Botswana Medicines Regulatory Authority

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Date of Approval (DD/MM//YY)

Table of Contents

Revision status sheet

Page No.	Changes made	Issue No.	Process owner (Title)	Reviewers Name	Date

1. PREAMBLE

The guidelines for conducting clinical trials in Botswana were partly derived from WHO Handbook for Good Clinical Research Practice (GCP) and other guidelines for conducting clinical trials from the region that is South Africa, Zimbabwe and Tanzania.

Good Clinical Practice (GCP) is an international ethical and scientific standard for conducting biomedical and behavioral research involving human participants. The objective of this guideline is to provide a unified standard across Botswana. GCP is widely accepted and expected in all research involving human participants. GCP is not specific to a protocol, but rather is general and applicable to all protocols.

Good Clinical Practice (GCP) is a system of shared responsibilities between clinical investigators, industry/sponsors/monitors, institutions/ethics committees, and government regulators. Each party must understand and execute his/her responsibilities. Clinical research with investigational medicines, biologics and devices is a privilege, which comes with responsibilities for Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). GCP ensures the protection of clinical trial patients/participants and that clinical trials produce accurate credible data by defining standards and responsibilities.

Anyone directly involved in the design or conduct, oversight, or management of research involving human participants, including research site staff, back-up staff, contractors, subcontractors, and consultants who perform key study functions, should complete the GCP training. Non-study staff at the research site who provide standard care or other non-study related services should be encouraged to complete the GCP training, but they are not required to do so.

This guideline should be read in conjunction with other ICH guidelines relevant to the pharmaceutical development of investigational products and conduct of clinical trials.

2. PURPOSE

The principles in this guideline may be applied to all clinical investigations involving human participants, such as those involving an investigational product, a marketed drug, a medical device, or a behavioral intervention. To achieve compliance, this guideline should be used in conjunction with the Guideline for clinical trial application and authorization in Botswana.

3. LEGAL CONSIDERATIONS

These guidelines were developed in accordance with the various 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, and

b) Medicines and Related Substances Regulations, 2019

4. CLINICAL TRIAL APPLICATION

4.1 Application Requirements to Conduct Clinical Trials in Botswana.

4.1.1 An application to conduct clinical trial shall be made to BoMRA in prescribed form accompanied by the prescribed fee in accordance with MRS Regulations 2019 Section 55.

4.1.2 Applicants are required to submit their applications through our Records Management Unit at BoMRA.

4.1.3 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 (PV and CT) Department to approval.

4.1.4 This timeline excludes 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.

4.1.5 For clinical trials for emergency preparedness, the expedited timeline for review and approval may be reduced to 10 -15 working days subject to submission of a complete application. This timeline excludes when the applicant is addressing the queries raised.

4.1.6 Applicants are required to submit their applications through our Records Management nit at BoMRA.

4.1.7 After approval of the clinical trial application, the principal investigator shall report all SAEs which may occur in the study population to BoMRA as per the stipulated SAE reporting timelines.

4.2 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.

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

4.2.2 Unregistered medicines/ vaccines/ medical devices

4.2.3 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

4.2.2 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.

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

4.2.5 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.

4.2.6 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.

5. ABBREVIATIONS

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

5.1 ADR- Adverse Drug Reaction

5.2 AE- Adverse Event

5.3 AVAREF- African Vaccine Regulatory Forum

5.4 BoMRA- Botswana Medicines Regulatory Authority

5.5 CIOMS- Council for International Organizations of Medical Sciences

5.6 COA- Certificate of Analysis

5.7 CRF- Case Report Form

5.8 CRO- Contract Research Organisation

5.9 DSMB- Data Safety Monitoring Board

5.10 GCP- Good Clinical Practice

5.11 GMP- Good Manufacturing Practice

5.12 **GPP-** Good Pharmacy Practice

5.13 **HRDC-** Health Research & Development Committee

5.14 **IB-** Investigation Brochure

5.15 **ICH-** International Council on Harmonisation

5.16 **IDMC-** Independent Data-Monitoring Committee

5.17 **IREC-** Independent Research Ethics Committee

5.18 **IRB-** Institutional Review Board

5.19 **MRSA-** Medicines and Related Substance Act

5.20 **PVAC-** Pharmacovigilance Advisory Committee

5.21 **QA-** Quality Assurance

5.22 **QC-** Quality Control

5.23 **SOP-** Standard Operating Procedure

5.24 **SPC-** Summary of Product Characteristics

6. DEFINITIONS

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

6.1 Adverse Event (AE): Any undesirable experience occurring to a participant during a clinical trial, whether considered related to the investigational product(s). 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.

6.2 Serious Adverse Events (SAE): Any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect (ICH definition 1997).

6.3 Adverse Drug Reaction (ADR): A response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function. In the pre-approval clinical experience with a new medicinal product or its new intended usages, particularly as the therapeutic dose(s) may not be established, this includes all unintended responses to any dose. The phrase responses to a

medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

6.4 Adverse event following immunization (AEFI): Any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

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

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

6.7 Audit (of a trial): A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

6.8 Audit Certificate: A declaration of confirmation by the auditor than an audit has taken place.

6.9 Audit Report: A written evaluation by the sponsor's auditor of the results of the audit.

6.10 Audit Trail: Documentation that allows reconstruction of the course of events.

6.11 Blinding/Masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware and double-blinding usually refers to the participant(s), Investigator(s), and monitor and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

6.12 Case Report Form (CRF): A printed, optical or electronic document designed to record all of the protocol required information. There should be assurance of accurate input and presentation and it should allow verification.

6.13 Certified Copy: A paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

6.14 Clinical Trial [ICH: E6 (R2)]: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and

excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

6.15 Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference medical product in a clinical trial. Compliance (in relation to clinical trials): Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

6.16 Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a participant's identity and/or medical records.

6.17 Contract: A written, dated and signed agreement between the investigator(s), institutions and sponsor that sets out any arrangements on delegation and distribution of tasks and obligations and if appropriate on financial matters. The protocol may serve as a basis for a contract.

6.18 Co-ordinating Investigator: An investigator assigned the responsibility for the coordination of investigators at different.

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

6.20 Direct Access: Permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical trial. Any party with direct access should take reasonable precautions to maintain confidentiality of participants' identities and sponsor's proprietary information.

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

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

6.23 Emergency: An outbreak of a disease with high mortality and which involves significant numbers of individuals, and which may have a danger of international transmission.

6.24 Epidemic: the occurrence in a community or a region of cases of an illness, specific health related behaviour or other health-related events clearly in excess of normal expectancy.

6.25 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).

6.26 Fast-track: Fast track is a process designed to facilitate the development and expedite the review of clinical trial applications for the conduct of clinical trials during emergencies Good Clinical Practice (GCP): Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

6.26.1 Good Clinical Practice (GCP) Grading: The following defines grading of non-conformance to GCP:

6.26.2 Minor: These are conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data.

6.26.3 Major: These are conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles.

6.26.4 Critical: These are conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered to be totally unacceptable and possible consequences.

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

6.28 Good Laboratory Practice (GLP) The principles of Good Laboratory Practice (GLP)define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which clinical, non-clinical health and environmental safety studies are planned, performed, monitored, recorded, r reported and archived.

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

6.30 Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the participant.

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

6.32 Inspection and/or GCP inspection: The act by BoMRA of conducting an official review of documents, facilities, records, and any other resources that are deemed to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CRO's) facilities, or at other establishments deemed appropriate by the BoMRA.

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

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

6.35 Investigators Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects There should be adequate data to justify the nature, scale and duration of the proposed trial.

6.36 Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial including a product with a marketing authorisation when used or assembled in a way different from the approved form, or when used for an unapproved indication or when used to gain further information about an approved use.

6.37 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.

6.38 Joint Review: This process involves a joint assessment of the application by the Authority (BoMRA) with the relevant IRBs and other receiving national drug regulatory agencies.

6.39 Monitor: A person appointed by the sponsor or CRO to oversee the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the SOP's, GCP and the applicable regulatory requirements.

6.40 Medical Institutions: Medical Institutions are defined as any public or private entity or agency or medical or dental facility where clinical trials may be conducted. Clinical trials should be conducted in medical institutions which possess adequate facilities, equipment, and a well-established organisation so that clinical observation evaluation and necessary procedures or treatments can be adequately and timely performed in the case of an emergency. A medical institution should establish an Ethics Committee to review and approve proposed clinical trial and to monitor the conduct of the approved trials.

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

6.42 Multicentre Trial: A clinical trial conducted according to one single protocol but at more than one site. It is carried out by more than one investigator. Nonclinical Study Biomedical studies not performed on human subjects.

6.43 Pandemic: an emergency occurring worldwide or over a wide area crossing international boundaries and affecting a large number of people 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 organisation's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

6.44 Participant Identification Code: A unique identifier assigned by the investigator to each trial participant to protect the participant's identity and used in lieu of the

participant's name when the investigator reports adverse events and/or other trial related data.

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

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

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

6.48 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 GCP and the applicable regulatory requirement(s).

