysing of efficacy parameters.

5.2.1.7 Safety

This will include:

i. Specification of safety parameters.

ii. The methods and timing for assessing, recording, and analyzing safety parameters.

iii. Procedures for eliciting reports of and for recording and reporting adverse events and co-occurring illnesses.

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

v. A clear description of study procedures and quantities of any body fluids to be collected for study analysis.
vi. The named composition of the Drug Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC), name of the Chairperson must be stated.

5.2.1.8 Statistics

This will include:

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).
iii. The number of participants planned to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each 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.
vi. Criteria for the termination of the trial.
vii. Procedure for accounting for missing, unused, and spurious data.
viii. 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).
ix. Procedures for reporting any protocol violations.
x. The selection of study participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).
xi. A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).
xii. The number of participants to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified.
xiii. Methods for data analyses and evaluation of results.

5.2.1.9 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit inspections from MCAZ/MRCZ and provide direct access to source data/documents.

5.2.1.10 Quality Control and Quality Assurance

i. In line with ICHE6(R2)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 MCAZ/MRCZ

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, in line with ICHE6 R (2).

5.2.2 Investigator's Brochure

5.2.2.1 The investigator's brochure must contain the following information in respect to the investigational medicinal product (IMP):

i. The physical, chemical and pharmaceutical properties.
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. Proof of current Good Manufacturing Practices (cGMP) as compliance of the IMP manufacturing site(s).
viii. Documentation on quality and manufacturing of the IMP (IMP dossier)
ix. Stability data for initial batches, certificates of analysis for three batches or batch analysis data for three batches
x. Name and address of the manufacturer(s) or manufacturing licenses.

5.2.2.2 More details are provided in ICH E6 (R2)-GCP guidelines and may be used when compiling information on this part.

5.2.2.3 For trial medicinal products included in the study, registered by the MCAZ, 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 SmPC of the product.
ii. Certificate of Analysis (CoA).
iii. cGMP certificate from a reference NRA.

NB: For products that are approved by other reference agencies such as USFDA, EMA, TGA 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.

5.2.3 Clinical Trial Pharmacy Protocol (Pharmacy Plan)

A pharmacy plan should be submitted for all Clinical Trial applications submitted to MCAZ. A clinical trial pharmacy protocol (pharmacy plan) is a policy document covering the safe handling of medicines used in clinical trials, including a statement listing the responsibilities that will be delegated to the pharmacy by the investigator and Pharmacist of Record. Pharmacy input into the development and review of this policy document is vital to ensure practicability and consistency with pharmacy procedures in general including environmentally required methods of expired/unused medical products destruction. The guideline on the requirements of the clinical trial pharmacy plan are available on the MCAZ website and should be complied with at the time of Clinical Trial application submission including submission of the completed pharmacy plan form.

5.2.4 Participant Insurance Cover for trial-related injuries

In line with MASCA Chapter 15:03 requirements, the sponsor is required to provide insurance cover for trial-related injuries for the participants of the study. Certificate of insurance or a letter confirming such insurance cover and the amounts set aside or limits is to be provided with the initial clinical trial application. The level of risk that participants will be exposed to will be different across phase I-IV trials and therefore the sponsor is required to provide insurance cover that will be adequate to match the risk involved in the clinical trial. For the purposes of the Act, a person conducting a clinical trial shall insure the persons participating in such trial for the sum determined by the Authority in respect of each person of: not less than one thousand United States dollars in respect of each person; or such other amount as the Authority may direct depending on the risk profile of the clinical trial.

5.2.5 Ethics approval and other relevant regulatory approvals

Parallel clinical trial applications to all regulators in Zimbabwe are encouraged to minimize the timelines for clinical trial approvals.

Research involving humans should satisfy the ethical standards and any other applicable internationally recognized ethics guidelines. Ethical approval to conduct a clinical trial in humans should be sought from the Medical Research Council of Zimbabwe (MRCZ). MRCZ approval, or proof of submission of an application for MRCZ approval in case of parallel submission should be submitted.

For clinical trials involving biological products approvals or proof of application to the local National Biotechnology Authority is required. The National Biotechnology Authority (NBA) of Zimbabwe is responsible for clearance of recombinant DNA products and issues Trial Release Permits and Facility Registration for clinical trials involving biological products.

The Research Council of Zimbabwe (RCZ) is mandated to register foreign researchers in terms of Section 27 of the Research Act [Chapter 10:22]. A foreign researcher is a non-Zimbabwean national and any person wishing to conduct research in Zimbabwe on behalf of a foreign institution, foreign organization or other foreign person. Authorization of foreign researchers should be obtained from Research Council of Zimbabwe (RCZ). If a researcher intends to transfer or export samples abroad for research purposes, they are required to obtain approval from RCZ to export the biospecimens and/or materials.

5.2.6 Proof of Provision of Data Safety Monitoring Board / Data Monitoring Committee/ Safety Monitoring Committee (DSMB/DMC/SMC)

Clinical trials are required to set up a DSMB/DMC/SMC for their studies. The sponsor shall appoint members of a DSMB/DMC/SMC by considering selection of individuals with relevant expertise (such statisticians, clinicians etc) , experience in clinical trials and in serving on other DSMB/DMC/SMCs, and absence of serious conflicts of interest. The Principal Investigator shall submit a DSMB/DMC charter with information on the aims and objectives of the DSMB/DMC, the composition of the DSMB/DMC/SMC, names of the chairperson and members and how meetings will be organized.

5.2.7 Monitoring Plan

Monitoring should be provided. The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. 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 emphasize 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.

5.2.8 Signed Declarations

Completed, signed and dated copies of the following forms are required to be submitted as part of the clinical trial application:

5.2.8.1 Submission Declaration by Principal Investigator (Appendix 4)
5.2.8.2 Joint Declaration by Sponsor and Principal Investigator concerning Sufficient Funds to Complete the Study (Appendix 5)
5.2.8.3 Declaration by Principal Investigator for GCP Compliance (Appendix 6)
5.2.8.4 Declaration by Co- and Sub-Investigators for GCP Compliance (Appendix 7)

5.2.9 Recruitment Advertisements (if applicable)

Any recruitment materials such as leaflets, brochures, posters, banners or advertisements flighted through televisions, radio programs, newspapers and any other media should be provided for approval by the MCAZ and ethics committees prior to distribution and must follow existing local rules and regulations.

5.2.10 Patient information leaflet(s) and informed consent forms

Version controlled and dated English and Vernacular Informed consent forms should be provided with the clinical trial application. The Informed Consent Forms should be in line with MRCZ Guidelines and templates

5.2.11 Pharmaceutical Dossier for new Investigational Medicinal Products

This requirement applies to Phase I, II and III clinical trials which involve new Investigational Medicinal Products. For clinical trials using well established Investigational Medicinal Products that have been registered and marketed in Zimbabwe or reference stringent regulatory authorities an updated Investigator's brochure or SMPC or package insert and prescribing information will suffice. The amount and depth of information that would be submitted to MCAZ depends on the clinical trial phase, novelty of the medicine, dosage form/route of administration and the known / suspected risks. For combination protocols (e.g. Phase I/II or II/III protocols), applicants should submit Quality data according to the requirements of the highest phase.

5.2.11.1 Quality Data - Module 3

This module should provide details on the chemistry, manufacturing and control of the Investigational Medical Product. Information on quality should be presented in the structured format as described in ICH M4Q. Supporting data to demonstrate quality of the investigational product, including relevant batch analyses results should be attached. If the comparator medicinal product is modified in any way in order to blind the trial (e.g., grinding of tablets, encapsulation of tablets), results of an in vitro study (e.g., comparative dissolution profiles for solid dosage forms) comparing

the unchanged and the modified product should also be submitted. For sterile products that are repackaged for blinding purposes, it should be demonstrated that sterility is maintained.

i. 3.2.S Active Pharmaceutical Ingredient (API)

Where some of the proprietary information on the API section is not available to the Principal Investigator/FPP Manufacturer, the API manufacturer can send the closed part of the Drug Master File (DMF) directly to MCAZ. The DMF will be held in strict confidence by MCAZ.

Section 3.2. S.1 General Information

3.2. S.1.1 Nomenclature

Information on the nomenclature of the API should be provided. For example:

(a) Recommended International Non-proprietary Name (INN);

(b) Compendial name, if relevant;

(c) Chemical name(s);

(d) Company or laboratory code;

(e) Other non-proprietary name(s) (e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN)); and

(f) Chemical Abstracts Service (CAS) registry number.

