LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

GUIDELINE FOR APPLICATION TO CONDUCT OF CLINICAL TRIALS IN LIBERIA

Date: February 2014

THIS GUIDELINE WAS PROMULGATED UNDER PART IV SECTION 2 (1 j & n) OF THE LIBERIA MEDICINES AND HEALTH PRODUCTS REGULATORY AUTHORITY ACT OF 2010

First Edition

February 2014

GUIDELINE FOR APPLICATION TO CONDUCT CLINICAL TRIALS IN LIBERIA

Foreword

This is the first edition of the guideline for application to conduct clinical trials in Liberia which has been drafted by a committee constituted by the Liberia Medicines and Health Products Regulatory Authority (LMHRA). The guideline has been made under Part IV Section 2(1 j & n) of the Liberia Medicines and Health Products Regulatory Authority Act, 2010. The edition is the first on the process of Clinical Trials in Liberia to have been drafted and to be implemented under the LMHRA's Act of 2010. The Authority has a legal responsibility of ensuring that all clinical trials obtain a written authorization from the LMHRA prior to commencement of study of any kind in Liberia.

It is therefore anticipated that all those who will be intending to conduct clinical trials in Liberia will herein oblige themselves with the aforementioned legal provisions and follow the procedures and requirements as set out in this guideline. The review process had evolved through drafting the guideline and consultation with stakeholders from various institutions before final approval by the LMHRA Management. The guideline therefore provides an up-to-date guidance on application requirements and standards of Good Clinical Practices (GCP) to be followed by all those who have interests in clinical trials in the country, to include research institutions, Medicines and Health Products Ethics Committee (MHEC), researchers, Contract Research Organizations (CROs), trial participants, trial applicants, Principal Investigators (PIs) and Sponsors alike.

It is the expectation of the LMHRA that the guideline will enable consistent and uniform documentation of applications and make it easier for the Authority to evaluate all clinical trials and make decisions on approval/non-approval based on clear and transparent outlined criteria. The Authority has also adopted for use the International Conference on Harmonization (ICH) of Technical requirements for Registration of Pharmaceuticals for Human Use - Tripartite Guideline for Good Clinical Practice (GCP). Applicants are therefore required to follow the LMHRA guideline along with the current GCP guideline when generating clinical trials data. As clinical trials are complex in nature and since review of technical guidelines in any scientific spectrum is unavoidable in order to keep pace and benefit from developments in science and technology, the LMHRA shall always welcome new ideas, opinions, and suggestions in this context that will assist in improvement of this guideline.

David Sumo (Pharm.)

MANAGING DIRECTOR

LMHRA

Acknowledgements

I am grateful to the hard working committee for their tireless effort in the draft of this policy document to guide all medicines and health products related clinical trials in the Republic of Liberia. This guideline has been drafted to outline application requirements and procedures for clinical trials.

The process to draft the guideline started in August, 2013 with a seven-man committee that worked along with the Department of Pharmacovigilance and Medicines Information of the Liberia Medicines and Health Products Regulatory Authority (LMHRA) to produce the first draft. The drafting team relied on their experiences, knowledge on clinical trials and available literatures (WHO, ICH-GCP, NIH, School of Pharmacy-University of Liberia, etc.).

I would like to express my profound gratitude to the Drafting Committee members, Pharm. Ezekiel F. Hallie, Pharm. Joseph N. Somwarbi, Pharm. Nathaniel Borley Comehn, Pharm. James D. K. Goteh, Pharm. Juwe D. Kercula and Mr. Theophilus Ndorbor, for the level of hard work and resources exerted in a timely development of this first draft. I would also like to express my sincere thanks and appreciation to all persons and institutions for their support.

David Sumo, Pharm.
Managing Director
LMHRA

Acronyms

ADRs	:	Adverse Drug Reactions
AEs	:	Adverse Events
API	:	Active Pharmaceutical Ingredient
BSE	:	Bovine spongiform encephalopathy
BUCHS	**:**	Bugando University College of Health Sciences
CoA	:	Certificate of Analysis
CRF	:	Case Report Form
CRO	:	Contract Research Organization
CTA	:	Clinical Trial Application Form
CTC	:	Clinical Trial Model Certificate
DMC	:	Data Monitoring Committee
DSMB	:	Data and Safety Monitoring Board
IEC	:	Independent Ethics Committee
GCLP	:	Good Clinical and Laboratory Practices
GCP	**:**	Good Clinical Practice
GMP	:	Good Manufacturing Practice
IB	:	Investigator's Brochure
ICH		International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	:	Independent Data Monitoring Committee
IMP	:	Investigational Medicinal Product
IP	:	Investigational Product
IRB	:	Institutional Review Board
LMHRA	:	Liberia Medicines & Health Products Regulatory Authority

LPB	**:**	Liberia Pharmacy Board
MOH/SW	:	Ministry of Health & Social Welfare
MTA	:	Material Transfer Agreement
NEC	:	National Ethics Committee
NF	**:**	National Formulary
PI	:	Principal Investigator
PIL	:	Principal Investigator List
QA	:	Quality Assurance
QC	:	Quality Control
REC	**:**	Research Ethics Committees (Independent /Institutional)
SAE	:	Serious Adverse Event
SUSARs	:	Suspected Unexpected Serious Adverse Reactions
SOPs	:	Standard Operating Procedures
TFDA	:	Tanzania Food and Drugs Authority
TSE	:	Transmissible Spongiform Encephalopathy
USP	:	United States Pharmacopoeia
WHO	:	World Health Organization
WMA	:	World Medical Assembly

Table of Contents

1.0 Introduction

Clinical trials are organized research studies directed on prospective human participants expected to determine the safety and effectiveness of new or unverified treatments. They are specifically designed to find better ways to treat, cure, prevent or diagnose diseases and/or conditions and to answer scientific questions.