6.49 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.

6.50 Randomization: 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.

6.51 Raw Data: Original and certified copies of documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recordings from automated instruments, X-rays, microfilm) related to a clinical trial.

6.52 Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guidance, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

6.53 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.

6.54 Recognition: The routine acceptance of the regulatory decision of another regulator or other trusted institution.

6.55 Risk Minimisation Measures (RMM): are interventions that are aimed at reducing the risk of adverse reactions experienced after exposure to a medicinal product or reducing the impact or severity of such adverse reactions. They allow for the use of medicinal products with serious safety issues, which would otherwise be deemed unsuitable for use, whilst ensuring that the risks are outweighed by the benefits in the population exposed to the medicinal product.

6.56 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction an evaluation of the trial. Source data are contained in source documents (original records or certified copies).

6.57 Source Document: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

6.58 Sponsor: An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a trial. Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

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

6.60 Sub-investigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

6.61 Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

6.62 Trial Master File (TMF): is the name of the collection of trial documents that GCP requires must be present before, during, and after the trial. The TMF maybe electronic (eTMF) and must include "any documentation that facilitates reconstructing and evaluating the trial conduct, as part of the TMF" such as completed forms, checklists and reports, generated from following quality system procedures; assay method validation report for analysis of IMP or metabolite(s) in clinical samples; documentation to demonstrate validation of trial specific builds of computer systems. Thus, it includes not just the core documents themselves, but any supporting document that shows the study quality system was followed.

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

6.64 Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

6.65 Validation of Computerized Systems: A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

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

6.67 Well-being (of the trial participants): The physical and mental integrity of the participants participating in a clinical trial.

7. SCOPE

These guidelines are for persons that wish to conduct clinical trials in Botswana. The medicines or medical products may either be registered or non-registered medicines. They

do not include veterinary and medical devices which will be covered in a separate guideline. The guidelines for conducting clinical trials are based mainly on the guidelines for Good Clinical Practice (GCP). This is an ethical and scientific standard for designing, conducting, recording, and reporting clinical trials on medicinal products in human beings. These guidelines are directed towards all those involved in clinical trials whether for academic purposes or for the generation of data intended for inclusion in the regulatory submissions for medicinal product.

8. Good Clinical Practice (GCP) Principles

The guidelines for conducting clinical trials in Botswana were derived from the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) E6(R2) and from the International Ethical Guidelines for Biomedical Research involving human participants prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with World Health Organization current guidance for clinical trials and WHO African Vaccine Regulatory Forum (AVAREF Clinical Trial guidelines for Emergency Preparedness, and CT Joint reviews.

8.1 13 Principles of Good Clinical Practice

Please note that all the following GCP principles are to be complied with:

8.1.1 Compliance with this standard provides public assurance that the rights, safety and well-being of participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that clinical trial data are credible.

8.1.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

8.1.3 The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.

8.1.4 The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

8.1.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

8.1.6 A trial should be conducted in compliance with the protocol that has received prior approval of the relevant authorities.

8.1.7 The medical care given to, and medical decisions made on behalf of participants should always be the responsibility of a qualified physician or, when appropriate of a qualified dentist registered in terms of the Botswana Health Professions Act.

8.1.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

8.1.9 Freely given informed consent should be obtained from every participant prior to clinical trial participation.

8.1.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. Laboratory results should be recorded in a flow chart.

8.1.11 The confidentiality of records that could identify participants should be protected, respecting privacy and confidentiality.

8.1.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

8.1.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

8.2 Protection of Study Participants

Clinical trials should be designed, conducted and analysed according to sound scientific principles to achieve their objectives; and should be reported appropriately. The essence of rational medicines development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated. The design of the study should maximize the achievement of the objectives of the study whilst protecting the rights of the study participants. Several levels of safeguards are in place to help protect the people who take part in clinical trials. There are still risks involved with any study, but these safeguards try to reduce the risk as much as possible. Three basic principles, as outlined in the Belmont Report from the late 1970s, should provide a basis for research involving humans:

8.2.1 **Respect for persons:** Understanding that all people should be respected and have the right to choose what treatments they receive.

8.2.2 **Beneficence:** Clinical trials should be designed in a way that protects people from harm by maximizing benefits and minimizing risks. The benefit should always out-weigh the risks and study participants should be made aware of the risks associated with the study.

8.2.3 **Justice:** Trying to ensure that all people share the benefits and burdens of research equally

8.3 Scientific and Social Value and Respect for Rights

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health. Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources. Therefore, researchers, sponsors, research ethics committees, and health authorities, must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information. Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted. Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.

8.4 Social value

Social value refers to the importance of the information that a study is likely to produce. Information can be important because of its direct relevance for understanding or intervening on a significant health problem or because of its expected contribution to research likely to promote individual or public health. The importance of such information can vary depending on the significance of the health need, the novelty and expected merits of the approach, the merits of alternative means of addressing the problem, and other considerations. For example, a well-designed, late phase clinical trial could lack social value if its endpoints are unrelated to clinical decision-making so that clinicians and policy-makers are unlikely to alter their practices based on the study's findings. Similarly, although replication serves an important role in scientific research, well designed studies that lack sufficient novelty may also lack social value. Researchers, sponsors, research ethics committees and relevant health authorities, such as regulator and policy-makers, must ensure that a study has sufficient social value to justify its associated risks, costs and burdens. In particular, there must be sufficient social value to justify risks to participants in studies that lack the prospect of potential individual benefit to them.

8.5 Scientific value

Scientific value refers to the ability of a study to produce reliable, valid information capable of realizing the stated objectives of the research. The requirement of scientific value applies to all health-related research with humans, regardless of funding source or degree of risk to participants. In part, this is because a diverse range of stakeholders (including patients,

clinicians, researchers, policymakers, industrial sponsors and others) rely on the information that research generates to make decisions that have important consequences for individual and public health. For example, evidence produced in early phase research provides the foundation for subsequent studies, and methodological shortcomings can derail promising avenues of research and squander valuable resources. Many other forms of research, such as clinical trials, health systems research, epidemiological studies or post-marketing studies, generate data that are relevant for clinical decision-making, health and social policy, or resource allocation. Ensuring that studies uphold high scientific standards is essential for maintaining the integrity of the research enterprise and its ability to fulfil its social function.

8.6 TYPES OF CLINICAL TRIALS

8.6.1 Phase I studies

Phase I studies relate to the safety of the drug under investigation usually in healthy volunteers. The aim is to assess major safety issues and understand how the drug is dealt with in the body.

8.6.2 Phase II studies

Phase II studies usually involve a small (usually randomized) trial investigating the potential benefits of a drug among patients with a particular disease. These trials are also used establish which therapies have the potential to be investigated in full-scale, phase III randomised trials while further assessing the safety of these therapies.

8.6.3 Phase III studies

Phase III trials are full-scale randomised controlled trials evaluating the benefits and safety of a drug against a placebo or standard therapy in a substantial number of patients. This is the key stage in establishing the impact of a drug and the majority of drug trials you have come across in this course relate to this type of trial. They may also be called 'pivotal' trials.

8.6.4 Phase IV studies

Phase IV studies relate to the stage after a medical product has been approved and involves the long-term monitoring of the safety of the drug. This phase has gained increasing importance as regulators and manufacturers realize that phases I-III trials cannot easily identify serious but rare adverse events. Hence more regulators are requesting post authorization safety studies as a condition for marketing approval. Treatment Intervention Studies and other investigational studies.

9.0 Regulatory Authorities Roles and Responsibilities

9.1 Botswana Medicines Regulatory Authority (BoMRA)

The Medicines Regulatory Authority was established under Section 3 of the Medicines and Related Substances Act ("MRSA") and referred to as the Botswana Medicines Regulatory Authority or BoMRA. The Authority is responsible for ensuring the safety, efficacy, and quality of medicines and related substances, which includes both human and veterinary medicines, medical devices, and cosmetics in Botswana.

Among others the Authority's key functions are stated under Section 4 of the MRSA and include:

Oversight and Regulation of Clinical Trials. This is done by promoting Good Clinical Practice (GCP) and adherence to Clinical Trials Regulations to protect the rights and wellbeing of Clinical trial participants (Patients). To strengthen regulatory oversight and control of Clinical trials in Botswana, BoMRA is working on establishing systems, structures, processes, and procedures.

BoMRA is responsible for the following activities:

9.1.1 Ensure efficient, effective, and ethical evaluation or assessment of medicines and related substances.

9.1.2 To provide scientific assessment of clinical trial applications for clinical trial conduct approval.

9.1.3 Ensure periodic assessment of SAEs, SUSARs and any other adverse drug reactions reported during the conduct of clinical trails.

9.1.4 To conduct announced and unannounced inspections.

9.2 Health Research Development Committee (NEC)

9.2.1 All clinical trials and medical research involving human participants shall undergo an independent ethics review by the national ethics committee, HRDC.

9.2.2 The HRDC shall review and approve a protocol in accordance with the relevant GCP and regulations.

9.2.3 An application for ethics review may be made parallel with the application to BoMRA for approval, however, a clinical trial involving human participants shall have both approvals to commence.