3.2. S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. This information should be consistent with that provided in section S 1.1. For API existing as salts, the molecular mass of the free base should also be provided.

3.2. S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the API.

3.2.S.2 Manufacturer

3.2.S 2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.S.2.2 Description of Manufacturing Process and Process controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. A summary of the expectations at each phase is provided below

Phase I Clinical Trial Applications:

A flow diagram of the synthetic process(es) should be provided that includes chemical structures and configurations of starting materials, intermediates and the API. In addition, all reagents (including chemical formulae), solvents and catalysts should be specified in the flow diagram.

Phase II Clinical Trial Applications:

In addition to the flow chart, a stepwise narrative description of the API manufacturing process should be provided. The use of all reagents, solvents, catalysts and auxiliary materials should be summarized in the manufacturing process description. Relevant process controls should be indicated where critical steps in the synthesis have been identified. The description of the manufacturing process at Phase II should be sufficiently detailed to address quality and safety concerns without being overly restrictive to process optimization. For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description, addressing critical process controls and safety concerns, should be provided at Phase II.

Phase III Clinical Trial Applications:

A detailed flow chart and narrative process description should be provided. The detailed description provided at Phase III should include critical steps identified in the process and relevant process controls (e.g. reaction times, pH, temperatures, etc.), including all purification steps.

In addition to the above information, the data provided for an API produced by fermentation should include:

i. Source and type of micro-organism used;
ii. Composition of media;
iii. Precursors;
iv. Additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and
v. Name and composition of preservatives.

For APIs of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for residues resulting from such treatments in the

API specification. Absence of toxic metals and radioactivity may also have to be confirmed.

3.2.S.2.3 Control of Materials

APIs or materials used in the synthesis which are of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and an attestation confirming this should be provided. For Phase II and Phase III Clinical Trial Applications, applicants should provide details of the starting materials for the synthesis of the API. The level of detail expected concerning controls on starting materials for synthesis increases as synthetic steps get closer to the final API. Generally, the "starting material for synthesis" is:

i. A synthetic precursor, one or more synthetic steps prior to the final intermediate
ii. A well-characterized, isolated and purified substance with the structure fully elucidated
iii. Controlled by well-defined specifications, which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities

For starting materials which are commercially purchased, the source and a copy of the provisional specifications is typically considered acceptable. For "starting materials for synthesis" which are manufactured in-house, a copy of the flow chart and provisional specifications for the starting material should be provided.

3.2.S.2.4 Controls of Critical Steps and Intermediates

Information in this section not required for Phase I or Phase II clinical trial applications. For Phase III Clinical trial applications, a summary of critical steps identified in the synthesis and the tests and tentative acceptance criteria for their control should be submitted. In-process controls or provisional specifications for isolated intermediates may be summarized here.

3.2. S.3 Characterizations

3.2. S.3.1 Elucidation of Structure and other Characteristics

For all Clinical Trial Applications, confirmation of structure based on synthetic route and spectral analyses should be provided. Copies of the actual spectra are not required for clinical trial applications, but should be availed to the Authority on request. Studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally includes elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), X-ray diffraction (XRD) and Mass Spectra (MS) studies. It is recognized that some

drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the API. If an API consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

3.2.S.3.2 Impurities

Summaries of the names, structures, and origin of the impurities should be provided. The origin refers to how the impurity was introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis", etc.). It should also be indicated if the impurity is a metabolite of the API. For Phase I Clinical Trial Applications, the structure (or other identifier, if not structurally characterized) as well as the origin should be provided. For Phase II and III Clinical Trial Applications, the impurity name (or identifier), structure (if characterized) and origin should be provided in the table for all specified impurities

3.2. S.4 Control of the Active Pharmaceutical Ingredient

3.2.S.4.1 Specification

Information in this section not required for Phase I Clinical Trial Applications. A summary of the specification for the Active Pharmaceutical Ingredient should be provided for Phase II and III clinical trials. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the Active Pharmaceutical Ingredient.

3.2.S.4.2 Analytical Procedures

Information in this section is not required for Phase I Clinical Trial Applications. For Phase II and III Clinical Trial Applications, a brief description of the analytical methods used for the Active Pharmaceutical Ingredient should be provided for all tests included in the Active Pharmaceutical Ingredient specifications (e.g. method type, column size, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for clinical trial applications, but should be available upon request.

3.2.S.4.3 Validations of Analytical Procedures

Information in this section is not required for Phase I clinical trial applications. For Phase II and III Clinical Trial Applications, the suitability of the analytical methods and a tabulated summary of the validation carried out should be provided (e.g. results or values for specificity, linearity, range, accuracy, precision, intermediate precision, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be provided for Clinical Trial Applications.

3.2. S.4.4 Batch Analyses

Description of batches and results of batch analyses should be provided. Batch analysis results for the API may be provided in either the Quality Overall. The batch number, batch sizes, and dates and sites of production should be stated for all batches. For Phase I Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial should be provided. For Phase II Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of API may be provided as supporting data, with a commitment that the batch analysis for the specific lot to be used in that protocol will be submitted prior to dosing. For Phase III Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial, or batches representative thereof, should be provided.

3.2.S.4.5 Justification of Specification

Information in this section is not required for Phase I Clinical Trial Applications. The sponsor should ensure the specification includes all the tests and acceptance criteria appropriate for the API, and that reasonable limits for impurities and residual solvents have been established. Acceptance criteria should be based on manufacturing experience, stability data and safety considerations.

3.2.S.6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. Available long-term and accelerated stability data for the API should be provided at each stage of development to support its storage (conditions and re-test period) and use in the manufacture of the FPP. The proposed storage conditions and re-test period (or shelf life, as appropriate) for the API should be reported.

3.2.S.7.2 Stability Protocol and Stability Commitment

If full long-term stability data supporting the re-test period is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or batches considered representative thereof, will be monitored according to the stability protocol. A summary of the stability protocol (in

tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.S.7.3 Stability Data

Results of the stability studies (e.g., long-term studies, accelerated studies, stress conditions, etc.) should be presented in an appropriate format. The actual stability results (i.e., raw data) used to support the clinical trial should be provided as an attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

ii. 3.2.P Drug product (or finished pharmaceutical product

3.2. P.1 Description and Composition of the FPP

A description of the FPP and its composition should be provided. The information provided should include the description of the dosage form, composition, type of container closure system used for accompanying reconstitution diluent, if applicable and the qualitative list of the components of the placebo samples used in the clinical trials.

3.2.P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application.

For Phase I Clinical Trial Applications, this section should only be completed for sterile products. For Phase II and III Clinical Trial Applications, to the extent possible, information pertaining to the following aspects of pharmaceutical development should be submitted:

i. The compatibility of the API with excipients listed in P.1 should be discussed. For combination products, a summary of investigations of the compatibility of the APIs with each other should be provided.
ii. A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between earlier clinical formulations and the formulation (i.e., composition) described in P.1 should be discussed, if applicable.
iii. The selection of the manufacturing process described in P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.
iv. The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of API in solution, sorption on injection

vessels, stability) should be addressed to provide appropriate and supportive information for labelling.

3.2.P 3 Manufacture

3.2.P 3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the FPP for the batches used in the clinical studies. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative office(s). An attestation should be provided in the Quality Overall Summary or as an Attachment confirming that the FPP to be used in the Local study was manufactured according to Good Manufacturing Practices.

3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. For sterile products, a complete narrative description of the manufacturing process should also be submitted *regardless of the clinical trial phase*. Furthermore, details of sterilization and lyophilization (if applicable) procedures should be provided for all clinical trial application. For Phase I Clinical Trial Applications, a flow chart of the manufacturing process should be provided clearly indicating the order of addition of components and a summary of unit operations (e.g. blending, screening, etc.). For Phase II Clinical Trial Applications, a flow chart and narrative description of the manufacturing process should be provided. For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description which addresses critical process controls, and safety and bioavailability concerns, should be provided at Phase II. For Phase III Clinical Trial Applications, flow chart and a detailed narrative description of the process should be provided. A summary of in-process controls and process parameters (e.g. mixing/blending time, temperature, pH for preparations of solutions) should be provided. The critical steps, process controls, intermediate tests and final product controls should be identified and described in additional detail.

Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Information in this section not required for Phase I or Phase II clinical trial applications. For Phase III Clinical Trial Applications, to the extent possible at the time of submission, applicants should provide information on the critical steps and intermediates. Tests and tentative acceptance criteria for controls on the critical steps in the FPP manufacturing process, where identified, and information on the quality and provisional controls on intermediates isolated during the process, where relevant, should be provided.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

This includes the specifications for all excipients, including those that do not appear in the final FPP (e.g., solvents). Confirmation should be provided that none of the excipients which appear in the FPP are prohibited for use in drugs.

3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). This information should include biological source, country of origin, manufacturer, and a brief description of the suitability of use based on the proposed controls. For gelatin for use in pharmaceuticals, supporting data should be provided which confirms that the gelatin is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE). Supporting information for excipients of human or animal origin should be provided as an attachment.

3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a FPP or by a new route of administration, full details of manufacture, characterization and controls should be provided, with cross-references to supporting safety data.

3.2.P. 5 Control of FPP

3.2.P.5.1 Specification(s)

Information in this section is not required for Phase I clinical trial applications. For Phase II and III inspections, a summary of the specification(s) for the FPP should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the dosage form.

3.2.P.5.2 Analytical Procedures

Information in this section is not required for Phase I clinical trial applications. For Phase II and III Clinical Trial Applications, a _brief description of the analytical methods used for the FPP should be provided for all tests included in the FPP specifications (e.g. reverse-phase HPLC, GC, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for clinical trial applications, although this information should be available upon request.

3.2.P.5.3 Validation of Analytical Procedures

Information in this section is not required for Phase I Clinical Trial Applications._For Phase II and III Clinical Trial Applications, data on suitability of the analytical methods and a tabulated summary of the validation information should be provided (i.e. results or values for specificity, linearity, range, accuracy, precision, robustness, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be submitted for clinical trial applications, although this information should be available upon request.

3.2.P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided. For Phase I Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial should be provided. For Phase II Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of FPP may be provided as supporting data with a commitment that the batch analysis for the specific lot(s) to be used in that protocol will be submitted prior to dosing. For Phase III Clinical Trial Applications, analytical results from the batch(es) to be used in the proposed clinical trial, or batch(es) considered representative thereof, should be provided.

3.2.P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously summarized in Section S.3.2 - *Impurities.* This information includes degradation products (e.g., from interaction of the Active Pharmaceutical Ingredient with excipients or the container closure system), solvents in the manufacturing process for the FPP, etc. This section may also be used to report any new impurities found in the FPP during stress testing (e.g. photostability testing).

3.2.P.6 Justification of Specification(s)

Information in this section is not required for Phase I Clinical Trial Applications. The sponsor should ensure the specification(s) includes all the

tests and acceptance criteria appropriate for the FPP, and that reasonable limits for degradation products have been established. Acceptance criteria should be based on manufacturing experience, stability data, and safety considerations. For impurities/degradation products which are unique to the FPP, acceptance criteria should be supported by appropriate toxicology and safety studies.

3.2.P.7 Container Closure System

A description of the container closure system(s) to be used in the clinical trial should be provided, including the materials of construction for each packaging component. This includes packaging components that are product contact surfaces, are used as a protective barrier to help ensure stability or sterility, are used for drug delivery and are necessary to ensure FPP quality during transportation. For sterile products, details of the washing, sterilization and depyrogenation should be submitted in this section. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), additional detail may be required.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. For sterile products, sterility should be reported at the beginning and end of shelf life. During development it is expected that sterility will be monitored on a routine basis (e.g. annual basis) until the shelf life has been determined with confidence. For parenteral products, sub-visible particulate matter should be reported at every test interval until a shelf life has been established. Bacterial endotoxins need only be reported at the initial test interval. For FPPs which are reconstituted or diluted prior to administration, stability and compatibility studies covering the entire in-use period should be provided. Furthermore, for products which are diluted or reconstituted into a secondary container closure system (i.e., infusion kit), compatibility data should be submitted to support in-use conditions in that specific container closure. Available long-term and accelerated stability data should be provided for the FPP at each stage of development to support its storage conditions and shelf-life.

3.2.P.8.2 Stability Protocol and Stability Commitment

If full long term stability data supporting the proposed shelf life is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or samples considered representative of the clinical batches, will be monitored throughout the duration of the clinical trial. A

summary of the stability protocol (e.g. tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.P.8.3 Stability Data

Results of the stability studies (e.g. long-term and accelerated studies) should be presented in an appropriate format. The actual stability results (i.e., raw data) used to support the clinical trial should be provided as an attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

5.2.11.2 Non Clinical Study Reports – Module 4

The goals of the pre-clinical /nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. The information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterize potential adverse effects that might occur under the conditions of the clinical trial to be supported.

Applicants are required to conduct pre-clinical studies according to the ICH guidance document M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and guidelines of the Organisation for Economic Cooperation and Development (OECD). For biotechnology-derived products the applicants should follow ICH S6 guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals. The Nonclinical Study Reports should be presented in the order described in the guidance M4S.

In accordance with ICH Guideline M3 the following are the minimum requirements per clinical trial application phase:

Clinical Trial Phase	Minimum Required Data
Phase 1	Repeated dose toxicity (2 Weeks) Safety Pharmacology Local tolerance Genotoxicity *in vitro* Male reproductive organs
Phase 2	Repeated dose toxicity (2 weeks to 6 months) Genotoxicity *in vivo*
Phase 3	Repeated dose toxicity (1 month – chronic)

	Reprotoxicity (Male and Female fertility, Embryofetal, Peri-post natal) Absorption, Distribution Metabolism and excretion

The data that is submitted to MCAZ from non-clinical safety studies should have originated in studies that have been conducted in compliance with the Principles of GLP. Laboratories that perform safety pharmacology and toxicology studies are required to have worked under the conditions of GLP. The applicant shall be required to submit evidence of GLP via a declaration letter signed by the director of the research facility testifying to have conducted the studies as per GLP compliance for each study, and the quality assurance (QA) statement must list all QA activities and confirm that the study report reflects the raw data.

The test facility itself should be part of a national compliance monitoring programme at the country of origin and be listed as a compliant facility. If this latter prerequisite cannot be complied with because of lack of a national compliance monitoring programme then applicant shall communicate this in writing.

This module is applicable to new Investigational products only. For products that have already been registered and marketed, an updated investigator's brochure is sufficient.

5.2.11.3 Clinical Study Reports - Module 5:
Clinical study reports will be required for clinical trial applications which are not for first in human (FIH) studies. The reports provide details on clinical experience in humans regarding the investigational product.

5.2.12 Additional attachments and requirements

Any other relevant attachments such as GCP certificates and CV/Resume's must be submitted with the application in line with the clinical trial application checklist

With regards to the capacity of the clinical trial site, all clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and any potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

The Principal investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through up to date Curriculum Vitae. The Investigator should be licensed under the Health Professions Act (Chapter 27.19). The Principal Investigator should ensure that he or she has sufficient time to conduct and complete the trial within the agreed time period, and

that any other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand.

