Botswana Medicines Regulatory Authority

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1. Purpose

The purpose of this guideline is to provide a framework for regulating the conduct of clinical trials in human participants in Botswana. This guideline outlines the information required by BoMRA from sponsors and applicants wishing to conduct clinical trials as well as defines the evaluation process for the conduct of clinical trials.

2. Scope

The guideline is applicable to Clinical Trials conducted in Botswana for human participants only.

3. Definitions and Abbreviations

3.1 Definitions

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

3.1.1 Adverse Drug Reaction (ADR)- In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

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

3.1.3 Amendment (to the protocol)- See Protocol Amendment.

3.1.4 Assent- A term used to express willingness to participate in research by persons who are too young to give informed consent.

3.1.5 Blinding- 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 subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

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

3.1.7 Clinical Trial/Study- 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.

3.1.8 Clinical Trial/Study Report- A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

3.1.9 Confidentiality- Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

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

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

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

3.1.13 Deviation- Accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data.

3.1.14 Good Clinical Practice (GCP)- A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

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

3.1.16 Independent Research Ethics Committee (REC)-An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may

differ among countries but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

3.1.18 Informed Consent-A process by which a subject 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. Informed consent is documented by means of a written, signed and dated informed consent form.

3.1.19 Inspection- The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

3.1.20 Annual Clinical Trial/Study Report- A report of annual results and their evaluation based on analyses performed during the course of a trial.

3.1.21 Investigational Medicinal Product- A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

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

3.1.23 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 subjects.

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

3.1.25 Monitoring Report- A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

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

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

3.1.28 Protocol- A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced

documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

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

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

3.1.31 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.

3.1.32 Randomization-The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

3.1.33 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 and evaluation of the trial. Source data are contained in source documents (original records or certified copies)

3.1.34 Source Documents-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).

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

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

3.1.37 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.

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

3.2 Abbreviations

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

3.2.1 ADR - Adverse Drug Reaction

3.2.2 AE - Adverse Event

3.2.3 BoMRA - Botswana Medicines Regulatory Authority

3.2.4 COA - Certificate of Analysis

3.2.5 CRF - Case Report Form

3.2.6 CRO - Contract Research Organisation

3.2.7 DSMB - Data Safety Monitoring Board

3.2.8 GCP - Good Clinical Practice

3.2.9 GMP - Good Manufacturing Practice

3.2.10 HRDC - Health Research Development Committee

3.2.11 IB - Investigation Brochure

3.2.12 ICH - International Council on Harmonisation

3.2.13 IDMC - Independent Data-Monitoring Committee

3.2.14 IEC - Independent Ethics Committee

3.2.15 IREC - Independent Research Ethics Committee

3.2.16 IRB - Institutional Review Board

3.2.17 MRSA - Medicines and Related Substance Act

3.2.18 QA - Quality Assurance

3.2.19 QC - Quality Control

3.2.20 SOP - Standard Operating Procedure

3.2.21 SPC -Summary of Product Characteristics

4 Guidelines

4.1 Guideline for the Conduct of Clinical Trials in Human Participants

The aim of this guideline is to provide a framework for regulating the conduct of clinical trials in human participants in Botswana. This guideline outlines the information required by BoMRA from sponsors and applicants wishing to conduct clinical trials as well as defines the evaluation process for the conduct of clinical trials. This guideline is not intended as a comprehensive guide on Good Clinical Practice (GCP) and should be read in conjunction with relevant international GCP guidelines. This guideline has been prepared in accordance with the following GCP guidelines:

a) International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (ICH E6).

b) Guideline for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants (South Africa, 2000)

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:

4.2.1.1. Unregistered medicines/ vaccines/ medical devices

4.2.1.2. 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 as described in paragraph 2.1 above must be made on a form and accompanied by an application fee as determined by the regulatory authority.

4.2.3. No person may conduct a clinical trial using investigational products included in paragraph 2.1 above without prior authorization from BOMRA.

4.2.4. 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.

4.2.5. 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.

4.3 Responsibilities Relating to Clinical Trials:

An application to conduct a clinical trial may be made by a pharmaceutical company (sponsor), clinical research organization (CRO), or in the case of investigator initiated academic research studies, by the research institution or principal investigator.