9.2.4 The Ethics Committee should obtain all the information relating to the trial including, protocol, investigators brochure, patient consent forms, insurance for participants, current CVs for investigators and literature detailing rationale for the study.

9.3 NEC Composition and Functions

National Health Research Ethics Committee (NHREC), Health Research and Development Division, collaborates closely with BOMRA, the clinical research institutes, and trial investigators to promote Good Clinical Practise (GCP) and adherence to Clinical Trials Regulations in order to protect the rights and well-being of clinical trial participants and to strengthen regulatory oversight and control of clinical trials in Botswana.

The NHREC has specific functions for research and development, coordination, and oversight. The functions are stated as follows:

9.3.1 To act as a clearing house for biomedical and bio-behavioral research conducted in Botswana.

9.3.2 To advise and coordinate the formulation of explicit national policies on biomedical and bio-behavioural research, development of regulatory documents and research priorities.

9.3.3 To work in close co-operation with various institutions, sectors, and organizations in Botswana to co-ordinate all biomedical and bio-behavioural research activities.

9.3.4 To establish ethics committees/IRBs, Community Advisory Boards (CABs) and any other research developmental bodies and institutions.

9.3.4 The NEC includes clinicians and non – clinicians. The composition is as follows:

(a) Epidemiologist / Research methodology expert

(b) Academicians

(c) Pharmacologist

(d) Members of the community(layperson/theologist)

(e) Lawyer

9.4 The National Ethics Committee should consider the following:

9.4.1 The suitability of the investigator for the proposed trial in relation to his/her qualifications, experience, supporting staff, and available facilities.

9.4.2 The suitability of the protocol in relation to the objectives of the study.

9.4.3 The potential for reaching sound conclusions with the smallest possible exposure of participants.

9.4.4 The justification of predictable risks and inconvenience weighed against the anticipated benefits for the participants and/or others.

9.4.5 The adequacy and completeness of the written information to be given to the participants, their relatives, guardians and, if necessary. Legal representatives.

9.4.6 The means by which initial recruitment is to be conducted and by which full information is to be given, and by which consent is to be obtained. All written information for the participant and/or legal representative must be submitted in its final form.

9.4.7 Provision for compensation/treatment in the case of injury or death of a participant, and any insurance or indemnity to cover the liability of the investigator and sponsor involved in the clinical trial.

9.4.8 The extent to which investigators and participants may be rewarded/compensated for participation.

The suitability of the study population, whether they constitute a vulnerable group, if so whether the study is justified and whether sufficient measures to protect their interest are in place.

9.4.9 That the number of participants to be recruited is adequate to demonstrate the predicted effect.

9.4.10 The risk-benefit analysis takes full awareness of benefits and harms beyond the life of the study itself, particularly in relation to chronic life-threatening conditions.

9.4.11 If placebos are to be used, whether their use can be justified.

9.4.12 That by their participation in a clinical study the participants or other persons in the establishment or clinical centre are not denied timely access to medical personnel investigations, equipment, or procedures.

9.4.13 The means by which initial recruitment is to be conducted and by which full information is to be given and informed consent is to be obtained.

9.4.14 All written information for the participant and/or legal representative must be submitted in its final form; the adequacy and completeness of the written information to be given to the participants, their relatives, guardians and, if necessary, legal representatives.

9.4.15 That the application allows the participants and/or their representatives' adequate time to consider the patient information package before informed consent is sought.

9.5 Informed Consent

9.5.1 The principles of informed consent in the current revision of the Helsinki Declaration should be implemented in each clinical trial.

9.5.1.1 Information should be given in both oral and written form whenever possible. No participant should be coerced or unduly influenced to participate or continue to

participate in a trial. The participant, legal representative or guardian should be given ample opportunity to enquire about the details of the trial and be allowed sufficient time to decide whether they wish to participate. The information should make clear that refusal to participate or withdrawal from the trial at any stage is without any disadvantages for the person's subsequent care.

9.5.1.2 The participant must be made aware and consent that personal information may be scrutinised during audit by BoMRA, and that personal information will be treated confidentially and will not be publicly available.

9.5.1.3 None of the information concerning the trial should contain any language that causes the participant/legal representative or guardian waive or appear to waive any legal rights or that releases or appears to release the investigator and/or sponsor from liability for negligence. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should be submitted to BoMRA for review and approval before use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that might be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

9.5.1.4 The participant must have access to information about procedures for compensation and treatment should he/she be injured/disabled by participating in the trial.

9.5.1.5 The language used in the oral and written information about the trial including the informed consent form should be as non-technical as practical and should be understandable to the participant or their representative. Both the English and vernacular version should be made available. Evidence of back translation and who performed it will be required.

9.5.1.6 Prior to participation in the trial, the written informed consent form should be signed and personally dated by the participant. An impartial witness should sign the consent form to attest that the participant/legal representative gave consent freely. A copy of the signed and dated consent form should be given to the participant/representative before trial commences.

9.5.2 Informed consent discussion and the written informed consent discussion and the written consent form should include explanations of the following:

9.5.3 Does the trial involve research.

9.5.4 The purpose of the trial.

9.5.5 The trial treatment(s) and the probability for random assignment to each treatment.

9.5.6 The trial procedures to be followed, including all invasive procedures.

9.5.7 The participant's responsibilities.

9.5.8 Those aspects of the trial that are experimental.

9.5.9 The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.

9.5.10 The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.

9.5.11 The alternative procedure(s) or course(s) of treatment that may be available to this participant, and their important potential benefits and risks.

9.5.12 The compensation and/or treatment available to the participant in the event of trial-related injury.

9.5.13 The anticipated prorated payment, if any, to the participant for participating in the trial.

9.5.14 The anticipated expenses, if any, to the participant for participating in the trial.

9.5.15 That the participant's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time.

9.5.16 That the participants' identity will remain confidential whether results of the trial are published or not published. That BoMRA and other authorized persons will be granted direct access to the participants' original medical records for verification of trial procedures and data.

9.5.17 That should any new information that is relevant to the participants willingness to continue participating in the trial become available it will be conveyed to them in a timely manner.

9.5.18 The contact persons for further information about the trial or whom to contact in the event of trial-related injury.

9.5.19 That the participant may be requested to terminate participation in the trial.

9.5.20 The expected duration of the trial.

9.5.21 The approximate number of participants involved in the trial.

10. The Investigator

Investigators should satisfy the following:

10.1 The 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.

10.2 The investigator should be thoroughly familiar with the characteristics and appropriate use of the investigational product as described in the protocol, current investigator's brochure, in the product information and in other information sources.

10.3 Have a clear understanding and willingness to obey the ethical and legal requirements of the trial.

10.4 To permit monitoring and auditing of the trial and inspection by BoMRA or appointed representatives.

10.5 Keep a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

10.6 The investigator should not have been found guilty of any misconduct under the Health Professions Act and Regulations.

10.7 The Principal Investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in the country and who is responsible for the conduct of the clinical trial at a clinical site. A principal investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area.

10.8 All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical Practice (GCP) within the last three years.

10.9 Upon signing the application, all parties accept the responsibility that all applicable regulations and requirements will be adhered to. Furthermore, all parties are responsible for ensuring that the trial is based on and implemented according to well-founded ethical and scientific principles, which are expressed in the Helsinki Declaration and its current revisions as well as in the local and international guidelines for GCP.

10.10 Adequate Resources. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

10.11 The investigator should have adequate number of qualified staff and adequate facilities for the duration of the trial to conduct the trial properly and safely. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, investigational product and their trial-related duties and functions.

10.12 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual, or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial related duties and functions performed and any data generated.

10.13 Medical Care of Trial Participants

10.14 A qualified medical practitioner should be responsible for all trial-related medical decisions. The qualified medical practitioner should also be licensed with the Botswana Health Professions Council (BHPC). The medical care given to, and medical decisions made on behalf of the participants must always be the responsibility of a qualified medical practitioner. During and following a participant's participation in a trial, the investigator should ensure adequate medical care is provided to a participant for any adverse events including clinically significant laboratory values related to the trial. The participant should be informed when medical care is needed for intercurrent illness for which the investigator becomes aware.

11. INVESTIGATOR RESPONSIBILITIES

11.1 Before initiating a trial, the investigator should have the written dated approval from BoMRA and HRDC.

11.2 The investigator should conduct the trial according to the approved protocol.

11.3 The investigator should not implement any deviation from or changes to the protocol without prior review and approval of the BoMRA except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes.

11.4 The investigator should establish the SOP for investigational products (IP).

11.5 The IP(s) should be kept by a designated person who maintain records of the delivery process and who ensures that the product is processed and stored correctly.

11.6 The designated person should maintain an inventory of the IP at the site, those used by each participant and the return to sponsor or alternative disposition of unused product(s).

11.7 The investigational product(s) should be used only on the participants participating in the trial.

11.8 The investigator should ensure that the IP are used only in accordance with the approved protocol.

11.9 The investigator should ensure that if there is blinding, it is maintained but there should be criteria establishment for breaking of code.

