MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDELINES FOR CONDUCT OF CLINICAL TRIALS IN KENYA

September 2016

Citation of is Document

This Guideline is in the public domain and may be reproduced or adapted on condition that the recommended citation is made.

Recommended Citation

Guidelines for Conduct of Clinical Trials In Kenya, Pharmacy and Poisons Board, September 2016.

Contact the following for clarifications, comments or suggestions:
Registrar Pharmacy and Poisons Board,
P. O. Box 27663-00506 Nairobi, Kenya
Tel: +254 20 3562107 +254 733 884411 / 720 608811
admin@pharmacyboardkenya.org or pv@pharmacyboardkenya.org

PPB/MIP/CT/GUD/003	**GUIDELINES FOR CONDUCT OF CLINICAL TRIALS IN KENYA**	**Revision No. 1**	**Effective Date 1st Sept 2016** **Review Date: 31st Aug 2019**

Prepared by Quality Assurance Officer

Sign..... .....

Date.....10th August 2016 .....

Checked by Director Medicines Information and Pharmacovigilance

Sign.....

Date.....17/8/2016.....

Checked by Head, Quality Management

Sign.....

Date....23/8/2016.....

Authorized by Deputy Registrar

Sign.....

Date.....23/8/16.....

Table of Contents

Abbreviations and Definition of Terms

The meanings 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.
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.
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.

Term	Abbreviation	Meaning
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).
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.
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)	***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.
Emancipated Minors		A child who has been granted the status of adulthood by a court order or other formal arrangement.

Term	Abbreviation	Meaning
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.
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. A sponsor, institution, IRB or regulatory authority conducts it.

Term	Abbreviation	Meaning
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.
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.
Minor		All individuals from the ages of birth until the legal age of adulthood which is 18 years in Kenya.
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.
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.
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.
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 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.
Pharmacy and Poisons Board	***PPB***	The National legal Drug Regulatory Authority established by Cap 244 laws of Kenya.

Term	Abbreviation	Meaning
Protocol		A document that 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).
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.

Term	Abbreviation	Meaning
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).
Sponsor		An individual, company, institution or organization which takes legal responsibility for the initiation, management and/or financing of a clinical trial.
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).
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.

Acknowledgements

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

The Ministry of Health
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.

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. Bernhards Ogutu
8. Dr. George Osanjo

The ECCT Secretariat

1. Mr. George Muthuri
2. Dr. Edward Abwao
3. Dr. Lydia Tuitai
4. Ms Mary Njeri

PPB QMS Team

1. Dr. Ronald Inyangala
2. Dr. Felistas Yano

Preface

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.

Dr K. C. Koskei OGW
Registrar, Pharmacy and Poisons Board

Legal Framework

The regulation for the conduct of clinical trials is governed according to Pharmacy and Poisons Act, Cap 244 Laws of Kenya Subsidiary Legislation, Pharmacy and Poisons (Registration of Drugs) Rules,

(1A) Any person wishing to carry out a clinical trial in the country shall apply to the Board for approval before engaging in such study involving investigational products.

(1B) An application under paragraph (1A) shall be accompanied by the fees set out in Part B of the Second Schedule

Introduction

Clinical trials are a very important part in the process of drug development. In the recent past, Africa and Kenya in particular has seen increased numbers of requests for approval to conduct clinical trials. In order to facilitate research and the continuous discovery of medicines, but to also ensure the safety, well being of participants and integrity of the data generated, PPB has developed this new guideline.

As the institution responsible for the regulation of medicines and also the final approval of conduct of clinical trials in Kenya, the Pharmacy and Poisons Board developed the first guidelines on conduct of clinical trials in the year 2011. Since then, there are a number of changes that have taken place necessitating the development of this second edition.

Some of the additions in this edition are;

1. Safety reporting timelines; the document gives a guidance on how these reports are to be submitted to PPB
2. Studies involving children; The requirements for carrying out studies involving children has also included in this version
3. Phase One studies
4. Clinical trial insurance
5. Labelling and relabeling of investigational products. In order to guide investigators on this important activity, a section has been dedicated to labelling and relabeling of the investigational products
6. Data Safety and Monitoring Boards
7. Product Accountability and Disposal
8. Updated checklist for submission of applications; for efficient review of the submitted protocols, the checklist for submission has been updated taking note of the frequent finding of the previous reviews

This guideline has been developed to address the concerns that clinical trials investigators had with the previous edition and to also update the document as per the current practise around the world.

In addition the guideline also gives the process of review approval and monitoring of the clinical trials in Kenya

SECTION ONE

1. Application Requirements

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

1.1.1. Unregistered medicines, vaccines or medical devices

1.1.2. Registered medicines where the proposed clinical trials are outside the conditions of approval for registration. These may include changes to:

1.1.2.1.1. Indications and clinical use

1.1.2.1.2. Target patient population(s)

1.1.2.1.3. Routes of administration

1.1.2.1.4. Dosage regimens

1.1.3. Comparative bioavailability trials

1.1.4. Studies intended to generate data on a product that is registered in Kenya based on foreign generated data.

1.1.5. Studies to establish Bioequivalence for registration of generic products

1.1.6. Studies to identify any adverse reactions to one or more medicinal products

1.1.7. Studies to generate information on the absorption, distribution, metabolism and excretion of one or more medicinal products;

1.1.8. Or any study that is going to use an investigational product/medicine/device on human beings.

1.1.9. Post- Marketing clinical trials (Phase IV) of registered medicines

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

1.3. 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.

1.4. An application must be made by completing the appropriate application form (Annex 1; ***FOM 001/MIP/CLT/014***) 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

1.5. An application to conduct a clinical trial shall include all the documents as indicated in Annex 2 (***FOM 001/MIP/CLT/015***)

NB **Any application that does not meet the listed requirements will not be accepted for review.**

2. Procedures for Acceptance, Review and Approval of Applications

Application

2.1. 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.

2.2. On receipt, the application will be screened for completeness prior to acceptance according to the receipt SOP (***PPB/MIP/CLT/SOP/003***).

2.3. Application Reference Number:

2.4. 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.

Review

2.5. Applications will be reviewed according to Standard Operating Procedures of the Unit (***PPB/MIP/CLT/SOP/004, PPB/MIP/CLT/SOP/005***)

2.6. Each member prior to reviewing the application will declare conflict of interest in the study and should have no financial or personal interests, which could affect their impartiality.

2.7. The reviewers shall be independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence

2.8. Confidentiality will be maintained at all times during review.

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

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

2.11. 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.

2.12. The review shall consider among other things;

2.12.1. Reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;

2.12.2. Compliance with the requirements concerning the manufacturing and import of investigational medicinal products and auxiliary medicinal product,

2.12.3. Compliance with the labelling requirements;

2.12.4. The completeness and adequateness of the investigator's brochure.

2.13. 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.

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

2.15. 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

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

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

3.3. Kenya Medical and Dentists Practioners Board should duly have registered the medical doctor in the study team responsible for the clinical care of patients in a trial.

3.4. The Pharmacists responsible for the test article should be duly registered by the Pharmacy and Poisons Board

3.5. 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.

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

4. Investigator

4.1. Investigators shall satisfy the following:

4.1.1. The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through an up to date Curriculum Vitae.

4.1.2. The investigator should have a current practice licence from the Kenya Medical Practitioners and Dentist Board

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

4.1.4. Have a clear understanding and willingness to obey the ethical, GCP and legal requirements in the conduct of the trial.

4.1.5. To permit monitoring and auditing of the trial and inspection by PPB or appointed representatives.

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

4.1.7. The Principal Investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in Kenya and who is responsible for the conduct of the clinical trial at a clinical site.

4.1.8. A Principal Investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area.

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

4.1.10. Have adequate to carry out the study

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

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

Adequate Resources

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

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

4.6. The study should have adequate fund to carry out the clinical trial to its conclusion

Medical Care of Trial Subjects

4.7. A qualified medical practitioner should be responsible for all trial-related medical decisions. The qualified medical practitioner should also be licensed with the Kenya Medical and Practitioners' Board. In addition, they must have the annual Practice License.

4.8. The medical care given to, and medical decisions made on behalf of the subjects must always be the responsibility of a qualified medical practitioner or when appropriate a qualified dentist registered with the Kenya Medical and Practitioners' Board

4.9. During and following a subject's participation in a trial, the investigator should ensure adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the trial.

4.10. The subject should be informed when medical care is needed for inter-current illness for which the investigator becomes aware.

4.11. Before initiating a trial the Principal Investigator should have the written and dated approval from the Pharmacy and Poisons Board and other relevant bodies.

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

4.13. The investigator shall not implement any deviation from or changes to the protocol and Informed Consent Form without prior review and approval of the

4.14. PPB and ERC except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes or is based on issues relating to the immediate safety of subjects already recruited into the trial.

4.15. The investigator shall establish SOPs for investigational products (IP):

4.16. A Pharmacist who shall maintain records of the delivery process and who ensures that the product is processed and stored correctly should keep the IP(s).

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

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

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

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

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

4.22. The investigator shall guarantee the authenticity and confidentiality of the research data, the trial subjects' details and information provided by sponsor.

4.23. The investigator shall ensure that all data is accurately collected and recorded.

4.24. The investigator shall ensure that all serious adverse events are reported promptly to the PPB within timelines specified in this Guideline

4.25. Proper protection procedures or treatments should be administered to trial subjects with serious adverse events.

4.26. The investigator shall submit all relevant trial data to PPB in a timely manner for validation, auditing and inspection.

5. Sponsor

5.1. The Sponsor shall be responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and regulatory requirements.

5.2. The sponsor shall be responsible for availing insurance cover for the study participants and ensure that the clinical trial institution, CRO and researchers have sufficient insurance cover for the clinical trial.

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

5.4. The Sponsor shall agree with investigator(s) on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical report.

5.5. Prior to the initiation of the clinical trial, the agreement between the sponsor and investigators should be in writing as part of the protocol submitted for PPB's approval or in a separate agreement.