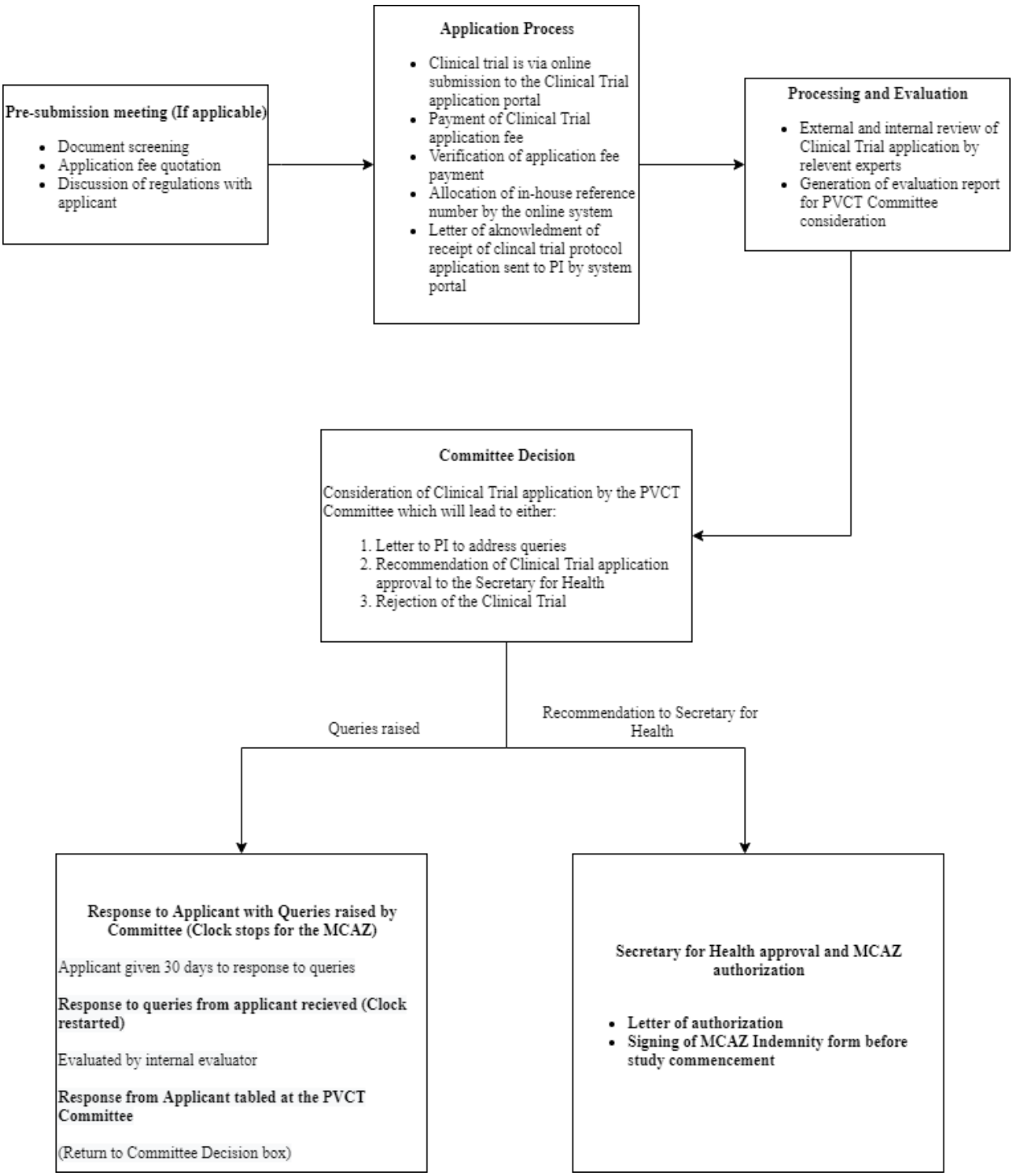
5.3 Application Review and Authorization

5.3.1 The application will be reviewed by external and internal experts appointed by the MCAZ. There is a confidentiality agreement between MCAZ and reviewers, and Committee members 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 MCAZ Director-General.

5.3.2 The reviewers will generate an evaluation or assessment report that will be tabled at the Pharmacovigilance and Clinical Trial Committee (PVCT) where a recommendation to the Secretary for Health and Child Care for approval of the application will be made in line with MASCA [Chapter 15:03].

5.3.3 If an application is approved by the Secretary for Health and Child Care, the MCAZ will issue a clinical trial authorization form for the clinical trial with conditions of authorization to be adhered to. The clinical trial authorization will be valid up to the proposed duration of the study as indicated in the application form (MC10). The validity period may be extended on submission of an amendment application. Below is a flow chart of the review processes that are involved in the authorization of a clinical trial. Once a clinical trial is approved, the Principal Investigator is required to complete and sign the Indemnity Form appended to the authorization certificate and return it to MCAZ prior to commencement of the clinical trial.

Figure 1: Flow chart of the Clinical Trial application review process



5.4 Expedited Review of Applications

5.4.1 The Authority has an expedited review pathway for clinical trial applications. This pathway can be used in the case of public health emergencies or at the request of a Principal Investigator. The timeline for review **by the Authority** will be 15-30 working days subject to submission of a complete application. The fees for the expedited review pathway will be as stipulated by the Authority from time to time.

5.5 Reliance Model

5.5.1 The MCAZ employs the reliance model **approach** for clinical trial **investigational products.** The MCAZ implements the reliance model especially for 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 countries and countries considered to be trustworthy by the Authority. 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 of investigational products, as well as the design of clinical trials. The Authority will however maintain its regulatory responsibilities for decision-making.

5.6 Post-Clinical Trial Authorization Monitoring requirements

5.6.1 Amendments

i. Clinical Trial Amendments to an authorized clinical trial protocol are required to be submitted for review and approval by the MCAZ. Applications for an amendment to an authorized clinical trial protocol shall be made on the appropriate form (Appendix PVF 82: Application for a Clinical Trial Protocol Amendment) and will attract an application fee as stipulated in the fee schedule.

ii. If the amendment is considered (by the DSMB and/or PI) as urgent and crucial to protect life or well-being of trial participants or the community, the change may be effected immediately, and the investigator must inform the IRB/IEC and the MCAZ as soon as possible - by telephone followed by a written full explanation and submission of the protocol amendment application.

iii. If the amendment affects the safety of the trial participants (e.g. changes to dose, regimen, concomitant medication, monitoring, etc.) the amendment must be submitted in full and approval in writing from the MCAZ must be obtained prior to implementation.

iv. If the amendment is unlikely to impact participant safety (e.g. change of investigator (except PI), endpoint assay, laboratory, statistical analysis, etc.) the full detail of the change must be submitted to the MCAZ in writing. The amendment must be implemented after receipt of approval by the MCAZ.

v. The following information must be supplied when applying for an amendment to an authorized clinical trial protocol:

   a. A cover letter from the PI.

b. Each amendment should be in bold and the words/statements removed stricken through, e.g. strikethrough. A Table in a covering letter should detail all amended parts of the protocol. The reasons or justification for the amendments must be provided.
c. The possible consequences for participants already enrolled must be described. If the amendments affect the participants; inclusion and/or exclusion criteria, dosage regimen, safety, visits etc. an amended ICF may be required.
d. Any additional risks or safety issues should be highlighted.
e. The amended supporting documents should be appended, including any new relevant publications.

vi. The clinical trial amendment application will be considered by the PVCT Committee for approval/rejection and approval/rejection of the amendment will be communicated to the applicant in writing. The timeline is 20 working days excluding time taken to address queries raised. Early submission of a complete clinical trial amendment to MCAZ at least 2 weeks before the next monthly PVCT Committee meeting will reduce the approval timeline.

5.6.2 Reporting of Clinical Trial Safety Reports to MCAZ (AEs, ADRs SAEs and/or AEFIs), product defects, DSMB/DMC reports, and/or protocol deviations/ violations.

5.6.2.1 It is a mandatory requirement in terms of MASCA [Chapter 15:03] for the applicant to report all types of safety reports (AEs, ADRs and/or AEFIs) to the MCAZ within 7 days of the PI becoming aware of them. Reports of serious adverse events (SAEs) during the trial must be reported promptly to the MCAZ within 48 hours of occurrence of being know by the principal investigator/investigators. You are required to submit an online safety report on the MCAZ e-PV system. The reporting form for SAEs may be used and is now available on https://e-pv.mcaz.co.zw/

5.6.2.2 In addition, safety report study summaries such AE/ADR/SAE/AEFI logs should also be submitted.

5.6.2.3 Product defect(s) of the investigational product(s) and other study medicines are also required to be reported in line with the MCAZ product defect form and MCAZ Notification Guidelines of a Product Defect available on MCAZ website www.mcaz.co.zw

5.6.2.4 Data Safety Monitoring Board (DSMB)/Data Monitoring Committee and other types of safety reports in relation to the benefit/risk assessment of the study safety and subsequent protocol amendments or clarification memorandums should also be submitted to MCAZ on the online e-CTR platform available on *https://e-ctr.mcaz.co.zw/*

5.6.2.5 Reports on Protocol Deviation(s) and Violation(s) including the corrective action taken should also be submitted to MCAZ.

5.6.3 Annual Progress Reports

PI's are required to submit annual progress reports for all running CTs by completing the Clinical Trial Annual Progress Reporting Form for Investigators by the 31st of January annually. The form is to be accompanied by all relevant attachments. A Provision for annual renewal of clinical trials may be included when the MASCA [Chapter 15:03] is amended in the future however applicants and researchers will be notified of the requirement thereof.

