Botswana Medicines Regulatory Authority

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Date of Approval (DD/MM//YY)

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13	Added "6.2 When to Submit an Application to Conduct a Clinical Trial"	1.0	Manager Clinical Trials and Research	Tshetsana Senau	16/01/2024

1.0 INTRODUCTION

1.1 Clinical Trials or medical research on a medicine can be defined as an investigation in humans or animals intended to:

a. Discover or verify the clinical pharmacological or pharmacodynamic effects of an investigational medicinal products or medical device.
b. Identify any adverse reaction to an investigational medicinal product or medicinal product; or
c. Study the absorption, distinction, metabolism and the excretion of an investigational medicinal product or medical device, with the object of ascertaining the safety and efficacy of the IMP or medical device, in accordance with MRSA 2013 *(Part 1)*.

1.2 The review and approval process in Botswana is expected to take up to 90 working days from the time the completed application is received by BoMRA for approval. This timeline excludes the time when the applicant is addressing the queries raised. We encourage all applicants to work in coordination with BoMRA to enable the achievement of these timelines. Clinical trials for emergency preparedness, the expedited timeline for review and approval may be reduced to 15 working days subject to early submission of a complete application.

1.3 All Clinical Trials applications submitted to BoMRA will be evaluated with the same evaluation process as per BOMRA guidelines regardless of the applicant, either local or international.

For further information refer to the Medicines and Related Substances Regulations of 2019 for fees Statutory, Botswana Good Clinical Trial Practice (GCP) Guidelines.

2.0 PURPOSE

This guideline outlines the information required by BoMRA from sponsors and applicants wishing to conduct clinical trials as well as defines the evaluation process for the conduct of clinical trials. To achieve compliance, this guideline should be used in conjunction with the Guidelines for Good Clinical Practice in Botswana BOMRA/PCT/CT/P01/G02.

3.0 SCOPE

This is an application guideline for all those who wish to conduct clinical trials in human participants in Botswana.

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 Botswana and the steps that the Authority will take to review, evaluate, and authorize the conduct of clinical trials. Applicants are recommended to approach Pharmacovigilance and Clinical Trials (PV and CT) department at BoMRA for clarification. Applicants are

required to submit their applications through Records Management Unit at BoMRA. The application fee schedule is available as Appendix 5.

4.0 LEGAL CONSIDERATIONS

These guidelines were developed in accordance with the laws, regulations, policies and guidelines governing conduct of clinical trials. This guideline does not replace nor supersede any aspect as described in any one of the Acts or the Regulations within the Acts. The laws, regulations, policies, and guidelines applied are listed below:

a) Medicines and Related Substances Act, 2013,

b) Medicines and Related Substances Regulations, 2019 Section 55(1) which states that: *The applicant shall apply to the authority in Form19 set out in Schedule 4, accompanied by a fee set out in Schedule 5.*

5.0 DEFINITIONS AND ABBREVIATIONS

5.1 Definitions

For the purpose of this guideline, the following definitions shall apply:

5.1.1 Adverse Drug Reaction (ADR): All noxious and unintended responses to a medicinal product related to any dose in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established.

5.1.2 Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational)product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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

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

5.1.5 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 incountry

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.

5.1.6 Case Report Form (CRF): A printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each trial participant.

5.1.7 Clinical Trial/Study: Any investigation in human participants 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.

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

5.1.9 Co-ordinating Investigator: An investigator assigned the responsibility for the co-ordination of investigators at different centers participating in a multicenter trial.

5.1.10 Contract Research Organization (CRO)- A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

5.1.11 Documentation- All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

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

5.1.13 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).

5.1.15 Expedited Review: 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.

5.1.16 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.

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

5.1.18 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

5.1.19 Clinical Trial Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) 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 organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

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

5.1.21 Investigator- A physician, dentist or other qualified person who conducts a clinical trial at a trial site.

5.1.22 Investigator's Brochure-A compilation of the clinical and nonclinical data on the investigational product(s)which is relevant to the study of the investigational product(s) in human participants.