4.4. Investigator

4.4.1 Investigator's Qualifications and Agreements

The investigator (s) should: be qualified by education, training and experience to assume responsibility for the proper conduct of the trial, meet all the qualifications specified by the applicable regulatory requirement (s), provide evidence of such qualifications through up to date curriculum vitae and/or other relevant documentation as required by BoMRA

4.4.2 The investigator should be thoroughly familiar with the appropriate use of the investigational products (s), as described in the protocol, in the current Investigator's brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.4.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by BoMRA.

4.4.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties / responsibilities

4.5 Adequate Resources

4.5.1 The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

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

4.5.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.5.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product (s), and their trial-related duties and functions.

4.6 Medical Care of Trial Subjects

4.6.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.6.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values. The investigator/institution should inform a subject when medical care is needed for intercurrent illness (es) of which the investigator becomes aware.

4.6.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.6.4 Although a subject is not obliged to give his/her reason (s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason (s), while fully respecting the subject's rights.

4.7. Communication with BoMRA

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

4.7.2 As part of the investigator's/institution's written application to BoMRA the investigator/institution should provide BoMRA with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to BoMRA.

4.8. Compliance with Protocol

4.8.1 The investigator/institution should conduct the trial in compliance with the protocol agreed by the sponsor and, if required, by BoMRA and the ethics committee. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.8.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/ from BoMRA, 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).

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

4.9 Sponsor

4.9.1 Quality Assurance and Quality Control

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.

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

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

4.10. Contract Research Organization (CRO)

4.10.1 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.

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

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

4.10.4 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.

4.11 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.

4.12. Trial Design

4.12.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

4.12.2 For further guidance on Clinical Trial Protocol and Protocol Amendment (s), the ICH Guideline for Structure and Content of Clinical Study reports, and other appropriate ICH guidance on trial design, protocol and conduct may be referred to.

4.13. Trial Management, data Handling and Report Keeping

4.13.1 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. For this guideline, a qualified person is one registered and in good standing with the Botswana Health Profession Council and Botswana Nursing and Midwifery of Botswana.

4.13.1.1 The sponsor may consider establishing an independent data-monitoring committee (IDMC)/ Data and safety monitoring board (DSMB) 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/DSMB should have written operating procedures and maintain written records of all its meetings.

4.13.1.2 When using electronic trial data handling and/or remote electronic trial data systems, it is recommended the sponsor complies with the US FDA's part 11 of Title 21 of the Code of Federal Regulations: Electronic Records; Electronic Signatures, or should:

a) Ensure and document that the electronic data processing system (s) conforms to the standards /requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation).

b) Maintains SOPs for using these systems.

c) 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).

d) Maintain security system that prevents unauthorized access to the data.

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

f) Maintain adequate backup of the data.

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

h) If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

i) The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject.

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

k) If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions, BoMRA and IEC/HRDC.

l) Any transfer of ownership of the data should be reported to BoMRA.

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications 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.

4.14. Information on Investigational Product(s)

4.14.1 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.

4.14.2 The sponsor should update the Investigator's brochure as significant new information becomes available (see 4.23 Investigator's Brochure).

4.15 Manufacturing, Packaging, Labelling, and Coding of Investigational Product(s)

4.15.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

4.15.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light and heat), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

4.15.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

4.15.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency but does not permit undetectable breaks of the blinding.

4.15.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

4.16 Supplying and handling Investigational Product(s)

4.16.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

4.16.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval from BoMRA)

4.16.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from

subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s).

The sponsor should:

a) Ensure timely delivery of investigational product(s) to the investigator(s).

b) Maintain records that document shipment, receipt, disposition return and destruction of the investigational product(s) as per the prescribed MRSA regulations of 2019.

c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaims).

d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition as per the prescribed MRSA regulations of 2019.

4.16.4 The sponsor should:

a) Take steps to ensure that the investigational product(s) are stable over the period of use.

b) Maintain records of the batches of the investigational product(s) used in the trials , an IMP and Comparator sample should be sufficient to reconfirm specifications.

4.17. Record Access

4.17.1 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.

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

4.18 Monitoring

4.18.1 Purpose

The purposes of trial monitoring are to verify that:

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

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

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

4.18.2 Selection and Qualifications of Monitors

a) Monitors should be appointed by the sponsor.

b) 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.

c) 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).

4.18.3 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.