The Liberia Medicines and Health Products Regulatory Authority Act of 2010, provides for the regulation and control of clinical trials in the country. **Part V Section 5(1)** of the Act prohibits any person/organization to conduct a clinical trial on any medicines and health products without a written authorization from the Authority. **Section 5(2)** provides that the conditions for authorization of such Clinical Trial shall be stipulated in regulations promulgated by the Authority that shall provide for the issuance, renewal, suspension, cancellation and revocation of such authorizations. In this regard, any person wishing to conduct a clinical trial of a medicines and health products shall submit to the Authority an application in prescribed form signed by him/her and accompanied with prescribed fees, an Ethical Clearance Certificate issued by any approved institute for clinical research and any other relevant information as required by the LMHRA. This guideline has therefore been developed so as to provide guidance on current minimum standards required for authorization to conduct clinical trials involving medicines and health products in Liberia. It articulates among other things, including application procedures, good clinical practice (GCP) requirements and ethical principles for clinical research involving human participants. Ethics are as important as scientific considerations when reviewing clinical protocols for research, this is an important aspect emphasized in this document.

The LMHRA has requirements for qualifications and responsibilities of investigators and monitors. It also has requirements concerning informed consent and procedures for trial amendments. Other requirements include reporting of Serious Adverse Events (SAEs)/Suspected Unexpected Serious Adverse drug Reactions (SUSARs), requirements concerning Data Safety Monitoring Board (DSMB) or alternatively known as Data Monitoring Committee (DMC), as well as the regular submission of progress reports, procedures for termination of clinical trials and a snapshot on inspection of trial sites. Various forms and tools have also been attached as appendices to aid in the application process. These shall be filled in and submitted together with the documentation as specified in the guideline.

1.1 Relevance of this Guideline

The relevance of this guideline is to provide Liberia with clearly expressed standards of good clinical practice in clinical study that are also applicable to local realities and contexts and to

ascertain that clinical trial carried out on human participants are designed and conducted according to strict scientific and ethical principles within the basis of good clinical practice. Compliance with these standards provides the public with assurance that the rights, safety and well-being of trial participants are safeguarded and that clinical trial data are trustworthy.

1.2 Definition of terms

In the context of this guideline the following words/phrases are defined as adopted from WHO:

The Act - The Liberia Medicines and Health Products Regulatory Authority Act of 2010 and regulations relating to clinical trials made under the Act.

Adverse Drug Reactions - All noxious and unintended responses to a clinical trial medicinal product related to any dose or all unintended noxious responses to a registered medicinal product which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event -Any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product and which does not necessarily have a usual relationship with the treatment. An adverse event (AE) can therefore beany unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

Applicant - A person applying to conduct a clinical trial which may include a sponsor, contract research organization or in the case of investigator-initiated academic research studies, research institution or principal investigator.

Audit of a trial - A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms are consonant with those found in hospital files and other original records.

Audit Certificate - A declaration of confirmation by the auditor that an audit has taken place

Audit Report - A written evaluation by the sponsor's auditor of the results of the audit

Authority– Liberia Medicines and Health Products Regulatory Authority (LMHRA)

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

Case Report Form - A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Clinical Trial/Study - A systematic study on medicinal product(s) in human participants (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into four phases.
A brief description of the individual phases, based on their purposes as related to clinical development of medicinal products, is given below:

Phase I - These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

Phase II - These trials are performed in a limited number of study participants and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III - Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV - Studies performed after marketing of the medicinal product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post marketing surveillance, or assessment of therapeutic value or treatment strategies.
Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new medicinal products.
Clinical Trial/Study Report - A clear and accurate written description of a trial/study of any therapeutic or prophylactic agent conducted in human study participants in which the clinical and statistical description, presentations and analyses are fully integrated into a single report.

Comparator Product - A medicinal or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Confidentiality -Maintenance of the privacy of trial participants including their personal identity and all personal medical information.

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.

Coordinating Committee - A committee that a sponsor may organize to coordinate the conduct of a multi-center trial.

Coordinating Investigator - An investigator assigned the responsibility for the coordination of investigators at the different centers participating in a multi-center trial.

Contract Research Organization - 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.

Data and Safety Monitoring Board - 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.

Direct Access - Permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical trial. LMHRA inspectors with direct access should take all reasonable precautions to maintain the confidentiality of study participants' identities and sponsor's proprietary information.

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.

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

Ethical Clearance - An authorization to conduct a clinical trial issued by the Medicines and Health Products Ethics Committee based on ethical issues related to trials involving human participants in Liberia.

Good Clinical Practice - A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial study participants are protected.

Good Manufacturing Practice - That part of quality assurance which ensures that investigational products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current LMHRA GMP Guideline.

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

study participant or the study participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the study participant.

Independent Ethics Committee - An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of participants in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

Informed Consent - A participant's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (see Appendix 11).

Inspection - The act of conducting an official review of documents, facilities, records, and any other resources that are deemed necessary by LMHRA to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities or at other establishments deemed appropriate by LMHRA.

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

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.

Investigator - A physician, dentist or other qualified person who conducts a clinical trial at a trial site. See also Sub-investigator.

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

Legally Acceptable Representative - An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective study participant, to the study participant's participation in the clinical trial.

Material Transfer Agreement - A written agreement entered into by a provider and a recipient of research material. The purpose of the MTA is to protect the intellectual and other property rights of the provider while permitting research with the material to proceed.

Monitor- A person appointed by, and responsible to, the sponsor or Contract Research Organization (CRO) for the monitoring and reporting of progress of the trial and for verification of data.

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.

Multi-center 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.

Pre-clinical Studies - Biomedical studies not performed on human study participants.

Principle Investigator - A person responsible for the conduct of the clinical trial at a trial site who is a pharmacist, physician, dentist or other qualified person, and a member of good standing of a professional health association. If a trial is conducted by a team of individuals at a trial site, the principle investigator is the responsible leader of the team. See also Sub-investigator.

Protocol - A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

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

Quality Assurance - All those planned and systematic actions that are established to ensure that the trial is performed and the credible data are generated, documented (recorded), and reported incompliance with LMHRA requirement(s).

Quality Control - 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.

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

Serious Adverse Event - or Serious Adverse Drug Reactions (Serious ADR)

Any untoward medical occurrence that at any dose: a) that results in death, b) that is life threatening, c) that requires hospitalization or prolongation of existing hospitalization, d) that results in persistent or significant disability/incapacity, or e) that is a congenital anomaly/birth defect.

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

Source Documents - Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, study participants' 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, study participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

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

Standard Operating Procedures - Detailed written instructions to achieve uniformity of the performance of a specific function.