5.6.4 The Final Report

In line with the provisions of Sections 22 and 24 of the Medicines and Allied Substances Control Act (Chapter 15:03) it is an offence to disseminate or publish clinical trial results without prior submission of the same results to the MCAZ. As such, it is a mandatory requirement for the applicant (researcher/PI/sponsor) to submit a **preliminary report 3 months** after completion of the study and a **final report 6 months** after completion of the study including any publications. The final report should follow international expectations (ICH E3 and ICH E6R (2) for clinical trial reporting. This must be a completed and comprehensive description of the study and its outcomes are given. The protocol, statistical and clinical aspects should be integrated in order to obtain a final study report that is consistent with the study data generated. A final report is also required for a study that may be prematurely stopped due to safety reasons or other reasons.

5.6.5 Importation, Management and Destruction of Investigational Products

5.6.5.1 All study investigational products and other trial-related medical products shall be approved for importation, exportation or destruction by the MCAZ. Approval to import or export products for clinical trials shall only be granted to clinical research entities whose study has been approved by The Authority. Applicants are required to submit an application for authorisation to import investigational products. The application shall contain the following:

i. A cover letter stating the full name and address of the innovator and /or manufacturer, the study Sponsor and the recognized clinical research entity, the name/description of the investigational product, placebo and quantity to be imported;
ii. The quantity and source of each investigational product and trial-related products to be imported;
iii. Shipment documents and invoices of the IMP purchased/ to be purchased indicating quantities;
iv. A certificate of analysis of investigational products for all batches of each product to be imported;
v. Lot Release certificate(s) (where applicable) for all batches to be imported.

5.6.5.2 On submission of the above, an application for an import permit will be processed within five (5) working days.

5.6.5.3 The Principal Investigator shall notify the Authority within 48 hours of each consignment of investigational product batches received. The notification shall include the following details: Name of product(s), Quantities received and Batches received. The investigational product shall be appropriately labelled with the approved labels to indicate that samples are for the conduct of clinical trials only. The label shall bear the following as the basic information:

i. For Clinical Trial purposes ONLY
ii. Trial name
iii. Expiry date (if applicable)
iv. Dosage (if applicable)
v. Investigational Product identity number.

5.6.5.4 Products imported may be inspected by officials of the Authority at the port of entry before they are released to the recognized clinical research entity.

5.6.5.5 For investigational products purchased locally, the Principal Investigator shall document the source, proof of purchase, quantities purchased and Certificate of Analysis for each batch of Investigational Products. Copies of all documents on investigational products, whether purchased locally or imported shall be kept on-site for verification and accountability during GCP inspections.

5.6.5.6 Leftover, expired, used or broken Investigational Products may be destroyed upon authorization by the MCAZ and the study Sponsor. As such, an official request to dispose of the Investigational Products, indicating the type, quantity of each product to be destroyed and the method of destruction shall be made to the Authority. The destruction certificate/letter confirming destruction shall be submitted to the MCAZ. For more information on the destruction of investigational products please refer to the MCAZ pharmacy guidelines for investigational products

5.6.6 Clinical Trial application process and importation of study medical products during public health Emergency

5.6.6.1 In cases where the country has been declared to be in a public health emergency disaster by the President or Minister of Health, the WHO or any other designated person, expedited regulatory review pathway for CT's will be employed in line with the African Vaccine Regulatory Forum (AVAREF) Strategy and Guidance for Emergency Preparedness. 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.

5.6.6.2 The emergency procedure will involve joint review/inspections, data sharing and communication with MRCZ to speed up approval of the Clinical Trial. Parallel/ simultaneous ethical and regulatory review is be encouraged. A timeline of 10 working days is recommended for processing of Clinical Trial Applications where the product is already registered for other indication/s, or for old products which are known and 15 working days for novel products. These timelines are for the entire process from receipt of Clinical Trial Application to the final decision, with exception of clock stops in line with the African Vaccine Regulatory Forum (AVAREF) Strategy and Guidance for Emergency Preparedness. The documentation to be submitted will be the same as outlined in section 3.1, however, this will be dealt with on a case by case basis. Researchers are encouraged to have pre-submission meetings with MCAZ to discuss their protocol and any anticipated problems so that the approval process will be shortened. The MCAZ will also coordinate with relevant stakeholders such as WHO, AVAREF, MRCZ and others when necessary to achieve the desired result.

5.6.6.3 To initiate the submission process, the applicant should send an email of intention to the MRCZ and MCAZ, with a copy to the AVAREF Secretariat. The MRCZ and MCAZ will then set up a pre-submission meeting (via a mutually convenient medium) with the applicant and communicate the meeting outcome to AVAREF Secretariat. E-mail contacts and phone numbers for all countries are available on the AVAREF Website.

5.6.6.4 Applications for the importation of study medical products will also be expedited and be processed within 3 working days of receipt of the application. Any post-authorisation amendments will be processed within 5 working days of receipt of the application.

5.6.7 Good Clinical Practice (GCP) inspections

5.6.7.1 The MCAZ will conduct pre-trial, trial and post-trial GCP inspections in line with the MASCA [Chapter 15:03] mandate to monitor clinical trials from start to finish. Inspections may be routine or may be triggered by issues arising during the assessment of the protocol, annual reports, amendments or protocol deviations or by other information such as previous inspection experience. Risk-based approach will be considered for the inspection frequency and scheduling. The MCAZ may inspect the study site(s), the sponsor or the manufacturer of the medical products, to ensure compliance with GCP and the inspection may be done with/without notification. Combined inspections may be conducted with MCAZ or MRCZ from time to time. Aspects of the study that will be inspected may include but not be limited to:

i. The facilities and staff where the studies will be conducted, as approved by the MCAZ.
ii. Compliance with the approved protocol and any amendment(s) to the protocol, if they are any.
iii. Accurate, complete and current records according to the protocol.
iv. Serious adverse event(s) and adverse event(s) reporting according to MCAZ requirements.
v. More information on GCP inspections is provided in the Guidelines for Good Clinical Practice in Zimbabwe and Guidelines for Conducting Good Clinical Practice (GCP) Inspections in Zimbabwe

5.6.8 Safety Notifications

5.6.8.1 Any update to the following documentation should be submitted as soon as it becomes available to the study team:

i. Investigator's Brochure
ii. Package Inserts
iii. Safety reports from all active sites
iv. Notifications of safety signals.
v. Emergency preparedness and response plans
vi. Information distributed to participants during the course of the study.

5.6.9 Uploading approved clinical trial application on the Clinical Trials Registry platform

The MCAZ e-CTR application system also has a provision for a Clinical Trial Registry platform. The Principal Investigator is however also required to upload the approved clinical trial application onto a publicly accessible registry platform such as the WHO recommended Pan African Clinical Trials Registry (PACTR) platform.

5.7 Validity of clinical trials authorization

The validity period of each clinical trial shall be stated on the MCAZ clinical trial authorisation communication sent to the Principal Investigator. Applications for clinical trials renewals should be submitted to MCAZ for approval if the Principal Investigator wishes to extend the clinical trial beyond the expiry date of the clinical trial stated in the authorisation form. Applications for the renewals of clinical trials should be submitted 3 months before the expiry date and shall be processed within 60 calendar days. A cover letter stating the reasons and justifications for the extension of the study should be submitted to the Authority together with a copy of progress report of the clinical trial.