4.18.4 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:

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

b) 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.

c) Verifying, for the investigational product(s):

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

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

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

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

v. 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:

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

d) Verifying that written informed consent was obtained before each subject's participation in the trial.

e) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

f) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.

g) Verifying that the investigator is enrolling only eligible subjects.

h) Reporting the subject recruitment rate.

i) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

j) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

4.18.5 Sharing of Clinical Trial data

The PI is required to notify BoMRA in writing the intent to share clinical trial data for scientific presentations or any other intention. The authority shall provide acceptance of the same in writing.

4.19. Ethical Assessment:

4.19.1 A clinical trial that has received approval from the BoMRA may only proceed once authorisation from HRDC has been obtained and clearance has also been obtained from a recognized Research Ethics Committee for a particular trial site as required.

4.19.2 Ethical evaluations of clinical trials of Drugs must take place in accordance with the principles of Good Clinical Practice as well as the Declaration of Helsinki and its current revisions.

4.20 Insurance of Trial Subjects:

4.20.1 All subjects must be satisfactorily insured against possible injuries that might arise during the conduct of the clinical trial.

The sponsor and PI should ensure that the insurance offered cover all contingencies that require reimbursement or compensation.

4.21 Good Clinical Practice (GCP)

4.21.1 Applicants must be able to demonstrate that clinical trials are conducted according to generally accepted principles of good clinical practice.

4.21.2 Trials must be conducted in accordance with the applicable regulatory requirement(s)

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

4.21.4 The rights, safety, and wellbeing of the trial subjects are the most important considerations and must prevail over interests of science and society.

4.21.5 The available non-clinical and clinical information on an investigational drug must be adequate to support the proposed clinical trial.

4.21.6 Clinical trials must be scientifically sound, and described in a clear, detailed protocol.

4.21.7 A trial must be conducted in compliance with a protocol that has received regulatory and ethics approval prior to initiation.

4.21.8 The medical care given to, and medical decisions made on behalf of, subjects must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

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

4.21.10 Freely given informed consent must be obtained from every subject prior to clinical trial participation.

4.21.11 All clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation and verification.

4.21.12 The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

4.21.13 Investigational Drugs must be manufactured, handled, and stored in accordance with applicable good manufacturing practices (GMP) and must be used in accordance with the approved protocol.

4.21.14 Systems with procedures that assure the quality of every aspect of the trial must be implemented.

4.22 The Clinical Trial Protocol:

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

4.22.1 General Information

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

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

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

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

e) 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).

f) 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).

g) 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.

4.22.2 Background Information

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

b) A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.22.2c Summary of the known and potential risks and benefits, if any, to human subjects.

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

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

e) Description of the population to be studied.

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

4.22.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial should be included.

4.22.4 Trial Design

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

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

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

c) A description of the measures taken to minimize/avoid bias, including:

i. Randomization

ii. Blinding

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

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

f) A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial

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

h) Maintenance of trial treatment randomization codes and procedures for breaking codes.

i) 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.

4.22.5 Selection and withdrawal of Subjects

a) Subject inclusion criteria

b) Subject exclusion criteria

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

i. When and how to withdraw subjects from the trial/investigational product treatment.

ii. The type and timing of the data to be collected for withdrawn subjects.

iii. Whether and how subjects are to be replaced

iv. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

4.22.6 Treatment of Subjects

a) 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 subjects for each investigational product treatment/trial treatment group/arm of the trial.

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

c) Procedures for monitoring subject compliance.

4.22.7 Assessment of Efficacy

a) Specification of the efficacy parameters.

b) Methods and timing for assessing, recording, and analyzing of efficacy parameters.

4.22.8 Assessment of Safety

a) Specification of safety parameters.

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

c) Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illness.

d) The type and duration of the follow-up of subjects after adverse events

4.22.9 Statistics

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

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

c) The level of significance to be used.

d) Criteria for the termination of the trial.

e) Procedure for accounting for missing, unused, and spurious data.

f) 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).

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

4.22.10 Direct Access to Source Data/Documents

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

4.22.11 Quality Control and Quality Assurance

(Refer to sponsor responsibilities)

4.22.12 Ethics

Description of ethical considerations relating to the trial.