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

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

5.8. An updated Investigator's Brochure shall be submitted whenever available but at least once year.

5.9. The Sponsor shall obtain the investigator's/institutions' agreement on the following items:

5.9.1. The conduct of the trial in compliance with Good Clinical Practices and with the approved protocol;

5.9.2. To be in compliance with procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol.

5.10. The sponsor and all investigators shall sign and date the protocol of the trial to confirm the agreement.

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

5.12. The Sponsor shall ensure that the IP's (including active comparator(s) and placebo) is manufactured in accordance with Good Manufacturing

Practices and are adequately packed and labelled in a manner that protects the blinding if applicable. In addition the labelling should comply with the regulatory requirements

5.13. The Sponsor shall determine for the IP's, acceptable storage temperature and conditions, storage times, reconstitution fluids and procedures and devices for product infusion if any.

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

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

5.16. The sponsor shall appoint qualified and suitable trained individuals to monitor the trial.

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

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

5.19. The sponsor should report to the PPB and all relevant institutions, all adverse events occurring during the course of the trial. The sponsor should expedite reporting all serious adverse events to PPB and the Ethics Committee, the sponsor and the investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects.

5.20. When a trial is prematurely terminated or suspended by the sponsor/investigators, PPB should be informed as soon as possible of the decision to terminate/suspend the trial and the reasons thereof by the sponsor/investigators.

5.21. When the trial is prematurely terminated, the sponsor shall submit a report to the PPB within 15 (fifteen) days.

5.22. When the trial is completed, the sponsor should submit a preliminary report to PPB within 30(thirty) days and final report within 180 days

5.23. Sponsors and investigators have an ethical obligation to ensure that biomedical research projects contribute effectively to national or local capacity building.

5.24. Capacity building may include, but is not limited to, the following activities:

5.24.1. Developing technologies appropriate to health-care and biomedical research,

5.24.2. Training of research and health-care staff,

5.24.3. Educating the community from which research subjects will be drawn.

5.25. External sponsors are ethically obliged to ensure the availability of:

5.25.1. Health-care services that are essential to the safe conduct of the research treatment of subjects who suffer injury as a consequence of research intervention;

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

Sponsor responsibilities:

5.26. The following responsibilities are expected of the sponsor on the IMP:

5.26.1. Make the application to PPB for the granting of approval to carry out the clinical trial.

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

5.26.3. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s)

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

5.26.5. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

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

5.26.7. 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.

5.26.8. After the end of the trial, submit an executive summary report of the study within 30 days and submit a copy of the Clinical Study Report within 180 days. The report should conform at least to the consolidated system of reporting trials (CONSORT) unless otherwise specified in the conditions specified in the approval letter

5.26.9. The report shall include a short but comprehensive summary of the essential findings of trial and of its methodology and course

6. Clinical Trial Protocol

6.1. 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.

6.2. The clinical trial study protocol must contain at least the following:

General Information

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

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

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

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

6.7. 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.

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

6.9. Name(s) and address (es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

6.10. Justification and need for the study.

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

6.11.1. A summary of findings from non-clinical studies that potentially have clinical significance

6.11.2. Summary from clinical trials that are relevant to the trial.

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

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

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

6.11.6. Description of the population to be studied.

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

Trial Objectives and Purpose

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

Trial Design

6.13. A description of the clinical trial design should include:

6.14. 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.

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

6.16. A description of the measures taken to minimize/avoid bias, including Randomization and Blinding.

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

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

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

6.20. Maintenance of trial treatment randomization codes and procedures for breaking codes/blind (for safety reasons).

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

Selection and withdrawal of study participants

6.22. This will include:

6.22.1. Inclusion criteria.

6.22.2. Exclusion criteria.

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

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

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

6.22.6. Whether and how participants are to be replaced.

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

Treatment of study participants

6.23. 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.

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

6.25. 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).

6.26. Procedures for monitoring participant's compliance.

6.27. Procedures put in place to ensure Post Trial Access to research participants

Assessment of Efficacy

6.28. This will include:

6.28.1. Specification of the efficacy parameters.

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

Assessment of Safety

6.29. This will include:

6.29.1. Specification of safety parameters.

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

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

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

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

Statistics

6.30. This will include:

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

6.30.2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.

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

6.30.4. The level of significance to be used.

6.30.5. Criteria for the termination of the trial.

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

6.30.7. 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).

6.30.8. Procedures for reporting any protocol violations.

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

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

6.30.11. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.

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

6.30.13. The level of significance to be used.

6.30.14. Criteria for the termination of the trial.

6.30.15. Methods for data analyses and evaluation of results.

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

6.30.17. 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).

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

6.31. There should be a statistical analysis plan (SAP) for each trial.

6.32. A statistician should:

6.32.1. Write and sign off on the analysis plans before the trial data is available and before any analysis has started

6.32.2. Describe in the protocol or SAP the hypotheses being tested and how conclusions will be drawn, the analyses that will be done, the procedures for dealing with missing data and avoiding bias, and the selection of subjects to be included in the analyses

6.32.3. Put sample tables and listings in the SAP, to show how data will be presented

6.32.4. Include any planned interim analyses in the SAP

6.32.5. Describe and justify in the trial report any deviations from the SAP

6.32.6. Ensure all steps of the data management, reporting and analysis process have fully validated procedures to avoid the potential for errors. These procedures would normally be included in a company's Standard Operating Procedures library.

Direct Access to Source Data/Documents

6.33. 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.

Quality Control and Quality Assurance

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

6.35. The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by PPB.

6.36. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements, made by the sponsor with the principal investigator and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

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

6.38. Choice of investigators

6.39. Monitors and monitoring plan

7. Research Involving Children

7.1. The sponsor should briefly summarize available information on the

7.1.1. Pathophysiology of the disease,

7.1.2. Methods of diagnosis, and

7.1.3. Currently available treatments and/or prevention strategies in the pediatric population, including neonates.

7.2. The sponsor should also include available information on the incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population.

7.3. The sponsor should provide evidence and assumptions on key differences between the disease in adults and in the pediatric population.

7.4. Before undertaking research involving children, the investigator must ensure that:

7.4.1. The research might not equally well be carried out with adults;

7.4.2. The purpose of the research is to obtain knowledge relevant to the health needs of children;

7.4.3. A parent or legal representative of each child has given permission;

7.4.4. No incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

7.4.5. The agreement (assent) of each child has been obtained to the extent of the child`s capabilities; and,

7.4.6. A child`s refusal to participate or continue in the research will be respected.

7.4.7. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

7.4.8. The informed consent forms, assent forms and the patient information sheets should also be in another language other than English and Kiswahili that the parent or legal representative understand.

7.5. Pediatric patients should be given medicines that have been appropriately evaluated for their use.

7.6. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, the development of pediatric formulations of those products.

7.7. Drug development programs should include the pediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the pediatric population.

7.8. Obtaining knowledge of the effects of medicinal products in pediatric should be done without compromising the well being of pediatric patients participating in clinical trials.

7.9. The decision to proceed with a pediatric development program for a medicinal product should be determined by:

7.9.1. The prevalence of the condition to be treated in the pediatric population

7.9.2. The seriousness of the condition to be treated

7.9.3. The availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments

7.9.4. Whether the medicinal product is novel or one of a class of compounds with known properties

7.9.5. Whether there are unique pediatric indications for the medicinal product

7.9.6. The need for the development of pediatric-specific endpoints

7.9.7. The age ranges of pediatric patients likely to be treated with the medicinal product

7.10. Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues

7.11. Potential need for pediatric formulation development

7.12. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.

7.13. Pharmacokinetic studies should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

7.14. Relative bioavailability comparisons of pediatric formulations with the adult oral formulation should be done in adults.

7.15. Definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in whom the medicinal product is likely to be used should be conducted in the pediatric population.

7.16. For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may provide sufficient information for dosage selection.

7.17. In addition to the other requirements, the application should also include;

7.17.1. Non clinical safety data

7.17.1.1. Genotoxicity

7.17.1.2. Reprotoxicity (fertility, pre and post natal development)

7.17.1.3. Carcinogenicity (if required)

7.17.1.4. Juvenile animal studies (in some cases, e.g. neonatal use)

7.17.2. Pharmaceutical properties

7.17.3. Pharmacokinetics

7.17.3.1. Absorption

7.17.3.2. Distribution

7.17.3.3. Metabolism

7.17.3.4. Excretion

7.17.4. Pharmacodynamics

Specific and General

7.18. In addition, the following will also be important

7.18.1. The trial will provide useful answers to the study population

7.18.2. The medicine fulfils a need of the population in which it is studied ("is relevant")

7.18.3. Children are adequately monitored and protected

7.18.4. There is direct benefit for the child, or if no direct benefit, there is no more than minimal risk (*probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests)*

7.18.5. The trial results will be published

7.18.6. There are provisions for end-of-trial treatment

7.19. Ages are defined in completed days, months, or years and the following classification applies;

7.19.1. Preterm newborn infants

7.19.2. Term newborn infants (0 to 27 days)

7.19.3. Infants and toddlers (28 days to 23 months)

7.19.4. Children (2 to 11 years)

7.19.5. Adolescents (12 to 18 years)

Practical considerations to facilitate pharmacokinetic studies

7.20. The volume of blood withdrawn should be minimized in paediatric studies. Blood volumes should be justified in protocols.

7.21. The following blood volume limits for sampling are recommended (although are not evidence-based). If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time.

7.22. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight.

7.23. Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected blood loss should be detailed in any trial protocol, and should be detailed in the patient information sheet.

7.24. Use of sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample

7.25. Use of laboratories experienced in handling small volumes of blood for pharmacokinetic

7.26. Analyses and for laboratory safety studies (blood counts, clinical chemistry)

7.27. Collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis

7.28. The use of indwelling catheters, etc., to minimize distress

7.29. Use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient. Techniques include:

7.30. Sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall "population area-under-the-curve"

7.31. Population pharmacokinetic analysis using the most useful sampling time points derived from modelling of adult data

Efficacy

7.32. The potential for extrapolation of efficacy from studies in adults to paediatric patients or from older to younger paediatric patients should be considered

7.33. Where efficacy studies are needed, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups.

7.34. Measurement of subjective symptoms such as pain requires different assessment instruments for patients of different ages.