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 make important trial-related decisions (e.g. associates, residents, research fellows).

Trial participant- An individual who participates in a clinical trial either as a recipient of the investigational medicinal product(s) or as a control.

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

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

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).

Vulnerable Study participants - Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such a 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 study participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

2.0 Application Procedure

An application to conduct a clinical trial is required for the following categories of medicines:

1. Unregistered medicines
2. Registered medicines where the proposed clinical trials are outside the conditions of approval. These may include changes to:
   a. Indications and clinical use
   b. Target patient population(s)
   c. Routes of administration
   d. Dosage
3. An application must be made by completing an application form (Appendix 1) accompanied by a fee as prescribed in Appendix 11. Any application that will not be accompanied by proof of payment will not be accepted.
   a. Fees may be paid directly to the LMHRA's account or by bank transfer to:
      Liberia Medicines and Health Products Regulatory Authority (LMHRA)
      Bank: **ECOBANK, Liberia Ltd**
      Account number: **001-113472105440**

4. Approval by LMHRA to conduct post-marketing clinical trials of a registered medicine within the approved conditions of registration of such a medicine is not required.
5. 2.4.1 The application shall be submitted in the English Language, both electronic and hard copy. Processing of application shall only begin upon receipt of the hard copies. Four copies word formatted, Times New Roman, font size 12, shall be submitted in sealed envelope.

6. Applications should be submitted to the following address:
   Liberia Medicine and Health products Regulatory Authority (LMHRA)
   VP Road, Tubman Boulevard
   Old Road, Sinkor
   1000 Monrovia, 10 Liberia
   West Africa

7. An application to conduct a clinical trial shall include:
   Cover letter, duly filled in, signed and stamped application form (Appendix 1)
8. General investigational plan
9. Capacity building plans including training and updating of staff that will be involved in the clinical trial
10. Protocol (study protocol and investigators, copies or description of CRFs to be used, facilities and IEC data, informed consent forms and information given to participants)
11. Investigator's Brochure or prescribing information data sheet

12. Declarations by sponsor, investigators and monitor(s) in prescribed format (Appendices 2-4)
13. Financial declaration by Sponsor and/or Principal investigator in prescribed format (Appendix 5)
14. Certified copy of insurance of study participants
15. Ethical clearance or a copy of acknowledgement of submission of study protocol from the Medicines and Health Products Ethics Committee
16. Curriculum vitae (CV) of investigator(s) (see Appendix 6 for recommended format)
17. Investigational medicinal product dossier
18. An application to conduct a clinical trial may be made by a sponsor or the sponsor's agent who must also submit a power of attorney attesting that he is a duly appointed agent.
19. A statement by the applicant must be provided indicating that all information contained therein, or referenced by the application is complete, accurate and not misleading.
20. In the case of multi-center trials, a coordinating investigator must also sign the application form.
21. If the trial is part of an international study, information regarding the other Participating countries must be provided including the part of the trial that will be carried out locally.
22. LMHRA will only process an application upon receipt of a completed application together with the prescribed fees.
23. Processing of application shall take a period of five (5) months upon receipt of submission whereby the outcome of the application shall be communicated to the applicant within this period.

3.0 Qualifications and Responsibilities of Sponsors, Investigators and Monitors:

1. Sponsors, investigators and monitors should assume responsibilities as provided in the GCP guidelines.
2. The principal investigator (PI) engaged in clinical trials must have a university degree in pharmacy, pharmacology, toxicology, biochemistry or medicines and related fields and must be competent with practical experience within the relevant professional area. The principal investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area and shall be responsible for the conduct of the clinical trial at a clinical trial site.
3. In case of multi-center studies where the PI is not a resident of Liberia, the appointed national principal investigator must be the resident and shall assume full responsibilities for all local clinical trial sites.
4. All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical and Laboratory Practices (GCLP) within the last two years. Evidence of attending GCLP course should also be submitted.

4.0 Study Protocol

The clinical trial study protocol shall have at least the following:

4.1 General Information

1. Protocol title, identification number and date. Any amendment(s) shall also bear the amendment number(s) and date(s).
2. Name and address of the sponsor and monitor (if other than the sponsor).
3. Name, title and contact details of the sponsor's medical expert (or dentist when appropriate) for the trial.
4. Name, title and contact details of the investigator (s) who is (are) responsible for conducting the trial, and the contact details of the trial site (s).
5. Name, title and contact details of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
6. 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.

4.2 Background Information

1. Name and description of the investigational product (s).
2. A summary of findings from pre-clinical studies that potentially have clinical significance and from clinical trials (if investigated elsewhere) that are relevant to the trial.
3. Summary of the known and potential risks and benefits of the studied product as observed in both animal and human testing.
4. Description of and justification for the route of administration, dosage, dosage regimen, and duration of treatment period(s).
5. A statement that the trial shall be conducted in compliance with the study protocol, GCP and LMHRA requirement(s).
6. Description of the population to be studied (e.g. age group and sex).
7. Reference literatures and data that are relevant to the trial that provide background for the trial.

4.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial shall be provided as to convince the Authority.

4.4 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:

1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
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.
3. A description of the measures taken to minimize/avoid bias, including:
    a. Randomization.
    b. Blinding.
4. A description of the trial treatment(s), 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).
5. The expected duration of subject participation, a description of the sequence and duration of the trial periods, including follow-ups, if any.
6. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, at any/all parts of the trial.
7. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
8. Maintenance of trial treatment randomization codes and procedures for breaking codes.
9. The identification of any data to be recorded directly on the case report forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered as source data.

4.5 Selection and withdrawal of study participants

1. Provide participants' inclusion criteria.
2. Provide participants' exclusion criteria.
3. Provide participants' withdrawal criteria (i.e. terminating investigational product trial treatment) and procedures specifying:
    a. When and how to withdraw participants from the trial/investigational product treatment.
    b. The type and timing of the data to be collected for withdrawn participants.
    c. Whether and how participants are to be replaced.

4.6 Treatment of study participants

During the participation of all subjects in the trial, the below documentations are required:

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 duration including follow-up period(s) for participants for each investigational product trial treatment.
2. Medication(s)/treatment(s) permitted (including rescue medications) and those not permitted before and/or during the trial.
3. Procedures for monitoring participants' compliance.