4.22.13 Data Handling and Record Keeping

4.22.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

4.22.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

4.22.16 Supplements

(Note: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline)

4.22.17 To facilitate evaluation as well as provide guidance on the relevance of the study, the protocol should clearly indicate the complete development plan for the trial and the investigational product. This should include the following:

a) A plan for the possible discontinuation of previous treatment

b) The rationale for the use of placebo products

c) Follow-up of trial subjects after the conclusion of the trial

d) A plan for involvement of other personnel

e) The state of readiness in case of complications

f) A plan for the publication of the results (publishing plan)

g) A description of how special lists of the trial subjects and forms relating to the trial subjects will be kept for each trial subject included in the trial

4.23. The Investigator's Brochure:

4.23.1 The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration; and safety monitoring procedures.

The Investigator's Brochure also provides insight to support the clinical management of the study subjects during the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an Investigator's Brochure, but the contents of the Investigator's Brochure should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an Investigator's Brochure and provides suggestions for its layout. It is expected that they type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive Investigator's Brochure may not be necessary. A basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the

investigator. If a marketed product is being studied for a new use (i.e. a new indication), an Investigator's Brochure specific to that new use should be prepared. The Investigator's Brochure should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised Investigator's Brochure.

Generally, the sponsor is responsible for ensuring that an up to-date Investigator's Brochure is made available to the investigator(s) and the investigators are responsible for providing the up-to-date Investigator's Brochure to the responsible Institutional review Boards/Independent Ethics Committees. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal Investigator's Brochure is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

4.23.2 General Considerations

The IB should include:

a) Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

b) Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

c) Contents of the Investigator's Brochure

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

i) Table of Contents

ii) 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.

iii) 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.

iv) 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(s) should also be given. Any structural similarities to other known compounds should be mentioned.

v) Non-clinical Studies

Introduction:

The results of all relevant non-clinical 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 he investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following as appropriate, if known/available:

- Species tested
- Number and Sex of animals in each group
- Unit dose (e.g. milligram/kilogram (mg/kg)
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

    Nature and frequency of pharmacological or toxic effects

    Severity or intensity of pharmacological or toxic effects

    Time to onset of effects

Reversibility of effects

Duration of effects

Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the doses response of observed effects, the relevance to humans and any aspects to be studies in humans. If applicable, the effective and non-toxic 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.

i. Non-clinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studies 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)).

ii. Pharmacokinetic 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.

iii. 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:

• Single dose

• Repeated dose

• Carcinogenicity

• Special studies (e.g. irritancy and sensitisation)

• Reproductive toxicity

• Genotoxicity (mutagenicity)

vi)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, pharmacodynamic, 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.

i. Pharmacokinetics

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

1. Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution and elimination).

2. Bioavailability of the investigational product (absolute, where possible,

and/or relative) using a reference dosage form.

3. Population subgroups (e.g. gender, age, and impaired organ function)

4. Interactions (e.g. product-product interactions and effects of food)

5. Other pharmacokinetic data (e.g. results of population studies performed within clinical trial(s)).

ii. Safety and efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamic, 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).

iii. 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 summarised (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.

vii) Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the non-clinical and clinical data and should summarise 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 is based on previous human experience and on the pharmacology of the investigational product.

4.24 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 a dossier in addition to Investigator's brochure.

4.24.1 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

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

4.24.1.2 Where allowed/required, the investigator/institution may/should assign some or all of 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.

4.24.1.3 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.

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

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

4.24.1.6 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.

4.24.2 Chemistry and Manufacturing:

4.24.2.1 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.

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

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

a) Drug Substance:

b) Names and Source

c) The physical address of the manufacturer of the clinical trial substance

d) Method of Manufacture

e) 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.

f) Physicochemical Properties and Structure Elucidation

g) A brief description of the ag substance and some evidence to support its chemical structure should be submitted.

h) Impurities

i) Specifications and Test Methods and Batch Analyses

j) 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.

k) Stability and Packaging [refer to BOMRA Stability guidelines]

4.24.2.4 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:

4.24.2.5 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.

4.24.2.6 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.

4.24.2.7 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.

4.24.2.8 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

4.24.2.9 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 non-pyrogenicity 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.

4.24.2.10 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.

4.24.2.11 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.

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

4.24.3. 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.

4.24.4 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.

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

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

4.24.7 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).

4.25. Labelling and Dispensing of Trial Medications:

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

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

b) The name, number or identifying mark of the Drug

c) The expiration date of the Drug

d) The recommended storage conditions for the Drug

e) The lot number of the Drug

f) The name and address of the sponsor

g) The protocol code or identification

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

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

4.25.3 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.

4.26 Requirements Concerning Informed Consent:

4.26.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement (s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the BoMRA written approval of the written informed consent form and any other written information to be provided to subjects.

4.26.2 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 receive the BoMRA approval in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.26.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.26.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor or their agents from liability for negligence.