5.1.23 Investigational Medicinal 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 authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

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

5.1.25 Monitor: The person responsible for ensuring that the study is performed at the agreed progression and that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

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

5.1.27 Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

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

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

5.1.30 Principal Investigator- A person responsible for the conduct of the clinical trial at a trial site who is a physician, dentist or other qualified person, resident in the country and a member of good standing of a professional council. If a trial is conducted by a team of individuals at a trial site, the principal investigator is the responsible leader of the team.

5.1.31 Protocol- A document that describes the objective(s), design, methodology, statistical considerations, and organization 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.

5.1.32 Protocol Amendment- A written description of a change(s) to or formal clarification of a protocol.

5.1.33 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.

5.1.34 Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

5.1.35 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.

5.1.36 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.

5.1.37 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.

5.1.38 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.

5.1.39 Sponsor-An individual, company, institution, or organization, which takes responsibility for the initiation, management, and/or financing of a clinical trial.

5.1.40 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.

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

5.1.42 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 participants 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.

5.2Abbreviations

5.2.1 ADR- Adverse Drug Reaction
5.2.2 AE- Adverse Event
5.2.3 BoMRA- Botswana Medicines Regulatory Authority
5.2.4 COA- Certificate of Analysis
5.2.5 CRF- Case Report Form
5.2.6 CRO- Contract Research Organisation
5.2.7 DSMB- Data Safety Monitoring Board
5.2.8 GCP- Good Clinical Practice
5.2.9 GMP- Good Manufacturing Practice
5.2.10HRDC- Health Research Development Committee
5.2.11IB- Investigation Brochure
5.2.12ICH- International Council on Harmonisation
5.2.13IDMC- Independent Data-Monitoring Committee
5.2.14IREC- Independent Research Ethics Committee
5.2.15IRB- Institutional Review Board

5.2.16MRSA- Medicines and Related Substance Act
5.2.17QA- Quality Assurance
5.2.18QC- Quality Control
5.2.19SOP- Standard Operating Procedure
5.2.20SmPC-Summary of Product Characteristics

6.0 GUIDELINE

Administrative and General Information

This section describes the application procedure for clinical trial applications.

All applications and supporting documents shall be in English. Participants information sheets and Informed Consents shall be in both English and Setswana. Submissions shall be presented in electronic format in Compact Disc (CDs). The information shall be compiled in accordance with these guidelines. Where information is required in the application forms its location shall be cross referenced in the submission.

6.0.1 Payment of fees

New clinical trial applications and amendments shall be accompanied by an application fee as prescribed in the Medicines and Related Substances Regulations of 2019 (MRSR, 2019) in force at the time of application. Applicants should submit payments in accordance with Finance Department Policies. Any application that will not be accompanied by appropriate fees will not be accepted.

6.0.2 Documentation for Clinical Trial Application

This includes a complete Clinical Trial Application Form **BOMRA/PCT/CT/P01/F01** available on the BoMRA website and attachment of relevant documents. The application shall be delivered physically or by courier to BoMRA head office located at Plot 112, Finance Park Gaborone, P.O.Box 2 Gaborone Station Botswana. An application to conduct a clinical trial shall include the following, as per the approved checklist **BOMRA/PCT/CT/P01/F04.**

To conduct a clinical trial in Botswana:

i. The applicant (Principal investigator) shall be resident in Botswana.
ii. The conduct of the trial shall be approved by the National Medicines Regulatory Authority (BoMRA) and the Health Research and Development Committee (National Ethics Committee).

6.0.3 When to Submit an Application to Conduct a Clinical Trial:

Before initiating the clinical trial (s), the sponsor (or the sponsor and the investigator, is required to submit the required application (s) to BoMRA for review, acceptance, and/or permission to conduct the trial(s). The submission should be dated, signed by the Principal Investigator, and contain sufficient information as detailed under clinical trial application checklist.

6.0.3.1 An application in the prescribed format, for approval to conduct a clinical trial is required for the following categories of medicines:

6.0.3.2 Unregistered medicines/ vaccines/ medical devices

6.0.3.3 Registered medicines / Vaccines where the proposed clinical trials are outside of the conditions of approval.

These may include changes to:

a) indication(s) and clinical use

b) target patient population(s)

c) route(s) of administration

d) dosage regimen(s)

e) Bioavailability and Bioequivalence studies

6.0.3.4 An application for authorization to conduct a clinical trial shall be made on a form and accompanied by an application fee as determined by the regulatory authority.