7.35. In paediatric patients with chronic diseases, the response to a medicinal product may vary among patients not only because of the duration of the disease and its chronic effects but also because of the developmental stage of the patient.

Safety

7.36. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting.

7.37. Unintended exposures to medicinal products (accidental ingestions, etc.) may provide the opportunity to obtain safety and pharmacokinetic information and to maximize understanding of dose-related side effects.

7.38. Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in paediatric patients.

7.39. Long-term studies or surveillance data, either while patients are on chronic therapy or during the post-therapy period, may be needed to determine possible effects on skeletal, behavioural, cognitive, sexual, and immune maturation and development.

Post marketing information

7.40. Normally the paediatric database is limited at the time of approval. Therefore, post marketing surveillance is particularly important. In some cases, long-term follow-up studies may be important to determine effects of certain medications on growth and development of paediatric patients.

7.41. Post marketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the paediatric population or additional information for the entire paediatric population.

Ethics

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

7.42.1. Patient Information leaflets (PIL) and Informed Consent Forms (ICF) for any proposed archiving of biological specimens for later research or for genetics research.

7.42.2. Treatment and/or management of participants and their disease condition(s) after completion of trial

7.42.3. Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and PPB requirements

7.42.4. Any arrangement for the follow-up of trial study participants after the conclusion of the trial.

7.42.5. Insurance and indemnity measures

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

7.42.7. Identification of the provider and recipient

7.42.8. Definition of the trial and how the material will and will not be used

7.42.9. Maintenance of confidentiality of background or supporting data or information, if any

8. Insurance Cover

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

8.2. The insurance cover shall be provided by an insurer that is registered by Insurance Regulatory Authority of Kenya

8.3. For all sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provide prior to study initiation
8.4. Sponsors and Principal Investigators shall ensure insurance cover for clinical trial participants and shall submit as evidence a certificate of insurance cover for participants.
8.5. The certificate of insurance certificate must be duly executed by the insurance company under a valid insurance policy which makes explicit reference to the proposed study.
8.6. The insurance policy shall grant cover for compensation of study participants for injury that is causally linked to the clinical trial activities and must cover the liability of investigator and sponsor of the clinical trial, without excluding any damage that may be attributed to negligence.
8.7. Self-insurance of clinical trial participants such as by the NHIF will not be sufficient.
8.8. In addition, the study investigators shall be required to have Professional Indemnity insurance cover for the period of the trial
8.9. Clinical Trial Host Institution shall have in place, appropriate insurance at a level sufficient to meet potential liability of its Investigators(s), those acting on behalf of investigators and its research members;

9. Publication Policy

9.1. Publication policy, if not addressed in a separate agreement, need to be stipulated.
9.2. The Board shall be informed of any results that will be publicly released at least 14 days before this information is publicly released

10. Requirements Concerning Informed Consent

10.1. 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.
10.2. Prior to the beginning of the trial, the investigator should obtain Ethical Clearance from the ethics committee on record before applying for PPB approval.
10.3. 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.
10.4. 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.

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

10.6. 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.

10.7. 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.

10.8. 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.

10.9. 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.

10.10. 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.

10.11. 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.

10.12. 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.

10.13. 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:

10.13.1. That the trial involves research.

10.13.2. The purpose of the trial.

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

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

10.13.5. The participant's responsibilities.

10.13.6. Those aspects of the trial that are experimental.

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

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

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

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

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

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

10.14. 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.

10.15. 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.

10.16. 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.

10.17. 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.

10.18. 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.

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

10.20. The expected duration of participating in the trial.

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

10.22. 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.

10.23. 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.

10.24. 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. The age od ascent will be greater than 12 years but less than 18 years. Those parents less than 18 years can consent for their children to participate in clinical trials as emancipated minors.

11. The Investigator's Brochure

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

11.1.1. The physical, chemical and pharmaceutical properties

11.1.2. The pharmacological aspects including its metabolites in all animal species tested

11.1.3. The pharmacokinetics and metabolism including its biological transformation in all animal species tested

11.1.4. Toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study

11.1.5. Results of clinical pharmacokinetic studies

11.1.6. Information regarding safety, pharmacodynamics, efficacy and dose responses that were obtained from previous clinical trials in humans.

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

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

12. Investigational New Drug Dossier

12.1. 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.

12.2. 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:

12.2.1. Required details on Active Pharmaceutical Ingredient (API)
12.2.2. Nomenclature
12.2.3. Name and address of the manufacturer
12.2.4. Physicochemical properties
12.2.5. Route of synthesis and summary of manufacturing process
12.2.6. Documented evidence of structure and stereochemistry
12.2.7. Characterization of impurities
12.2.8. Specifications and their justifications
12.2.9. Batch analyses
12.2.10. Validation of analytical procedures
12.2.11. Container closure system
12.2.12. Stability studies

12.3. Required details on Investigational Medicinal Product (IMP)
12.4. Name, strength and dosage form
12.5. Description and composition
12.6. Name and address of the manufacturer
12.7. Pharmaceutical development
12.8. Description of manufacturing process including flow diagram and Controls of Critical Steps and Intermediates
12.9. Manufacturing information for novel excipients.
12.10. Specifications and their justifications (including excipients)
12.11. Batch analyses
12.12. Validation of analytical procedures
12.13. Characterization of impurities
12.14. Certificates of analysis (CoAs) of the clinical batches of the test product, placebo and modified comparator.
12.15. Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathy (TSE) certificates for excipients of human or animal origin
12.16. Stability studies
12.17. Container closure system
12.18. 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.

12.19. 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.

12.20. 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.

12.21. 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.

13. Phase One Clinical Trials

Non-clinical aspects

13.1. The application should demonstrate the relevance of the animal model used

13.2. Qualitative and quantitative differences may exist in biological responses in animals compared to humans. For example, differences in affinity for molecular targets, tissue distribution of the molecular target, cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.

13.3. Where there is evidence of species-specificity of action from in vitro studies with human cells compared with cells from a test species, the value of the in vivo response of the test species may be significantly reduced in terms of predicting the in vivo human response. It should be noted that a similar response in human and animal cells in vitro is not necessarily a guarantee that the in vivo response will be similar.

13.4. Animal studies with highly species-specific medicinal products therefore, may:

13.4.1. Not reproduce the intended pharmacological effect in humans;

13.4.2. Give rise to misinterpretation of pharmacokinetic and pharmacodynamics results;

13.4.3. Not identify relevant toxic effects.

13.5. A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process.

13.6. High species-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans much more difficult, but does not imply that there is always an increased risk in first-inhuman trials.

13.7. The demonstration of relevance of the animal model(s) may include comparison with humans of:

13.7.1. Target expression, distribution and primary structure.

13.7.2. Pharmacodynamics

13.7.3. Binding and occupancy, functional consequences, including cell signalling if relevant.

13.7.4. Data on the functionality of additional functional domains in animals, if applicable,

13.7.5. Metabolism and other pharmacokinetic aspects

13.7.6. Cross-reactivity studies using human and animal tissues (e.g. monoclonal antibodies).

13.8. The search for a relevant animal model should be documented and justified in detail.

13.9. Where no relevant species exists, the use of homologous proteins or the use of relevant transgenic animals expressing the human target may be the only choice. The data gained is more informative when the interaction of the product with the target receptor has similar physiological consequences to those expected in humans. The use of in vitro human cell systems could provide relevant additional information.

13.10. The relevance and limitations of all models used should be carefully considered and discussed fully in the supporting documentation.

Pharmacodynamics

13.11. Pharmacodynamics studies should address the mode of action, and provide knowledge on the biology of the target. The primary and secondary pharmacodynamics should be conducted in in vitro animal and human systems and in vivo in the animal models. These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, duration of effect and dose-response.

13.12. A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps in order to increase the likelihood to detect significant pharmacological effects with low doses and to identify active substances with U-shaped or bell-shaped dose-response curves.

13.13. Since a low dose is to be administered to humans in the first-in-human trial, this is of high importance.

Pharmacokinetics

13.14. Standard pharmacokinetic and toxic kinetic data should be available in all species used for safety studies before going into human

13.15. Exposures at pharmacodynamics doses in the relevant animal models should be determined especially when pharmacodynamics effects are suspected to contribute to potential safety concerns.

Safety Pharmacology

13.16. Standard core battery data should be available before the first administration in humans

13.17. Additional studies to investigate effects in other organ systems should be

carried out on a case by case basis. In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using in vitro studies, including human material.

Toxicology

13.18. The toxicology programme should be performed in relevant animal species and include toxicokinetics.

13.19. When factors influencing risk are identified, the inclusion of additional endpoints should be considered, on a case-by-case basis.

13.20. Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. The use of homologous products or transgenic model approach or of in vitro human cell systems could provide relevant additional information.

13.21. Animal models that are thought to be similar to the human disease may provide further insight in the pharmacological action, the pharmacokinetics, (e.g. disease-related expression of the target) as well as dosing in patients and safety (e.g., evaluation of undesirable promotion of disease progression). Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals.

13.22. The scientific justification for the use of these animal models of disease to support safety should be provided.

Estimation of the First Dose in Human

13.23. The estimation of the first dose in human is an important element to safeguard the safety of subjects participating in first-in-human studies. All available information has to be taken in consideration for the dose selection and this has to be made on a case-by-case basis. Different methods can be used.

13.24. In general, the No Observed Adverse Effect Level (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant animal species adjusted with allometric factors or on the basis of pharmacokinetics gives the most important information. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials.

13.25. For investigational medicinal products for which factors influencing risk have been identified, an additional approach to dose calculation should be taken.

13.26. Information about pharmacodynamics can give further guidance for dose selection.

13.27. In order to further limit the potential for adverse reactions in humans, a safety factor may be applied in the calculation of the first dose in human. This should take into account criteria of risks such as the novelty of the active substance, its biological potency and its mode of action, the degree of species

specificity, and the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL. The safety factors used should be justified.

13.28. When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used, unless justified.

13.29. Other approaches may also be considered in specific situations, e.g. for studies with conventional cytotoxic IMPs in oncology patients.

Investigator Site Facilities and Personnel

13.30. First-in-human trials should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early phase trials (i.e. phase I-II) and medical staff with appropriate level of training and previous experience of first-in-human studies.