11.10 The investigator or a person designated by the investigator should explain the correct use of the IP to each participant and should check at appropriate intervals during the trial that each participant is following the instructions. In the case where the IP is administered to the participant, the proper administration should be ensured.

11.11 The investigator should ensure that the participants have signed and dated the consent form or given their consent in an acceptable form before participating in the trial.

11.12 The investigator should guarantee the confidentiality of the research data, the trial participants' details and information provided by sponsor.

11.13 The investigator should ensure that all data is accurately collected and recorded.

11.14 The investigator should ensure that all serious adverse events are reported promptly to the BoMRA, sponsor and the Ethics Committee.

11.15 Proper protection procedures or treatments should be administered to trial participants with serious adverse events.

11.16 The investigator should submit all relevant trial data to BoMRA and

sponsor in a timely fashion for validation, auditing and inspection.

12. SPONSOR

12.1 The sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The quality management system should use a risk-based approach as described below:

12.2 Critical process and data identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

12.3 Risk identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

12.4 Risk evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring.

b) The extent to which such errors would be detectable.

c) The impact of such errors on human subject protection and reliability of trial results.

12.5 Risk control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

12.6 Risk communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

12.7 Risk review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

12.8 Risk reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

12.9 Risk management

It comprises systematic discovery and communication of specific known and unknown risks of medicinal products as well as the plan to address and minimize those risks. It strives to ensure that the benefits of a medicine or medical product outweigh the risks in clinical practice by identifying potential risks prior approval, evaluating actual risks in context of the benefits during clinical practice, and implementing risk minimization measures.

13. CONTRACT RESEARCH ORGANIZATION (CRO)

13.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a Contract Research Organization, but the ultimate responsibility for the quality and

integrity of the trial data always resides with the sponsor. The Contract research Organization should implement quality assurance and quality control.

13.2 Any trial-related duty and function that is transferred to and assumed by a Contract research Organization should be specified in writing.

13.3 Any trial-related duties and functions not specifically transferred to and assumed by a Contract Research Organization are retained by the sponsor.

13.4 All references to a sponsor in this guideline also apply to a Contract research Organization to the extent that a Contract Research Organization has assumed the trial related duties and functions of a sponsor.

13.5 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant (s) may be appointed for this purpose.

13.6 Quality assurance and quality control

13.6.1 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 requirement(s).

13.6.2 The sponsor is responsible for selecting investigators according to the availability of adequate clinical trial environment facilities and resources. In addition, the sponsor should ensure that the investigator has sufficient training, qualifications and capability.

13.6.3 The sponsor should agree with investigators on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical report. Prior to the initiation of the clinical trial, the agreement between the sponsor and investigators should be in writing as part of the protocol or in a separate agreement.

13.6.4 The sponsor, in a written document, may agree to transfer all related activities of the clinical trial to the designated research activities of the clinical trial to the designated research institutions. However, all responsibility for the trial lies with the sponsor.

13.6.5 The sponsor should provide an up to date Investigator's brochure, which includes information about the products with respect to their physical, chemical, pharmacokinetic and pharmacodynamic properties obtained from animals as well as human participants and currently available results of relevant clinical trials.

13.6.6 The sponsor should obtain the investigators/institutions agreement on the following items: The trial is to be conducted in compliance with Good Clinical Practices with the protocol agreed to by the sponsor; and to be in compliance with procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol.

13.6.7 The sponsor and all investigators should sign and date the protocol of the trial to confirm the agreement. The sponsor should agree with investigators on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical report. Prior to the initiation of the clinical trial, the agreement between the sponsor and investigators should be in writing as part of the protocol or in a separate agreement sponsor, in a written document, may agree to transfer all related activities of the clinical trial to the designated research activities of the clinical trial to the designated research institutions. However, all responsibility for the trial lies with the sponsor.

13.6.8 The sponsor should ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages for the duration and in the trial population to be studied.

13.6.9 The sponsor should ensure that the IP's (including active comparator(s) and placebo) is manufactured in accordance with Good Manufacturing Practices and are adequately packed and labelled in a manner that protects the blinding if applicable. In addition, the labelling should comply with the regulatory requirements.

13.6.10 The sponsor should determine for the IP's, acceptable storage temperature and conditions, storage times, reconstitution fluids and procedures and devices for product infusion if any.

13.6.11 In blinded trials, the coding system for the IP's should include a mechanism that permits rapid identification of the products in case of a medical emergency but does not permit undetectable breaks of the blinding.

13.6.12 If formulation changes are made to the IP or comparator products during the clinical development, the results of pharmaceutical and pharmacokinetic profile of the product should be available to BoMRA prior to the use of the reformulated IP in clinical trials.

13.6.13 The sponsor should appoint qualified and suitable trained individuals to monitor the trial.

13.6.14 The sponsor should provide insurance or should indemnify the investigator/institution against claims arising from the trial except for claims that arise from malpractice and/ or negligence.

13.6.15 The sponsor policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries. The sponsor should provide insurance cover for all trial participants.

13.6.16 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

13.6.17 The sponsor should report to BoMRA, all adverse events occurring during the trial. The sponsor should expedite reporting all serious adverse events to the Ethics Committee and BoMRA. The sponsor and the investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial participants.

13.6.18 When a trial is prematurely terminated or suspended by the sponsor/investigators, the Ethics Committee and BoMRA should be informed of the decision to terminate/suspend the trial and the reasons thereof by the sponsor/investigators.

13.6.19 Whether the trial is completed or prematurely terminated, the sponsor should submit a report to BoMRA and NEC within 30 (thirty) days.

13.6.20 The external sponsor should strengthen local capacity for ethical, scientific review, biomedical research and provide healthcare services as described in sections 20, 21 of the International Ethical Guidelines for Biomedical Research involving Human Participants (CIOMS 2002)

13.6.21 Ethical obligation of external sponsors to provide healthcare services

13.6.22 External sponsors are ethically obliged to ensure the availability of:

a) Health-care services that are essential to the safe conduct of the research.

b) Treatment of participants who suffer injury as a consequence of research.

c) Intervention; and Services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

14. MONITOR

13.7 Purpose The purposes of trial monitoring are to verify that:

13.8 The rights and well-being of human subjects are protected.

13.9 The reported trial data are accurate, complete, and verifiable from source documents.

13.10 The conduct of the trial is following the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

13.11 Selection and Qualifications of Monitors

13.12 Monitors should be appointed by the sponsor.

13.13 Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

13.14 Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

13.15 Extent and Nature of Monitoring

The sponsor should ensure that trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meeting, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

13.16 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

13.17 Acting as the main line of communication between the sponsor and the investigator.

13.18 Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, those facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

13.19 Verifying, for the investigational product(s):

13.19.1 That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

13.19.2 that the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s)

13.19.3 Those subjects are provided with necessary instruction on properly using handing, storing, and returning the investigational product(s).

13.19.4 That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

13.19.5 That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor:

13.19.6 Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

15. Clinical Trial Records and Reports

15.1 The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants.

15.2 The objective of data storage and processing is to record, store and transfer the information obtained from the trial participants during the conduct of the trial, and to transform the data adequately and efficiently for retrospective validation and evaluation of the progress and conduct of the trial.

15.3 With respect to blinded clinical trials, the blindness should be completely maintained from the generation of random codes for allocation of treatments to the time of decision for revelation of random codes.

15.4 The protocol, documents, case report forms, Informed Consent Forms and other trial- related documents should be retained for at least 10 years by the sponsor; and the trial participants documents should be retained for at least 10 years by the medical institution. The participant identification codes should be retained by the investigator and the sponsor for at least 10 years.

15.5 All records and their duplicates required by the Guidelines should be kept at the trial related sites for the duration of the above-mentioned retention period and should always be available for inspection by BoMRA. The inspector should be allowed to photocopy or duplicate the records by other electronic and/or optical means. Upon request of the monitor, auditor, IRB/IEC, or BoMRA, the investigator/institution should make available for direct access all requested trial related documents.

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

15.7 The sponsor must submit requested records within 48 hours if safety concerns arise.

15.8 Additionally, BoMRA can request the submission of additional information within seven days to facilitate an inspection of a site.

15.9 The sponsor must maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:

15.10 A copy of all versions of the investigator's brochure for the drug.

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

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

15.13 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 drug may endanger the health of the clinical trial participants or other persons, destruction of the drug.

15.14 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.

15.15 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 BoMRA for that clinical trial site.

15.16 Records in respect of the shipment, receipt, disposition, return and destruction of the drug.

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

15.18 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 BoMRA for that clinical trial site.

15.19 Record Access

15.20 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source

data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

15.21 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring.