6.0.3.5 No person may conduct a clinical trial using investigational products included in paragraph above without prior authorization from BOMRA.

6.0.3.6 A clinical trial authorized by the BoMRA must be conducted in accordance with guidelines for Good Clinical Practice (GCP) as may from time to time be determined by the Authority.

6.0.3.7 Approval by the Regulatory Authority to conduct post-market clinical trials of a registered medicine within the approved conditions of registration of such a medicine is not required. The authority should be notified of such a trial.

6.1 Check list for Clinical Trial application:

CHECKLIST

No.	Mark (x)	Item
1.	☐	Cover letter addressed to the CEO, BoMRA, duly signed by the Principal investigator with list of documents submitted and their version number and date
2.	☐	Completed clinical trial application form
3.	☐	Clinical trial protocol including site specific addendums and version numbers
4.	☐	Informed consent form(s)
5.	☐	Product information if the investigational medical product is registered in Botswana: summary of product characteristics, patient information leaflet/package insert, and labelling
6.	☐	Investigator's brochure
7.	☐	If applicable, synopsis of previous trials with the investigational medical product(s)
8.	☐	If applicable, electronic copies of key peer reviewed publications to support the application.
9.	☐	Copy/ies of patient recruitment advertisement(s) (if applicable) and questionnaires used in the study
10.	☐	Investigational medical product dossier for products that are not registered in the country
11.	☐	Product information and certificate of analysis for the concomitant and rescue

		medications
12.	☐	GMP certificate for the site(s) producing the IMP(s)
13.	☐	Certificate(s) of analysis of the IMP(s)
14.	☐	Certificate(s) of accreditation for the central laboratories
15.		Signed declaration by the principal investigator
16.	☐	Workload forms for investigators
17.	☐	Signed curriculum vitae for all key staff participating in the conduct of the clinical trial, eg national principal investigator, principal and/or co-investigators, study coordinator, regional and local monitor, contract research affiliate, etc
18.	☐	Signed joint financial declaration between the sponsor and the principal investigator/institution
19.	☐	Signed declaration by the sub-investigators and key staff participating in the clinical trial
20.		Signed declaration by the regional monitor
21.	☐	Proof of registration on PACTR or WHO or other primary accessible registry
22.	☐	Clinical Trials Insurance
23.	☐	Proof of professional indemnity (malpractice insurance)
24.	☐	Valid GCP certificates for the investigators

25.	☐	Proof of registration for the investigator with a professional statutory body like Botswana Health Professional council
27.	☐	Study budget
28.	☐	Evidence of submission to the national ethics committee
29.	☐	Data Safety Monitoring Board charter and composition (As applicable)
30.	☐	Proof of application fee Payment

The following documents shall be attached:

6.1.1 Study Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization 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.

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.

Background Information

I. Justification for the study.

II. Name and description of the investigational product(s), including:
   a. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
   b. 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, and BoMRA 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.

6.1.2 Trial Objectives and Purpose

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

Trial Design:

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

I. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

II. A description of the type/design of the trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

III. A description of the measures taken to minimize/avoid bias, including:
   a. Randomization
   b. Blinding

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

V. The expected duration of participant 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, parts of trial and entire trial

VII. Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s), if any.

VIII. Maintenance of trial treatment randomization codes and procedures for breaking codes.

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

Selection and withdrawal of participants

I. Participant inclusion criteria

II. Participant exclusion criteria

III. Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

a. When and how to withdraw participants from the trial/investigational product treatment.

b. The type and timing of the data to be collected for withdrawn participants.

c. Whether and how participants are to be replaced

d. The follow-up for participants withdrawn from investigational product treatment/trial treatment.

6.1.3 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 rescue medication) 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 compliance.

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

6.1.4 Assessment of Efficacy

This will include:

i. Specification of the efficacy parameters.

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

6.1.5 Assessment of Safety

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 event and intercurrent illness.

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 Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC), name of the Chairperson should be stated.