13.31. They should also understand the investigational medicinal product, its target and mechanism of action.

13.32. Units should have immediate access to equipment and staff for resuscitating and stabilizing individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of Intensive Care Unit facilities.

13.33. Procedures should be established between the clinical research unit and its nearby Intensive Care Unit regarding the responsibilities and undertakings of each in the transfer and care of patients.

13.34. First-in-human trials should preferably be conducted as a single protocol at a single site.

13.35. When different sites are involved this should be justified and an appropriate plan needs to be in place to assure the well-being of all trial participants and to assure an adequate information communication system. This information system should ensure that new safety findings are transmitted to all participating sites and that the integrity of the study design is not compromised.

13.36. The following criteria for all first-in-human trials should be discussed in the clinical trial application. These criteria should be taken into account on a case-by-case basis.

Mode of Action

13.37. While a novel mechanism of action might not necessarily add to the risk per se, consideration should be given to the novelty and extent of knowledge of the supposed mode of action. This includes the nature and intensity (extent, amplification, duration, reversibility) of the effect of the medicinal product on the specific target and non-targets and subsequent mechanisms, if applicable.

13.38. When analyzing risk factors associated with the mode of action, aspects to be considered should include:

13.38.1. Previous exposure of human to compounds that have related modes of action.

13.38.2. Evidence from animal models (including transgenic, knock-in or knock-out animals) for the potential risk of serious, pharmacologically mediated toxicity

13.38.3. Novelty of the molecular structure of the active substance(s), for example a new type of engineered structural format, such as those with enhanced receptor interaction as compared to the parent compound.

13.38.4. Nature of the target. The target in human should be discussed in detail. Beyond the mode of action, the nature of the target itself might impact on the risk inherent to a first administration to humans, and sponsors should discuss the following aspects, based on the available data:

13.38.4.1. The extent of the available knowledge on the structure, tissue distribution (including expression in/on cells of the human immune system), cell specificity, disease specificity, regulation, level of expression, and biological function of the human target including "downstream" effects, and how it might vary between individuals in different populations of healthy subjects and patients.

13.38.4.2. Description of polymorphisms of the target in relevant animal species and humans, and the impact of polymorphisms on the pharmacological effects of the medicinal product.

13.38.4.3. Relevance of animal species and models. The Sponsor should compare the available animal species to humans taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects.

13.39. Where available animal species/models or surrogates are perceived to be of questionable relevance for thorough investigation of the pharmacological and toxicological effects of the medicinal product, this should be considered as adding to the risk.

Quality aspects

13.40. The requirements are the same for all investigational medicinal products regarding physico-chemical characterization and, additionally biological characterization of biological products.

13.41. Quality attributes should not, in themselves, be a source of risk for first-in-human trials. However, these quality attributes are to be considered in a risk assessment preceding a first-in-human trial.

13.42. Specific points to be considered are:

13.42.1. Determination of strength and potency. To determine a safe starting dose, the methods used for determination of the strength and/or the potency of the product need to be relevant, reliable and qualified.

13.42.2. For a biological medicinal product, the lack of a bioassay measuring the functional or biological activity should be justified.

13.42.3. Qualification of the material used. The material used in non-

clinical studies should be representative of the material to be used for first in- human administration.

13.43. It is important to have an adequate level of quality characterisation even at this early point of development.

13.44. A characterisation of the product including its heterogeneity, degradation profile and process-related impurities should be performed. Particular attention should be given to impurities that could be pharmacologically active and/or toxic. Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug product.

13.45. When moving from non-clinical studies to first-in-human administration, there should be sufficient assurance that product differences, should they occur, would not have an adverse impact on clinical characteristics of the product, especially safety. Furthermore, during the early development of a product, significant modifications to the manufacturing process frequently occur. Particularly in the case of complex molecules, these modifications can potentially result in subtle changes to the active substance that may not be detectable in characterisation studies but can affect biological properties and could have clinical consequences.

13.46. Given the fact that major clinical decisions are based on the non-clinical data it is important to show that these data remain valid.

13.47. Further non-clinical studies may be needed with the product intended for use in the first-in-human trial in the following situations:

13.47.1. Where there are differences in the product quality attributes of the non-clinical and clinical material and adverse clinical consequences may result from such differences.

13.47.2. Where there are differences in the manufacturing process and the limitations of product characterisation, including biological assays, cannot assure that the material used in nonclinical studies is representative of the material to be used in clinical studies.

Reliability of very small doses

13.48. Applicants should demonstrate that the intended formulation of the doses to be administered provides the intended dose. There is a risk of reduced accuracy in cases where the medicinal product needs to be diluted, to prepare very small doses, or the product is provided at very low concentrations as the product could be adsorbed to the wall of the container or infusion system. This might lead to an overestimation of the safety of the initial clinical doses and non-clinical safety data. Therefore, compatibility of the product with primary packaging materials and administration systems should be investigated, where relevant.

Clinical aspects

13.49. The safety of participants in first-in-human clinical trials should be

enhanced by identification and planned mitigation of factors associated with risk which should be demonstrated in the application

13.50. Key aspects of the trial should be designed to mitigate those risk factors, including:

13.50.1. Study population;

13.50.2. Trial sites;

13.50.3. First dose;

13.50.4. Route and rate of administration;

13.50.5. Number of subjects per dose increment (cohort);

13.50.6. Sequence and interval between dosing of subjects within the same cohort;

13.50.7. Dose escalation increments;

13.50.8. Transition to next dose cohort;

13.50.9. Stopping rules;

13.50.10. Allocation of responsibilities for decisions with respect to subject dosing and dose escalation.

13.51. In general, the higher the potential risk associated with an investigational medicinal product (IMP) and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study.

13.52. The protocol should describe the strategy for managing risk including a specific plan to monitor for and manage likely adverse events or adverse reactions as well as the procedures and responsibilities for modifying or stopping the trial if necessary.

13.53. It is recognized that placebo is often included as part of the design of Phase I studies. The study design including randomization schemes should take this into account. Any decisions taken with respect to subsequent dosing at the same dose level and or to dose escalation, should take into account the number of subjects that might have received either placebo or the active medicinal product. There should always be rapid access to the treatment allocation codes when relevant.

13.54. For first-in-human trials where there is uncertainty about the risk it is recommended that a confirmatory pharmacodynamics measure is identified that can show the pharmacological effect and link with the preclinical experience.

Monitoring and communication of adverse events/reactions

13.55. The trial design should provide a specific plan for monitoring for adverse events or adverse reactions and relevant reporting system to sponsor and PPB.

13.56. The mode of action of the investigational medicinal product, findings in the non-clinical toxicity studies and any anticipated responses should be used to identify likely adverse reactions.

13.57. All clinical staff should be trained to identify those reactions and how to

respond to those or any other adverse events or reactions.

13.58. There should be constantly available rapid access to the treatment allocation codes when relevant.

13.59. In cases where there is a predictable risk of a certain type of adverse reaction occurring in humans, a treatment strategy should be described in the protocol. This should include the availability of specific antidotes where they exist, a clear plan of availability of supportive treatment emergency facilities and medical staff.

13.60. The length of the monitoring period and nature of monitoring within and if deemed appropriate outside the research site should be justified on the grounds of pharmacokinetics, pharmacodynamics and safety endpoints as part of the strategy to manage risks in the clinical trial.

13.61. Special consideration should be given to potential long-term consequences on physiological systems and potential long-term safety problems.

13.62. Communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) is particularly important. Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to PPB.

14. Labelling:

14.1. 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:

14.1.1. Statement indicating that the product is for "*clinical trial purpose only*"

14.1.2. Name, number or identifying mark

14.1.3. Recommended storage conditions

14.1.4. Name and address of the sponsor

14.1.5. Protocol code or identification

14.1.6. The writing "Keep out of reach of children"

14.1.7. Name, address and telephone number of the sponsor, contract re search organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding)

14.1.8. Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency

14.1.9. The batch and/or code number to identify the contents and packaging operation;

14.1.10. A trial reference code allowing identification of the trial, site, investigator and sponsor, if not given elsewhere;

14.1.11. The trial participant identification number/treatment number

and, where relevant, the visit number

14.1.12. The name of the investigator (if not included above)

14.1.13. Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial participant or person administering the product)

14.1.14. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity

Re-labelling

14.2. 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.

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

14.4. The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP).

14.5. Any request for re-labelling should be accompanied by certificate of analysis of the product from PPB recognized laboratory. After issue of a go ahead, the re-labelling shall be carried out under the supervision of a Pharmaceutical Inspector on the ground.

14.6. Any re-labelling of Investigational Product requires the prior approval of PPB. In general it is recommended that wherever possible investigational product is not relabelled. It is however accepted that in certain cases it is necessary to re-label and as such we will, review applications for the extension of expiry dates based on sufficient evidence being provided by the applicant that an extended expiry date is warranted.

14.7. It is required that re-labelling be performed in accordance with the GMP requirements *"In case of use date extension, an additional label should be affixed to the investigational medicinal product. This additional label should include the new use date and repeat the batch number. It may be superposed on the old use date, but, for quality control reasons not on the original batch number. This operation may be performed on site by the clinical trial monitor(s) or the clinical trial site pharmacist, in accordance with specific and standard operating procedures and under contract if applicable. The operation should be checked by a second person. Documented evidence of this additional labelling should be available in the trial documentation and in the batch records."*

14.8. Provide a written justification and evidence (copies of re-analysis supporting extension of expiry date)

14.9. Please ensure that a sample of the label you intend to use for re-labelling is submitted with your application. It is essential that all packaging levels, primary and secondary, are relabelled and that, where appropriate, re-labelling seals are used to re-seal opened packaging.

14.10. PPB will not approve re-labelling of product if the proposed additional label, obscures the original labelling. At all times the original label, consistent with the import licence, should be visible.

14.11. PPB requires that Investigational Product is maintained in its original packaging. Packaging is an integral component of Good Manufacturing Practice and as such can only be performed by a GMP authorized unit; PPB will consider applications for the extension of expiry dates only.