6.0 KEY RELEVANT DOCUMENTS

6.1 Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]
6.2 Statutory Instrument 150 of 1991 and MCAZ current gazetted fee schedule
6.3 Guidelines for Good Clinical Trial Practice in Zimbabwe Revision 1_ June 2020
6.4 ICH E6R (2) GCP, ICHE8, ICHE9, ICHE2A to E2F guidelines and other applicable ICH guidelines for pharmaceutical development of a medical product.
6.5 Mak, T. K. *et al.* (2020) 'Global regulatory agility during covid-19 and other health emergencies', *BMJ*. British Medical Journal Publishing Group, 369, p. m1575. doi: 10.1136/bmj.m1575.
6.6 WHO Media release: African regulatory agencies, ethics committees to expedite COVID-19 clinical trial reviews accessible on https://www.afro.who.int/health-topics/immunization/avaref
6.7 AVAREF Guideline for Joint and Assisted Reviews of Clinical Trial Applications for National Regulatory Authorities (NRAs) and Ethics Committees (EC)
6.8 Health Canada - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals, File 08-134763-687
6.9 Appendix 1: MC10 New Clinical Trial Application Form
6.10 Appendix 2: Checklist For Completeness Of An Application To Conduct A Clinical Trial
6.11 Appendix 3: Recommended Format For CV's Of Individuals Participating In Clinical Trials
6.12 Appendix 4: Submission Declaration by Principal Investigator
6.13 Appendix 5: Joint Declaration By Sponsor And Principal Investigator Concerning Sufficient Funds To Complete Study
6.14 Appendix 6: Declaration By Principal Investigator For GCP Compliance
6.15 Appendix 7: Declaration By Co- And Sub-Investigators For GCP Compliance

7.0 HISTORY

<table>
<tr><th colspan="3">DOCUMENT HISTORY</th></tr>
<tr><td>Revision Number</td><td>Date Approved</td><td rowspan="2">Date Reviewed:

Reason for Change and Amendments
Continuous improvement to comply with current best practices

The following changes/amendments were done from Revision 0 to Revision 1

Section 1.0 changed from “This is an application guideline for all those who wish to conduct clinical trials in human participants.” to “This is an application guideline for all those who wish to conduct clinical trials of a medicine in human participants in Zimbabwe in line with Section 17(1) of the Medicines and Allied Substances Control Act (MASCA) Chapter 15:03. When assessing if a study falls under the definition of a clinical trial requiring authorization from MCAZ, the following questions should be considered:
1.1. Is your study a clinical trial of medicinal products?
1.2. Is the study objective to study the therapeutic, diagnostic or preventive effect of one or more medicinal products?
1.3. Is the study objective to identify or investigate adverse reactions from one or more medicinal products?
1.4. Is the study objective to study the pharmacological effect (pharmacodynamics) of one or more medicinal products?
1.5. Is the study objective to study the absorption, distribution, metabolism or excretion (pharmacokinetics) of one or more medicinal products?
If the answer is yes to either of the questions above, then the study falls under the definition of a clinical trial requiring written authorization by MCAZ”

Section 2.0 changed from “The Medicines Control Authority of Zimbabwe has updated the application guidelines for clinical trials authorization in Zimbabwe in line with the Medicines Allied Substance Control Act (MASCA) Chapter 15:03 and Statutory Instrument (SI 150) and other local and international requirements. To achieve compliance, this guideline should be used in conjunction with the Guidelines for Good Clinical Practice in Zimbabwe; Version 1, June 2020” to “The Medicines Control Authority of Zimbabwe has updated the application guidelines for clinical trials authorization in Zimbabwe in line with the Medicines Allied Substance Control Act (MASCA) Chapter 15:03</td></tr>
<tr><td>0</td><td>July 2021</td></tr>
</table>

		and Statutory Instrument (SI 150) and other local and international requirements. To achieve compliance, this guideline should be used in conjunction with the Guidelines for Good Clinical Practice in Zimbabwe: **Changed from "**5.1 Documentation for clinical trial application" **to** "5.1 Pre-submission Meetings/Enquiries for Clinical Trial Applications" **Changed from** "5.1.1 Study Protocol" **to** "5.2.1 Study Protocol" **Changed from** "5.1.2 Trial objectives and purpose" **to** "5.2.1.3 Trial objectives and purpose" **Changed from** "5.1.3 Treatment of study participants" **to** "5.2.1.5 Treatment of study participants" **Changed from** "5.1.4 Assessment of Efficacy" **to** " 5.2.1.6 Assessment of Efficacy" **Changed from "**5.1.5 Safety" **to** "5.2.1.7 Safety" **Changed from** "5.1.6 Statistics" **to** "5.2.1.8 Statistics" **Changed from "**5.1.7 Direct Access to Source Data/Documents" **to** "5.2.1.9 Direct Access to Source Data/Documents" **Changed from** "5.1.8 Quality Control and Quality Assurance" **to** " 5.2.1.10 Quality Control and Quality Assurance" **Changed from** "5.2 Investigator's Brochure" **to** "5.2.2 Investigator's Brochure" **Changed from** "5.3 Clinical Trial Pharmacy Protocol (Pharmacy Plan)" **to** "5.2.3 Clinical Trial Pharmacy Protocol (Pharmacy Plan)" **Added "Section 5.2.5**: Ethics approval and other relevant regulatory approvals: Parallel clinical trial applications to all regulators in Zimbabwe are encouraged to minimize the timelines for clinical trial approvals. Research involving humans should satisfy the ethical standards and any other applicable internationally recognized ethics guidelines. Ethical approval to

		conduct a clinical trial in humans should be sought from the Medical Research Council of Zimbabwe (MRCZ). MRCZ approval, or proof of submission of an application for MRCZ approval in case of parallel submission should be submitted. For clinical trials involving biological products approvals or proof of application to the local National Biotechnology Authority is required. The National Biotechnology Authority (NBA) of Zimbabwe is responsible for clearance of recombinant DNA products and issues Trial Release Permits and Facility Registration for clinical trials involving biological products. The Research Council of Zimbabwe (RCZ) is mandated to register foreign researchers in terms of Section 27 of the Research Act [Chapter 10:22]. A foreign researcher is a non-Zimbabwean national and any person wishing to conduct research in Zimbabwe on behalf of a foreign institution, foreign organization or other foreign person. Authorization of foreign researchers should be obtained from Research Council of Zimbabwe (RCZ). If a researcher intends to transfer or export samples abroad for research purposes, they are required to obtain approval from RCZ to export the bio-specimens and/or materials." **Added "Section 5.2.6** Proof of Provision of Data Safety Monitoring Board / Data Monitoring Committee/ Safety Monitoring Committee (DSMB/DMC/SMC): Clinical trials are required to set up a DSMB/DMC/SMC for their studies. The sponsor shall appoint members of a DSMB/DMC/SMC by considering selection of individuals with relevant expertise (such statisticians, clinicians etc , experience in clinical trials and in serving on other DSMB/DMC/SMCs, and absence of serious conflicts of interest. The Principal Investigator shall submit a DSMB/DMC charter with information on the aims and objectives of the DSMB/DMC, the composition of the DSMB/DMC/SMC, names of the chairperson and members and how meetings will be organized." **Added "Section 5.2.7 Monitoring Plan:** Monitoring should be provided. The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. 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 emphasize 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." **Added** "5.2.9 Recruitment Advertisements (if applicable): Any recruitment materials such as leaflets, brochures, posters, banners or advertisements flighted through televisions, radio programs, newspapers and any other media should be provided for approval by the MCAZ and ethics committees prior to distribution and must follow existing local rules and regulations." **Added "5.2.10** Patient information leaflet(s) and informed consent forms: Version controlled and dated English and Vernacular Informed consent forms should be provided with the clinical trial application. The Informed Consent Forms should be in line with MRCZ Guidelines and templates" **Added "5.2.11** Pharmaceutical Dossier for new Investigational Medicinal Products**:** This requirement applies to Phase I, II and III clinical trials which involve new Investigational Medicinal Products. For clinical trials using well established Investigational Medicinal Products that have been registered and marketed in Zimbabwe or reference stringent regulatory authorities an updated Investigator's brochure or SMPC or package insert and prescribing information will suffice. The amount and depth of information that would be submitted to MCAZ depends on the clinical trial phase, novelty of the medicine, dosage form/route of administration and the known / suspected risks. For combination protocols (e.g. Phase I/II or II/III protocols), applicants should submit Quality data according to the requirements of the highest phase." **Added "5.2.11.1** Quality Data - Module 3: This module should provide details on the chemistry, manufacturing and control of the Investigational Medical Product. Information on quality should be presented in the structured format as described in ICH M4Q. Supporting data to demonstrate quality of the investigational product, including relevant batch analyses results should be attached. If the comparator medicinal product is modified in any

		way in order to blind the trial (e.g., grinding of tablets, encapsulation of tablets), results of an in vitro study (e.g., comparative dissolution profiles for solid dosage forms) comparing the unchanged and the modified product should also be submitted. For sterile products that are repackaged for blinding purposes, it should be demonstrated that sterility is maintained i. 3.2.S Active Pharmaceutical Ingredient (API) ….. 3.2.S 1 General Information 3.2.S 1.1 Nomenclature 3.2.S 1.2 Structure 3.2.S 1.3 General Properties 3.2.S 2 Manufacture 3.2.S 2.1 Manufacturer(s) 3.2.S 2.2 Description of Manufacturing Process and Process Controls 3.2.S 2.3 Control of Materials 3.2.S 2.4 Controls of Critical Steps and Intermediates 3.2.S 3 Characterisation 3.2.S 3.1 Elucidation of Structure and other Characteristics 3.2.S 3.2 Impurities 3.2.S 4 Control of the Drug Substance 3.2.S 4.1 Specification 3.2.S 4.2 Analytical Procedures 3.2.S 4.3 Validation of Analytical Procedures 3.2.S 4.4 Batch Analyses 3.2.S 4.5 Justification of Specification 3.2.S.6 Container Closure System 3.2.S.7 Stability 3.2.S.7.1 Stability Summary and Conclusions 3.2.S.7.2 Stability Protocol and Stability Commitment 3.2.S7.3 Stability Data ii. 3.2.P Drug product (or finished pharmaceutical product….. 3.2.P. 1 Description and Composition of the Drug Product 3.2.P.2 Pharmaceutical Development 3.2.P.3 Manufacture 3.2.P.3.1 Manufacturer(s) 3.2.P.3.2 Batch Formula 3.2.P 3.3 Description of Manufacturing Process and Process Controls 3.2.P 3.4 Controls of Critical Steps and Intermediates

