REPUBLIC OF KENYA

PHARMACY AND POISONS BOARD

GUIDELINES FOR APPLICATIONS TO CONDUCT CLINICAL TRIALS IN KENYA

PREPARED BY

EXPERT COMMITTEE ON CLINICAL TRIALS

February 2011

Foreword

Clinical trials include any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

The Pharmacy and Poisons Board is the national drug regulatory authority in Kenya established under Cap 244 Laws of Kenya. The importance of Research and Development in the attainment of national health, social and economic goals is well recognized. The Pharmacy and Poisons Board as the national drug regulatory authority has the mandate to ensure that clinical trials involving the use of new investigational drugs and older drugs for new conditions or diseases or investigational devices in human subjects are in compliance with national regulations including procedures to protect the safety of all participants.

As part of Board's continuing process of improving its efforts to facilitate clinical research, ECCT has developed these guidelines to assist clinicians, researchers and scientists be familiar with the procedures required for the conduct of drug-related clinical trials in the country. This will enhance and expand research activities and capabilities in the country. The guidelines provide the pharmaceutical industry, sponsors and investigators with the specific procedures required in the application for permission to conduct clinical trials in Kenya.

These guidelines have been developed to provide information for researchers on the current minimum requirements for authorization to conduct clinical trials involving investigational drugs, medical devices or herbal drugs in Kenya. The guidelines stipulate, among other things, application procedures for obtaining approval to conduct clinical trials (including clinical trials application form), procedures for approval of protocol amendments, requirements for reporting serious adverse events (SAEs)/suspected unexpected serious adverse events (SUSARs), requirements concerning data and safety monitoring board (DSMB), submission of progress reports, procedures for termination of clinical trials, and information on inspection of trial sites.

All researchers are encouraged to be conversant and implement this guideline in their practice.

Signed
Dr. F. Kimani MBChB, MMed, MBS
Director of Medical Services
Ministry of Medical Services

Signed
Dr S. K. Sharif MBChB, MMed, MSc, MBS
Director of Public Health and Sanitation
Ministry of Public Health and Sanitation

Acknowledgements

The Pharmacy and Poisons Board acknowledges the contribution of the following in the research and compilation of these guidelines:

The Ministry of Medical Services
The Ministry of Public Health and Sanitation
Our stakeholders, partners and clients

We take this early opportunity to thank all the researchers, investigators, sponsors, pharmaceutical manufacturers, distributors, retailers and respondents who offered their valuable contributions to the editing of this guideline.

We thank the trial participants who will be the ultimate beneficiaries of this guideline.

Special thanks go to the Management Sciences for Health- Strengthening Pharmaceutical Services (MSH-SPS) for their support in organising the initial meeting to prepare the first document.

LIST OF CONTRIBUTORS

The Pharmacy and Poisons Board acknowledges the immense contribution of the following for their research, compilation and commitment in developing this guideline.

The ECCT members

1. Dr. Kipkerich Koskei
2. Dr. Fred Siyoi
3. Prof. Gilbert Kokwaro
4. Prof. Walter Jaoko
5. Dr. Rashid Aman
6. Dr. Monique Wasunna
7. Dr. Berhards Ogutu
8. Dr. George Osanjo
9. Dr. Juma Rashid
10. Dr. Willis Akhwale

The ECCT Secretariat

1. Mr. George Muthuri
2. Dr. Edward Abwao
3. Dr. Jayesh Pandit

Contents

Abbreviations and Definition of Terms

The meaning of the following words used in these guidelines are as defined herein.

Term	Abbreviation	Meaning
Adverse Drug Reaction	***ADR***	All noxious and unintended responses to a clinical trial study or interventional 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	***AE***	Any untoward medical occurrence in a patient or clinical investigation study participant administered a study or intervention product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavourable 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		An institution applying to conduct a clinical trial – Sponsor/sponsor representative
Assent		A child's affirmative agreement to participate in research, where the child is below the age of the majority but old enough to understand the proposed research in general, its expected risks and possible benefits and the activities expected of them as subjects.

Term	Abbreviation	Meaning
Audit		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 study protocol and whether data reported are consistent with those on records at the site.
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.
Blinding/Masking		A procedure in which study participants, investigators or data analysts 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) and data analyst(s) being unaware of the treatment assignment(s).
Case Report Form	***CRF***	A form used to record data on each trial subject during the trial, as defined by the study protocol.
Clinical Trial	***CT***	Clinical trials are systematic studies aimed at determining the safety and efficacy of drugs or devices. Clinical trials are generally classified into Phases I to IV.
Clinical Trial Report		A 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		A medicinal or marketed product (Active or placebo) used as a reference in a clinical trial.

Term	Abbreviation	Meaning
Confidentiality		Maintenance of the privacy of trial participants including their personal identity and all personal medical information.
Contract Research Organization	***CRO***	An individual or organization contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
Data and Safety Monitoring Board or may also be called a Independent Data Monitoring Committee (IDMC) or an Independent Data Monitoring Board (IDMB)	***DSMB***	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.
Division of Medicines Information and Pharmacovigilance		The Division at the PPB at the time being responsible for the issues of pharmacovigilance and clinical trials.
Documentation		All records, in any form, that describes the methods, conduct, and/or results of a clinical trial, the factors affecting a trial, and the actions taken.
Drug		Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and accompanying information.

Term	Abbreviation	Meaning
Emancipated Minors		A child who has been granted the status of adulthood by a court order or other formal arrangement.
Essential Documents		Documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced.
Ethical Clearance		An authorization issued by an NCST accredited ethics committee to conduct a clinical trial in Kenya.
Good Clinical Practice	***GCP***	A standard for the design, conduct, performance, and 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	***GMP***	That part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.
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	***IEC***	A committee that has been formally designated to approve, monitor, and review biomedical and behavioural research involving humans with the aim to protect the integrity, rights, safety and welfare of the research subjects.

Term	Abbreviation	Meaning
Informed Consent		A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Audit		The act of conducting an official review of documents, facilities, records, and any other resources deemed to be related to the clinical trial and that may be located at the trial site, at the sponsor's and/or CRO's facilities. It is conducted by a sponsor, institution, IRB or regulatory authority.
Interim Clinical Trial/Study Report		A report of intermediate results and their evaluation based on analyses performed during the course of a trial.
Investigational New Drug	***IND***	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's Brochure	***IB***	A compilation of the clinical and non-clinical data on the investigational product(s) relevant to the study of the investigational product(s) in human study participants.