14.12. The relabeling process report should then be submitted to PPB within seven days of carrying out the activity

15. Safety Reporting

15.1. The Sponsor or the Principal Investigator should provide initial reports of SUSARs 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.

15.2. The SUSAR and SAE reports can also be submitted to the Board through the online system at www.pv.pharmacyboardkenya.org

15.3. In addition to the expedited reporting, sponsors shall submit, once a year throughout the clinical trial or on request a safety report to PPB, taking into account all new available safety information received during the reporting period. The aim of the annual safety report is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety conditions of subjects included in the concerned trial(s).

15.4. The safety report shall include a summary of SAEs and SUSARs.

15.5. The SUSAR/SAE Log should include:

15.6. Patient ID

15.7. Age

15.8. Type of SUSAR/SAE

15.9. Start date of the SUSAR/SAE

15.10. End date of the SUSAR/SAE

15.11. Reason for reporting the event as an SAE

15.12. Relation to investigational drug

15.13. Outcome of the SAE

15.14. Initial Serious / fatal reactions (local) shall be reported within **seven days** and follow up reports afterwards within eight days

15.15. Non-serious (local) reports should be provided within fifteen days

15.16. Any serious adverse event to the investigational product shall receive immediate medical attention and reported to the board.

15.17. The SAE report form shall be completed and detailed information such as laboratory results submitted to enable causality assessment.

15.18. All fatal cases shall be accompanied by a formal autopsy report where available.

15.19. In exceptional circumstances where a formal autopsy is not practicable, provision of a verbal autopsy report shall be submitted.

15.20. Any frequent adverse event to the product shall receive immediate medical attention and reported to PPB within seven (7) days.

15.21. The Principal Investigator is required to submit follow-up information as soon as it becomes available.

15.22. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes.

15.23. All additional information should be clearly marked as update information and should include the Protocol Number and Participant Number.

15.24. The SUSARs to be reported include;

15.24.1. SUSARs which occur within the concerned trial

15.24.2. SUSARs which occur outside the concerned trial

15.25. Foreign regulatory decisions that affect the safety or use of the product under study shall be reported to PPB within seven days through a detailed report

15.26. Literature reports that affect the safety of the product under study shall be submitted within fifteen days thorough a detailed report and a copy of the publication

15.27. Notification of change in nature, severity or frequency of risk factors for the product under study shall be submitted within 28 days

15.28. New information impacting on risk benefit profile of product or conduct of trial shall be submitted within fifteen days

16. Requirements Concerning Data and Safety Monitoring Board

16.1. The Pharmacy and Poisons Board recommends the formation of a Data Safety and Monitoring Board to monitor trials, when:

16.1.1. The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;

16.1.2. There are *a priori* reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;

16.1.3. There is prior information suggesting the possibility of serious toxicity with the study treatment;

16.1.4. The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;

16.1.5. The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;

16.1.6. The study is large, of long duration, and multi-center.

16.2. The following issues related to DSMB shall be submitted to PPB:

16.2.1. Composition of DSMB or SMC

16.2.2. Copy of the DSMB/SMC Charter

16.2.3. DSMB or SMC reports which should be submitted to PPB within two weeks of the deliberations and in the request for annual approval.

16.3. Factors that may be considered when appointing members to DSMB include

16.3.1. Relevant expertise,

16.3.2. Experience in clinical trials and

16.3.3. Serving on other DSMBs, and

16.3.4. Absence of serious conflicts of interest

16.4. The objectives and design of the trial and the scope of the responsibilities given to the DSMB determine the types of expertise needed for a particular DSMB.

16.5. Composition may include

16.5.1. Clinicians with expertise in relevant clinical specialties

16.5.2. Biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data.

16.5.3. Toxicologists,

16.5.4. Epidemiologists, and

16.5.5. Clinical pharmacologists,

16.5.6. For trials with unusually high risks or with broad public health implications, the DSMB may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials.

16.5.7. Prior DSMB experience is important when considering the committee as a whole; it is highly desirable that at least some members have prior DSMB service. Prior DSMB experience is particularly important for the statistical DSMB member if there is only one statistician serving on the DSMB.

16.5.8. Some trials may require participation of other types of scientists.

16.5.9.

16.6. We recommend that sponsors establish procedures to:

16.6.1. Assess potential conflicts of interest of proposed DSMB members;

16.6.2. Ensure that those with serious conflicts of interest are not included on the DSMB;

16.6.3. Provide disclosure to all DSMB members of any potential conflicts that are not thought to impede objectivity and thus would not preclude service on the DSMB;

16.6.4. Identify and disclose any concurrent service of any DSMB member on other DSMBs of the same, related or competing products.

17. Manufacturing and import of Investigational products

17.1. Investigational medicinal products shall be manufactured by applying manufacturing practice, which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability of data generated in the clinical trial ('good manufacturing practice').

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

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

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

17.4.1. Drug Substance:

17.4.1.1. Names and Source

17.4.1.2. Method of Manufacture

17.4.1.3. Physicochemical Properties and Structure Elucidation

17.4.1.4. Impurities

17.4.1.5. Specifications and Test Methods and Batch Analyses

17.4.1.6. Stability and Packaging

17.4.2. Dosage Form:

17.4.2.1. Source

17.4.2.2. Developmental Pharmaceutics

17.4.2.3. Formulation and Method of Manufacture and Packaging

17.4.2.4. Specifications and Test Methods and Batch Analyses

17.4.2.5. Stability

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

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

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

18. Pharmacy

18.1. All clinical trial sites should have a designated Pharmacy that is secure and access controlled and shall be under the control of a validly qualified Pharmacist.

18.2. The pharmacy should have;

18.2.1. Facilities and equipment reflecting the types of trial that the investigator does including Biosafety Level Cabinets if required.

18.2.2. The right environment, such as directional airflow that is controlled/monitored for particles, microbiological contamination and temperature.

18.2.3. A designated storage area, with a quarantine area, for the investigational products

18.2.4. The right equipment, such as a laminar flow cabinet to prepare sterile products

18.2.5. Procedures to comply with GMP

18.2.6. A rigorous quality management system

18.3. The study products should be stored in designated areas under conditions and for times recommended by the sponsor.

18.4. Storage areas should:

18.4.1. Have adequate space for different study products to be stored apart

18.4.2. Be temperature-controlled and, if appropriate, humidity monitored, with alarm controls

18.4.3. Be protected from direct sunlight

18.4.4. Be mapped to identify and avoid using hot and cold spots, if appropriate

18.4.5. Be secure

18.4.6. Be accessible only to authorized staff

18.4.7. Have records for logging study products in and out

Pharmacy Staff

18.5. The pharmacy staff must be suitably qualified and experienced, and sufficient in number for the type and amount of work that the pharmacy undertakes.

18.6. A pharmacist may delegate work to pharmacy technicians or assistants, but must supervise their work and will be overall responsible for their work.

18.7. A pharmacist should have overall responsibility for investigational products and marketed medicines, including emergency medicines.

Product Handling, Accountability and Disposal:

18.8. All clinical trial sites shall have a Pharmacist as part of the core study team

18.9. The role of the Pharmacy in relation to clinical research shall be:

18.9.1. To safeguard subjects and health care professionals by ensuring that IMPs are appropriate for use and are procured, handled stored and used safely and correctly.

18.9.2. To ensure that IMPs are managed and dispensed to patients in accordance with the protocol.

18.9.3. To ensure that all pharmacy clinical trials procedures comply with relevant guidelines and regulations.

18.9.4. All pharmacy teams involved in the setting up of clinical trials and dispensing of trial medication must adhere to GCP which ensures

18.9.4.1. The protection of participants involved in trials and

18.9.4.2. The credibility of the data generated in the trial.

18.10. All investigational products shall be under the care and responsibility of a Pharmacist registered and with annual practice licence of the board

18.10.1. The Study Pharmacist shall maintain;

18.10.1.1. Certify QP release statement

18.10.1.2. QP declaration

18.10.1.3. IMP certificate of analysis

18.10.1.4. Viral safety studies and data (if applicable)

18.10.1.5. BSE-/TSE-free certificate(s)

18.10.1.6. Master randomization list

18.10.1.7. IMP code breaks

18.10.1.8. IMP prescription template

18.10.1.9. IMP accountability log template

18.10.1.10. IMP destruction log template

18.10.1.11. Temperature log template

18.10.1.12. Temperature deviation log template

18.10.1.13. IMP recall information

18.10.2. The study products shall be stored according to the required storage instructions of the manufacturer

18.10.3. All clinical trial sites shall maintain;

18.10.3.1. Local dispensing/pharmacy procedure SOPs

18.10.3.2. IMP ordering and shipping records

18.10.3.3. Acknowledgement of receipt

18.10.3.4. Completed IMP prescriptions

18.10.3.5. IMP accountability log

18.10.3.6. IMP storage records

18.10.3.7. IMP temperature records

18.10.4. Records of temperature and humidity control and monitoring shall

be maintained and these may be subject of inspection by PPB

18.10.5. If the investigational drug is subject to the Controlled Substances Act, the pharmacist shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

18.10.6. An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub investigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

18.10.7. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug.

18.10.8. All study products will be destroyed after a written permission from the board

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

18.10.9.1. Date(s) and quantity received for each product

18.10.9.2. Balance of the study medication(s)

18.10.9.3. Drug Destruction Certificate, and/or written evidence return to the used/unused drug supplies to country of origin (whichever applicable).

18.10.9.4. PPB should be provided with a report of shipment to the sponsor of destruction of the remaining test articles

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

18.11. When a clinical trial is taking place in a hospital all Investigational Medicinal Products (IMPs) should be stored and dispensed by the pharmacy and managed to the same standards as licensed medicines. IMPs must not be stored in offices, clinics or ward areas unless by prior agreement with pharmacy.

Accountability at Trial Site

18.12. The pharmacist should keep records of each stage of the handling and use of the investigational product, such as:

18.12.1. Receiving and assessing its condition on arrival, and notifying the findings to the sponsor

18.12.2. Dispensing or manufacturing it

18.12.3. Giving each subject the dose or doses specified by the protocol

18.12.4. Returning unused product to the sponsor or delegate,

18.12.5. Destroying it, as instructed by the sponsor with the approval of PPB

18.12.6. Keeping an inventory

18.12.7. Reconciling the entire IMP received from the sponsor.

18.13. These records should include the dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the investigational product and to the trial subjects.