6.1.6 Statistics

I. A description of the statistical methods to be employed, including timing of any planned interim analysis (es).

II. The number of participants planned to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified. Reasons for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

III. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

IV. The level of significance to be used.

V. Criteria for the termination of the trial.

VI. Procedure for accounting for missing, unused, and spurious data.

VII. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

VIII. Procedures for reporting any protocol violations.

IX. The selection of participants to be included in the analyses (e.g., all randomized participants, all dosed participants, all eligible participants, evaluable participants.

X. Methods for data analyses and evaluation of results.

6.1.7 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 trial-related monitoring audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.1.8 Quality Control and Quality Assurance

I. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

II. The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

III. Quality control should be applied to each stage of data collection and handling to ensure that all data are reliable and are 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 ICH GCP guidelines.

6.2 Communication with BoMRA

6.2.1 Before initiating a trial, the investigator/institution should have a written and dated approval from BoMRA for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements), and any other written information intended to be provided to trial participants.

6.2.2 All communication sent to BoMRA shall be addressed to the CEO and attention to Director- PV and CT, duly signed by the PI.

6.3 The Investigator's Brochure:

A compilation of the clinical and nonclinical data on the investigational product(s)which is relevant to the study of the investigational product(s) in human participants.

Full description is provided in the accompanying GCP guideline of Botswana.

Contents of IB includes;

a) Title Page

b) Confidentiality Statement

c)Contents of the Investigator's Brochure

i) Table of Contents Summary

ii) Introduction

iii) Physical, Chemical and Pharmaceutical Properties and Formulation

iv)Non-clinical Studies

a. Non-clinical Pharmacology
b. Pharmacokinetic and Product Metabolism in Animals
c. Toxicology

v)Effects in Humans

a. Pharmacokinetics
b. Safety and efficacy
c. Marketing experience

vi) Summary of Data and Guidance for the Investigators

6.4 Participant Insurance Cover for trial-related injuries

All trials submitted to BoMRA for approval shall be insured against possible injuries to trial participants that might arise during the conduct of the clinical trial.

6.5 Additional attachments

Informed consent forms and other relevant attachments such as GCP certificates and CV/Resume should be submitted with the application in line with the clinical trial application checklist.

6.6 Application Review Process

6.6.1 The application will be reviewed by Clinical trial officers at BoMRA. The reviewers will generate an evaluation or assessment report.

6.6.2 The reviewed protocol is tabled at the Pharmacovigilance Advisory Committee meeting where a regulatory decision of the application will be made. The initial review by the CT officers and the committee review may result in queries that need to be addressed by the applicant/PI.

6.6.3 Approval

BoMRA may approve conduct of the trial or may reject the application with written reasons for rejection.

6.6.4 Authorization of a Clinical Trial

When an application is approved BoMRA will write a letter of approval to the applicant with conditions of approval to be adhered to.

6.6.5 Expedited Review of Applications

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 working days subject to submission of a complete application.

6.7 Reliance Model

6.7.1 BoMRA employs the reliance model approach for clinical trial investigational products. BoMRA implements the reliance model especially 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.

6.7.2 The approach facilitates conducting regulatory reviews and evaluations in a timely manner and at the same time, accelerates the evaluation process without compromising the quality, safety, and efficacy of investigational products, as well as the design of clinical trials. The Authority will however maintain its regulatory responsibilities for decision-making.

6.8 Post-Clinical Trial Authorization Monitoring requirements

6.8.1 Clinical Trial Amendments:

Clinical Trial Amendment form is available on the BoMRA website:

I. Applications for amendments to clinical trial protocols and investigational product/s shall be submitted to BoMRA for approval prior to their implementation using Application for Clinical Trial Amendment Protocol form **BOMRA/PCT/CT/P01/F02** with the prescribed fee.
II. The applicant shall submit the original wording, revised wording, and rationale for the change including a copy of a complete protocol incorporating all amendments.
III. Such amendments shall also be approved by HRDC prior to implementation.
IV. Approval shall be obtained for the following amendments to the clinical trial protocol:
V. Changes that affect patient selection and monitoring
VI. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc.)

VII. Changes that affect patient discontinuation

VIII. Changes that result in the extension of the duration of the clinical trial

IX. Changes to the chemistry and manufacturing information that may affect Medicine safety and quality (For example: specifications for the Medicine where the limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and, the addition of new raw materials, solvents, reagents, catalysts, or any other material used in the manufacture of the Medicine substance.)