3.2.P 4 Control of Excipients
3.2.P 4.1 Specifications
3.2.P 4.5 Excipients of Human or Animal Origin
3.2.P 4.6 Novel Excipients
3.2.P 5 Control of Drug Product
3.2.P 5.1 Specification(s)
3.2.P 5.2 Analytical Procedures
3.2.P 5.3 Validation of Analytical Procedures
3.2.P 5.4 Batch Analyses
3.2.P 5.5 Characterisation of Impurities
3.2.P 5.6 Justification of Specification(s)
3.2.P 7 Container Closure System
3.2.P 8 Stability
3.2.P 8.1 Stability Summary and Conclusions
3.2.P 8.2 Stability Protocol and Stability Commitment
3.2.P 8.3 Stability Data**"**

Added Section "5.2.11.2 Non Clinical Study Reports – Module 4: The goals of the pre-clinical /nonclinical safety evaluation generally include a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. The information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterize potential adverse effects that might occur under the conditions of the clinical trial to be supported. Applicants are required to conduct pre-clinical studies according to the ICH guidance document M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and guidelines of the Organisation for Economic Cooperation and Development (OECD). For biotechnology-derived products the applicants should follow ICH S6 guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals. The Nonclinical Study Reports should be presented in the order described in the guidance M4S. In accordance with ICH Guideline M3 the following are the minimum requirements per clinical trial application phase:

Clinical Trial Phase	**Minimum Required Data**

		<table><tr><td>Phase 1</td><td>Repeated dose toxicity (2 Weeks) Safety Pharmacology Local tolerance Genotoxicity *in vitro* Male reproductive organs</td></tr><tr><td>Phase 2</td><td>Repeated dose toxicity (2 weeks to 6 months) Genotoxicity *in vivo*</td></tr><tr><td>Phase 3</td><td>Repeated dose toxicity (1 month – chronic) Reprotoxicity (Male and Female fertility, Embryofetal, Peri-post natal) Absorption, Distribution Metabolism and excretion</td></tr></table> The data that is submitted to MCAZ from non-clinical safety studies should have originated in studies that have been conducted in compliance with the Principles of GLP. Laboratories that perform safety pharmacology and toxicology studies are required to have worked under the conditions of GLP. The applicant shall be required to submit evidence of GLP via a declaration letter signed by the director of the research facility testifying to have conducted the studies as per GLP compliance for each study, and the quality assurance (QA) statement must list all QA activities and confirm that the study report reflects the raw data. The test facility itself should be part of a national compliance monitoring programme at the country of origin and be listed as a compliant facility. If this latter prerequisite cannot be complied with because of lack of a national compliance monitoring programme then applicant shall communicate this in writing. This module is applicable to new Investigational products only. For products that have already been registered and marketed, an updated investigator's brochure is sufficient." **Added** "5.2.11.3 Clinical Study Reports - Module 5: Clinical study reports will be required for clinical trial applications which are not for first in human (FIH) studies. The reports provide details on clinical experience in humans regarding the investigational product." **Added "5.2.12 A**dditional attachments and requirements: Any other relevant attachments such as GCP certificates and CV/Resume's must be submitted with the application in line with

		the clinical trial application checklist. With regards to the capacity of the clinical trial site, all clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and any potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed. The Principal investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through up to date Curriculum Vitae. The Investigator should be licensed under the Health Professions Act (Chapter 27.19). The Principal Investigator should ensure that he or she has sufficient time to conduct and complete the trial within the agreed time period, and that any other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand." **Changed from** "5.4 Participant Insurance for trial related injuries" **to** "5.2.4 Participant Insurance for trial related injuries" **Changed from** "5.5 Additional Attachments" **to** "5.2.12 Additional attachments and requirements" **Changed from** "5.6 Application Review Process" **to** "5.3 Application Review Process" **Changed from** "5.7 Reliance model" **to** "5.5 Reliance model" **Changed from** "5.8 Post-clinical trial authorization monitoring requirements" to "5.6 Post-clinical trial authorization monitoring requirements" **Changed from** "5.9 Reporting of Clinical Trial Safety Reports to MCAZ (AEs, ADRs SAEs and/or AEFIs), product defects, DSMB/DMC reports, and/or protocol deviations/violations" **to** "5.6.2 Reporting of Clinical Trial Safety Reports to MCAZ (AEs,

		ADRs SAEs and/or AEFIs), product defects, DSMB/DMC reports, and/or protocol deviations/violations" **Changed from** "5.10 Annual Progress Reports" **to** "5.6.3 Annual Progress Reports **Changed from** "5.11 The Final Report" **to** "5.6.4 The Final Report" **Changed from** "5.12 Importation, Management and Destruction of Investigational Products" **to** "5.6.5 Importation, Management and Destruction of Investigational Products" **Changed from** "5.13 Clinical Trial application process and importation of study medical products during public health Emergency" **to** "5.6.6 Clinical Trial application process and importation of study medical products during public health Emergency" **Changed from** "5.14 Good Clinical Practice (GCP) inspections" **to** "5.6.7 Good Clinical Practice (GCP) inspections" **Changed from** "5.15 Safety Notifications" **to** "5.6.8 Safety Notifications" **Changed from** "5.16 Uploading approved clinical trial application on the Clinical Trials Registry platform" **to** "5.6.9 Uploading approved clinical trial application on the Clinical Trials Registry platform"

APPENDICES

Appendix 1: MC 10 Form

CONFIDENTIAL MEDICINES CONTROL AUTHORITY

MEDICINES AND ALLIED SUBSTANCES CONTROL ACT [CHAPTER 15:03]

APPLICATION FOR AUTHORIZATION TO CONDUCT A CLINICAL TRIAL

(To be submitted in triplicate)

1. Particulars of applicant

If an individual: Full names ……

Date and place of birth ……

Qualifications ……..

Address (Home) ……..

(Business) ……...

If a company: Name of company ……..

Physical address ……..

. ……..

Registered office ……

Postal address ……

Telephone number ……...

Position of person in the company who is making the application on behalf of the company

……...

State the main field of manufacture of the company, if applicable .....……..

……

2. State the name of the medicine, its chemical composition, graphic and empirical formulae, animal pharmacology, toxicity and teratology as well as any clinical or field trials in humans or animals, or any other relevant information and supply reports, if any

……...

3. State any adverse or possible reactions to the medicine ……...

4. State therapeutic effects of the medicine ……

5. (a) Has the medicine been registered in the country of origin? YES/NO* If YES a valid certificate of registration in respect of such medicine issued by the appropriate authority established for the registration of medicines in the country of origin shall accompany this application.

If NO state details ……

(b) Have clinical trials been conducted in the country of origin? YES/NO*

If YES state details ……

If NO give reasons why ……

……...

(c) Has an application for the registration of the medicine been made in any other country? YES/NO* If YES state details including the date on which the application was lodged

……....

(d) Has the medicine been registered in any other country? YES/NO*

If YES state details ……..

(e) Has the registration of the medicine been rejected, or refused, deferred or cancelled in any country? YES/NO*

If YES. state details …… ……..

(f) What is the status of the medicine in Zimbabwe?