4.7 Assessment of Efficacy

The below required documentations should be provided:

1. Specifications of the efficacy parameters.
2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.

4.8 Assessment of Safety

1. Specification of safety parameters.
2. The methods and timing for assessing, recording, and analyzing safety monitoring arameters.
3. Procedures for eliciting reports of and for recording and reporting adverse events and inter-current illnesses.
4. The type and duration of the follow-up of subjects after adverse events.

4.9 Statistics

1. A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
2. The number of subjects planned to be enrolled. In multi-center trials, the numbers of enrolled subjects 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.
3. The level of significance to be used.
4. Criteria for the termination of the trial.

5. Procedure for accounting for missing, unused and spurious data.
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).
7. The selection of study participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

4.10 Direct Access to Source Data/Documents

The sponsor shall ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit LMHRA inspection(s), providing direct access to source data/documents.

4.11 Quality Control and Quality Assurance

There should be mechanism for good quality control and quality assurance.

4.12 Pharmaceutical and Health products Ethics

Description of ethical considerations relating to the trial shall include the following issues:

1. Choice of investigators
2. Monitors and monitoring plan
3. Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and LMHRA requirements
4. Indemnity measures for the participants
5. Patient Information leaflets and Informed Consent forms for any proposed archiving of biological specimens for later research or for genetics research.
6. Treatment and/or management of participants and their disease condition(s) after completion of trial
7. Institutional ethics committee capacity to monitor site and conduct of trial
8. Provide an explanation if minimum recommended compensation for a participant is not being provided.
9. Follow-up of trial study participants after the conclusion of the trial
10. In case of transfer of materials, provide Material Transfer Agreement
11. (MTA) highlighting among other things, the following:
    a. Identification of the provider and recipient
    b. Identification of the material and the volume of material

c. Definition of the trial and how the material will and will not be used.
d. Maintenance of confidentiality of background or supporting data or information, if any
e. Indemnification and warranties (where applicable)

12. Data handling and record keeping should be done in conformity with WHO guidelines

4.14 Publication Policy

Publication policy, if not addressed in a separate agreement.

5.0 The Investigator’s Brochure

The investigator's brochure must contain at least the following information in respect to the investigational medicinal product:

1. The physical, chemical and pharmaceutical properties
2. The pharmacological aspects including its metabolites in all animal species tested
3. The pharmacokinetics and metabolism including its biological transformation in all animal species tested
4. Toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study
5. Results of clinical pharmacokinetic studies
6. Information regarding safety, pharmacodynamics, efficacy and dose responses that were obtained from previous clinical trials in humans if available. More details could be found in WHO-GCP guidelines and may be followed when compiling information on this part.

6.0 Requirements concerning Informed Consent

1. In obtaining and documenting informed consent, the investigator shall comply with Medicines and Health Products Ethics Committee (MHEC) requirement(s) and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki (Appendix 11).
   Prior to the beginning of the trial, the investigator should obtain Ethical Clearance from MHEC and LMHRA approval.
2. Informed consent to study participants shall be administered in English and all information to be given to study participants both oral and written must be in English. The consent form together with the accompanying information shall be in English.
3. The written informed consent form and any other written information to be provided to participants shall be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written informed consent form, and written information should receive MHEC and LMHRA approval in advance of use. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information shall be documented.
4. Neither the investigator, nor the trial staff, shall coerce or unduly influence a participant to participate or to continue to participate in a trial.
5. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant'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.
6. The investigator, or a person designated by the investigator, shall fully inform the participant or, if the participant is unable to provide informed consent, the participant's legally acceptable representative, of all pertinent aspects of the trial including the written information and the MHEC and LMHRA approval.
7. 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 participant or the participant's legally acceptable representative and the impartial witness, where applicable.
8. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the participant or the participant'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 participant or the participant's legally acceptable representative.

9. Prior to participation in the trial, the written informed consent form shall be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.
10. If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness shall be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participant, is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to participate in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness shall sign and personally date the consent form. By signing the 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 participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative.
11. Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants shall 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. The trial procedures to be followed, including all invasive procedures.
    e. The participant's responsibilities.
    f. Those aspects of the trial that are experimental.
    g. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, fetus, or nursing infant.
    h. The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
    i. The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
    j. The compensation and/or treatment available to the participant in the event of trial-related injury.
    k. The anticipated prorated payment, if any, to the participant for participating in the trial.
    l. The anticipated expenses, if any, to the participant for participating in the trial.
    m. That the participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.

n. That the LMHRA will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by LMHRA and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.

o. That records identifying the participant will be kept confidential and will not be made publicly available. If the results of the trial are published, the participant's identity will remain confidential.

p. That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participating in the trial.

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

r. The foreseeable circumstances and/or reasons under which the participation in the trial may be terminated.

s. The expected duration of participating in the trial.

t. The approximate number of participants involved in the trial.

12. Prior to participation in the trial, the participant or the participant'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 participants. During participation in the trial, the participant or the participant'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 participants.
13. When a clinical trial includes participants who can only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g., minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant should sign and personally date the written informed consent.
14. In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented LMHRA approval to protect the rights, safety and well-being of the participant and to ensure compliance with MHEC and LMHRA requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

7.0 Investigational Medicinal Product (IMP) Dossiers

1. Clinical trial investigational medicinal products must be manufactured in accordance with Good Manufacturing Practices (GMP). 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.
2. Chemistry and manufacturing information for IMP(s) which have not been registered by LMHRA should be presented in a concise manner and shall include the following:

7.1 Active Pharmaceutical Ingredients (API)

1. Nomenclature
2. Name and address of the manufacturer
3. Physicochemical properties
4. Route of synthesis and manufacturing process
5. Documented evidence of structure and stereochemistry
6. Characterization of impurities
7. Specifications and their justifications
8. Batch analyses
9. Validation of analytical procedures
10. Container closure system
11. Stability studies