X. The clinical trial amendment application will go through the similar process of assessment and approval as the original protocol submitted.

6.8.2 Clinical Trial Records:

a) The sponsor shall record, handle and store all information in respect of a clinical trial in order to ensure that the clinical trial is conducted in accordance with good clinical practices and in a way that allows its complete and accurate reporting as well as its interpretation and verification.

b) The sponsor shall keep all records related to the conduct of a clinical trial in a format that facilitates verification for the purpose of an inspection.

c) The sponsor shall submit requested records within 48 hours if safety concerns arise.

d) Additionally, BOMRA can request the submission of additional information within seven days to facilitate an inspection of a site.

e) The sponsor shall maintain complete and accurate records in respect of the use of a medicine in a clinical trial, including:

I. A copy of all versions of the investigator's brochure for the IMP.

II. Records of all adverse events in respect of the IMP that have occurred locally or internationally, including information that specifies the indication for use and the dosage form of the Medicine at the time of the adverse event.

III. Records in respect of the enrolment of clinical trial participants, including information sufficient to enable all clinical trial participants to be identified and contacted in the event that the use of the Medicine may endanger the health of the clinical trial participants or other persons.

IV. Records in respect of the shipment, receipt, disposition, return and destruction of the Medicine.

V. For each clinical trial site, an undertaking from the principal investigator that is signed and dated by the principal investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that the principal investigator will conduct the clinical trial in accordance with good clinical practices.

VI. For each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Committee and Regulatory Authority for that clinical trial site.

VII. Records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change.

6.9 Reporting of Serious Adverse Events (SAEs)/Suspected Unexpected Serious Adverse Reactions (SUSARs)

Safety Reporting

Applicants shall report SAEs which may occur during conduct of clinical trials. These serious adverse events may be related to the investigational medicinal product (IMP) or the conduct of the trial in accordance with the submitted protocol. SAE's which the protocol or IB have identified as not needing immediate reporting may not be reported immediately as evaluated by BoMRA.

NB: This guidance is in alignment with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Integrated Addendum to ICH E2B(R1): Good Clinical Practice E2B(R2).

a) The entity responsible for reporting SAEs shall be clearly identified and provided in the clinical trial application or IB.
b) Fatal or life-threatening SAEs and SUSARs should be reported to BoMRA within 24 hours by e-mail followed by a complete report within 72 hours.
c) If it is neither fatal nor life threatening, the sponsor shall report within 15 calendar days after becoming aware of the information.
d) Other suspected unexpected serious adverse reactions (SUSAR) from foreign entities shall be reported within 30 days after becoming aware of the information.

6.9.1 Submission of SAE Reports

The applicant and the sponsor shall submit local or foreign suspected Serious adverse Events by completing the Council for International Organizations of Medical Sciences (CIOMS) I Form BOMRA/PCT/CT/P01/G02 (Annex 1) within 72 hours of first knowledge by the applicant.

6.9.2 Reports of concerns discovered during safety analyses.

The sponsors shall submit to BoMRA any additional information that the authority may request, as soon as possible, but no later than 15 calendar days after receiving the request.

Further new information which may be discovered during the conduct of the trial with suspicion to impact the benefit/risk balance of the trial shall be reported within 72hours providing a detailed report in narrative format.

6.9.3 Post SAE Report Submission

The applicant or the Sponsors shall perform an evaluation of all submitted SAEs related to the reported SAE and include scientific literature from similar incidences and provide a progress report within 90 calendar of the occurrence of the SAE. A follow up of this progress report should then be provided as part of the annual report or on request by the Authority for the duration of the trial.

6.10 Annual Report

The applicant conducting the clinical trial shall submit a progress report to BoMRA on an annual basis a month/ 30 days after the completion of the year in the format as per BOMRA/PCT/CT/P01/F02

6.11 End of Study report

The applicant should submit a full report of the trial findings from the date of initiation of the clinical trial upon completion of the trial, this should be submitted to BoMRA withing 90 days of the completion of the study and shall follow Application for Clinical Trial Protocol Amendment form- BOMRA/PCT/CT/P01/F02.