15.22 Case Report Form (CRF)

The Investigator should ensure that collection procedures, storage and retrieval of data meets minimum requirements for quality and facilitates verification, validation, audit and inspection. In addition, investigations and findings are accurately and completely documented in the CRF, which should be signed and dated by the authorized individuals. Any change or correction to a CRF, as well as the process of duplicating raw data, should not obscure the original entry. Changes and corrections should be made by crossing out the old entries and should be initiated and dated by the individual who makes the correction. Entry and corrections of the electronic data should only be made by the authorized personnel. Any correction or deletion of electronic data should be documented and recorded. Reasons for the corrections should be given in every case. In addition to the data required by the protocol, other data may be recorded on the CRF and this data should be clearly marked as additional data.

15.23 Trial Data

Laboratory values with the normal reference ranges should be recorded or attached to CRF. In addition, the investigator should evaluate and comment on the laboratory values outside acceptable ranges or values that differ importantly from previous values. Adequate security and protection should be provided in the computer system for the accuracy of the database. Any printout of the data, as well as duplicates, must be signed and dated. The Monitor should apply appropriate methods to avoid any omission of the data and logically inconsistent data, any missing data identified by computer should be clearly documented and labelled.

15.24 Electronic Data

Validated, error-free data processing programmes with adequate use documentation should be used. Adequate security and protection should be provided in the computer system for the accuracy of the data directly entered into the computer database. Any printout of the data, as well as duplicates, must be signed and dated. Procedures for corrections made at data entry, as well as documentation of corrections in the audit records, should be provided for the electronic data processing and management system or for the network system for remote data entry. SOPs should be maintained for using electronic systems. The SOPs should cover system setup, installation and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning. The responsibilities of the sponsor, investigator and other parties with

respect to the use of these computerized system should be clear, and the users should be provided with training in the use of the systems. The SOPs should also clearly state those who have access to the electronic systems and timed maintenance of the electronic system.

15.25 Validation of Data

15.25.1 The sponsor should be responsible for the accuracy of the transformation of the data during the data processing. The sponsor should compare the original data, observations and findings with the processed and transformed data.

15.25.2 If data transformation is required during data processing, the method of transformation should be validated for what it purports to do. The transformation procedures should be explained in a written document.

15.25.3 The sponsor should maintain a signature list of the individuals who are authorized to make data changes, and institute an adequate security system prevent any data change by unauthorized personnel.

15.25.4 In order to ensure the conclusion of the trial can be derived sequentially from the raw data, all observations findings, especially the reliability of the trial, should be subjected to re-validation.

15.25.5 Quality control procedure should be enforced to each step of data processing to ensure that all data are reliably and correctly processed. It is recommended that the sponsor or the medical institution appoint individuals, who are not involved with the trial, to conduct audits independently.

15.25.6 All relevant documents specified in the guidelines, including application forms, should be made available for inspection and audit by the sponsor or by BoMRA.

15.25.7 Trial sites, medical institutions, laboratories, and all data (including raw data) and documents should be made available for inspection by BoMRA.

15.26 Identification of Trial Participants

The Investigator should keep a detailed and confidential record which can identify the trial participants at any time. The sponsor should use an unambiguous identification coding system that allows identification of all the data reported for each participant.

15.27 Annual Progress Reports

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

15.28 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 must follow BOMRA/PCT/CT/P01/F02.

15.29 Statistical Analysis

15.29.1 It is recommended that a biostatistician participates in the planning, execution, analysis, and other relevant aspects of clinical trials.

15.30 Random allocation and Blinding

The process of random allocation of treatments to the trial participants should be documented. Both the Investigator and the sponsor should keep the sealed random code of each trial participant. When a blinded trial is conducted, the circumstances of breaking the random codes should be precisely and clearly stated. The time and reason for revelation of random codes should be clearly and unambiguously recorded on the CRF.

15.31 The following issues should be addressed in the statistical analyses.

15.31.1 Statistical methods and primary clinical therapeutic end points should be described in the protocol. Any deviation(s) from the original statistical plan specified in the approved protocol should be described and justified in the final report. The possibility and timing of any planned interim analysis should also be described in the protocol. Estimation of the number of participants planned to be enrolled and the corresponding statistical power of the trial and clinical interpretation should also be described and justified in the protocol.

15.31.2 The Investigator and Monitor are responsible for the quality assurance of the data and the statistician is responsible for the reliability and efficiency of data processing and management.

15.31.3 The results of statistical analysis should not rely solely on statistical significance but also emphasize the interpretation of the clinical significance, such as estimation of the therapeutic effect and the magnitude of the treatment difference as well as the correspondence intervals.

15.31.4 The statistical procedures applied to missing, unused, and surplus data should be described and justified.

15.31.5 Interim Analysis and Stopping Rules

An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. It is a tool that is meant to protect the participants and prevent exposure to unnecessary risk, especially for phase I and II trials. Because the number, methods, and consequences of these comparisons affect

the interpretation of the trial, all interim analyses should be carefully planned and described in the protocol. The stopping guidelines and their properties should be clearly described in the protocol or amendments. The potential effects of early stopping on the analysis of other important variables should also be considered. This material should be written or approved by the data monitoring committee when the trial has one. The execution of an interim analysis should be a completely confidential process because un-blinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should be informed only about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures.

16. Management of Investigational Medicinal Products (IMPs)

16.1 Clinical trial investigational medicinal products must be manufactured in accordance with Good Manufacturing Practices (GMP). If a reference product, i.e. an active comparator or a placebo is used in the clinical trial, GMP certificate of the relevant manufacturer (if different from the test product manufacturer) should also be submitted as stated in the ***Guidelines for Importation of Investigational Medicinal Product BOMRA/IL/IE/P02/G01.*** 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.

16.2 Certificates of analysis (COAs) must be provided for all investigational and comparator products.

16.3 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 Botswana.

16.4 If the pharmaceutical or chemical properties of the investigational product have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified. This, for instance, applies to impurities and degradation products.

16.5 Pharmaceutical and/or chemical alterations in an investigational product that is used in an ongoing clinical trial, and that may affect the quality, safety and/or efficacy of the medicinal product must immediately be reported to BoMRA. If the composition of the medicinal product is altered, additional bioavailability or bioequivalence studies may be required.

16.6 In cases where an extension of the shelf life for the finished medicinal product is desired, an application for this must be submitted to BoMRA. In such cases stability

data or certificates of analysis (CoAs) from reanalysis of the relevant batches must be submitted.

16.7 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).

16.8 The management records of the investigational products should document quantities, delivery, receipt, disposition, return, and destruction of the investigational products. The Investigator should not provide the investigational products to any individuals who are not trial participants.

16.9 The sponsor should ensure that the investigational products are adequately packaged and labelled for clinical trial use only. In addition, the labelling should comply with the specifications specified in the protocol including at least the following information:

16.10 A statement indicating that the drug is an investigational drug to be used only by a qualified investigator.

(a) The name, number or identifying mark of the drug

(b) The expiration date of the drug

(c) The recommended storage conditions for the drug

(d) The batch/ lot number of the drug

(e) The name and address of the sponsor

(f) The protocol code or identification

(g) The name and address of the premises where the clinical trial is to be carried out.

(h) The sponsor should retain the batch samples of the investigational products until at least two years after the approval of a marketing application or after the conclusion of the clinical trial for unapproved marketing application.

16.11 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 BoMRA. As stated in the BOMRA/IL/IE/P05/G04 ***and MRSA 2019 Section 59***

16.12 Investigators in the trial should provide information on restrictions on the uses of the IP in any country.

16.13 Trial medications must be stored and dispensed by the pharmacy or the pharmaceutical department at the trial site in accordance with good dispensing practices. The general principle is that investigational products used in clinical trials should be handled in the same way as registered medicines.

17. Placebo

17.1 The use of placebo alone as trial treatment for some participants is not acceptable where there is known treatment.

17.2 Should use of a placebo be part of the protocol, there should be proper rationale and justification in accordance with the ICH-CGP. In principle, the placebo may be used as a comparator when there is no evidence that an existing treatment is more effective than the placebo or where no proven treatment exists. The use of the placebo should also be justifiable in that it will not pose a risk of serious or irreversible harm to participants.

17.3 When an established effective intervention exists, placebo may be used as a comparator without the established effective intervention only if:

a) Compelling scientific reasons indicate use of placebo; and

b) Delaying or withholding the established effective intervention poses no more than a minor increase over minimal risk of harm to the participant; and

c) There is a Risk Minimisation Plan, including using effective mitigation procedures.

18. QUALITY MANAGEMENT

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The quality management system should use a risk-based approach as described below.

18.1 Critical Process and Data Identification: During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

18.2 Risk Identification: The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, and informed consent process)

18.3 Risk Evaluation: The sponsor should evaluate the identified risks, against existing risk controls by considering:

18.4 The likelihood of errors occurring

18.5 The extent to which such errors would be detectable.

18.6 The impact of such errors on human subject protection and reliability of trial results

18.7 Risk Control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

18.8 Risk Communication: The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

18.9 Risk Review: The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

18.10 Risk Reporting: The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, section 9.6 Data Quality Assurance)

19. QUALITY ASSURANCE AND QUALITY CONTROL

19.1 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 requirement(s).

19.2 The sponsor is responsible for securing agreement from all involved parties to ensure d direct access 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.