Term	Abbreviation	Meaning
Legally Acceptable Representative		An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Material Transfer Agreement	***MTA***	A written agreement entered into by a *provider* and a *recipient* of research material, aimed at protecting the intellectual and other property rights of the provider while permitting research with the material to proceed.
Minor		All individuals from the ages of birth until the legal age of adulthood which is 18 years in Kenya.
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-centre Trial		A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one Principal Investigator.
Participant/study Participant		An individual who participates in a clinical trial, either as a recipient of the investigational product or as a control
Phase I Clinical Trial		The purpose of these trials is to obtain preliminary data on safety of investigational products such as medicines or vaccines, or devices. These studies are carried out in a small number of healthy volunteers.

Term	Abbreviation	Meaning
Phase II Clinical Trial		The purpose of these trials is to demonstrate therapeutic activity of medicines, or immunogenicity of vaccines, and to determine appropriate dose ranges or regimens. In addition, these trials obtain additional safety data. These studies are routinely carried out in patients. They are frequently split into two phases IIA (proof of Concept) and IIB (Dose finding). These studies provide early efficacy data.
Phase III Clinical Trial		These are large trials aimed at determining efficacy of the investigational product. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use. The information obtained in this phase and the other two phases is used for licensure of the investigational product. Safety data is also collected in Phase III Trials. Phase IIIB are studies conducted just before or during regulatory filing to provide evidence to support product claims and to demonstrate safety in larger and more diverse populations.
Phase IV Clinical Trial		These are studies performed after registration of the medicinal product for use by the general public. It is often referred to as Post-Marketing Surveillance Studies, these are studies designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with the widespread use.
Pre-clinical Studies		Non Human studies of product development.

Term	Abbreviation	Meaning
Pharmacy and Poisons Board	***PPB***	The National legal Drug Regulatory Authority established by Cap 244 laws of Kenya.
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.
Protocol Amendment		A written description of change(s) to or a formal clarification of a study protocol.
Periodic Safety Update Report	***PSUR***	A report containing update safety data pertaining to a registered/approved medicinal product for human use, as well as a scientific evaluation report regarding the product's benefits and risks.
Principal Investigator	***PI***	An appropriately qualified person responsible for the conduct of the clinical trial. If there is more than one trial site in Kenya, there shall be a Coordinator who will be responsible for all the sites in Kenya. For clinical trials conducted in Kenya the site PI must be resident in the country. The Principal Investigator is the leader of the team and can delegate responsibilities to sub-investigators.
Quality Assurance	***QA***	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with good clinical practice (GCP) requirement(s).

Term	Abbreviation	Meaning
Quality Control	**QC**	The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.
Randomization		The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Serious Adverse Event	**SAE**	Any untoward medical occurrence that at any dose: - Results in death, - is life threatening, - Requires hospitalization or prolongation of existing hospitalization, - Results in persistent or significant disability/incapacity, or - 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 reconstruction 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).

Term	Abbreviation	Meaning
Sponsor		An individual, company, institution or organization which takes legal responsibility for the initiation, management and/or financing of a clinical trial.
Sub-Investigator		Any individual member of the clinical trial team designated and supervised by the principal investigator at a trial site to perform critical trial-related procedures and/or make important trial-related decisions.
Suspected Unexpected Serious Adverse Reaction	***SUSAR***	A serious adverse reaction that is not Identified in practice, severity or frequency by the reference safety information.
Trial Site		A facility with appropriate infrastructure to support the conduct of a specific clinical trial.
Vulnerable Study Participants		Individuals whose decision to participate in a clinical trial may be unduly influenced by the expectation of benefits associated with participation, or by coercion. This includes but is not limited to medical students, members of the uniformed forces, prisoners, minors, orphans, homeless, unemployed, refugees and the mentally challenged.

INTRODUCTION

This document is intended to provide guidance on the format and contents of application for authorisation to conduct clinical trials in Kenya, the amendments to clinical trial application and the declarations at the end of a clinical trial.

In Kenya, the Pharmacy and Poisons Board (PPB) is the authority mandated, by Cap 244 Laws of Kenya, to regulate clinical trials.

The Pharmacy and Poisons Board recognizes the importance of Research and Development of new medicines, medical devices or procedures in the attainment of national health, social and economic goals. Clinical research must nonetheless be conducted under conditions that satisfy ethical and scientific quality standards.

PPB will endeavour to provide a regulatory environment that avoids unnecessary delays in the clinical trial authorisation process while providing safeguards for quality, efficacy and public health.

Consequently the Expert Committee on Clinical Trials (ECCT) of the PPB has developed these guidelines to assist clinicians, researchers, pharmaceutical industry, sponsors and investigators to easily navigate the Kenyan clinical trial authorisation process.

The guidelines provide information on the current minimum requirements for authorisation to conduct clinical studies involving investigational drugs, medical devices or herbal drugs. It provides an application form and specifies procedures for approval of protocol amendments. It gives requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs). Also provided is information regarding data and safety monitoring board (DSMB), submission of progress reports, procedures for termination of clinical trials and inspection of trial sites.

The appropriate forms have been attached as appendices at the end of the guidelines. We hope you find this document beneficial in your daily practice in clinical research.

We undertake to review these guidelines and incorporate up-to-date practices, as may be necessary for our setting. Hence, your feedback is valuable to us. Do send us your comments.

Signed

Dr. K. C. Koskei OGW

Registrar, Pharmacy and Poisons Board

SECTION ONE

1. APPLICATION REQUIREMENTS

An application to conduct a clinical trial is required for any study that intends to use human subjects for the testing of:

1. Unregistered medicines, vaccines or medical devices
2. Registered medicines where the proposed clinical trials are outside the conditions of approval for registration. These may include changes to:
    a. Clinical indications
    b. Target population(s)
    c. Routes of administration
    d. Dosage
3. Studies intended to generate data on a product that is registered in Kenya based on foreign generated data.
4. Or any study that is going to use an investigational product/device on human beings.

Post-marketing clinical trials (Phase IV) of registered medicine, is provided for within the approved conditions of registration of such a medicine and approval is not required from the ECCT.

An application to conduct a clinical trial should be made by a sponsor or sponsor's representative and is known as the Applicant.