4.26.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval by BoMRA

4.26.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.26.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.26.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.26.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.26.10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research

b) The purpose of the trial

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

d) Other medicines that may/may not be taken at the same time as the trial medication. Non-prescription medications and complementary products should be mentioned specifically

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

   ii. Criteria for selection that apply to the subject

   iii. The subject's responsibilities

   iv. Those aspects of the trial that are experimental

e) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

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

g) The alternative procedure (s) or course (s) of treatment that may be available to the subject, and their important potential benefits and risks.

h) The compensation and/or treatment available to the subject in the event of trial-related injury.

i) The anticipated prorated payment, if any, to the subject for participating in the trial.

j) The anticipated expenses, if any, to the subject for participating in the trial.

k) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

l) That the monitor (s), the auditor (s), the IRB/IEC, and the regulatory authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

m) That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

n) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

o) The person (s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial related injury.

p) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

q) The expected duration of the subject's participation in the trial

r) The approximate number of subjects involved in the trial.

i. Follow-up treatment, if applicable

ii. Information about who the trial subject can contact. This should include details of the investigator, Research Ethics Committee and Regulatory Authority

iii. Information if biological fluids will be used and/or stored for pharmacogenetic sub studies. Participation in this part of the study should be voluntary and a separate informed consent must be obtained

4.26.11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.26.12. When a clinical trial (therapeutic or non-therapeutic) includes subject who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

Trials on under-aged subjects and subjects with reduced competence to consent.

4.26.12.1. Withdrawal of consent

4.26.12.2. Provision of new information to subjects as these become available

4.26.12.3. Pregnant and breast-feeding subjects must be excluded from participation in the study and safe contraceptives must be used by women of a childbearing age. Information concerning safe use of contraceptives for men, if this is relevant, must be provided

4.26.13. Additionally the patient should be informed if there are any amendments approved and implemented in the trial protocol and investigational product that relates to the patients enrolment, treatment follow up, and participation of the patient in the trial.

4.27. Clinical Trial Amendments:

4.27.1. Applications for amendments to clinical trial protocols and investigational product/s must be submitted to BoMRA for approval prior to their implementation.

4.27.2. The applicant must submit the original wording, revised wording, and rationale for the change including a copy of a complete protocol incorporating all amendments.

4.27.3. These amendments must also be presented to the site Research Ethics Committee for approval prior to implementation.

4.27.4. Approval must be obtained for the following amendments to the clinical trial protocol:

4.27.5. Changes that affect patient selection and monitoring

4.27.6. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)

4.27.7 Changes that affect patient discontinuation

4.27.8 Changes that result in the extension of the duration of the clinical trial

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

4.28 Clinical Trial Records:

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

4.28.2 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.

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

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

4.28.5. The sponsor must maintain complete and accurate records in respect of the use of a Drug in a clinical trial, including:

a) A copy of all versions of the investigator's brochure for the Drug.

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

c) Records in respect of the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the use of the Drug may endanger the health of the clinical trial subjects or other persons;

d) Records in respect of the shipment, receipt, disposition, return and destruction of the Drug;

e) 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;

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

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

4.29 Premature Termination /Suspension/withdrawal of a Trial

4.29.1 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:

4.29.2. 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.

4.29.3. 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.

4.29.4. 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.

4.30 Reporting of Adverse Drug Reactions and Adverse Events:

4.30.1 The term adverse Drug reactions is understood as adverse events where the connection to the trial medication cannot be excluded (possible or probable connection).

4.30.2 The sponsor must report serious adverse Drug reactions that emerge during trials as individual reports (one report per suspected event).

4.30.3 During the course of a clinical trial, the sponsor must inform BoMRA of any serious unexpected adverse Drug reaction in respect of the Drug that has occurred locally or internationally and defined as "an untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalisation of the trial subject (where the trial subject is an out-patient or a healthy person), prolongation of hospitalization of the trial subject (where the trial subject is an indoor-patient), persistent or significant disability or incapacity, congenital anomaly, birth defect or life threatening event.

4.30.3.1 If it is fatal or life threatening, report within 72hours after becoming aware of the information

4.30.3.2 If it is neither fatal nor life threatening, within 15 working days after becoming aware of the information.

4.30.4 The potential connection to the study drug must be clarified, and updated reports sent to BoMRA.

4.30.5 With regard to adverse Drug reaction that are serious and already known (described in Investigator's Brochure or the Summary of Product characteristics (SPC) these cases must be reported as soon as the necessary information are available and not later than 15 working days.