19.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

19.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

19.5 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a Contract/ Clinical Research Organization (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

19.6 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing and submitted for regulatory approval by BoMRA as protocol amendments.

19.7 The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

19.8 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

19.9 All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

20. CLINICAL TRIAL PROTOCOL

20.1 The contents of a trial protocol should generally include the following topics.

20.2 General Information

20.3 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

20.4 Name and address of the sponsor and monitor (if other than the sponsor).

20.5 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

20.6 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

20.7 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

20.8 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).

20.9 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.

21. Background Information

21.1 Name and description of the investigational product(s).

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

21.3 Summary of the known and potential risks and benefits, if any, to human participants.

21.4 Description and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

21.5 A statement that the trial will be conducted in compliance with the protocol, GMP, GCP and the applicable regulatory requirement(s).

21.6 Description of the population to be studied.

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

21.8 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

22. Trial Design

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

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

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

22.3 Use of placebo alone as a trial treatment for trial participant is not acceptable where there is known treatment.

22.4 A description of the measures taken to minimize/avoid bias, including randomization and/or Blinding.

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

22.6 The expected duration of participant participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

22.7 A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

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

22.9 Maintenance of trial treatment randomized codes and procedures for breaking codes.

22.10 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.

22.11 Selection and Withdrawal of Participants

22.11.1 Participant inclusion criteria.

22.11.2 Participant exclusion criteria.

22.11.3 Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying: When and how to withdraw participants from the trial/investigational product treatment. The type and timing of the data to be collected for withdrawn participants. Whether and how participants are to be replaced. The follow-up for participants withdrawn from the investigational product treatment/trial treatment.

23. Treatment of Participants

23.1 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.

23.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

23.3 Procedures for monitoring participant compliance.

23.4 Assessment of Efficacy

23.5 Specifications of the efficacy parameter

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

23.7 Assessment of Safety

23.8 Specifications of the efficacy parameter

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

23.10 Procedures for eliciting reports of and for recording and reporting adverse event and Inter-current illnesses.

23.11 The type and duration of the follow-up o participants after adverse events

24. Statistics

24.1 A description of the statistical methods to be employed, including timing of any planned interim analysis.

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

24.3 The level of significance to be used.

24.4 Criteria for the termination of the trial.

24.5 Procedures for accounting for missing, unused and spurious data.

24.6 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. The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, valuable participants).

24.7 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, Institution Review Boards (IRB)/Institution Ethical Committees (IEC) review, and regulatory inspection(s) providing direct access to source data/documents.

24.8 Quality Control and Quality Assurance of Data and Procedures

24.9 To ensure the conclusion of the trial can be derived sequentially from the raw data, all observations findings, especially the reliability of the trial, should be subjected to re-validation.

24.10 Quality control procedure should be enforced to each step of data processing to ensure that all data are reliably and correctly processed.

24.11 It is recommended that the sponsor or the medical institution appoint individuals, who are not involved with the trial, to conduct audits independently.

24.12 All relevant documents specified in the guidelines, including application forms, should be made available for inspection and audit by the sponsor or by the BoMRA.

24.13 Trial sites, medical institutions, laboratories, and all data (including raw data) and documents should be made available for inspection by the BoMRA.

24.14 Ethics Description of ethical considerations relating to the trial.

24.15 The trial design must be customised appropriately for the local setting to ensure that local realities are considered and appropriately integrated into the design.

24.16 BoMRA and HRDC must review proposals carefully to ensure that feasible and appropriate modifications are made for the local context.

25. Data Handling and Record Keeping

25.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

25.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

25.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

25.3.1 Ensure and document that the electronic data processing system(s) conform(s) to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

25.3.2 Maintains SOPs for using these systems.

25.3.3 Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

25.3.4 Maintain a security system that prevents unauthorized access to the data.

25.3.5 Maintain a list of the individuals who are authorized to make data changes.

25.3.6 Maintain adequate backup of the data.

25.3.7 Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

25.3.8 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an ambiguous participant identification code that allows identification of all the data reported for each participant.

25.3.9 The sponsor, or other owners of the data, should retain all of the sponsor specific essential documents pertaining to the trial.

25.3.10 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of Botswana.

25.3.11 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 15 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

25.3.12 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

25.3.13 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

25.3.14 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor, as stated in the ICH Guideline.

25.3.15 These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

25.4 Insurance of Trial Participants for trial related injuries.

The sponsor shall provide insurance cover for trial related injuries for the participants of the study. Certificate of insurance or a letter confirming such insurance cover shall be submitted to the authority.

25.5 Publication Policy

Publication policy should include a plan for the publication of the results (publishing plan).

25.6 Contents of the Investigator's Brochure (IB)

The IB should contain the following sections, each with literature references where appropriate:

25.6.1 Table of Contents

25.6.2 Summary: A brief summary (preferably not exceeding two pages) should

be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

25.6.3 Introduction: A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

25.6.4 Physical, Chemical, and Pharmaceutical Properties and Formulation: A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula (e), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

25.6.5 Nonclinical Studies: Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available:

25.6.6 Species tested.

25.6.7 Number and sex of animals in each group.

25.6.8 Unit dose (e.g., milligram/kilogram (mg/kg));

25.6.9 Dose interval.

25.6.10 Route of administration.

25.6.11 Duration of dosing.

25.6.12 Information on systemic distribution.

25.6.13 Duration of post-exposure follow-up.

25.6.14 Results, including the following aspects:

25.6.15 Nature and frequency of pharmacological or toxic effects.

25.6.16 Severity or intensity of pharmacological or toxic effects.

25.6.17 Time to onset of effects.

25.6.18 Reversibility of effects.

25.6.19 Duration of effects.

25.6.20 Dose response.

25.6.21 Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. The data that is submitted to BoMRA from nonclinical 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. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on an mg/kg basis.

25.6.22 Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)). Pharmacokinetics and Product Metabolism in Animals A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and

the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

25.6.23 Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

a. Single dose

b. Repeated dose

c. Carcinogenicity

d. Special studies (e.g., irritancy and sensitization)

e. Reproductive toxicity

f. Genotoxicity (mutagenicity)

25.6.24 Effects in Humans: Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing. Pharmacokinetics and Product Metabolism in Humans A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available: Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination). Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form. Population subgroups (e.g., gender, age, and impaired organ function). Interactions (e.g., product-product interactions and effects of food). Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

25.6.25 Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data.

Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed. The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

25.6.26 Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

25.6.27 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.

25.6.28 Information on Investigational Product(s)

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosage and duration, and in the trial population to be studied. The sponsor should update the Investigator's brochure as significant new information becomes available.

25.6.29 Investigational Medicinal Product (IMP) (s)

The Investigational Medicinal Product is 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. In case of a new drug application or when a product is not registered in Botswana but elsewhere, the applicant should submit a dossier in addition to Investigator's brochure.

25.6.30 Quality of Investigational Medicinal Products Formulations used in clinical studies should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of Drug development. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses.

25.6.31 Responsibility for investigational product (s) accountability at the trial site (s) rests with the investigator/institution.

25.6.32 Where allowed/required, the investigator/institution may/should assign some or all the investigator's/institution's duties for investigational product(s) accountability at the trial site (s) to an appropriate pharmacist or any other as authorised according to the Drugs and Related Substances Act who is under the supervision of the investigator/institution.

25.6.33 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product (s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product (s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product (s) received from the sponsor.

25.6.34 The investigational product (s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement (s).

25.6.35 The investigator should ensure that the investigational products are used only in accordance with the approved protocol.

25.6.36 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product (s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

25.7 Chemistry and Manufacturing:

Clinical trial investigational medicinal products must be manufactured in accordance with the code of Good Manufacturing Practice (GMP) including Good Manufacturing Practice for Investigational Medicinal Products. This implies that the manufacture of the investigational product may be subject to control and inspection in the same way as in the case of marketed medicinal products.

25.8 Certificates of analysis (COAs) must be provided for all investigational and comparator products.

25.9 Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner and should include the following:

25.9.1 Drug Substance:

25.9.2 Names and Source

25.9.3 The physical address of the manufacturer of the clinical trial substance

25.9.4 Method of Manufacture

25.9.5 A brief description of the manufacturing process, including a list of reagents, solvents and catalysts used should be submitted. This may be submitted as a detailed flow diagram. More information may be needed to assess the safety of biotechnology-derived medicines or those extracted from human or animal sources.

25.9.6 Physicochemical Properties and Structure Elucidation

25.9.7 A brief description of the drug substance and some evidence to support its chemical structure should be submitted.

25.9.8 Impurities

25.9.9 Specifications and Test Methods and Batch Analyses

25.9.10 A brief description of the test methods used should be submitted. Proposed acceptance limits supported by analytical data of the clinical trials material should be provided. Validation data and established specifications need not be submitted at the initial stage of development. For some well characterized, therapeutic biotechnology derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety.