For multi site trial in Kenya, there shall only be one application filed by the Sponsor but there shall be Coordinating PI who shall be responsible for all the sites. In addition, the application should have the site specific addendum which should have the details of the sites including the infrastructure and staff capability to conduct the study.

An application must be made by completing the appropriate application form (**Annex 1**) and submitting this together with the required supporting documents and an application fee of USD 1,000.00 (or its equivalent in Kenya Shillings at the prevailing bank rates) Application forms and application guidelines can be downloaded from the PPB website: **www.pharmacyboardkenya.org**

An application to conduct a clinical trial shall include all the documents as indicated in **Annex 2**.

Applications shall be submitted to the following address:

The Registrar
Pharmacy and Poisons Board
P.O. Box: 27663-00506
Nairobi, Kenya
Tel: (020) – 3562107, 2716905/6, 0720608811, 0733884411
Fax: (020) - 2713431/2713409
E-mail: pv@pharmacyboardkenya.org

Attention: Clinical Trials Unit, Division of Medicines Information and Pharmacovigilance

NB **Any application that does not meet the listed requirements will not be accepted or reviewed.**

2. PROCEDURES FOR ACCEPTANCE, REVIEW AND APPROVAL OF APPLICATIONS

All applications to conduct a clinical trial will be received at the Clinical Trial Unit of Division of Medicines Information and Pharmacovigilance of the Pharmacy and Poisons Board.

On receipt, the application will be screened for completeness prior to acceptance.

Application Reference Number:
When an application for a Clinical Trial is accepted, an acknowledgement of receipt will be issued with a reference number for each application. This PPB/ECCT reference number must be quoted in all correspondence concerning the application in the future.

Applications will be reviewed according to Standard Operating Procedures of the Unit.

Conflict of interest will be declared by each member prior to reviewing the application.

Confidentiality will be maintained at all times during review.

PPB may approve the trial application or reject it specifying reasons for rejection.

The decision of the PPB (Approval, Request for Additional Information or Rejection) will be communicate to the applicant within 30 days of the receipt of a valid application

Approval for importation of investigational products and comparator will be dependent on approval to conduct the clinical trial.

In the case of rejection, the applicant may appeal and provide additional information to satisfy PPB requirements. In specific cases, PPB may decide to refer the matter to external experts for recommendation.

All decisions will be communicated to the applicant in writing stating whether the trial has been approved as it is, or if it requires certain corrections or if it has been rejected.

Importation of the Investigational Product will be made to the trade department of PPB by the applicant upon receipt of necessary approval of the research protocol.

3. QUALIFICATIONS AND RESPONSIBILITIES OF INVESTIGATORS, SPONSORS AND MONITORS

The Principal investigator engaged in clinical trials must be appropriately qualified to conduct the study, with relevant practical experience within the professional area, and must be a resident of Kenya.

For multi site studies in Kenya, the coordinating investigator, should be a Kenyan resident and should assume full responsibility for the trial.

All investigators in a clinical trial must have had formal training in Good Clinical Practices (GCP) within the last three years. Evidence of attending GCP course should also be submitted. Otherwise it is the responsibility of the sponsor to organize this training before the study can be implemented.

The sponsors, Investigators, and monitors should assume responsibilities as provided in the ICH – GCP guidelines.

4. CLINICAL TRIAL PROTOCOL

A Clinical Trial Protocol is a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial as defined in the ICH GCP guidelines Chapter 6.

The study protocol should be written in Times New Roman font size 12 with line spacing of “1.5”. The clinical trial study protocol must contain at least the following:

4.1 General Information

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

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

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

- Name, title, address, and telephone number(s) of the sponsor's medical expert for the trial.

- Name and title of the investigator(s) who is (are) responsible for conducting the trial, their address and telephone number(s) including updated mobile numbers.

- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

- 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

- Justification and need for the study.

- Name and description of the investigational product(s), including;

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

  b. Summary of the known and potential risks and benefits, if any, to human subjects.

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

- A statement that the trial will be conducted in compliance with the protocol, GCP, national and PPB requirements.

- Description of the population to be studied.

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

4.3 Trial Objectives and Purpose

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

4.4 Trial Design

A description of the clinical trial design should include:

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

4.5 Selection and withdrawal of study participants

This Will include :

- Inclusion criteria.

- Exclusion criteria.

- Withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

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

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

  c. Whether and how participants are to be replaced.

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

4.6 Treatment of study participants

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.

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

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

- Procedures for monitoring participant's compliance.

4.7 Assessment of Efficacy

This will include:

- Specification of the efficacy parameters.

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

4.8 Assessment of Safety

This will include:

- Specification of safety parameters.

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

- Procedures for eliciting reports of and for recording and reporting adverse events and co-occurring illnesses.

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

- A clear description of study procedures and quantities of any body fluids to be collected for study analysis.

4.9 Statistics

This will include:

- Frequency of DSMB meetings if applicable.

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

- The number of subjects planned to be enrolled. In multicentre 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.

- The level of significance to be used.
- Criteria for the termination of the trial.

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

- 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).

- Procedures for reporting any protocol violations.

- 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 should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit inspections from PPB providing direct access to source data/documents.

4.11 Quality Control and Quality Assurance

The protocol should contain a description on how to maintain quality control and quality assurance of the study such as:

1. Choice of investigators

2. Monitors and monitoring plan

4.12 Ethics

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

1. Patient Information leaflets (PIL) and Informed Consent Forms (ICF) for any proposed archiving of biological specimens for later research or for genetics research.
2. Treatment and/or management of participants and their disease condition(s) after completion of trial
3. Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and PPB requirements
4. Any arrangement for the follow-up of trial study participants after the conclusion of the trial.
5. Insurance and indemnity measures

In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:

1. Identification of the provider and recipient
2. Identification of the material and the volume of material
3. Definition of the trial and how the material will and will not be used
4. Maintenance of confidentiality of background or supporting data or information, if any
5. Indemnification and warranties (where applicable)

4.13 Data Handling and Record Keeping

The protocol should contain a description on the handling of data and how records will be kept (CRFs)

4.14 Publication Policy

Publication policy, if not addressed in a separate agreement, need to be stipulated.