7.2 Investigational Medicinal Product (IMP)

1. Name, strength and dosage form
2. Description and composition
3. Name and address of the manufacturer
4. Pharmaceutical development
5. Description of manufacturing process including flow diagram and process validation.
6. Manufacturing information for novel excipients.
7. Specifications and their justifications (including excipients)
8. Batch analyses
9. Validation of analytical procedures
10. Characterization of impurities
11. Certificates of analysis (CoAs) and Bovine spongiform encephalopathy (BSE) /transmissible spongiform encephalopathy (TSE) certificates for excipients of human or animal origin

12. Stability studies
13. Container closure system
14. If the pharmaceutical or chemical properties of the IMP have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified.
15. Pharmaceutical and/or chemical alterations in the IMP that are used in an ongoing clinical trial and that may affect the quality, safety and/or efficacy of the IMP must immediately be reported and justified to LMHRA.
16. In cases where an extension of shelf life for the IMP is desired, an application for this must be submitted to LMHRA. In such cases stability data and certificates of analysis (CoAs) from reanalysis of the relevant batches must be submitted.
17. In case of IMP(s) which have been registered by LMHRA, a cross reference to the part of the dossier containing chemistry and manufacturing information should be declared.
18. Information on preclinical pharmacology and toxicology studies done must be submitted. In case information on preclinical studies was submitted in phase I study application, a summary of preclinical studies for the late phase trials (i.e. phase II and III) should be submitted.
19. Information on human experience data and previous clinical studies done mustbe submitted and in accordance with applicable GCP guidelines.
20. Labeling
21. Investigational medicinal products (including registered products) used in clinical trials must be properly labeled and contain the following minimum information:
22. Statement indicating that the product is for “clinical trial purpose only”
23. Name, number or identifying mark
24. Recommended storage conditions
25. Manufacturer’s address
26. Protocol code or identification
27. Re-labeling of any remaining IMP from previously manufactured batches must be performed in accordance with established written procedures and GMP principles.

8.0 Clinical Trial Amendments

1. Application for amendment(s) to a previously authorized clinical trial shall be made in forms (Appendices 6 and 7), whichever is applicable, and shall be accompanied with amendment fees as prescribed in the Fees and Charges Regulations enforced at the time of application.
2. The applicant must submit the description of the proposed amendment including reasons thereof.
3. Original wording, revised wording and rationale for the change(s) including a copy of complete protocol incorporating all amendments should also be submitted, where applicable.
4. The applicant must also submit supporting data for the amendment, including:
    a. Updated overall risk-benefit assessment
    b. Possible consequences for participants already in the trial
    c. Possible consequences for the assessment of trial results summaries of data
5. LMHRA approval must be obtained for the following amendments:
    a. Changes that affect patient selection and monitoring
    b. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc.)
    c. Changes that affect patient discontinuation
    d. Addition/deletion of an investigational site
    e. Change of principal investigator
    f. Changes that result in the extension of duration of a trial
    g. Changes that relate to the chemistry and manufacturing information that may affect drug safety and quality (For example: specifications for the IMP where limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and addition of new raw materials, solvents, reagents, catalysts or any other materials used in the manufacture of the API).
6. The application for amendment(s) shall be accompanied by Ethical Clearance or authorization from the MHEC.

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

1. All serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) should be reported to LMHRA within 8 working days and for fatal ones within 24 hours of their occurrence.
2. Form attached (Appendix 9) should be used when reporting, followed by detailed written reports. When completing the form, the application number and/or protocol number should be included.
3. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should also be reported.
4. For reported deaths, additional information (e.g., autopsy reports and terminal medical reports) should be submitted.
5. The relationship between SAE(s)/SUSARs and the IMP must be established, evaluated, clarified and submitted to LMHRA for further assessment.

10.0 Requirements concerning Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

For trials that will involve Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) to monitor trials, the following issues related to DSMB/DMC must be submitted:

1. A broad statement of the aims and objectives of the DSMB/DMC
2. Terms of Reference
3. Composition of the DSMB/DMC
4. Qualifications of the DSMB/DMC members
5. Specific roles including responsibilities of statisticians
6. The role of statistical stopping rules
7. Relationship with the principal investigators and trial management team
8. Clarification of the decision-making powers
9. How DSMB/DMC meetings will be organize.
10. Whether the DSMB/DMC will be blinded to treatment
11. What options a DSMB/DMC can recommend
12. In what form and to whom decisions shall be conveyed
13. Who the DSMB/DMC will report to
14. The role of the DSMB/DMC in the publication of results
15. Disclosure of competing interests of DSMB/DMC members

11.0 Submission of Progress Reports

The sponsor and/or PI must submit progress reports to LMHRA on a quarterly basis depending on the duration of the clinical trial from the date of initiation of the clinical trial.

12.0 Termination of Clinical Trial

12.1 Premature termination

If a clinical trial is terminated by the principal investigator or sponsor in its entirety, the principal investigator or sponsor must inform LMHRA not later than 15 days after the date of the termination; and must:

1. Provide LMHRA with the reason(s) for the termination and its impact on the proposed or ongoing clinical trials in respect of the investigational medicinal product including issues related to accountability and disposal of investigational products as well as maintenance of records.
2. As soon as possible, inform all co-investigators of the termination and of the reasons for the termination and advice them in writing of potential risks to the health of clinical study participants or other persons including ensuring that patients continue to receive medical care.

12.2 Revoking of LMHRA's Clinical Trial Approval

LMHRA may revoke the authorization to conduct a clinical trial if the Authority is of the opinion that the safety of the study participants in the trial is compromised or that the scientific reasons for conducting the trial have changed.

12.3 End of trial (Study closeout)

1. After the trial has been conducted and closed, the sponsor and/or principal investigator shall submit a closing report within 30 working days. This should be followed by a final study report within six months after trial closure unless otherwise justified. The structure and content of the final study report should be acceptable to LMHRA in line with the guidelines.
2. Any unexpected safety issue that changes the risks-benefit analysis and is likely to have an impact on trial participants should be reported together with proposed actions to be taken.

13.0 Inspection of Clinical Trial Sites

1. The Authority may inspect clinical trial (investigator) sites, sponsor's office, data management center, contract research organization (CRO) or any other establishment related to the trial as it will be deemed appropriate by the Authority to ensure that the generally accepted principles and/or requirements of GCP and LMHRA are met.
2. The objectives of inspection will be to ensure that participants are not Subjected to undue risks, to validate the quality of data generated and/or to Investigate complaints.
3. The Authority may use the information collected as a result of the inspections to ensure compliance with regulatory requirements and may take enforcement action where necessary.

