MCAZ Medicines Control Authority of Zimbabwe

106 Baines Avenue
Tel: +263-4-736981-7
708255/792165, 0772 145 191/2/3
Email: mcaz@mcaz.co.zw
Website: www.mcaz.co.zw

P.O. Box 10559
Harare
Zimbabwe

REF: B/279/35/11/2022

CIRCULAR 11 of 2022

Date: 11th May 2022

To: All clinical trial applicants, pharmaceutical industry, clinical trial sponsors and researchers

RE: Revised MCAZ clinical trial guidelines in line with the Medicines and Allied Substance Control Act [*Chapter 15:*03], current Good Clinical Trial Practice (GCP) requirements including the revised clinical trial authorization certificate

In line with the Medicines and Allied Substance Control Act (MASCA) [Chapter 15:03] and current good regulatory practices, the Medicines Control Authority of Zimbabwe has revised guidelines and updated the clinical trial authorization certificate as listed in Table 1 below.

Table 1: List of clinical trial guidelines and certificate of authorization for clinical trial application

Document Title	Reference Number	Current Approved Version (as at 20/4/2022)	Effective Date	Summary of Changes
Guidelines for Good Clinical Trial Practice in Zimbabwe	MCAZ/PVCT/ GL-04	Revision 2_February 2022	25 February 2022	Refer to Annex 1
Guidelines for Clinical Trial Application and Authorization in Zimbabwe	MCAZ/PVCT/ GL-05	Revision 1_February 2022	4 March 2022	Refer to Annex 2
Guidelines for Conducting Good Clinical Practice (GCP) Inspections in Zimbabwe	MCAZ/PVCT/ GL-01	Revision 0_May 2021	7 May 2021	Not applicable
Pharmacy Guidelines for Investigational Medicinal Products		Revision 1_June 2020	10 June 2020	Not applicable
MCAZ Form MC19 - Clinical Trial Authorization Certificate	Form MC 19	Form MC 19	25 February 2022	Updated template in line with section 44 of the Medicines and Allied Substance Control (General) Regulations and inclusion of a validity period

You are required to familiarize and comply with all these guidelines in line with the effective dates of the approved guidelines as well as all applicable legislation, including the Medicines and Allied Substance Control Act (MASCA) [Chapter 15:03]. The guidelines are accessible on the MCAZ website via the following URL: https://www.mcaz.co.zw/documents/pharmacoviligence-n-clinical-trials-docs/guidelines/

Please note that if expedited clinical trial application evaluation for authorization is required, you are required to submit the clinical trial application on the electronic Clinical Trials Registry (e-CTR) system accessible on the following URL: https://e-ctr.mcaz.co.zw/ by the 15th of every month for consideration at the next Pharmacovigilance and Clinical Trials Committee Meeting, which is routinely held every first week of the month. Applications submitted after the date will be processed in meetings to come.

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

.....

R. T. Rukwata (Mr)
ACTING DIRECTOR-GENERAL

Guidelines for Clinical Trial Practice in Zimbabwe Summary of Changes from Revision 1 _July 2021 to Revision 2_February 2022		
Revision Number	Date Approved	
2	25 February 2022	**Date Reviewed**: February 2022 **Reason for Change and Amendments** Continuous improvement in line with current WHO GBT indicators The following changes/amendments were done from **Revision 1** to **Revision 2**
		1.0 APPLICATION **Changed from** This is revision 1 of May 2020 of the Good Clinical Trial Practice guidelines for use by all those who wish to conduct clinical trials in Zimbabwe. **Changed to** This Good Clinical Trial Practice guidelines for use by all those who wish to conduct clinical trials in Zimbabwe.
		3.0 BACKGROUND AND INTRODUCTION **Changed from** ……. This timeline **excludes** clock stops when the applicant is addressing the queries raised. For clinical trial application for emergency preparedness however if complete information is submitted, the approval trial may be reduced to 15-30 working-days. We encourage all applicants to submit complete applications and address queries raised promptly with MCAZ of the application **Changed to** ……. This timeline **excludes** clock stops when the applicant is addressing the queries raised. 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. We encourage all applicants to submit complete applications and address queries raised promptly.
		5.0 GUIDELINES **5.15 Changed from** 5.15 …… authorization of foreign researchers and/or importation of Specimen Transfer Agreement (STA) must be obtained from Research Council of Zimbabwe (RCZ). The National Biotechnology Authority (NBA) is responsible for clearance of some genetically modified organisms (GMOs). **5.15 Changed to**