5. REQUIREMENTS CONCERNING INFORMED CONSENT

In obtaining and documenting informed consent, the investigator should comply with the NCST accredited Ethics Committee requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. This should be as indicated in ICH GCP Guideline 4.8.10.

Prior to the beginning of the trial, the investigator should obtain Ethical Clearance from the ethics committee on record before applying for PPB approval.

Informed consent to study participants shall be administered in either English or Kiswahili and local spoken language of the area, where applicable. The same information will be given to participants in a written format. Copies of the English Informed Consent should be submitted to PPB.

The written informed consent form and any other written information to be provided to participants should 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 ERC favourable opinion and lodged with PPB in advance of use.

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

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.

The investigator, or a person designated by the investigator, should 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 ethics and PPB approval.

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.

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.

Prior to participation in the trial, the written informed consent form should 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.

If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to 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 should 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.

The informed consent discussion, the written informed consent form and any other written information to be provided to participants should include, as a minimum, explanations of the following:

1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.

5. The participant's responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
10. The compensation and/or treatment available to the participant in the event of trial-related injury.
11. The anticipated prorated payment, if any, to the participant for participating in the trial.
12. The anticipated expenses, if any, to the participant for participating in the trial.
13. 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.
14. That the PPB 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 PPB and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.
15. 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.
16. 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.
17. 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.
18. The foreseeable circumstances and/or reasons under which the participation in the trial may be terminated.
19. The expected duration of participating in the trial.
20. The approximate number of participants involved in the trial.

Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated (same day as that signed for approval to participants) 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.

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.

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 PPB approval to protect the rights, safety and well-being of the participant and to ensure compliance with NEC and PPB 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.

6. 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.
7. More details are provided in ICH-GCP guidelines and may be followed when compiling information on this part.

For registered products being investigated for new conditions, latest PSUR, certificate of analysis and GMP inspection certificate should also be submitted.

7. INVESTIGATIONAL NEW DRUG (IND) DOSSIER

Clinical trial investigational new drug must be manufactured in accordance with Good Manufacturing Practices (GMP). This implies that the manufacture of the investigational medicinal product may be subject to GMP inspection by PPB in the same way as the case of marketed drug products.

Chemistry and manufacturing information for IND(s) which have not been registered by PPB should be presented in a concise manner and should include the following:

Required details on Active Pharmaceutical Ingredient (API)

1. Nomenclature
2. Name and address of the manufacturer
3. Physicochemical properties
4. Route of synthesis and summary of 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

Required details on 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 Controls of Critical Steps and Intermediates
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) of the clinical batches of the test product, placebo and modified comparator.

12. Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathy (TSE) certificates for excipients of human or animal origin
13. Stability studies
14. Container closure system

If the pharmaceutical 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.

Pharmaceutical 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 PPB.

In cases where an extension of shelf life for the IMP is desired, an application for this must be submitted to PPB. In such cases stability data must be submitted.

In case of IMP(s) which have been registered by PPB, a cross reference to the part of the dossier containing chemistry and manufacturing information should be declared.

Labeling:

Investigational medicinal products (including registered products) used in clinical trials must be properly labelled. A final copy/version of the labelling must be submitted for approval and should contain the following minimum information:

1. Statement indicating that the product is for "*clinical trial purpose only*"
2. Name, number or identifying mark
3. Recommended storage conditions
4. Name and address of the sponsor
5. Protocol code or identification
6. The expiry date
7. The writing "Keep out of reach of children"

Re-labeling

Any re-labelling of remaining IMP from previously manufactured batches must be performed in accordance with GMP principles and is limited to extension of expiry date where sufficient evidence is available to support such extension.

Sponsor responsibilities:

The following responsibilities are expected of the sponsor as regards the IMP:

1. Ensure timely delivery of investigational product(s) to the investigator(s).
2. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s)
3. Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
4. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.
5. Take steps to ensure that the investigational product(s) are stable over the period of use.
6. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

Product Accountability and Disposal:

A product Accountability/Disposal report shall be submitted to PPB within 3 months from the Last Patient Out date. The report should include:

1. Date(s) and quantity received for each product
2. Balance of the study medication(s)
3. Drug Destruction Certificate, and/or written evidence return to the used/unused drug supplies to country of origin (whichever applicable).

PPB shall be informed in writing of any possible delay in submission of the report where the delay is unavoidable.

8. SAFETY REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Initial reports of SUSARs should be provided by the Sponsor to PPB as soon as possible but within seven calendar days of the notification of the SUSARs with follow up reports being provided within a further eight calendar days.

A summary of SAEs and SUSARs shall be submitted every six months from the day of approval of the study.

For PSURs, these shall be submitted at the following times from the time of authorization, for all medicinal products:

- At least 6 monthly after authorization and until the placing on the market
- At least 6 monthly for the first two years after being placed on the market
- Annually for the subsequent two years
- Thereafter at three-yearly intervals
- Immediately upon request

9. REQUIREMENTS CONCERNING DATA AND SAFETY MONITORING BOARD (DSMB)/DATA MONITORING COMMITTEE (DMC)

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

1. Composition of DSMB
2. DSMB reports which should be submitted to PPB within two weeks of the deliberations.

10. PROTOCOL AMENDMENTS

Any new information which affects the conduct/management of the trial, safety of the subjects and manufacture of the product necessitating changes to, protocol, consent form and trial sites, etc will require immediate submission of the amended documents to PPB upon receipt of favourable opinion from the ethics committee/ institutional review board (IRB) of record.

A copy of the favorable opinion letter from ethics committee on record should be submitted to PPB.

PPB acknowledgment must be obtained for all amendments especially the following:

1. Changes that affect patient selection and monitoring
2. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
3. Changes that affect patient discontinuation
4. Addition/removal of an investigational site
5. Change of Principal Investigator
6. Changes that result in the extension of duration of a trial

11. INFORMATION ON ONGOING TRIALS

The sponsor and/or PI must submit progress reports to PPB on a six months basis from the date of initiation of the clinical trial. The progress report should contain:

1. SAE/SUSARs Log
2. DSMB Report for all trials where DSMB has been established.
3. Number of trial subjects enrolled.

In addition, for multi site trials in Kenya, the Sponsor must submit a summarised report for all the sites that should contains the above.