14.0 Appeals

As provided in Part VIII Section 1 (5 XI bi) Liberia Medicines and Health Products Regulatory Authority Act of 2010, any person who is aggrieved by a decision of the Authority of not granting authorization for the conduct of any specified activity may make his/her representation within thirty days to the Authority and shall be accorded administrative hearing. If no such representation is submitted by the applicant within the said period or if after consideration of any comments so submitted the Authority is still not satisfied it shall reject the application.

15.0 References

Department of Health. (2000). Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, DoH, Johannesburg.
European Union (EU) Clinical Trials Directive 2001/20/EC

General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996). ICH - Tripartite Guideline, Guideline for Good Clinical Practice, Recommended for Adoption at Step 4 of the ICH Process on 1 May 1996 by the ICH Steering Committee.

Southern Africa Development Community. (2004). Draft Guideline on Regulating the Conduct of Clinical Trials in Human Participants, SADC, Gaborone.

Tanzania Food and Drug Administration (TFDA) (February, 2009), Guidelines for Conducting Clinical Trials in Tanzania

World Health Organization. (1995). Guidelines for good clinical practice (ICH-GCP) for trials on pharmaceutical products, Technical Report Series No. 850, Annex 3,WHO, Geneva.

World Medical Association (2000). Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Study participants, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. Amended by the 29th WMA

16.0 Appendixes

Appendix 1: Format for Clinical Trial Application Form (CTA)

Applicant's letterhead
To be completed by Applicants for all Clinical Trials
Study Title:
Protocol No:
Version No:
Date of protocol:
Investigational medicinal product's name, number or identifying mark
Comparator product (if applicable):
Concomitant medications (if applicable):
Applicant
Sponsor's name, signature and stamp
Sponsor's agent,
Contact Person:
Address:
Telephone Number:
Fax Number:
E-mail address:

FOR OFFICIAL USE ONLY
Date original application received:
Application/Reference No.:
Application Fee paid:
Signature:
Date:

(All future communications to LMHRA regarding the application should quote the above application/reference number).

Acknowledgement of Receipt of Application (To be completed by LMHRA receiving officer). Cover sheet to be sent to the applicant once details above are completed.
Receipt of the application is hereby acknowledged.
Name:
Signature:
Date: Stamp:

SECTION 1: FORMAT FOR CHECKLIST AND TABLE OF CONTENTS (indicate pages)

1. Covering letter
2. Completed application form
3. General investigational plan
4. Capacity building plans including training and updating of staff involved in the clinical trial
5. Investigator's Brochure or prescribing information data sheet
6. Protocols (study protocol and investigators, facilities and IEC data, informed consent forms and information given to participants}
7. Declarations by Sponsor, monitors and investigators in prescribed format
8. Financial joint declaration by Sponsor and Principal investigator
9. Certified copy of indemnity of study participants
10. Investigational medicinal product dossier:
    - Chemistry, manufacturing and quality control data of active ingredient and finished product/dosage form
    - Pharmacology and toxicology data
    - Previous human experience data
    - Prototype product label

Note: Incomplete applications shall not be processed

SECTION 2: ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title of the Study:
Protocol Number/Identification:
Version number
Date of final protocol:

Part 1: CONTACT DETAILS (Name/Address/Tel/Mobile/Fax/E-Mail)

1.1 Applicant:
1.2 Sponsor:
1.3 Local contact person:
1.4 National principal investigator:
1.5 International principal investigator: (if applicable)
1.6 Monitor:
1.7 Study coordinator:

Part 2: DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

2.1 Name(s) and details of IMP to be used in trial:

[A summary of the chemistry and manufacturing data, formulation, composition, excipients and strength should be provided. Complete chemistry and manufacturing data should be included in the investigator's brochure. Product(s) registration number(s) and date(s) of registration, if applicable,

shall be included]

2.2 Name(s) and details (as above) of comparator product(s) and product registration number(s) and date(s) of registration if applicable: [As in 2.1, where applicable. Prescribing information sheet for registered comparator products should be included]

2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and product registration number(s) if applicable [As in 2.1, where applicable. Prescribing information sheet for registered products should be included]

2.4 If any of the above products are marketed locally, explain whether locally sourced products will be used in the trial:

2.5 Details of packaging, storage conditions and shelf-life of IMP:

2.6 Registration status of IMP, for the indication to be tested in this trial, in other countries [i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary]

Part 3: DETAILS OF INVESTIGATORS AND TRIAL SITE(S)

3.1 Details of investigator(s):

[Designation and title of principal investigators/investigators) Include

Name/Address/Tel/Mobile/Fax/E-Mail]

3.2 Current work-load of investigator(s):i

[Number of studies currently undertaken by investigators as principal and/or

co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work and non-trial work]

3.3 Details of Trial Site(s):

[Name of site, physical address, contact details, contact person, etc]

3.4 Capacity of Trial Site(s):

[Number of staff, names, qualifications, experience -- including study coordinators, site facilities, emergency facilities, other relevant infrastructure]

Part 4: TRIAL STUDY PARTICIPANTS

4.1 Number of local participants:

4.2 Total number of participants worldwide (where applicable):
4.3 Total enrolment in each local site/centre: [If competitive enrolment, state minimum and maximum number per site.]
4.4 Volunteer base from which local participants will be drawn
4.5 Retrospective data indicating potential of each site to recruit required number of participants within envisaged duration of trial: [Attach as an appendix if necessary]

Part 5: OTHER DETAILS

5.1 Provide an explanation if the trial is to be conducted locally only and not in the host country of the applicant / sponsor:
5.2 Estimated duration of trial:
5.3 Details of other Regulatory Authorities to which applications to conduct this trial have been submitted, but approval has not yet been granted. Include date(s) of application:
5.4 Details of other Regulatory Authorities which have approved this trial. Include date(s) of approval and number of sites per country:
5.5 Details of other Regulatory Authorities or Research Ethics Committees which have rejected this trial, if applicable, and provide reasons for the rejection:
5.6 Details of and reasons for this trial having been suspended at any stage by other Regulatory Authorities, if applicable:
5.8 If any sub-studies are proposed as part of this protocol, indicate whether these will also be conducted locally. If not, please explain:

Part 6: ETHICS

6.1 Ethics Committee responsible for each site, date of approval or date of application:
6.2 Attach copy of response(s) positive or negative made by, and/or conditions required by Ethics Committee(s) [if available]
6.3 Details of capacity building component of the trial, if any:
6.4 Details of GCP training of investigators, monitors, study co-coordinators in terms of conducting this trial:
6.5 Detailed monitoring plan for each site: [Attach as an appendix if necessary]
6.6 Details of trial indemnity: [e.g. insurer, policy holder, policy number, insurance cover, period of validity]
6.7 Details of possible conflict of interest of any person(s)/organization(s) who/which will be involved in the trial:
6.8 Remuneration/compensation to be received by investigators, trial participants or others: [Indicate breakdown of costs to be covered, if applicable. Indicate compensation to be received by participants for travel and incidental expenses. This is subject to discussion and agreement with the Authority.]

SECTION 3: DECLARATION BY THE APPLICANT

Title of the Study:
Protocol No:
Version No:
Date of Protocol:
Study investigational medicinal product:
I/We, the undersigned have submitted all requested and required documentations, and have disclosed all information which may influence the approval of this application.

I/We, hereby declare that all information contained therein, or referenced by, this application is complete and accurate and is not false or misleading.
I/We, agree to ensure that if the above said clinical trial is approved, it will be conducted according to the submitted protocol and all applicable legal, ethical and regulatory requirements.

Applicant: _____ Date: _____

National Principal Investigator: _____ Date: _____

National Co-coordinator/Other: _____Date: _____

Appendix 2: Declaration by Principal Investigator

Name:
Title of the study:
Protocol and site:
I, the undersigned, declare that:
1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and understand the responsibilities and obligations of the
Principle Investigator (PI) within the context of this study.

2. I have notified the Liberia Medicines and Health Products Regulatory Authority (LMHRA) of any aspects of the study with which I do not/am unable to, comply. (If applicable, this may be attached to this declaration.)

3. I have thoroughly read, understood, and critically analyzed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).

4. I will conduct the trial as specified in the protocol and in accordance with LMHRA requirements and ICH – GCP principles.

5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, recruit the required number of suitable participants within the stipulated time.

6. I shall not commence the trial before written authorization from the Medicines and Health Products Ethics Committee and the LMHRA unless it has been obtained.

7. I will obtain informed consent from all participants or if their legal representatives.

8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.

9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions].

10. I have*/have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with ICH-GCP (*Attach details).

11. I have*/have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details).

11. I will submit all required reports within the stipulated time-frames.

Signature: …… Date: ……..

Witness: …….. Date: ……

Appendix 3: Declaration by Co- and Sub-Investigator

Name:
Title of the study:
Protocol number:
Principal Investigator's Name:
Site:
I, the undersigned, declare that:
1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and understand the responsibilities and obligations of the Investigator within the context of this study.

2. I will carry out my role in the trial as specified in the protocol and in accordance with Good Clinical Practice (ICH - GCP).

3. I will not commence with my role in the trial before written authorization from Medicines and Health Products Ethics Committee and the LMHRA unless it has been obtained.

4. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or their legal representatives.

5. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.

6. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions).

7. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.

8. I will submit all required reports within the stipulated time-frames.

Signature: …….. Date: ……

Witness: ……. Date: ……

Appendix 4: Declaration by Monitor

Name:
Title of the study:
Protocol number:
Site:
I, the undersigned, declare that:
1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH - GCP) and understand the responsibilities and obligations of the clinical trial monitor within the context of this study.

2. I have notified LMHRA of any aspects of the above with which I do not/am unable to comply. (If applicable, this may be attached to this declaration.)

3. I will carry out my responsibilities as specified in the trial protocol and in accordance with LMHRA requirements and ICH–GCP.

4. I declare that I have no financial or personal relationship(s) which may inappropriately influence me in monitoring this clinical trial.

5. I have*/have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with GCP. (*Attach details.).
6. I have*/have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details).

7. I will submit all required reports when needed.

Signature: …… Date: ……

Witness: ……. Date: ……

Appendix 5: Joint Declaration by Sponsor (or Representative) and

Principal Investigator (or National Principal Investigator)

Concerning Sufficient Funds to complete the Study
Title of the study:
Protocol:

I, _____ (sponsor/sponsor's agent) and I, _____ (Principal Investigator/National Principal Investigator) do hereby declare that sufficient funds have been made available to complete the above mentioned study.

Signed: …… Date: …….
SPONSOR (or Agent)

Address:

Contact details:

Signed: ……. Date: ……

PRINCIPAL INVESTIGATOR (or National PI)

Address:

Contact details:

Appendix 6: Application for Clinical Trial Protocol Amendment

APPLICATION FOR APPROVAL OF:
PROTOCOL AMENDMENT
INCREASE IN NUMBER OF STUDY PARTICIPANTS
CHANGES IN DOSE/REGIMEN OF INVESTIGATIONAL MEDICINAL PRODUCT

Title of the study:

Protocol Number:

Date:

1. APPLICANT
1.1 Name:
1.2 Address:
1.3 Telephone:
1.4 Email:

2. **TRIAL PARTICULARS** (original application)
2.1 Trial Approval Number:
2.2 Date of Approval of original protocol:
2.3 Principal Investigator(s) approved for this trial:
Number of local sites approved for this trial:
Number of participants approved for this trial:

3. AMENDMENT PARTICULARS(Please list requests for approval)
3.1 Does the applicant wish to increase the number of local study participants participating in this trial? Yes, No
3.2 Does the applicant wish to change the dose/regimen of the investigational medicinal product? Yes, No
3.3 Does this amendment request require a new consent form to be signed by the participant? Yes, No
If "Yes" please submit new Principal Investigators List (PIL) together with this application.
Protocol Amendment Number:
Version Number and Date of Protocol Amendment (for each document submitted):
General motivation for the proposed amendment: [List all of the issues included in the amendment and provide the rationale for each amendment]
Details of the proposed protocol amendment: [For each amendment, provide reasons for amendment and clearly highlight changes to the original protocol; this can be done either as "old text" replaced with "new text" or with the old text deleted with a line through it and the new text in bold and underlined]
3.4 Will this amendment apply to all approved site(s)? Yes, No
If No: Specify the investigator(s)/site(s) for which the amendment will apply:

4. **ETHICS COMMITTEE APPROVAL**

4.1 Have the Research Ethics Committee(s) responsible for each center to which this amendment applies been notified? Yes, No
4.2 Research Ethics Committee(s) responsible:
4.3 Date of application to Ethics Committee:
4.4 Date of approval by Ethics Committee:

I/We, the undersigned, agree to conduct/manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility shall sign this form).