6.12 Importation, Management and Destruction of Investigational Products

6.12.1 All study investigational products and other trial-related medical products shall be approved for importation, exportation or destruction by the BoMRA. 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. Clinical trial approval letter issued by BoMRA

iii. The quantity and source of each investigational product and trial-related products to be imported.

iv. 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.

vi. Lot Release certificate(s) (where applicable) for all batches to be imported.

6.12.2 On submission of the above, an application for an import permit will be processed as per Guidelines for Import/Export of Medicines- BOMRA/IL/IE/P02/G01.

6.12.3. 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.

6.12.4 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.

6.12.5 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 trial inspections conducted by the Authority.

6.12.6 Destruction of Investigational Products

Leftover, expired, used, or broken Investigational Products should be destroyed to prevent them from being abused.

a.) The sponsor is responsible for ensuring that all returned, rejected, leftover or expired IMPs are destroyed or re-exported back to the sponsor.

b) IMPs should not be destroyed without prior consultation and approval of the sponsor.

c) As such, an official request to dispose of the Investigational Products, indicating the type, quantity of each product and batch numbers to be destroyed and the method of destruction shall be made by the sponsor to BoMRA for approval.

d) The destruction certificates/letter confirming destruction shall be kept on site for verification and accountability during trial inspections by BoMRA. The official request for destruction shall also be kept as a record for inspection by BoMRA.

e) All destructions of IMPs shall be done in accordance with MRS Regulations 2019 Section 59.

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

6.13.1 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 for the related trial protocols may be employed.

6.13.2 The emergency procedure may involve joint review assessments, reliance and data sharing to speed up approval of the Clinical Trial. Simultaneous ethical and regulatory review submissions is encouraged. A timeline of 15 working days is recommended for processing Clinical Trial Applications where the product is already registered for other indication/s, or for old products which are known and 30 working days for new products. These timelines are for the entire process from receipt of Clinical Trial Application to the final decision. Researchers are encouraged to have pre-submission meetings with BoMRA to discuss their protocol and any anticipated problems so that the approval process will be shortened.

6.13.3 Applications for the importation of study medical products may also be expedited and be processed within 2 working days of receipt of the application. Refer to Guideline for Import/Export of Medicines **BOMRA/IL/IE/P02/G01** for information on importation of investigational medicinal products.

6.14 Clinical Trial Inspections

6.14.1 BoMRA shall conduct clinical trial inspections to monitor clinical trials from start to finish as per inspection plan. Inspections may be routine or may be triggered by a cause like issues arising during the assessment of annual reports, protocol amendments, or by other information such as previous inspection experience. BoMRA 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. BoMRA and NEC (HRDC) may conduct combined inspections 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 BoMRA

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 BoMRA requirements.

v. More information on GCP inspections is provided in the Botswana Good Clinical Trial Practice Guideline.

6.15 Safety Notifications

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

i. Investigator's Brochure

ii. Package Inserts

iii. Safety reports from all active sites

v. Notifications of safety signals.
vi. Emergency preparedness and response plans
vii. Information distributed to participants during the study.

6.16 Uploading approved clinical trial application on the Clinical Trials Registry platform.

The Principal Investigator is required to upload the approved clinical trial application onto a publicly accessible CT registry platform such as the WHO CT registry or Pan African Clinical Trials Registry (PACTR).

7.0 REFERENCES

7.1 Medicines and Related substances Act of 2013

7.2 MRSA regulations of 2019

7.3 Guidelines for Good Clinical Trial Practice in Botswana Revision 1_ June 2020

7.4 ICH E6R (2) GCP, ICHE8, ICHE9, ICHE2A to E2F guidelines and other applicable ICH guidelines for pharmaceutical development of a medical product.