	Tick (√) whichever is appropriate
Registered	
Unregistered	
Application for registration has been submitted	

6. State the name(s), address(es) and telephone numbers) and qualifications of the person(s) who will conduct the trial

……

Name	Qualifications	Address and telephone number (Business)	Address and telephone number (Home)
…….	…….	…….	……...
…….	…….	…….	……...
…….	…….	…….	……...

7. State the name, physical address and telephone number of the institution or the places where the trial will be conducted

……..……..

8. State the purpose of the trial and the reasons therefor

……

9. State the time period for the trial ……..

10. Description of the type of trial (e.g. controlled, open) trial design (e.g. parallel groups, crossover technique), blind technique (e.g double blind, simple blind) randomisation (e.g. method and procedure) or any other type of trial

…….

11. Description of participants (e.g. age group of persons or animals, type or class of persons or animals, sex, etc.)

…… ……

12. Criteria for inclusion or exclusion of participants ……

……

13. Number of participants expected to take part in the trial and a justification thereof (e.g. based on statistical considerations)

……...

14. Administration route, dosage, dosage interval and period for the medicine being tested and the medicine being used as a control

……...

15. Control groups (placebo, other therapy, etc.) ……...

……...

16.(a) State whether any other medicine will be given concomitantly. YES/NO*

If YES, state the name of the medicine …….

(b) State whether a person already on another medicine will be given the experimental medicine at the same time or whether the participant will be taken off the other medicine.

……..

17.Recording of effects: give a description of the methods of recordings and times of recordings

……..

……..

18. State clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out

…… ……

……..

19. State the method of recording adverse reactions and provisions for dealing with same and other complications

…… .

……..

20. State antidote ……

21. State the procedure for the keeping of participant lists and participant records for each participant taking part in the trial +

……

……..

22. State where the trial code will be kept and how it can be broken in the event of an emergency …… ……

……..

23. State the measures to be implemented to ensure the safe handling of medicines and to promote and control compliances with the prescribed instructions

……..

……..

24. Evaluation of results, state the description of methodology (e.g. statistical methods)

……..

25. State how the persons or owners of animals are to be informed about the trial ……...

……..

26. State how the staff involved are to be informed about the way the trial is to be conducted and about the procedures for medicine usage and administration and what to do in an emergency ……

……..

27. State whether there are any ethical or moral considerations relating to the trial, giving details

……..

……..

28. State the name and address of the company who will insure all the participants in the proposed trial ++

……..

……..

29. State the amount of insurance in respect of each participant ……...

……..

30. State the quantity of the medicine for which exemption is required if the medicine is not registered

……..

31. Particulars of persons who will take part in the clinical trial+++

……..

Name	**Occupation**	**Adress**	**Date and place of birth**

1. …….. …….. …… ……..

2. …….. …….. …… ……..

3. …….. …….. …… ……..

32. Particulars of animals that will take part in the clinical trial.

Kind and breed of animal ……..

……

Age of animal, if known ……..
Name and addresses of owners of animals.

Name **Address**

1. …….. ……..

2. …….. ……..

33. Attached is a sample of the medicine, together with methods of analysis and storage conditions.

Date …….. ……

Signature of applicant

Countersignature of medical superintendent or senior medical officer if the clinical trial is to be conducted in a hospital or a medical institution.++++

Date …… …….

Notes

**Delete the inapplicable*
+, item 21: Records should permit easy identification of individual participants.
++, item 28: A letter from the insurance company shall be attached to the application indicating the insurance company's consent to the propose insurance and a copy of the proposed insurance policy.
+++, item 31: The consent of each person or the guardian of such person who will participate in the trial is required to be attached to the application Form M.C. 17.
The consent of each owner of an animal which will participate in the trial is required to be attached to the application in Form M.C. 18.
++++, This item should be countersigned by a veterinary surgeon if the trial is to be conducted in a veterinary hospital.

FOR OFFICIAL USE ONLY

1.Director General's comments on the application ……..

…… ……..

2. Authority's comments on the application ……

3. Application approved/disapproved by the Secretary.

Comments ……

……..

Date …… …….

Secretary for Health

Appendix 2: Checklist For Completeness Of An Application To Conduct A Clinical Trial

MCAZ Medicines Control Authority of Zimbabwe

PVF 06

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

CHECKLIST FOR COMPLETENESS OF AN APPLICATION TO CONDUCT A CLINICAL TRIAL

☐ **Clinical Trial Application Ref. no……Received Date……..**

- ☐ Covering letter
- ☐ Application fee
- ☐ Fully completed application MC 10 form in triplicate
- ☐ Protocol (Including relevant questionnaires, etc.)
- ☐ Patient information leaflet(s) and informed consent(s) including vernacular versions and English back translations
- ☐ Investigators brochure and/or all package insert(s)
- ☐ Investigator's CV(s) in required format
- ☐ Signed declaration(s) by investigator(s) to comply with GCP
- ☐ CV(s) and signed declaration(s) by study coordinator and/or monitor
- ☐ Monitoring plan by sponsor/PI/monitor throughout study
- ☐ Signed Declaration by sponsor and national PI to comply with GCP
- ☐ Signed financial declaration by sponsor and national PI for study sponsorship
- ☐ Pharmacy plan for local trial site
- ☐ MCAZ Pharmacy license (where applicable)
- ☐ Details of study medicines and concomitant medicines including GMP certificates
- ☐ Proof of participants' insurance certificate and if necessary:
- ☐ Letter endorsing generic insurance certificate
- ☐ Ethics approval, in country of origin and local MRCZ approval, or copy of letter applying for ethics committee approval
- ☐ Proof of approval of study by the National Regulatory Authority in country of origin
- ☐ Copy/ies of recruitment advertisement(s) (if applicable)
- ☐ Electronic versions of the application form + protocol on CD or flash disk
- ☐ Proof of Provision of Data Safety Monitoring Board (DSMB/DMC) Committee
- ☐ Proof of application to the local Bio Safety Board for biological products e.g. vaccines
- ☐ Pharmaceutical dossier for a new investigational drug (NID) product including stability data generated from 3 batches to support the shelf life claim and storage conditions. **N.B:** If study products are generic products not yet registered and specifically manufactured as 'trial batches' for the study then a pharmaceutical dossier is also required

Comments/Action plan……
……
……
……

Officer: ……..**Signature**…… **Date**……..

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Appendix 3: Recommended Format For CV's Of Individuals Participating In Clinical Trials

MCAZ Medicines Control Authority of Zimbabwe

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PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

RECOMMENDED FORMAT FOR CV'S OF INDIVIDUALS PARTICIPATING IN CLINICAL TRIALS

1. **Study Title:**
   _____
   _____
   _____
2. **Protocol Number:** _____
3. **Designation:** _____
   [e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Coordinator, Regional Monitor, Local Monitor, Clinical Research Associate]
4. **Personal Details:**

   Name: _____
   Work Address: _____
   Telephone Number: _____ Fax Number: _____
   Cell 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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Appendix 4: Submission Declaration by Principal Investigator

Medicines Control Authority of Zimbabwe

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PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

SUBMISSION DECLARATION FORM

DECLARATION BY APPLICANT

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

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

I/We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and all applicable legal, ethical and regulatory requirements.

Name	Signature	Date

Name	Signature	Date

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Appendix 5: Joint Declaration By Sponsor And Principal Investigator Concerning Sufficient Funds To Complete Study

Medicines Control Authority of Zimbabwe

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PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

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

(Name)

(Address)

(Contact details)

_____ _____

Signed Date

PRINCIPAL INVESTIGATOR

(Name)

(Address)

(Contact details)

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Appendix 6: Declaration By Principal Investigator For GCP Compliance

MCAZ Medicines Control Authority of Zimbabwe

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PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

DECLARATION BY PRINCIPAL INVESTIGATOR FOR GCP COMPLIANCE

Name: _____

Title of Trial:

_____

_____

_____

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 MCAZ 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 MCAZ 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.

Signature: _____ Date: _____

Witness: _____ Date: _____

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Appendix 7: Declaration By Co- And Sub-Investigators For GCP Compliance

Medicines Control Authority of Zimbabwe

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PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

DECLARATION BY CO- AND SUB-INVESTIGATORS FOR GCP COMPLIANCE

Name: _____

Title of Trial:

_____

_____

_____

Principal Investigator's Name: _____

Site: _____

Designation: _____

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 MCAZ 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.

Signature: _____ Date: _____

Witness: _____ Date: _____

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