Applicant:_____ Date:_____

Appendix 7: Application for Additional Investigator(s), Change of Investigator(s) or Additional Clinical Trial Site(s)

APPLICATION FOR APPROVAL OF:
CHANGES IN INVESTIGATOR(S) AT APPROVED SITE (includes additional investigators)
ADDITIONAL SITE(S)

Title of the study:
Protocol number:
Date:

1. APPLICANT
Name:
Address:
Telephone:
Email:

2. **TRIAL PARTICULARS (original application)**

Trial approval number:
Date of approval of original protocol:
Principal investigator(s) approved for this trial:
Number of local sites approved for this trial:
Number of participants approved for this trial:

3. **INVESTIGATOR'S DETAILS**

3.1 Name and address of additional Investigator(s)/Changes to Investigators: [Proof of ICH - GCP training must be provided for investigators who have not previously participated in clinical trials]
3.2 Summarize other ongoing/planned studies at the site involving the investigator:
[Provide details of studies, including numbers of study participants, whether the investigator is involved in research in a full-time or part-time capacity, and any other details that may affect the capacity of the site at any one time]
3.3 Date of application to Ethics Committee:
3.4 Date of approval by Ethics Committee:
3.5 Is CV for the additional investigator(s) attached? Yes, No
3.6 Is the declaration of Intent attached? Yes, No(If yes, attach declaration)

4. **CAPACITY OF THE SITE**

Describe how the site is structured so as to be able to take on the work for which this application is being made: [Give details of support staff, facilities, back-up and any other relevant infrastructure].

5. **RATIONALE FOR APPLICATION**

5.1 Briefly explain the reason for the new investigator/s or site(s):

I/We, the undersigned, agree to conduct/manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility should sign this form).

Applicant: ……. Date: …….

Appendix 8: SAE Reporting Form (refer to ADR reporting form)

Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form or ADR form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

Appendix 9: Good Clinical Practice (GCP) Principles (adopted from ICH-GCP)

1. Applicants must be able to demonstrate that clinical trials are conducted according to generally accepted principles of good clinical practice.
2. Trials must be conducted in accordance with the applicable regulatory requirement(s).

3. Before a trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the individual trial study participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
4. The rights, safety, and wellbeing of the trial study participants are the most important considerations and must prevail over interests of science and society.
5. The available non-clinical and clinical information on an investigational medicinal product must be adequate to support the proposed clinical trial.
6. Clinical trials must be scientifically sound, and described in a clear, detailed protocol.
7. A trial must be conducted in compliance with a protocol that has received regulatory and ethics approval prior to initiation.
8. The medical care given to, and medical decisions made on behalf of, study participants must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
9. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
10. Freely given informed consent must be obtained from every study participant prior to clinical trial participation.
11. All clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation and verification.
12. The confidentiality of records that could identify study participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
13. Investigational medicinal product must be manufactured, handled, and stored in accordance with applicable good manufacturing practices (GMP) and must be used in accordance with the approved protocol.
14. Systems with procedures that assure the quality of every aspect of the trial must be implemented.

Appendix 10: World Medical Association (WMA) Declaration of Helsinki (Ethical principles for medical research involving human study participants)

As adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996and the52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of clarification on paragraph 29 added by the WMA General Assembly,
Washington 2002

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principle to provide guidance to physicians and other participants in medical research involving human study participants. Medical research involving human study participants includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, " A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human study participants.
5. In medical research on human study participants, considerations related to the well-being of the human study participant should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human study participants is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the a etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research population is vulnerable and need special

protection. The particular needs of the economically and medically disadvantaged must be recognized. Special
attention is also required for those who cannot give or refuse consent for themselves, for those who may be study participant to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human study participants in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirements should be allowed to reduce or eliminate any of the protections for human study participants set forth in this Declaration.
B. Basic Principles for all Medical Research
10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human study participant.
11. Medical research involving human study participants must conform to general accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animal used for research must be respected.
13. The design and performance of each experimental procedure involving human study participants should be clearly formulated in an experimental protocol.
This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is
performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for study participants.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical human research involving study participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human study participant must always rest with a medically qualified person and never rest on the study participant of the research, even though the study participant has given consent.
16. Every medical research project involving human study participant should be preceded by careful assessment of predictable risk and burdens in comparison with foreseeable benefits to the

study participant or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research project involving human study participants unless they are confident that the risk involved has been adequately assessed and can be satisfactorily managed. Physicians should cease any investigations if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human study participants should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the study participant. This is especially important when the human study participants are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the result of the research.

20. The study participants must be volunteers and informed participants in the research project.

21. The right of research study participants to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the study participant, the confidentiality of every patient's information and to minimize the impact of the study on the study participant's physical and mental integrity and on the personality of the study participant.

22. In research of human beings, each potential study participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The study participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the study participant has understood the information, the physician should then obtain the study participant's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the study participant is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research study participant who is legally incompetent, physically or mental incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the

population represented and this research cannot instead be performed on legally competent persons.

25. When a study participant deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reason for involving research study participants with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligation. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicity available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principle laid down in this Declaration should not be acceptable for publication.

C. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to patients who are research study participants.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
Footnote: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be study participant to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Appendix 11: Fees for Clinical Trials in Liberia

No.	Service	Cost
1	Application to conduct Clinical Trial (LMHRA)	US$3,000.00
2	Application to conduct clinical trial (Ethics Committee Review)	US $ 2, 000.00
3	Fast track for clinical trial application (time shortens by half)	Double the cost for registration and analysis for the application
4	Amendments for major changes in clinical trials	US500.00

5	Amendments for minor changes in clinical trials	US$250.00