7.7 AVAREF Guideline Inspections of Clinical Trial Applications for National Regulatory Authorities (NRAs) and Ethics Committees (EC)

7.8 Guideline for conducting Good Clinical Practice in human Clinical trials. BOMRA/PCT/CT/P01/G02

8.0 RECORDS

8.1 Clinical Trial Application From **BOMRA/PCT/CT/P01/F01**

8.2 Application for Clinical Trial Protocol Amendment Form8 **BOMRA/PCT/CT/P01/F02**

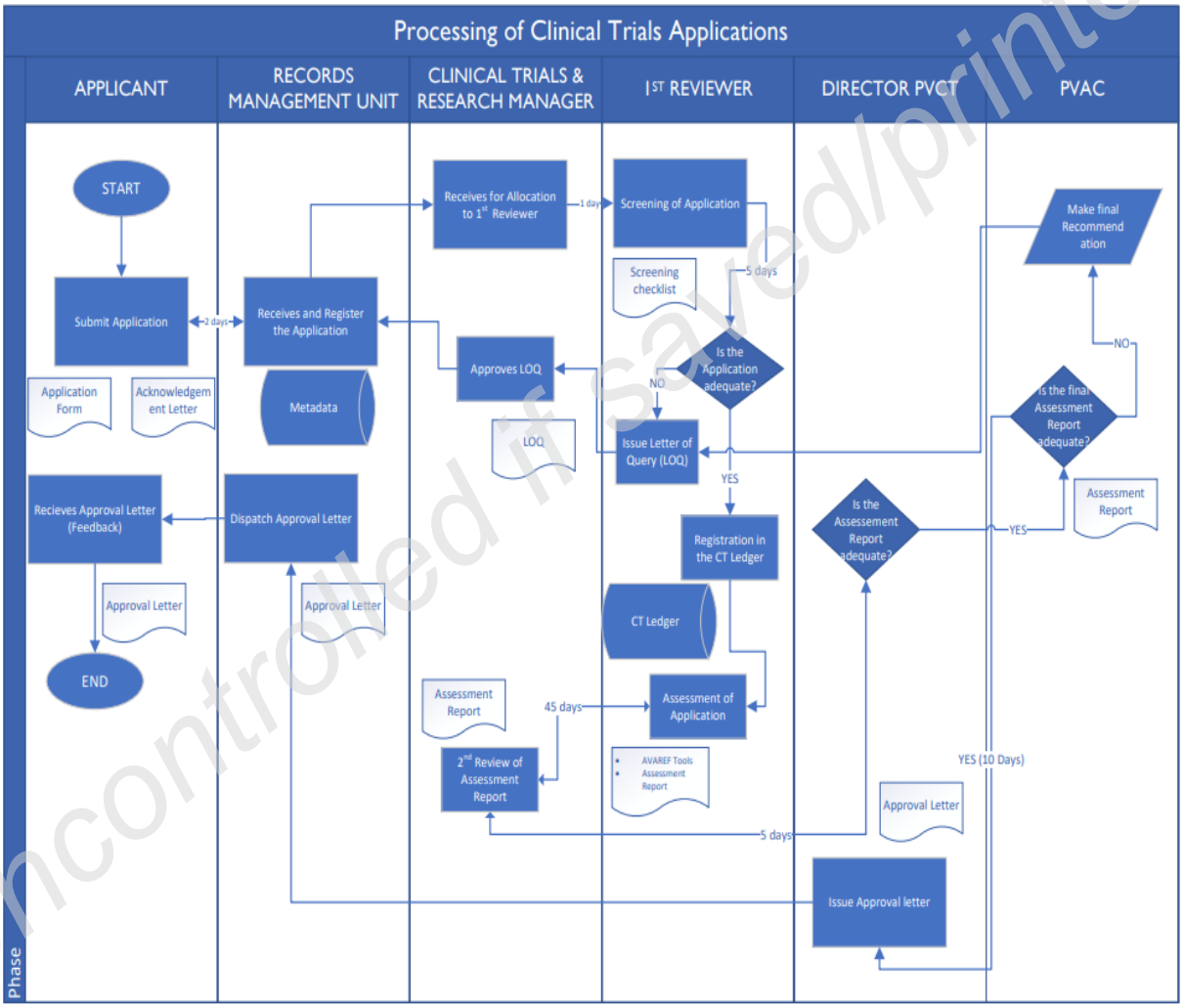
8.3 Checklist for Clinical Trial Application **BOMRA/PCT/CT/P01/F04**

9.0 APPENDICES

9.1 Appendix 1: Process Flow Chart of the Review of Clinical Trial Applications

9.2 Appendix 2: Process Flow Chart for Application for Amendment

Appendix 1: Process Flow Chart for Review of Clinical Trial Applications



Appendix 2: Process Flow Chart for Review of Clinical Trial Amendments