25.9.11 Stability and Packaging [refer to BOMRA Stability guidelines]

25.9.12 Drug Product: Sponsors are reminded that, under present regulations, references to the current edition of the reference books may be used to satisfy some of these requirements, when applicable. Information on the drug product should be submitted in a summary report containing the following items:

25.9.13 A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those which may not appear, but which are used in the manufacturing process: A list of usually no more than one or two pages of written information should be submitted. The quality of the inactive ingredients should be cited. For novel excipients, additional manufacturing information may be necessary.

25.9.14 Where applicable, the quantitative composition of the investigational new Drug product, including any reasonable variations that may be expected during the investigational stage: A summary of the composition of the investigational new Drug product should be submitted. In most cases, information on component ranges is not necessary.

25.9.15 The name and address of the Drug product manufacturer: The full street address (es) of the manufacturer(s) of the clinical trial Drug product should be submitted.

25.9.16 A brief, general description of the method of manufacturing and packaging procedures as appropriate for the product: A diagrammatic presentation and a brief written description of the manufacturing process should be submitted, including sterilization process for sterile products. Flow diagrams are suggested as the usual, most effective, presentations of this information.

25.9.17 The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the Drug product: A brief description of the proposed acceptable limits and the test methods used should be submitted. Tests that should be submitted will vary according to the dosage form. For example, for sterile products, sterility and nonpyrogenicity tests should be submitted. Submission of a copy of the certificate for analysis of the clinical batch is also suggested. Validation data and established specifications need not be submitted at the initial stage of Drug development. For well-characterized, therapeutic, biotechnology- derived products, adequate assessment of bioactivity and preliminary specifications should be available.

25.9.18 Information to support the stability of the Drug substance during the toxicologic studies and the proposed clinical study(ies): A brief description of the stability study and the test methods used to monitor the stability of the Drug product packaged in the proposed container/closure system and storage conditions should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol should be submitted.

25.9.19 A brief general description of the composition, manufacture, and control of any placebo to be used in the proposed clinical trials Diagrammatic, tabular, and brief written information should be submitted.

25.9.20 A copy of all labels and labelling to be provided to each investigator a mock-up or printed representation of the proposed labelling that will be provided to investigators(s) in the proposed clinical trial should be submitted.

25.9.21 If the pharmaceutical or chemical properties of the investigational product have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified. This, for instance, applies to impurities and degradation products.

25.9.22 Pharmaceutical and/or chemical alterations in an investigational product that is used in an ongoing clinical trial, and that may affect the quality, safety and/or efficacy of the medicinal product must immediately be reported to the Regulatory Authority.

25.9.23 If the composition of the medicinal product is altered, additional bioavailability or bioequivalence studies may be required.

25.9.24 In cases where an extension of the shelf life for the finished medicinal product is desired, an application for this must be submitted to the Medicines Regulatory Authority. In such cases stability data or certificates of analysis (COAs) from reanalysis of the relevant batches must be submitted.

25.9.25 The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good

25.10 Manufacturing Practices (GMP).

25.10.1 Labelling and Dispensing of Trial Medications:

25.10.2 Investigational, comparator and /or placebo products used in a clinical trial must be properly labelled and contain the following information:

25.10.3 A statement indicating that the Drug is an investigational Drug to be used only by a qualified investigator.

25.10.4 The name, number or identifying mark of the Drug

25.10.5 The expiration date of the Drug

25.10.6 The recommended storage conditions for the Drug

25.10.7 The lot number of the Drug

25.10.8 The name and address of the sponsor

25.10.9 The protocol code or identification

25.10.10 The name and address of the premises where the clinical trial is to be carried out.

25.10.11 Registered products that are incorporated in the trial must also be labelled in accordance with the above.

25.10.12 Trial medications must be stored and dispensed by the pharmacy or the pharmaceutical department at the trial site in accordance with good dispensing practices. The general principle is that investigational products used in clinical trials should be handled in the same way as registered medicines.

25.11 Compliance with Protocol

25.11.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor, BoMRA, IRB/IEC and other applicable regulatory authorities.

25.11.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from BoMRA and the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

25.11.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

25.11.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the regulatory authorities, BoMRA and IRB/IEC for review and approval or favourable opinion.

25.12 Noncompliance

25.12.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

25.12.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority (ies).

25.13 Premature Termination or Suspension of a Trial

25.13.1 If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects. In addition

25.13.2 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and BoMRA and should provide BoMRA a detailed written explanation of the termination or suspension the trial.

25.13.3 If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform BoMRA and provide a detailed written explanation of the termination or suspension.

25.13.4 If BoMRA terminates or suspends its approval of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

26. Safety Reporting

26.1 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).

26.2 The entity responsible for reporting SAE's shall be clearly identified and provided in the clinical trial application or IB.

26.3 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.

26.4 If it is neither fatal nor life threatening, the sponsor shall report within 15 calendar days after becoming aware of the information.

26.5 Other serious unexpected serious adverse events (SUSAE) from foreign entities shall be reported within 30 days after becoming aware of the information.

27. Submission of SAE Reports

27.1 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. Accessible at the following link: https://cioms.ch/wp-content/uploads/2019/11/Fillable-Form_CIOMS-to-E2B.pdf

27.2 A detailed preliminary report in a narrative format should be submitted to BoMRA within 7 calendar days of first knowledge by the Applicant or Sponsor.

28. Reports of concerns discovered during safety analyses.

28.1 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.

28.2 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.

29. Post SAE Report Submission

29.1 The applicant or the Sponsors shall perform an evaluation of all submitted SAE reports related to the SAE report submitted and include scientific literature from similar incidences and provide a progress report within 6 months of the occurrence of the SAE. A follow up of this progress report should then be provided annually or on request by the Authority for the duration of the trial.

30. GCP Inspections

This will be conducted as per the AVAREF GCP Guide for the Inspection of Clinical Trials.

30.1 BoMRA has the responsibility for the inspections and investigations in all clinical trials pertaining to medicinal products for human use including vaccines and medical devices. Clinical studies should be conducted in accordance with applicable regulatory requirements which include regulations, ethical standards, BoMRA Guidelines for Good Clinical Practice, WHO Handbook for Good Clinical Research Practice, ICH guidelines and declaration and Helsinki requirements.

30.2 The Guidelines for Good Clinical Practice Inspection will integrate the principles of GCP as described in the BoMRA Guidelines for Good Clinical Practice, regulations and also to ensure that the clinical trials are carried out in accordance with the ethical principles that are reflected. This may include but may not be limited to conducting clinical trials in accordance with the approved protocol, that the data generated are accurate; that

participant enrolled in clinical trials are not subjected to undue risks and that the trial is conducted in accordance with the generally accepted principles of GCP.

30.3 Clinical trials may be inspected before a trial commences, while the trial is still on-going, or when the trial is completed. An inspection may also be conducted when triggered by a complaint or there is a suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct.

30.4 Inspections may be routine or may be triggered by issues arising during the assessment of the protocol, annual reports, amendments, or protocol deviations or by other information such as previous inspection experience.

30.5 An inspection may be conducted at the qualified investigator (clinical trial site), facility of the sponsor, Contract Research Organisation's (CRO) facilities and other establishment deemed BoMRA. The objectives of a GCP Inspection are to:

30.6 Ensure the rights, safety and well-being of study subjects have been protected.

30.7 Determine whether the trial was conducted in accordance with applicable regulatory requirements, ethical standards, and Botswana Guidelines for Good Clinical Practice.

30.8 Determine whether the data submitted in the protocol are credible and accurate and assure the integrity of scientific testing and study conduct.

30.9 Take corrective action to ensure compliance and enforcement actions when deemed necessary.

30.10 Some of the documentation and areas that will be analysed during a GCP inspection include:

30.11 The protocol, including amendments must be signed by the investigator.

30.12 Ethics Committee and regulatory approval documentation must be verified.

30.13 Signed informed consent documents must be validated.

30.14 The signatures need to be checked against evidence on patient files.

30.15 It must be determined whether written informed consent was obtained for all participants prior to the entry into the study and whether this was recorded in the participants medical records. A copy of the information presented orally must be obtained.

30.16 Participant records must be verified.

30.17 The condition, organization, completeness and legibility of the investigator's raw data files need to be described. It needs to be determined whether there is adequate documentation to assure that all inspected participants did exist and were available for the duration of their stated participation in the study. The raw data in the clinical investigator's records needs to be compared with the completed case record forms.

30.18 The following also need to be determined:

30.19 Whether the number and type of participants entered into the study were confined to the protocol limitations whether the inclusion and exclusion criteria as specified in the protocol were followed observations, information, and data condition of the participants at the time of entering into the trial.

30.20 Observations and data on the condition of the participant throughout participation in the investigation, including results of lab tests, development of unrelated illness and other factors which might alter the effects of the test article Records of exposure of the participant to the test article. Whether clinical laboratory testing (including ECGs X-rays and other special investigations), as noted in the case reports, can't be evaluated by the presence of completed laboratory reports in the source documents. The occurrence of SAEs and SAE logs will be checked and compared to the SAEs that were reported to BoMRA. All persons obtaining raw data or involved in the collection or analysis of such data need to be identified and have their signatures in the signature master file.