For annual renewal, the applicant will be required to submit a copy of the progress report, the updated IB of the investigational product and a copy of favourable opinion from the IEC of record. The applicant must receive an acknowledgement of this submission before proceeding with the study. ***These documents must be submitted to PPB at least six weeks before the expiry of the previous approval.***

12. POST TRIAL INFORMATION

A Final Report shall be submitted to the PPB at the end of the trial. Summary of the Clinical study Report must be submitted to PPB within one year of the end of the study.

PPB shall conduct a review that shall include scrutiny of Interim Reports, final report and any PPB Inspection Reports.

13. INSPECTION OF CLINICAL TRIAL SITES

The PPB may inspect clinical trial (investigator) sites, sponsor's office, data management centre, contract research organization (CRO) or any other establishment related to the trial as it will be deemed appropriate by the Board to ensure compliance with the applicable regulations, Good Clinical Practice and clinical trial protocol. The authorized officer of the board may contact the PI or sponsor for the date of inspection when required.

Such inspections may be before commencement of the trial, or at predetermined intervals, as required.

Routine inspections will be announced at least three weeks in advance of the inspection date. PPB has the right to conduct an unannounced inspection at its discretion.

The objectives of inspection will be to ensure that the generally accepted Principles of Good Clinical Practices are met, validate the quality of data generated and verify compliance to the clinical trial regulations.

The PPB may use the information collected as a result of inspections to ensure compliance with regulatory requirements and may take enforcement action where necessary.

The Inspections will include - but not be limited to:

1. The facilities and staff used for the trial: as approved by the PPB in the protocol.
2. Compliance with the approved Protocol, GCP and the applicable regulations
3. All amendments to the Protocol have been approved.
4. Accurate, complete and current records according to the Protocol.
5. SUSARs/SAEs are reported as required by the Protocol
6. Monitoring and auditing inspections conducted as required by the Protocol.

14. TERMINATION OF CLINICAL TRIAL

14.1 Premature termination:

The protocol should have a clear description of study stoppage rules indicating reasons, who takes the decision and how the decision will be communicated to PPB and ethics committee on record.

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

1. 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.

2. Provide PPB 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.

14.1 Withdrawal of PPB approval:

PPB may withdraw 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.

14.2 End of trial (Study closeout):

After the trial has been conducted and closed, the applicant shall submit a final study report or closing report for his site within 60 days. This also applies to the sponsor for a study carried out in Kenya. This should be followed by a final study report within one year after trial closure unless otherwise justified. The structure and content of the final study report should be as provided in the ICH guidelines.

14.3 Archiving

It is the responsibility of the investigator and the sponsor to archive safely all the documents related to the trial. All archiving for Kenyan trial site related documentation, shall be done within the country and not exported. The sponsor/applicant should inform ECCT in writing prior to destroying the trial documents. It should include the protocol number, date started and ended and the licence number.

15. CONDITIONS FOR CLINICAL TRIAL IMPORT LICENCE

15.1 Endorsement of Clinical Trial Import License

The Sponsor shall submit to PPB a copy of endorsed Clinical Trial Import License and/or evidence of delivery to the approved investigator(s)/trial centre(s) on importation and supply of each consignment of the product.

The product shall only be supplied to the investigator(s) at the trial centre(s) named in the application for the Clinical Trial Import Licence/Clinical Trial Exemption for the purpose and use as stated in the said application. No change in investigator, trial centre or trial protocol shall be made without prior notification and approval by PPB.

The principal investigator shall ensure that adequate precautions are taken for all study medication(s), such as storage in a securely locked cabinet, access to which is limited, to prevent theft or illegal distribution.

The principal investigator shall ensure that the study medication(s) be supplied only to subjects involved in the said trial.

15.2 Change of Information

The sponsor shall inform PPB of any change in information, or any information received by him that casts doubt on the continued validity of the data which was submitted with, or in connection with the application for the Clinical Trial Import Licence.

15.3 Discontinuation of Trial

The sponsor shall inform PPB of any decision to discontinue the trial to which the licence relates and shall state the reason for the decision.

SECTION TWO

HERBAL PRODUCTS

16. CHEMISTRY- MANUFACTURING- CONTROL (CMC) CONSIDERATIONS FOR HERBAL PRODUCTS

For conventional, chemically-defined drug products, general considerations are synthesis and/or purification of the active pharmaceutical ingredient (API), manufacturing of the product that is administered to the patient and control of these processes so that the API and product are made reproducibly. Since herbal products are manufactured from plant material, these considerations have to be translated into terms appropriate to this plant source.

16.1. Overview of CMC evidence needed to support clinical trials for herbal products

Unlike standard chemically-defined drugs, herbal products have often had substantial human use prior to clinical trial evaluation. To capitalize on the use of this information in protocols to evaluate these products, it is important that the chemistry, manufacturing, and control of the product to be used mimic that for the traditionally-used formulation.

Also unlike conventional drugs, herbal products are mixtures of at least partially uncharacterized constituents. It is postulated that being a mixture provides a therapeutic advantage, in that unknown constituents may combine in an additive or synergistic fashion with known constituents to provide more efficacy than would be provided by the known constituent alone. Thus, evaluation of herbal products does not require attempts to purify the medicines down to known or otherwise single chemical constituents.

For herbal products, “analysis of the active pharmaceutical ingredient(s)” may be best approached by analysis of one or more hypothesized active ingredient(s), analysis of a chemical constituent that constitutes a sizable percentage of the total ingredients, and a chemical fingerprint of the total ingredients. The latter two analyses are surrogates for analysis of the unknown constituents that contribute to efficacy.

Specifications for acceptable values of analytic data should reflect the best available standards. For herbal products, variation of content from batch to batch may be an issue, and several analytical procedures may be needed to adequately quantify their constituents.

Because herbal products are sourced from plants, levels of contaminating herbicides and pesticides as well as toxic contaminations must particularly be addressed. The presence of adulterants should also be considered.

Many herbal medicines are in fact polyherbal. Plants may either be mixed before extraction or the extracts may be combined. In either case, information on each individual plant species used must be collected.

Herbal products intended for administration to humans are clinical trial materials, and they should therefore be made following the principles of GMP. The production facility should have a current certificate of GMP.

16.2. Information needed to support a clinical trial for a herbal product

Information on the herbal product proposed for phase 1/2 studies

HERBAL SUBSTANCE:

i. Description of the plant: genus, species (cultivar where appropriate); region(s) and country(ies) of origin; time of harvest; parts to be harvested
ii. Plant processing: drying, mechanical disruption, solvent extraction (aqueous or
iii. organic solvents, others)
iv. Isolation, identification and purification of active ingredients
v. Analytical procedures
vi. Specification
vii. Storage conditions/shelf life.