		5.15…… authorization of foreign researchers and/or importation of Storage Transfer Agreement (STA) must be obtained from Research Council of Zimbabwe (RCZ). For clinical trials involving biological products, proof of application to the National Biotechnology Authority local Bio Safety Board 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.
		Section 5.2.5 was deleted
		Section 5.3.4 was deleted
		5.10.1 Changed from Clinical trial investigational medicinal products must be manufactured in accordance with Good Manufacturing Practices (cGMP) including Good Manufacturing Practice for Investigational Medicinal Products. This implies that the manufacture of the investigational product may be participant to control and inspection in the same way as in the case of marketed medicinal products. **5.10.1 Changed to** Clinical trial investigational medicinal products must be manufactured in accordance with current Good Manufacturing Practices (cGMP). This implies that the manufacture of the investigational medicinal product is subject to control and inspection in the same way as in the case of marketed medicinal products.
		5.10.3 Changed from Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner. and should include the following: 5.10.3.1 Drug Substance: ii. Names and Source iii. Method of Manufacture iv. Physicochemical Properties and Structure Elucidation v. Impurities vi. Specifications and Test Methods and Batch Analyses vii. Stability and Packaging 5.10.3.2 Dosage Form: ix. Source x. Developmental Pharmaceutics xi. Formulation and Method of Manufacture and Packaging xii. Specifications and Test Methods and Batch Analyses xiii. Stability

		5.10.3 Changed to Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner. Information on the specific requirements for the chemistry and manufacturing information is found in the Guidelines for Clinical Trial Application and Authorization in Zimbabwe.
		5.10.8 Changed from The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP). NB. Trialists may apply for exemption from some of the requirements of this section provided that such exemption shall be provided in writing by the MCAZ **5.10.8 Changed to** The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP).
		5.10.12 Changed from Expired investigational products should not be used and should be destroyed in line with guidelines for destruction of medical products and destruction certificate submitted to MCAZ**.** **5.10.12 Changed to** Expired investigational products should not be used and authorization for destruction of the products should be sought from the Authority. The investigational products should be destroyed in line with guidelines for destruction of medical products and destruction certificate submitted to MCAZ.
		5.13.1.17 Changed from ….. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. **5.13.1.17 Changed to** ….. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. 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 and should be GLP certified.
		5.14.1 Changed from The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC . The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

		5.14.1 Changed to The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor, MCAZ, IRB/IEC (MRCZ) and other applicable regulatory authorities.
		5.14.5 was deleted
		5.17.Changed from **Annual Renewal of Authorized Clinical Trials** The Principal Investigator is responsible for submitting the application for annual renewal to the MCAZ office in a timely manner. Submission of annual renewal will assist the authority in monitoring on-going clinical trials for participant safety and the quality of the medicines in the study**.** **5.17. Changed to** **Renewals of Authorized Clinical Trials** The validity period of each clinical trial shall be stated on the MCAZ clinical trial authorisation communication sent to the PI. Applications for clinical trials renewals should be submitted to MCAZ for approval if the PI 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.
		5.22.5.1 Changed from Reporting on the conduct of the trial shall conform to provisions mentioned above in this guideline. Monthly reports shall however be submitted to the Authority in the prescribed format. **5.22.5.1 Changed to** Reporting on the conduct of the trial shall conform to provisions mentioned above in this guideline.

<table>
<tr><th colspan="3">Guidelines for Clinical Trial Application and Authorization in Zimbabwe Summary of Changes from Revision 0 _July 2021 to Revision 1_February 2022</th></tr>
<tr><td>Revision Number</td><td>Date Approved</td><td rowspan="5">Date Reviewed: February 2022

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”</td></tr>
<tr><td rowspan="4">1</td><td rowspan="4">4 March 2022</td></tr>
<tr><td>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 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:</td></tr>
<tr><td>Changed from “5.1 Documentation for clinical trial application” to “5.1 Pre-submission Meetings/Enquiries for Clinical Trial Applications”</td></tr>
<tr><td>Changed from “5.1.1 Study Protocol” to “5.2.1 Study Protocol”</td></tr>
</table>

		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**
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." **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"

Guidelines for Clinical Trial Practice in Zimbabwe Summary of Changes from Revision 1 _July 2021 to Revision 2_February 2022		
Revision Number	Date Approved	
2	25 February 2022	**Date Reviewed**: February 2022 **Reason for Change and Amendments** Continuous improvement in line with current WHO GBT indicators The following changes/amendments were done from **Revision 1** to **Revision 2**
		1.0 APPLICATION **Changed from** This is revision 1 of May 2020 of the Good Clinical Trial Practice guidelines for use by all those who wish to conduct clinical trials in Zimbabwe. **Changed to** This Good Clinical Trial Practice guidelines for use by all those who wish to conduct clinical trials in Zimbabwe.
		3.0 BACKGROUND AND INTRODUCTION **Changed from** ……. This timeline **excludes** clock stops when the applicant is addressing the queries raised. For clinical trial application for emergency preparedness however if complete information is submitted, the approval trial may be reduced to 15-30 working-days. We encourage all applicants to submit complete applications and address queries raised promptly with MCAZ of the application **Changed to** ……. This timeline **excludes** clock stops when the applicant is addressing the queries raised. 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. We encourage all applicants to submit complete applications and address queries raised promptly.
		5.0 GUIDELINES **5.15 Changed from** 5.15 …… authorization of foreign researchers and/or importation of Specimen Transfer Agreement (STA) must be obtained from Research Council of Zimbabwe (RCZ). The National Biotechnology Authority (NBA) is responsible for clearance of some genetically modified organisms (GMOs). **5.15 Changed to**