30.21 After the completion of the GCP inspection, a closing meeting of the inspectors and study investigators teams will he held to discuss and clarify the findings. BoMRA inspectors will then submit a signed written letter and report to the principal investigate on for his/her signed responses with action plan on how to address the non -compliances. The findings will also be tabled at the Pharmacovigilance Advisory Committee (PVAC) and reinspection maybe conducted again soon to verify compliance.

30.22 Categories of GCP Inspection Findings

GCP Inspections are classified as "critical", "major" and "minor" according to the classification of GCP findings.

30.23 Critical:

Conditions, practices, or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.

a. Possible consequences: rejection of data and/or legal action required.

30.24 Major:

Conditions, practices, or processes that might adversely affect the rights, safety or

well-being of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles.

a. Possible consequences: data may be rejected and/or legal action required.

b. Remarks: observations classified as major, may include a pattern of deviations and/or numerous minor observations.

30.25 Minor:

Conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data.

a. Possible consequences: observations classified as minor, indicate the need for improvement of conditions, practices, and processes.

b. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

30.26 General Considerations

30.27 Considerations of clinical trial applications under these circumstances shall

be in relation to the existing Guidelines for the conduct of clinical trials in Botswana:

30.28 The Authority shall facilitate the processing and approval of clinical trials during public health emergencies.

30.29 The Authority may also request for the conduct of clinical trials during public health emergencies.

30.30 The Authority shall require that the Sponsor ensures the under listed:

30.31 An appropriate memorandum of understanding regarding consultations and further actions shall be agreed upon and signed by all parties involved. The memorandum of understanding shall be binding on all parties involved. Acceptable amendments to the memorandum of understanding shall be discussed during development of the memorandum of understanding. An application to provide of an investigational product being used in a clinical trial under emergency conditions to non-trial participants shall receive prior approval from the Authority.

30.32 Ethical Considerations

All the necessary ethical approvals shall be obtained for the study.

30.33 Submission of a Clinical Trial Application to BoMRA, evaluation & approval process

30.34 MRSA Chapter 55:1-6, mandatory requirements for submission and conduct of a clinical trial application are the same for emergency public health preparedness, except that the evaluation and approval timelines will be expedited to 15-30 working days and joint reviews with ECs/NRAs and WHO _AVAREF Joint review process may also be used.

30.35 In addition, the Sponsor as part of the application may request a joint review of the application.

30.36 Such applications shall be considered by the Authority on a case-by-case basis.

30.37 Applications for the joint review process shall be submitted at least 14 working days before the proposed date of the joint review.

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

30.39 The under listed prioritization criteria shall be applied in the selection of applications for review:

30.40 Epidemiology of the emergency.

30.41 Morbidity / mortality associated with the emergency and/or condition under study.

30.42 Supporting scientific data/information available of the investigational product at the time of submission.

30.43 Feasibility of the implementation of the trial design within the context of the emergency.

30.44 Risk: Benefit impact of the intervention and/or trial design including adaptive trial design to amend to more effective and/or safer treatment regimens as they become available with time.

30.45 Upon conclusion of a review the Authority shall within applicable timelines communicate its decision on the Application to the Applicant.

NB: Please also refer to the BoMRA Clinical Trial Application Guidelines

30.46 Reporting

30.47 Reporting on the conduct of the trial shall conform to provisions mentioned above in this guideline.

30.48 The Sponsor shall develop a communication plan and any communication plan developed shall receive prior approval from the Authority before implementation. The communication plan and related information, educative and communication material shall be developed based on the principle of trust, transparency, rapid communication and adequate dialogue.

30.49 A communication plan shall consist of at least:

30.50 Background and environmental analysis

30.51 Goals and objectives

30.52 The communications team

30.53 Identification of key stakeholders

30.54 Strategy for ongoing communication with stakeholders

30.55 Strategy for managing controversy—crisis communications.

30.56 Dissemination plan for trial results

30.57 Materials to support the trial.

30.58 Monitoring and evaluation

30.59 Any communication plan proposed shall be implemented through broad-based programs to engage all relevant key stakeholders.

30.60 Information to be provided shall also be in local languages and shall be targeted not only to trial participants but also to key stakeholders, including local officials, medical professionals, the media, traditional leaders, Ministry of Health and Child Care and others.

30.61 Information provided shall include at least:

30.62 Awareness about the emergency.

30.63 Awareness about existing supporting system.

30.64 Awareness about the general objective and intended impact of the proposed study.

30.65 Shall seek to secure public / civil society support for the trial.

30.66 Mechanisms and channels available to the public to provide feedback on the trial.

30.67 Mechanisms and channels to be used to provide further information on the trial to stakeholders including international bodies.

30.68 Information, education and communication materials to be used shall receive the appropriate IRB/IEC approval.

30.69 The Sponsor shall ensure that information flow mechanisms are developed between investigators and participating communities; and that community are adequately educated on all relevant aspects of trial before recruitment begins.

30.70 Summary of Roles of Botswana Medicines Regulatory Authority (BoMRA)

30.71 No person shall conduct a clinical trial of any medicine without the prior written authorization of the Authority as stated in the MRSA2019 (chapter 5:01), along with a granted approval of HRDC.

31. Records

31.1 Clinical Trial Application From BOMRA/PCT/CT/P01/F01

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

31.3 Checklist for Clinical Trial Application BOMRA/PCT/CT/P01/F04

32. References

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

32.2 CIOMS with WHO International Ethical Guidelines for Epidemiological Studies

32.3 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research involving Human Subjects (2016)

32.4 Declaration of Helsinki (2013)

32.5 ICH E6R (2) GCP, ICHE8, ICHE9, ICHE2A to E2F guidelines and other applicable ICH guidelines for pharmaceutical development of a medical product ICH_E6-R3_GCP-Principles

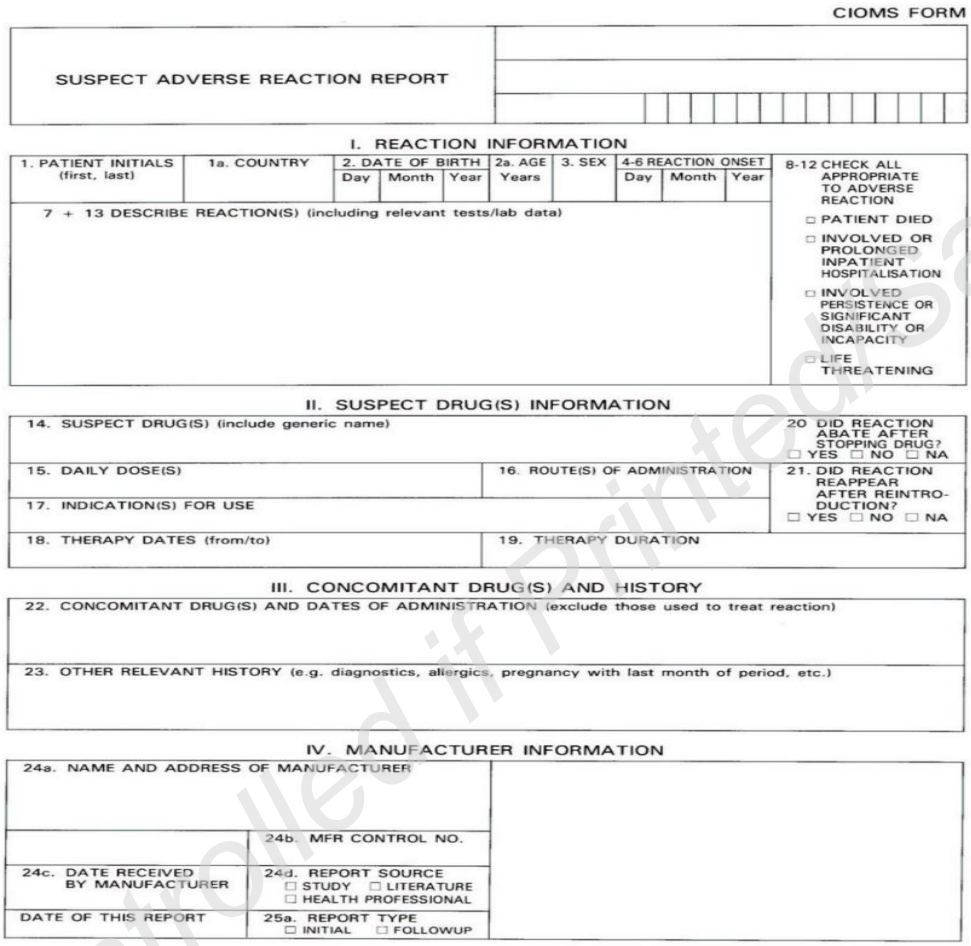
32.6 Guidelines for Good Clinical Trial Practice in Botswana Revision 1_ June 2020

32.7 Medicines and Related substances Act of 2013

32.8 MRSA regulations of 2019

32.9 World Health Organization WHO Technical Report Series, No. 850 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995)

Annex I CIOMS1 Form



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

2

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