HERBAL PRODUCT:

i. Amount of active ingredient
ii. List of excipients
iii. Type of product (tablet, capsule, etc.) and its method of manufacture
iv. Analysis of putative active ingredient(s) via chemical or biological parameters
v. Analysis of a sizeable chemical constituent (analytical marker compound)

16.3. Information on the herbal product proposed for phase 3 studies

Phase 3 trials are performed on large number of patients and are often carried out prior to registration and general use. Therefore, GMP standards are needed prior to phase 3 trials. In practice, this means performing generally the same procedures as for phase 1/2 trials, but more extensively and with more stringent oversight.

HERBAL SUBSTANCE:

i. As above for phase 1/2 trials. *In addition:*
ii. Statement that the plant is cultivated according to Good Agricultural Practices or harvested according to Good Wildcrafting Practices
iii. Reference batch.

HERBAL PRODUCT:

i. As above for phase 1/2 trials.
In addition:
ii. Environmental impact statement.

16. PRE-CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS

16.1. Introduction: Information needed for a conventional drug

Pre-clinical information generally needed to support a clinical investigation of a conventional drug consists of data on efficacy, toxicity, and pharmacokinetics.

Efficacy is demonstrated in enzyme/receptor assays, in vitro, and in animal models.

Toxicity is investigated:

- *in vitro* and in mice to assess genotoxicity
- *in vitro* to assess cytotoxicity
- in rodents to assess single-dose acute toxicity and maximum tolerated dose
- in one rodent model and one non-rodent model to investigate repeat dose (1, 3, 6, 9
- months) toxicological effects
- in a rodent model and in the rabbit to assess reproductive toxicity
- in the rat to assess carcinogenicity.

Pharmacokinetic analyses relate to:

- absorption of the drug from the gut after e.g. oral dosing, or mobilization from the injection site after injection
- distribution of the API around the body
- Rate of drug metabolism, the metabolic enzyme involved, and the nature of the metabolites produced.

Determination of the "No Adverse Effect Level (NOAEL) following administration to animals (rats) via the same route to be used in clinical studies.

16.2. Information needed to support a clinical trial for a herbal product

16.2.1. Efficacy

It is recommended that the appropriate literature sources be searched for all available evidence on efficacy. Examples of such sources are medical and scientific journals, pharmacopeia, and articles on traditional medicines. Only if there are obvious gaps in the information or the total amount of data is insubstantial should it be necessary to perform new efficacy experiments.

16.2.2. Toxicology

It is imperative that the appropriate literature sources (as above) be reviewed for the toxicities of the herbal products in prior human experiences or existing animal data. The need for additional non-clinical studies prior to clinical trials depends on the following considerations:

- Similarities between the new and old preparations, in terms of product characteristics, and usages in clinical settings.
- Scale and exposure (dosage/duration) of the proposed new clinical studies.
- Frequency and severity of any known toxicity.

Thus, in general, requirements for pre-clinical studies may range from none for early phase, small, studies using the same preparations that have been used extensively and without known safety problems, to a complete set of conventional toxicology studies for relatively new products in large phase 3 trials. For many herbal products, certain non-clinical studies may be necessary but can be conducted concurrently with the proposed clinical trials.

16.2.3. Pharmacokinetics

It is important that the active ingredient (s) is identified, and the pharmacokinetic profile of the active ingredients and their metabolites described.

17. CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS

Good Clinical Practice should be applied in all stages of clinical trials to ensure that quality and ethical requirements for clinical studies are met. It is expected that a traditional practitioner familiar with the product proposed for investigation be an integral member of the protocol development team, where those traditional practitioners exist. For all clinical trials, biostatisticians should be consulted to ensure that the sample size is sufficient to satisfy the primary endpoint/objective.

17.1. Introduction: Information needed for a standard intervention

Phase 1 studies are designed to determine safety associated with increasing doses in normal volunteers, as a precursor to phase 2 and phase 3 trials. In addition, phase 1 studies investigate toxicity and drug levels in states in which drug levels might be altered: the fed vs. the fasted state, in renal or hepatic impairment. Mechanisms of action are also investigated in phase 1.

Phase 2 studies evaluate the efficacy of a range of dosages in individuals with disease. Phase 2 studies typically start by evaluating the maximum tolerated dose determined in the prior phase 1 normal-volunteer studies. If this dose is effective, dose-ranging downwards would be investigated. If the phase 1 dose is ineffective, it is possible that higher doses will demonstrate efficacy and only mild intolerance, so dose-ranging upwards may be performed. Phase 2 dose-ranging studies utilize a relatively small number of patients per dosage group. Placebo and standard intervention groups may be included. If surrogate markers rather than disease endpoints are used in the phase 2 studies, it may be necessary to repeat dose-ranging in phase 3 trials with more valid disease endpoints. Phase 3 studies are expanded trials of safety and efficacy. They are performed after preliminary evidence suggesting efficacy for the intervention has been obtained, and are intended to gather the additional information about efficacy and safety that is needed to evaluate the overall benefit-risk ratio of the intervention and to provide an adequate basis for general clinical use. Phase 3 studies usually include large numbers (several hundred to several thousand) of subjects, may involve human populations with broader entrance characteristics than were used in the phase 2 trials, and involve statistical comparison of the intervention to standard and/or placebo interventions.

17.1.1. Important note on Phase I, Phase II and Phase III Trials

Development of safe and effective herbal products requires subjecting all such product to the different phases of clinical investigation of a new investigational product. The purpose of a clinical trial is to evaluate an intervention for a clinical condition. Positive (or negative) data can lead to a recommendation to use (or not to use) the treatment. Use of a suboptimal

dose that is safe but ineffective does not serve the needs of the community. Although the trial indicates only if the particular tested dose of the intervention was ineffective, the community may conclude that all doses of the intervention are ineffective and patients will be denied possible benefits from the intervention. The inappropriate rejection of an intervention, "because phase 2 studies did not precede a phase 3 trial, and a suboptimal dose was used in the phase 3 trial", is common for herbal medicines. For some herbal products, there may exist previous research that has determined the optimum dose for a treatment. For others, dose-ranging phase 2 studies will need to be performed prior to beginning more extensive phase 3 studies. Therefore, if the scientific literature does not contain scientifically valid dose-ranging data, the investigator should first perform phase 2 trials to generate these data.