Recall

18.13.1. The site must have a system for retrieving the investigational products promptly at any time.

Retention of samples

18.13.2. Manufacturers or importers of the investigational products must retain samples of each batch of bulk product, and the packaging components used for each finished batch, for at least two years after the trial.

19. Laboratories that Perform the Analysis of Clinical Trials Samples

19.1. Laboratories that conduct work in support of a clinical trial should be of suitable size, construction and location to meet the requirements of the work being performed.

19.2. The design of the facility should provide an adequate degree of separation of different activities to assure the proper conduct of the work.

19.3. The laboratory analysis should be organized and conducted in such a way that the findings are transparent and stand up to retrospective verification.

19.4. Roles and responsibilities within a laboratory should be established and documented prior to the initiation of analytical work.

19.5. It is the responsibility of laboratory management to ensure that laboratory personnel are appropriately educated, experienced and trainedand qualified to perform the roles and responsibilities assigned to them.

19.6. Laboratory management should ensure that each individual involved in the analysis of clinical trial samples has a current job description detailing the individual's role and responsibilities within the laboratory.

19.7. Laboratory management should ensure that there is a Quality Assurance programme with designated personnel and ensure that the quality assurance responsibility is being performed in accordance with regulatory requirements.

19.8. A named individual(s) who assumes responsibility for the conduct and reporting of the work should oversee the analysis or evaluation of clinical trial samples. This individual(s) should ensure that all laboratory work is performed in compliance with the clinical trial protocol, clinical trial protocol amendments, the contract, any associated work instruction and standard

operating procedures.

19.9. Prior to the initiation of any analysis, the persons designated as "laboratory management" should make provision to ensure that sufficient resources are available for the timely and proper conduct of the analysis in accordance with the clinical trial protocol, work instructions, associated methods and standard operating procedures.

19.10. Prior to the initiation of analytical work, lines of communication should be established and documented between the sponsor or their representative and the individual who is responsible for coordinating the laboratory analysis. It is particularly important that laboratory personnel know to whom they should report anomalous results, which may impact on trial subject safety.

19.11. Laboratory personnel should be fully aware of their roles and responsibilities with respect to the analysis or evaluation they are performing.

19.12. All staff involved in the analysis or evaluation of clinical trial samples should receive GCP training commensurate with their roles and responsibilities.

19.13. Laboratory staff should receive periodic GCP refresher training.

19.14. Laboratory personnel should receive an appropriate level of technical training prior to their participation in the analysis or evaluation of clinical trial samples. Specifically, laboratory management should ensure that staff is competent to perform the techniques required by the protocol, work instructions or associated methods.

19.15. A record of training should be maintained for each individual involved in the analysis or evaluation of clinical trial samples. Laboratory management should ensure a copy of this information is retained when staff leaves the organization.

19.16. If an individual has relevant experience that has been gained through previous employment, they should maintain a record of this experience in addition to a record of training provided by their current employer.

19.17. It is recommended that laboratory management to ensure the information they contain is up to date and remains relevant periodically review training records.

19.18. Contractual agreements between relevant parties should be in place prior to the initiation of any work.

19.19. Contracts and agreements between the laboratory and the sponsor should not conflict with the requirements outlined in the clinical trial protocol or work instruction

19.20. The laboratory's quality system should include a documented procedure for the drafting, agreement, review and revision of contracts.

19.21. The laboratory should be provided with a copy of the full clinical trial protocol (and amendments).

19.22. A mechanism should be agreed with the sponsor or their representative to ensure that any amendments to the clinical protocol that are relevant to the work of the laboratory are supplied accordingly.

19.23. All analysis or evaluation of clinical trial samples must be performed in accordance with the clinical trial protocol.

19.24. Appropriate procedures should be implemented to ensure effective and timely communication with the sponsor or their representative, regarding any serious deviations from the work instruction, clinical trial protocol or contract/agreement.

19.25. The impact of any deviations from the laboratory's standard operating procedures or documented policies should be assessed and documented.

19.26. Laboratories should not perform any work on clinical trial samples that is not specified in the clinical trial protocol.

19.27. If additional work is requested by the sponsor or their representative all relevant documentation must be amended prior to the initiation of the additional analysis or evaluation. The laboratory should seek assurance from the sponsor that the additional work does not conflict with the requirements of the clinical trial protocol, compromise the informed consent given by the trial subjects or impact on the ethics committee approval and/or the approval given by Pharmacy and Poisons Board

19.28. If unscheduled analysis or evaluation is required for urgent clinical reasons, e.g. as a result of adverse events, then it should not be delayed because it is not stipulated in the clinical trial protocol, the work instruction

19.29. Before placing work with a sub-contractor, the sponsor, or their representative, should be informed and, if necessary, the contract with the sponsor amended.

19.30. A contract or service level agreement should be implemented between the two laboratories prior to the initiation of any work. Any such contract or service level agreement should clearly state roles and delegated tasks and the scope and nature of the work that will be undertaken by the sub-contractor.

19.31. Care should be taken to ensure that contracts do not conflict with the requirements of the clinical trial protocol, work instruction or the contract between the analytical laboratory and the sponsor.

19.32. If analysis or evaluation of clinical trial samples is sub-contracted to another laboratory, the ability of the sub-contractor to perform the work must be assessed prior to its initiation.

19.33. Prior to the initiation of laboratory work, lines of communication should be established with the sponsor, or their representative, and with the investigators, to ensure that any issues that may impact on patient/subject safety are reported without delay. These may include, but are not limited to, the reporting of unexpected or out of range results and significant deviations from the protocol or work instructions.

19.34. Under most circumstances normal ranges should be established for safety tests prior to the start of analysis. If clinically significant deviations from these ranges are recorded, a mechanism should be in place to communicate this information to the sponsor or their representative and to the investigator as quickly as possible.

Sample labelling, receipt, storage and chain of custody

19.35. There should be a system for the sample management system taking care of samples from receipt to release of final result

19.36. The clinical trial samples should be labelled in such a way as to allow their unequivocal identification. A mechanism to track the movement of each sample from arrival to analysis or evaluation should be implemented and maintained.

19.37. Samples should be transported in such a way that their integrity and viability remains unaffected.

19.38. Where there is a requirement for samples to be refrigerated or frozen during transportation, measures should be taken to positively confirm that the samples were maintained at an appropriate temperature for the duration of time they were in transit.

19.39. Refrigerators or freezers used for the storage of clinical samples should be monitored to ensure they are operating within acceptable parameters.

Method validation

19.40. Analysis should be performed using appropriately validated methods with defined acceptance criteria where appropriate.

19.41. The validation of methods should be documented and, on completion, this documentation should be archived.

19.42. Relevant storage stability data must be available if samples are to be stored prior to analysis.

19.43. Routine system suitability tests, such as the analysis of quality control (QC) samples, should be considered and included in the analytical methodology as required.

19.44. It is important that analytical factors that may potentially affect clinical trial results are considered.

19.45. Acceptance criteria for each method of analysis and the circumstances that allow repeat analysis should be clearly defined and documented.

19.46. Repeat analyses should only be undertaken in accordance with a documented policy.

19.47. It is never acceptable to selectively report data; consequently, the rationale for performing the repeat analysis and the reason for the selection of the data points that will be reported should be transparent and should be documented.

19.48. All equipment used to conduct clinical analysis should be fit for its intended purpose. As a minimum, equipment should be regularly maintained by suitably qualified persons and any maintenance documented.

19.49. Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing, by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose. Any such tests should be documented and the records retained as long as the trial records to which the sample analyses relate (i.e. it may be necessary to retain the records beyond the decommissioning and retirement of the equipment).

19.50. Apparatus should be periodically inspected, cleaned, maintained and

calibrated according to standard operating procedures or the manufacturer's manuals. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement. Calibration frequency will be determined by management or their representatives and should be designed to ensure that all equipment remains fit for purpose.

Computerized systems

19.51. All computerised systems used for the capture, processing, reporting and storage of data should be developed, validated and maintained in ways which ensure the validity, integrity and security of the data.

19.52. Prior to use, all computerized systems should be subject to an appropriate level of validation. The primary aim of any validation process will be to demonstrate that the computerised system is fit for its intended purpose and can produce reliable and reproducible data. The scope of the validation should be linked to the level of functionality that will be utilised. Validation should be performed in accordance with a documented plan. All key aspects of the validation process should be documented and on completion, a suitably qualified person should assess results. When a computerised system is deemed fit for use the decision should be documented and authorised by laboratory management or their designated representative. Any limitations of the system should be clearly described in laboratory procedures.

19.53. For each computerised system, the components (e.g. hardware and software), which constitute the system, should be clearly defined. This information should be documented with the associated validation package.

19.54. If additional functionality is utilised which is beyond the scope of the original validation the need to perform additional validation must be considered and, in most cases, will be required.

19.55. If additional computerised systems are interfaced with an existing laboratory information management system (LIMS) the impact of the new equipment on the functionality of the LIMS should be assessed.

19.56. On completion, all records associated with the validation of a computerised system should be archived.

19.57. Computerised systems should be sited in appropriate locations. Consideration should be given to environmental conditions and other external factors, which may adversely impact on the systems performance.

19.58. Disaster recovery procedures should be considered for all computerised systems.

19.59. Laboratory policies should clearly define what constitutes a source document.

19.60. Source documents must always be archived and be sufficiently detailed to ensure they can be used to reconstruct the analysis, and any subsequent operation performed on the data, during or after the analysis.

19.61. Access to computerised systems should be controlled. The identity of those with specific access rights to computerised systems should be documented and subject to periodic review to ensure that the access restrictions remain current and appropriate.

20. Quality Assurance processes

20.1. Quality assurance processes should be developed to ensure that:

20.1.1. Patient safety and confidentiality are not compromised.

20.1.2. The analysis or evaluation of clinical trial samples is conducted in accordance with the principles of GCP.

20.1.3. Analysis or evaluation of samples is performed in accordance with the protocol and, where applicable, the contract/agreement, the work instruction and associated methods.