4.31 Submission of Reports:

4.31.1 Annual Report

The applicant conducting the clinical trial must 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

4.31.2 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

4.32 Inspection of Clinical Trials:

4.32.1 BoMRA may inspect clinical trial sites and trial sponsors to ensure that the generally accepted principles of good clinical practice are met this shall be done according to Clinical Trials inspection BOMRA/PCT/CT/P02

4.32.2 The objectives of the inspection will be to ensure that participants in clinical trials are not subjected to undue risks, to validate the quality of the data generated or to investigate complaints.

4.32.3 The Medicines Regulatory Authority may use the information collected as a result of these inspections to ensure compliance with the regulatory framework and may take action as deemed necessary.

4.33 The Clinical Trial Application:

4.33.1 BOMRA will undertake an assessment of a clinical trial only upon receiving fully completed applications.

4.33.2 The following are the requirements when submitting an application to conduct a clinical trial (ONE hard copy and an electronic copy):

a) Covering letter addressed to CEO, BoMRA Attention: Director, Clinical Trials Control and signed and dated by the Principal Investigator

b) Completed Application form

c) Cover sheet

d) Checklist

e) Final version of the Clinical Trial Protocol

f) Patient Information leaflet and Informed Consent form

g) Investigators Brochure and/or Package Insert

h) Signed investigator(s) CV(s) in required format

i) Signed declaration by Principal investigator(s)

j) Signed joint declaration by Sponsor/National Principal investigator

k) Signed declaration by Co- or Sub-investigators

l) Signed declaration by regional monitor and/or study coordinator

m) Electronic copies to be submitted in Microsoft Word format

n) Financial declaration by Sponsor and Principal investigator

4.33.3 Documentation must be arranged in separate folders. The extent of the documentation requirements will generally depend on the development phase of the investigational product.

4.34 Validity period of permission to initiate a clinical trial.

The permission to initiate clinical trial granted shall remain valid for a period of 12 months from the date of its issue, unless extended by BoMRA.

Appendix 1

CLINICAL TRIAL APPLICATION CHECKLIST

Clinical trial application checklist	
Full Title of the Trial	
Short Title	
Protocol No.	
Version No.	
Investigational medical product	
Sponsor	
Contact person	
Address	
Telephone No.	
Fax No.	
Cell No.	
Email address	
Date of application	

No.	Mark (x)	Item
1.		Cover letter including list of documents submitted and their version number and date
2.		Completed clinical trial application form including cover page
3.		Clinical trial protocol including site specific addendums
4.		Informed consent form(s)
5.		Product information if the investigational medical product is registered: summary of product characteristics, patient information leaflet/package insert, and labelling
6.		Investigator's brochure
7.		If applicable, synopsis of previous trials with the investigational medical product(s)
8.		If applicable, electronic copies of key peer reviewed publications to support the application.
9.		Copy/ies of patient recruitment advertisement(s) (if applicable) and questionnaires
10.		Investigational medical product dossier (If applicable)
11.		Product information and certificate of analysis for the concomitant and rescue medications
12.		GMP certificate for the site(s) producing the IMP(s)2
13.		Certificate(s) of analysis of the IMP(s)
14.		Certificate(s) of accreditation for the central laboratories
15.		Signed declaration by the applicant
16.		Signed declaration by the national principal investigator
17.		Workload forms for investigators
18.		Signed curriculum vitae for all key staff participating in the conduct of the clinical trial, e.g., national principal investigator, principal and/or co-investigators, study coordinator, regional and local monitor, contract research affiliate, etc

19.		Signed declaration(s) by each investigator(s)
20.		Signed joint financial declaration between the sponsor and the national principal investigator
21.		Signed declaration by the sub-investigators and key staff participating in the clinical Trial
22		Signed declaration by the regional monitor(s)
23.		Proof of registration on PACTR or other WHO primary accessible registry
24.		Active clinical trials insurance (Phase I, II, III)
25.		Proof of sponsor indemnification for investigators and trial site
26.		GCP certificates for the investigators
27.		Proof of registration of the key investigators with a professional statutory body (if applicable)
28.		Proof of professional indemnity (malpractice insurance)
29.		Study budget
30.		Evidence of submission to the national ethics committee
31.		Data Safety Monitoring Board charter and composition
32		Proof of Payment from BoMRA