For dose-ranging studies, clinical investigators should consult biostatisticians for examples of dose-ranging schemes, and decide which scheme best fits the needs of the particular clinical problem.

17.2. Information needed to support phase 2 trials

Although data from prior human experience may suggest confidence in the clinical safety of the product, it is important to verify tolerance in phase 2 trial patients. Both the literature review and the provisions in the protocol to be performed should focus on complete review of the clinical safety parameters.

Examples of safety parameters are:

Organ system	**Safety parameter**
Neurological:	lack of neurologic symptoms
Skin:	clinical evidence of lack of allergic reactions
Musculoskeletal:	lack of arthritis or myalgias, normal values of CPK
Gastrointestinal:	clinical evidence of tolerability
Liver:	normal values of SGOT or SGPT, alkaline phosphatase, Total bilirubin,
Kidney:	normal values of BUN or creatinine
Endocrine system	normal values of albumin or total protein, uric acid, glucose, cholesterol, amylase or lipase, sodium/potassium, calcium
Cardiovascular:	normal EKG and blood pressure
Hematopoietic:	normal values of complete blood count
Additionally:	more intensive investigation of any organ system likely to be particularly affected by the product

17.3. Information needed to support phase 3 trials

- Safety data. If the population has broader entrance characteristics compared to the populations of prior trials, the favourable safety profile shown for constricted populations in prior trials may or may not convey to the broader populations in the phase 3 trials. Arguments that the product is likely to be safe in the broader population should be stated, and the phase 3 protocol should include re-testing of the safety parameters. Another reason to re-test safety parameters in phase 3 trials is the greater chance of identifying rare adverse events with the large number of patients used in phase 3.

• Preliminary efficacy data from phase 2 trials.

• Evidence from dose-ranging trials that the chosen dosing regimen is likely to be the optimum regimen with respect to safety and efficacy.

All of the fundamental ethical principles of human participation in research apply equally to herbal remedies and research involving these compounds. Consent must be obtained, subject selection must be equitable, risks and benefits must be weighed and must be favourable to the potential participant, and experimental design must be sound. Concerns that particularly apply to clinical trials with herbal products include:

- Product adulteration (has it been documented?)
- Interactions between herbal remedies and other entities (rarely understood)
- Reproductive and organ toxicity data (may be minimal)
- Prior dose finding (likely to be incomplete).

ANNEXES

Annex 1

KENYA: CLINICAL TRIAL APPLICATION FORM

To be completed by the Sponsor or Sponsor's representative.

(To be submitted along with the necessary protocol as indicated in the GUIDELINES FOR APPLICATIONS TO CONDUCT CLINICAL TRIALS IN KENYA.)

Study Title:

Protocol No:

Version No: Date of Protocol:

Study Drug:

ECCT Ref number (if applicable):

Sponsor:

Contact Person:

Address:

Telephone Number: Fax Number:

Cell Number: E-mail address:

TICK AND PROVIDE NECESSARY DETAILS AS APPROPRIATE

2. NUMBER OF SITES

Single site in Kenya : yes ☐ no ☐

If yes, name of site……

Multiple sites in Kenya : yes ☐ no ☐

Number of sites anticipated in Kenya ( )

If yes list the sites……

Multiple countries: yes ☐ no ☐

Number of countries anticipated in the trial ( )

If yes above list the countries……

Does this trial have a data monitoring committee? yes ☐ no ☐

3. PARTICIPANTS (SUBJECTS)
3.1 Number of participants in Kenya: 3.2 Total enrolment in each Kenyan site: (if competitive enrolment, state minimum and maximum number per site.) 3.3 Total participants worldwide:

4.0 AGE SPAN	
Less than 18 years If yes specify:	yes ☐ no ☐
In Utero	yes ☐ no ☐
Preterm Newborn Infants (up to gestational age < 37 weeks)	yes ☐ no ☐
Newborn (0-28 days)	yes ☐ no ☐
Infant and toddler (29 days - 23 months)	yes ☐ no ☐
Children (2-12 years)	yes ☐ no ☐
Adolescent (13-17 years)	yes ☐ no ☐
18 years and over	yes ☐ no ☐
Adult (18-65 years)	yes ☐ no ☐
Elderly (> 65 years)	yes ☐ no ☐

5.0 DESIGN OF THE TRIAL	
Controlled If yes, specify:	yes ☐ no ☐
Randomised	yes ☐ no ☐
Open :	yes ☐ no ☐
Single blind :	yes ☐ no ☐
Double blind:	yes ☐ no ☐
Parallel group:	yes ☐ no ☐
Cross over :	yes ☐ no ☐
Other : If yes to other specify:	yes ☐ no ☐
If controlled, specify the comparator:	

Other medicinal product(s)	yes ☐ no ☐
Placebo	yes ☐ no ☐
Other If yes to other, specify :	yes ☐ no ☐

6.0 GROUP OF TRIAL SUBJECTS

Healthy volunteers	yes ☐ no ☐
Patients	yes ☐ no ☐
Specific vulnerable populations	yes ☐ no ☐
Women of child bearing potential	yes ☐ no ☐
Women of child bearing potential using contraception	yes ☐ no ☐
Pregnant women	yes ☐ no ☐
Nursing women	yes ☐ no ☐
Emergency situation	yes ☐ no ☐
Subjects incapable of giving consent personally If yes, specify :	yes ☐ no ☐
Others : *If yes, specify*	yes ☐ no ☐

7.0 GENDER

Female	☐
Male	☐

8.0 CO-ORDINATING INVESTIGATOR (*for multicentre trials in Kenya*)

Given name
Middle name, if applicable
Family name
Qualification
Professional address:

9.0 PRINCIPAL INVESTIGATOR *(for multicentre trial ; where necessary, use additional forms)*

Given name

Middle name, if applicable

Family name

Qualification

Professional address

10.0 ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED TRIAL RELATED DUTIES AND FUNCTIONS (repeat as needed for multiple organisations)

Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party? yes ☐ no ☐

Repeat as necessary for multiple organisations:
Organisation :
Name of contact person :
Address :
Telephone number :