20.1.4. The laboratories policies and SOPs are adhered to.

20.1.5. Trial data is recorded and reported accurately, legibly, completely and in a timely manner.

20.1.6. Trial data is archived.

20.1.7. Prior to the initiation of sample analysis or evaluation, it is often necessary to prepare a work instruction detailing the procedures, which will be used to conduct the analysis or evaluation.

20.1.8. Be purpose-built or adapted for the purpose

20.1.9. Have automated equipment for routine haematology, biochemistry and serology tests

20.1.10. Have procedures for analyser calibration and quality control

20.1.11. Regularly maintain all the equipment, including point-of-care equipment

20.1.12. Have a procedure for transporting samples safely and quickly from clinical areas to the laboratory

20.1.13. Have written procedures for all assays, and validate the assays

20.1.14. Have a stock control procedure to make sure that reagents and consumables are used within their expiry dates

20.1.15. Keep records, including source documents and final reports

20.1.16. Have a procedure for authorizing and releasing results

20.1.17. Have a procedure for 'flagging' and notifying medical staff of abnormal results

20.1.18. Have a laboratory information management system, and validate and backup the system

20.1.19. Provide protective clothing and safety equipment for staff

20.1.20. Have a central alarm system for all fridges and freezers

20.1.21. Have an internal audit programme.

21. Protocol Amendments

21.1. 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.

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

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

21.3.1. Changes that affect patient selection and monitoring

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

21.3.3. Changes that affect patient discontinuation

21.3.4. Addition/removal of an investigational site

21.3.5. Change of Principal Investigator

21.3.6. Changes that result in the extension of duration of a trial

22. Information on On-going Trials

22.1. The PI shall be responsible for updating the current status of the approved study at the clinical trials registry; www.ctr.pharmacyboardkenya.org

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

22.2.1. Copy of the progress report that should contain among others; the current status of the study, summary of the patients screened, failed screening, enrolled, withdrawn, lost to follow-up, and challenges

22.2.2. Summary of protocol deviations and protocol violations

22.2.3. Updated IB of the investigational product

22.2.4. Number of trial subjects enrolled.

22.2.5. Copy of the latest DSMB report

22.2.6. Copy of favourable opinion from the ERC of record.

22.2.7. Copy of annual practice licence for the investigators and Pharmacists

22.2.8. SAE Log that should include

22.2.8.1. Patient ID

22.2.8.2. Age

22.2.8.3. Type of SAE

22.2.8.4. Start date of the SAE

22.2.8.5. End date of the SAE

22.2.8.6. Reason for reporting the event as an SAE

22.2.8.7. Relation to investigational drug

22.2.8.8. Outcome of the SAE

22.3. The request for annual approval must be submitted at least six weeks before the expiry of the granted approval.

22.4. Request for annual approval shall also be accompanied by copies of annual practice licences of the Investigators, Pharmacists and copy of valid insurance covers for participants

22.5. The above documents must be submitted through www.ctr.pharmacyboardkenya.org

22.6. 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.***

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

23. Clinical Trial Master File

23.1. The sponsor and the investigator shall keep a clinical trial master file.

23.2. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial.

23.3. It shall be readily available, and directly accessible upon request, PPB

23.4. The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to PPB

23.5. Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this guideline.

24. Integrity of Data Generated

24.1. The sponsor shall put in place systems to ensure the integrity and traceability of the data generated from the study

24.2. The systems put in place should be able to prevent any willful misstatement, misrepresentation, manipulation, adulteration, rewriting, hiding, replacing of quality related documents, materials, activities or results.

25. Post Trial Information

25.1. A Final Report shall be submitted to the PPB at the end of the trial.

25.2. The executive summary report of the study shall be submitted to the Board within 30 days while a copy of the clinical study report should be submitted within 180 days of the study closure.

25.3. The Board shall be informed of any results that will be publicly released at least 14 days before this information is publicly released

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

26. Inspections

26.1. The Board may inspect clinical trial sites and trial sponsors to ensure that the generally accepted principles of good clinical practice are met.

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

26.3. The Board 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.

26.4. In order to be able to demonstrate compliance with the protocol and with the applicable regulations, a Clinical Trial Master File, containing relevant documentation to allow effective supervision, should be kept by the sponsor and by the investigator.

26.5. The clinical trial master file should be archived appropriately to allow for supervision after the clinical trial has ended.

26.6. The information generated in a clinical trial should be recorded, handled and stored adequately for the purpose of ensuring subject rights and safety, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation and effective inspection by PPB.

26.7. An investigator shall upon request from any properly authorized officer or employee of PPB, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator.

26.8. The authorized officer of the board shall contact the PI or sponsor for the date of inspection when required.

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

26.10. Routine inspections will be announced at least two weeks in advance of the inspection date.

26.11. PPB has the right to conduct an unannounced inspection at its discretion.

26.12. 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.

26.13. 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.

26.14. The Inspections will include - but not be limited to:

26.14.1. The facilities and staff used for the trial: as approved by the PPB in the protocol.

26.14.2. Compliance with the approved Protocol, GCP and the applicable regulations

26.14.3. All amendments to the Protocol have been approved.

26.14.4. Accurate, complete and current records according to the Protocol.

26.14.5. SUSARs/SAEs are reported as required by the Protocol

26.14.6. Monitoring and auditing inspections conducted as required by the Protocol.

27. Termination of Clinical Trial

27.1. Premature termination:

27.1.1. 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.

27.1.2. 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

27.1.2.1. 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.

27.1.2.2. 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.

27.2. Withdrawal of PPB approval:

27.2.1. 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.

27.3. End of trial (Study closeout):

27.4. The sponsor shall notify PPB of the end of a clinical trial taking place at a Kenyan site.

27.5. That notification shall be made within 15 days from the end of the clinical trial at the site.

27.6. After the trial has been conducted and closed, the applicant shall submit a copy of Clinical Study Report or closing report for his site within 60 days.

27.7. This should be followed by a final study report within one year after trial closure unless otherwise justified.

27.8. The structure and content of the final study report

27.9. Irrespective of the outcome of a clinical trial, the sponsor shall submit a summary of the results of the clinical trial to PPB. The content of that summary should be as provided in the ICH guidelines.

27.10. The report shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary shall have;

27.10.1. Clinical trial ECCT number

27.10.2. Name and contact details of the sponsor;

27.10.3. General information about the clinical trial (including where and when the trial was conducted,

27.10.4. The main objectives of the trial and an explanation of the reasons for conducting it)

27.10.5. Population of subjects

27.10.5.1. Age group breakdown and gender breakdown;

27.10.5.2. Inclusion and exclusion criteria);

27.10.6. Investigational medicinal products used;

27.10.7. Description of adverse reactions and their frequency;

27.10.8. Overall results of the clinical trial;

27.10.9. Comments on the outcome of the clinical trial;

27.10.10. Indication if follow up clinical trials are foreseen;

27.10.11. Indication where additional information could be found.

28. Archiving

28.1. It is the responsibility of the investigator and the sponsor to archive safely all the documents related to the trial.

28.2. All archiving for Kenyan trial site related documentation, shall be done within the country and not exported.

28.3. 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.

28.4. The study documents shall be archived for a minimum of ten years from the end of the study.

28.5. Records must be made available to PPB within 3 days if there is a concern regarding the use of a clinical trial drug and/or a risk to the health of the clinical trial subject. In any other case, records must be provided within 7 days of request.

29. Conditions for Clinical Trial Import Licence

29.1. The application for import permit shall be made online at the website; www.kentrade.go.ke

29.2. The following documents should then be attached

29.2.1. The proforma Invoice or Invoice.

29.2.2. The Ethical Committee favourable opinion Letter.

29.2.3. The ECCT Approval letter from Clinical trial Division of PPB

29.3. 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.

29.4. 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.

29.5. No change in investigator, trial centre or trial protocol shall be made without prior notification and approval by PPB.

29.6. 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.

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

29.8. Change of Information

29.9. 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 License.

29.10. Discontinuation of Trial

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

30. Kenya Clinical Trials Registry

30.1. All clinical trials taking place in Kenya shall be registered in the Kenyan Clinical Trials Registry at www.ctr.pharmacyboardkenya.org

30.2. The Principal Investigator of the study shall be required to log into the registry and set up an account.

30.3. The registry will be used for all future submissions to PPB.

30.4. The sponsor/PI is required to update the different status of the clinical trial as it progresses.

31. Sanctions

31.1. The following regulatory sanctions shall be applied to the sponsor and /or Principal Investigator in the case of non-compliance to the regulations in these guidelines:

31.1.1. Informed of non-compliance and advised on how this can be remedied.

31.1.2. Warning; The Board may issue a formal warning reminding the Sponsor or Principal Investigators of their regulatory obligations.

31.1.3. Black listing non-compliant Sponsor or Principal Investigator

31.1.4. The Board may consider making public a list of sponsors or Principal Investigators found to be seriously or persistently non-compliant.

31.1.5. Refusal to issue import permit of the study medications

31.1.6. Suspension of the study

31.1.7. Stopping of the study

1.1.1. Fining

SECTION TWO

HERBAL PRODUCTS

1. 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.

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 the known constituent alone would provide synergistic fashion with known constituents to provide more efficacy than. 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.

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)

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

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.

Information needed to support a clinical trial for a herbal product

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.

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.

Pharmacokinetics

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

2. 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.

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.

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.