		5.15…… authorization of foreign researchers and/or importation of Storage Transfer Agreement (STA) must be obtained from Research Council of Zimbabwe (RCZ). For clinical trials involving biological products, proof of application to the National Biotechnology Authority local Bio Safety Board 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.
		Section 5.2.5 was deleted
		Section 5.3.4 was deleted
		5.10.1 Changed from Clinical trial investigational medicinal products must be manufactured in accordance with Good Manufacturing Practices (cGMP) including Good Manufacturing Practice for Investigational Medicinal Products. This implies that the manufacture of the investigational product may be participant to control and inspection in the same way as in the case of marketed medicinal products. **5.10.1 Changed to** Clinical trial investigational medicinal products must be manufactured in accordance with current Good Manufacturing Practices (cGMP). This implies that the manufacture of the investigational medicinal product is subject to control and inspection in the same way as in the case of marketed medicinal products.
		5.10.3 Changed from Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner. and should include the following: 5.10.3.1 Drug Substance: ii. Names and Source iii. Method of Manufacture iv. Physicochemical Properties and Structure Elucidation v. Impurities vi. Specifications and Test Methods and Batch Analyses vii. Stability and Packaging 5.10.3.2 Dosage Form: ix. Source x. Developmental Pharmaceutics xi. Formulation and Method of Manufacture and Packaging xii. Specifications and Test Methods and Batch Analyses xiii. Stability

		5.10.3 Changed to Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner. Information on the specific requirements for the chemistry and manufacturing information is found in the Guidelines for Clinical Trial Application and Authorization in Zimbabwe.
		5.10.8 Changed from The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP). NB. Trialists may apply for exemption from some of the requirements of this section provided that such exemption shall be provided in writing by the MCAZ **5.10.8 Changed to** The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP).
		5.10.12 Changed from Expired investigational products should not be used and should be destroyed in line with guidelines for destruction of medical products and destruction certificate submitted to MCAZ**.** **5.10.12 Changed to** Expired investigational products should not be used and authorization for destruction of the products should be sought from the Authority. The investigational products should be destroyed in line with guidelines for destruction of medical products and destruction certificate submitted to MCAZ.
		5.13.1.17 Changed from ….. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. **5.13.1.17 Changed to** ….. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. 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 and should be GLP certified.
		5.14.1 Changed from The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC . The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

		5.14.1 Changed to The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor, MCAZ, IRB/IEC (MRCZ) and other applicable regulatory authorities.
		5.14.5 was deleted
		5.17.Changed from **Annual Renewal of Authorized Clinical Trials** The Principal Investigator is responsible for submitting the application for annual renewal to the MCAZ office in a timely manner. Submission of annual renewal will assist the authority in monitoring on-going clinical trials for participant safety and the quality of the medicines in the study**.** **5.17. Changed to** **Renewals of Authorized Clinical Trials** The validity period of each clinical trial shall be stated on the MCAZ clinical trial authorisation communication sent to the PI. Applications for clinical trials renewals should be submitted to MCAZ for approval if the PI 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.
		5.22.5.1 Changed from Reporting on the conduct of the trial shall conform to provisions mentioned above in this guideline. Monthly reports shall however be submitted to the Authority in the prescribed format. **5.22.5.1 Changed to** Reporting on the conduct of the trial shall conform to provisions mentioned above in this guideline.

<table>
<tr><th colspan="3">Guidelines for Clinical Trial Application and Authorization in Zimbabwe Summary of Changes from Revision 0 _July 2021 to Revision 1_February 2022</th></tr>
<tr><td>Revision Number</td><td>Date Approved</td><td rowspan="5">Date Reviewed: February 2022

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”</td></tr>
<tr><td rowspan="4">1</td><td rowspan="4">4 March 2022</td></tr>
<tr><td>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 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:</td></tr>
<tr><td>Changed from “5.1 Documentation for clinical trial application” to “5.1 Pre-submission Meetings/Enquiries for Clinical Trial Applications”</td></tr>
<tr><td>Changed from “5.1.1 Study Protocol” to “5.2.1 Study Protocol”</td></tr>
</table>

		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**
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." **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"