All tasks of the sponsor	yes ☐ no ☐
Monitoring	yes ☐ no ☐
Regulatory (e.g. preparation of applications to PPB & ethics committee)	yes ☐ no ☐
Investigator recruitment	yes ☐ no ☐
IVRS – treatment randomisation	yes ☐ no ☐
Data management	yes ☐ no ☐
E-data capture	yes ☐ no ☐
SUSAR reporting	yes ☐ no ☐
Quality assurance auditing	yes ☐ no ☐
Statistical analysis	yes ☐ no ☐
Medical writing	yes ☐ no ☐
Other duties subcontracted	yes ☐ no ☐

If yes to other please specify:

11.0 PRINCIPAL INCLUSION CRITERIA

List them here;

12.0 PRINCIPAL EXCLUSION CRITERIA

List them here;

13.0 PRIMARY END POINT(S) :

List them here;

14.0 SCOPE OF THE TRIAL – Tick all boxes where applicable	
Diagnosis	☐
Prophylaxis	☐
Therapy	☐
Safety	☐
Efficacy	☐
Pharmacokinetic	☐
Pharmacodynamic	☐
Bioequivalence	☐
Dose Response	☐
Pharmacogenetic	☐
Pharmacogenomic	☐
Pharmacoeconomic	☐
Others	☐
If others, specify:	
15.0 TRIAL TYPE AND PHASE	
Human pharmacology (Phase I) Is it:	☐
First administration to humans	☐
Bioequivalence study	☐
Other : If other, please specify	☐
Therapeutic exploratory (Phase II)	☐
Therapeutic confirmatory (Phase III)	☐
Therapeutic use (Phase IV)	☐

16.0 DESIGN OF THE TRIAL

Controlled yes ☐ no ☐

If yes, specify:

Randomised yes ☐ no ☐

Open : yes ☐ no ☐

Single blind : yes ☐ no ☐

Double blind: yes ☐ no ☐

Parallel group: yes ☐ no ☐

Cross over : yes ☐ no ☐

Other : yes ☐ no ☐

If yes to other specify:

If controlled, specify the comparator:

Other medicinal product(s) yes ☐ no ☐

Placebo yes ☐ no ☐

Other yes ☐ no ☐

If yes to other, specify :

17.0 INFORMATION ON PLACEBO (if relevant; repeat as necessary)

Is a there a placebo: yes ☐ no ☐

Pharmaceutical form :

Route of administration :

Composition, apart from the active substance(s):

Is it otherwise identical to the INDP? yes ☐ no ☐

If not, specify major ingredients :

18.0 Details of Site(s)
Name of site Physical address Contact details Contact person
19.0 Capacity of Site(s):
Number of staff, names, qualifications, experience -- including study co-ordinators, site facilities, emergency facilities, other relevant infrastructure)

20.0 OTHER DETAILS

20.1 If the trial is to be conducted in Kenya and not in the host country of the applicant / sponsor, provide an explanation:
20.2 Estimated duration of trial:
20.3 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application:
20.4 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country:
20.5 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection:
5.6 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities:

Annex 2

Requirements

The following are the requirements when submitting a clinical trial application.

1. Completed application form
2. Cover letter
3. Protocol
4. Patient Information leaflet and Informed consent form
5. Investigators Brochure/Package inserts or Investigational Medicinal Product Dossier (IMPD)
6. GMP certificate of the investigational product
7. Signed investigator(s) CV(s)
8. Financial declaration by Sponsor and/or PI
9. Signed Declaration by Sponsor or Principal investigator.
10. Indemnity cover and Insurance Certificate for the participants
11. Copy of favourable opinion letter from the local Institutional Review Board (IRB) and Ethics committee.
12. Copy of approval letter(s) from collaborating institutions or other regulatory authorities, if applicable
13. A signed statement by the applicant indicating that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading.
14. Where the trial is part of an international study, sufficient information regarding the other participating countries and the scope of the study in these countries.
15. For multicentre/multi-site studies, an addendum for each of the sites should be provided upon initial application.
16. Registration at the clinical trial registry at www.pharmacyboardkenya.org
17. Payment of application fee as prescribed below

A non-refundable application fee of US$ 1,000.00 (or equivalent in Kenya Shillings) per protocol, is to be paid in the form of at a Banker's Cheque drawn in favour of "Pharmacy and Poisons Board" at the PPB's accounts office on submission of the application wherein a receipt will be issued. Payment can also be made by electronic fund transfer (EFT) if required. All bank charges for EFT shall be borne by the applicant. Details for EFT payment should be obtained from PPB prior to such a transaction.

The application shall be submitted in both paper (4 bound copies) and electronic format (One copy in PDF format) via re-writable CD/Flash Disk.

NB: All controlled documents must be referenced with Version Control and Date.

Annex 3

Declaration by applicant:

We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and Kenyan legal, ethical, PPB requirements and principles of good clinical practice;

It is reasonable for the proposed clinical trial to be undertaken;

We will submit reports of suspected unexpected serious adverse reactions and safety reports according to applicable guidance;

We will submit a summary of the final study report to the PPB and the ethics committee concerned within a maximum 1 year deadline after the end of the study in all countries.

_____ _____

Name, Position and Contact details (Local contact) Date

_____ _____

Name and Contact details Principal Investigator / National Co-ordinating PI Date

This guidance should be followed unless it is otherwise justified in an application to the PPB.

References

1. Pharmacy and Poisons Act, CAP 244 Laws of Kenya.
2. Operation guidance: Information needed to support clinical trials of herbal products. *UNICEF/UNDP/World Bank/ WHO special Programme and Training in Tropical Diseases (TDR).*
3. Guideline for regulating the conduct of clinical trials in human participants. *SADC April 2004.*
4. Guidelines for Application to Conduct Clinical Trials in Tanzania Second Edition. *TFDA February 2009.*
5. Guidelines for Application to Conduct Drug Related Clinical Trials in Malaysia.
6. www.clinicaltrials.gov
7. ICH - GCP Guidelines for Clinical Trials. http://www.ich.org

Pharmacy & Poisons Board House
Lenana Road, Next to Lenana Conference Centre
P.O BOX 27663-00506, TEL 3562107, 2716905/6,
0720608811, 0733884411
Fax 2713431/2713409
www.pharmacyboardkenya.org