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

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 Application Form (*FOM 015/MIP/CLT/SOP/003*)

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:

Public Title:

Protocol No:

Version No: Date of Protocol:

Study Drug:

ECCT Ref number (if applicable):

Sponsor:

Contact Person:

Address:

Telephone Number: Fax Number:

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 yes □ no □

If yes specify:

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	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:	

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	yes □ no □
If yes, specify:	
Others:	yes □ no □
If yes, specify	
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 (*FOM010/MIP/CLT/SOP/003*)

Checklist for Submission of Request for Approval of New Application

No	Item	Yes/No
1.	Cover letter	
2.	Completed application form	
3.	The Study Protocol	
4.	Patient Information leaflet and Informed consent form	
5.	Investigators Brochure/Package inserts or Investigational Medicinal Product Dossier (IMPD)	
6.	Adequate data and information on previous studies and phases	
7.	Stability data of the investigational product	
8.	GMP certificate of the investigational product from the site of manufacture	
9.	Certificate of Analysis of the investigational product	
10.	Pictorial Sample of the investigational products. This sample should include the text of the labeling to be used	
11.	Signed investigator(s) CV(s) including that of study Pharmacist	
12.	Evidence of recent GCP training of the core study staff	
13.	DSMB Charter including the composition and meeting schedule	
14.	Detailed budget of the study	
15.	Financial declaration by Sponsor and/or PI	
16.	Signed Declaration by Sponsor or Principal investigator that the study will be carried out according to protocol and applicable laws and regulations.	
17.	Indemnity cover for PI and investigators	
18.	Insurance Certificate for the participants	
19.	Copy of favorable opinion letter from the local Ethics Review Committee (ERC).	
20.	Copy of current Practice Licenses for the Investigators and study Pharmacist	
21.	Copy of approval letter(s) from collaborating institutions or other regulatory authorities, if applicable	
22.	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.	
23.	For multicentre/multi-site studies, an addendum for each of the proposed sites including among other things the sites' capacity to carry out the study i.e personnel, equipment, laboratory etc	
24.	Registration at the clinical trial registry at www.ctr. pharmacyboardkenya.org	
25.	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.	
26.	Payment of fees	
27.	Four bound hard copies of all the above documents	
28.	Signed checklist	

Signed

Applicant Name……Sign…… Date……

PPB Staff Name. ……Sign…… Date……

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.

If required, payment can also be made by electronic fund transfer (EFT) to PPB Bank account. 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.

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

Annex 3 (FOM010/MIP/CLT/SOP/003)

Checklist for the Request for Annual Approvals of Clinical Trials

No.	Item	Yes/No
1.	Cover letter	
2.	Updated Investigators Brochure/Package inserts or Investigational Medicinal Product Dossier (IMPD)	
3.	Copy of current favorable opinion letter from the local Ethics Review Committee (ERC).	
4.	Request for annual approval at the clinical trial registry www.ctr.pharmacyboardkenya.org	
5.	Annual progress report	
6.	Latest Data Safety Monitoring Board (DSMB) report	
7.	SAE Cumulative log	
8.	Copy of the Annual Practice for the investigators and Pharmacist	
9.	Copy of the current indemnity cover of the investigators	
10.	Protocol Deviations and Violations Log	

Signed

Applicant Name……Sign…… Date……

PPB Staff Name. ……Sign…… Date……

Annex 4

Declaration by Applicant

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

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,

1. It is reasonable for the proposed clinical trial to be undertaken;
2. It will be conducted according to the submitted protocol
3. The study will be conducted according to Kenyan legal, ethical, and PPB requirements
4. The study will conducted according to principles of Good Clinical Practice
5. We shall ensure the safety and well being of study participants
6. We shall carry out the study so as to ensure the integrity of the data generated.
7. We will submit reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) and safety reports according to applicable guidance;
8. 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

Annex 5 (FOM014/MIP/CLT/SOP/003)

Declaration of Financial Disclosure/Conflict Of Interest

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

DECLARATION OF FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

_____

Protocol Title:	
Protocol Number:	
Study Site(s) Identification:	
Principal Investigator:	
Name of Person Completing this form:	
Study Role of person completing this form:	
Study Sponsor:	
Study Funded By:	

Note: For the purposes of this document the term "clinical investigator" includes the spouse (s) and all dependent children.

Read each of the statements in the left column and answer each statement with "True" or "False".If, during the course of the study any of your answers change from "True" to "False" then a new form must be completed.

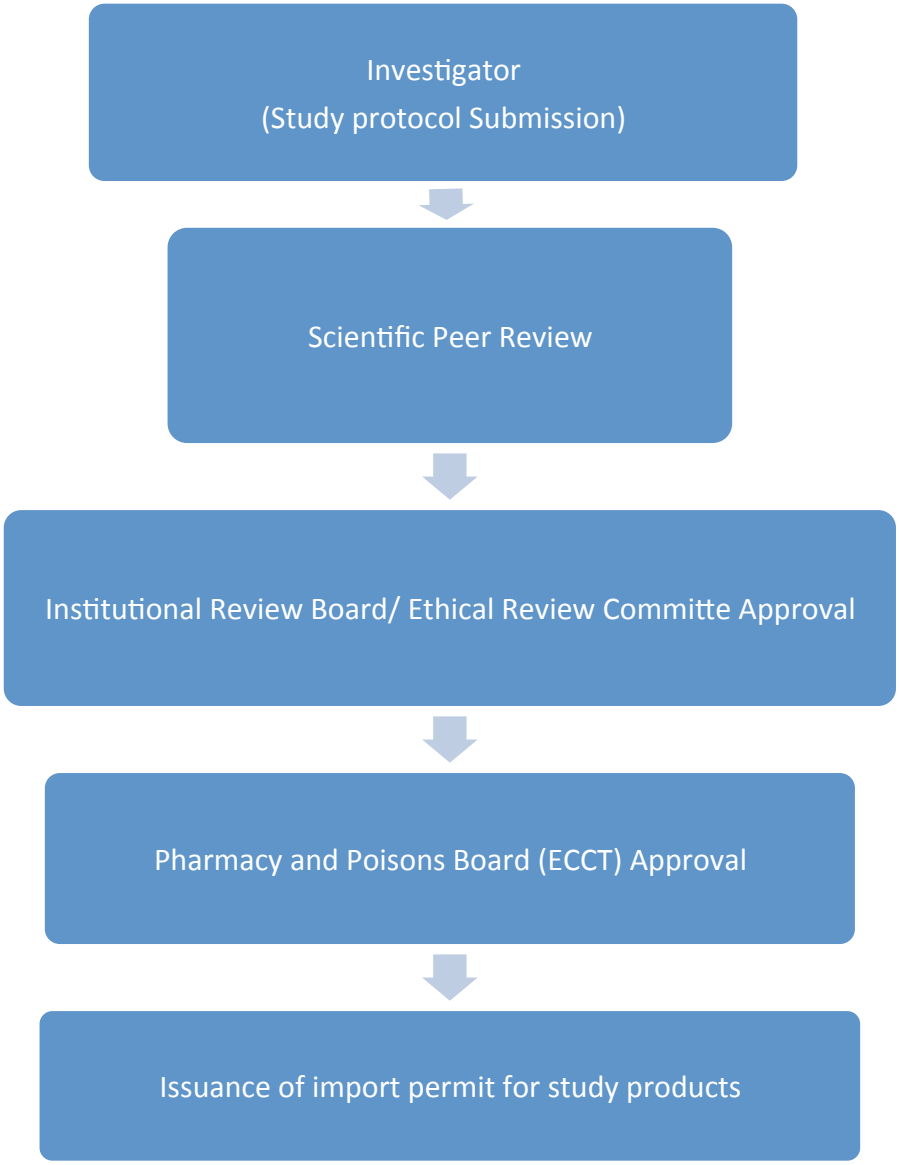
	True	False
I hold a significant equity interest in the Sponsor or Funding Company of the applied/listed clinical trial. This would include, for example, any ownership interest, stock options, Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) or other financial interest which may also include indirect investments such as a trust or holding company whose value cannot be easily		

determined through reference to public prices, or an equity interest exceeding USD $50,000. If "True" please describe:		
I am in receipt of significant payments of other sorts, the total of which exceeds USD $25,000, EXCLUDING the costs of conducting the trial or other clinical trials. This could include, for example, payments made to the investigator or the institution to support activities (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If "True" please describe:		
I hold a proprietary or financial interest in the test product such as a patent, trademark, copyright (including pending applications), or licensing agreement. If "True" please describe:		
I have financial arrangements whereby the value of the compensation could be influenced by the outcome of the trial. This could include, for example, compensation that is explicitly greater for a favourable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. If "True" please describe:		
To your knowledge, would the outcome of the study benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? If "True" please describe:		
DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge. Should there be any change to the above information (including changes to my financial interests and arrangements, or those of my spouse(s) and dependent children), I will promptly notify Pharmacy and Poisons		

Board and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the course of the trial or within one year after trial completion up to the publication of the final results.
Signature: Date:
Full Names of Clinical Investigator:

Annex 6

The Clinical Trials Approval Flow Chart



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 on Regulating the Conduct of Clinical Trial in Human Participants Zambia Medicines Regulatory Authority
6. Guidelines for Application to Conduct Drug Related Clinical Trials in Malaysia.
7. www.clinicaltrials.gov
8. ICH - GCP Guidelines for Clinical Trials. http://www.ich.org
9. Federal Regulations for Clinical Investigators
10. EU Regulations on Clinical Trials
11. EMA Note for Guidance on Clinical Investigation of Medicinal Products in The Paediatric Population (Cpmp/Ich/2711/99)
12. Guidelines for Good Clinical Practice In Ghana
13. USFDA Guidance for Clinical Trial Sponsors on Establishment and Operation of Clinical Trial Data Monitoring Committees
14. EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples
15. ABPI Guidelines for Phase 1 clinical trials 2012 Edition

Changes from edition 1 are;

1. Clarification on safety reporting timelines; the document gives a guidance on how these reports are to be submitted to PPB
2. Guide on studies involving children; The requirements for carrying out studies involving children has also included in this version
3. Information on Phase One studies
4. Requirement for Clinical trial insurance
5. Labelling and relabeling of investigational products. In order to guide investigators on this important activity, a section has been dedicated to labelling and relabeling of the investigational products
6. Information on Data Safety and Monitoring Boards
7. Product Accountability and Disposal
8. Submission of final study report
9. Updated checklist for submission of applications; for efficient review of the submitted protocols, the checklist for submission has been updated taking note of the frequent finding of the previous reviews
10. Updated checklists
11. Updated declaration forms

P. O. Box 27663 00506 Lenana Road Opposite Russian Embassy Nairobi,

Tel: +254-02-3562107/2716905/6, Fax: +254-02-2713431,

Website: www.pharmacyboardkenya.org

Email: info@pharmacyboardkenya.org