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REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDELINES FOR THE CONDUCT OF CLINICAL TRIALS IN KENYA

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
CT	Clinical Trial
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
ERC	Ethics Review Committee
IDMC	Independent Data Monitoring Committee (IDMC)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IP	Investigational product
IB	Investigator's Brochure
MABEL	Minimum Anticipated Biological Effect Level
MTA	Material Transfer Agreement
MABEL	Minimum Anticipated Biological Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PPB	Pharmacy and Poisons Board
PSUR	Periodic Safety Update Report
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

GLOSSARY OF TERMS

Adverse Drug Reaction: 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: 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

Active pharmaceutical ingredient (API): Means an active ingredient in any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or
to affect the structure or any function of the body of man or animals.

Applicant: An investigator or sponsor 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 participants.

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

Bioavailability: refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution vs. intravenous), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities in terms of peak (Cmax and Tmax) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects with respect to both efficacy and safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

Blinding/Masking

A procedure in which study participants, investigators or data analysts are kept unaware of the treatment assignment(s). Single-blinding usually refers to the study participant(s) being unaware and double-blinding usually refers to the study participant(s), investigator(s), and data analyst(s) being unaware of the treatment assignment(s).

Case Report Form: A form used to record data on each trial participant during the trial, as defined by the study protocol.

Clinical Trial: Any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, to discover or verify the effects of, identify any adverse reactions to investigational products, to study the absorption, distribution, metabolism, and excretion of the products with the object of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV.

Clinical Trial Report: A written description of a trial/study of any therapeutic or prophylactic agent conducted in human study participants in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Comparator: A medicinal or marketed product (Active or placebo) used as a reference in a clinical trial.

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

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

Contract Research Organization: An individual or organization contracted by the sponsor to perform one or more of a sponsor's trial- related duties and functions.

Coordinating Principal Investigator (CPI): An investigator designated for a multi-site clinical trial conducted within a single country to coordinate the implementation of the approved protocol across all participating sites. The Coordinating Principal Investigator facilitates communication among site investigators and the sponsor and ensures consistency in trial conduct across sites within that country.

Co-Principal Investigator (Co-PI): An investigator who shares significant scientific or operational responsibilities with the Principal Investigator for the conduct of a clinical trial, as defined in the study protocol or sponsor documentation. A Co-Principal Investigator may contribute to study leadership but does not replace the Principal Investigator as the primary regulatory contact unless formally designated.

Data and Safety Monitoring Board (DSMB)/ Independent Data Monitoring Committee (IDMC): 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.

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.

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 NACOSTI-accredited Ethics review committee (ERC) to conduct a clinical trial in Kenya.

Finished pharmaceutical product (FPP): Means a finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

Good Clinical Practice: 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: 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.

Indemnity: legal exemption from liability for damages

Independent ERC Committee: A committee that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans with the aim to protect the integrity, rights, safety and welfare of the research participants.

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

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

Insurance: The act, system, or business of insuring property, life, one's person, etc., against loss or harm arising in specified contingencies, as fire, accident, death, disablement, or the like, in consideration of a payment proportionate to the risk involved.

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

Investigational product: pharmaceutical form of an active ingredient, placebo, or medical device being tested, or used as a reference, in a clinical trial.

Investigational medicinal product: Any pharmaceutical product including a new product or existing product for new indication in 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.

Investigational medical device: Medical device being assessed for safety or performance in a clinical investigation

Investigator: A person responsible for the conduct of the clinical trial at a trial site.

In Vitro diagnostics: Means a device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Investigator's Brochure: 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 authorized under applicable law to consent, on behalf of a prospective participant, to the participant 's participation in the clinical trial.

Manufacturer: Means a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.

Material Transfer Agreement: 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.

Minimum Anticipated Biological Effect Level: Anticipated dose needed to result in a biological effect in participants of a clinical trial. It is a safety window based on pharmacological threshold. The minimal anticipated biological effect level is recommended as a useful approach to calculate the Safe Starting Dose, as it is the lowest dose that is active.

Minimum Anticipated Biological Effect Level: Anticipated dose needed to result in a biological effect in participants of a clinical trial. It is a safety window based on pharmacological threshold. The minimal anticipated biological effect level is recommended as a useful approach to calculate the Safe Starting Dose, as it is the lowest dose that is active.

Minor: All individuals from the ages of birth until the legal age of adulthood which is 18 years in Kenya.

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

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

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

Multi-Regional Clinical Trial (MRCT): A clinical trial conducted in more than one region/country under a single protocol, designed to support regulatory submissions in multiple regions by generating data that are applicable across those regions.

On-going stability study: Means the study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

No Observed Adverse Effect Level: The highest dose level that does not produce a significant increase in adverse effects (AEs) in comparison to the control group

No Observed Effect Level: Greatest concentration or amount of a substance, found by experiment or observation, that causes no alteration of morphology, functional capacity, growth, development, or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

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.

Phase II Clinical Trial: The purpose of these trials is to demonstrate therapeutic activity of medicines, or immunogenicity of vaccines, and to determine appropriate dose ranges or regimens. In addition, these trials obtain additional safety data. These studies are routinely carried out in patients. They are frequently split into two phases IIA (proof of Concept) and IIB (Dose finding). These studies provide early efficacy data.

Phase III Clinical Trial: These are large trials aimed at determining efficacy of the investigational product. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use. The information obtained in this phase and the other two phases is used for licensure of the investigational product. Safety data is also collected in Phase III Trials. Phase IIIB are studies conducted just before or during regulatory filing to provide evidence to support product claims and to demonstrate safety in larger and more diverse populations.

Phase IV Clinical Trial: These are studies performed after registration of the medicinal product for use by the general public. It is often referred to as Post-Marketing Surveillance Studies, these are studies designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with the widespread use.

Placebo: An inactive substance or treatment (inert substances with no pharmacologic activity) that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

Participant/study Participant: An individual who participates in a clinical trial, either as a recipient of the investigational product or as a control

Pre-clinical Studies: Non-Human studies for product development.

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: 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.

Quality Assurance: 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: 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 participant s to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- Results in death,

- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

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

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

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

Standard Operating Procedures (SOPs): Detailed written instructions to achieve uniformity of the performance of a specific function.

Sub- Investigator (Sub-I): Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions

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.

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1. The Ministry of Health
2. Our stakeholders
3. Partners and
4. 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.

FOREWORD

The Pharmacy and Poisons Board recognizes the importance of research and development of new medical products and health technologies 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 endeavor to provide a regulatory environment that avoids unnecessary delays in the clinical trial authorization process while providing safeguards for quality, efficacy, and public health. Consequently, these guidelines have been developed to assist clinicians, researchers, pharmaceutical industry, sponsors, and investigators to easily navigate the Kenyan clinical trial authorization process.

The guidelines provide information on the current minimum requirements for authorization to conduct clinical studies involving investigational products, health technologies, 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 Reactions (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 revised guidelines have been structured in a format that incorporates the principles and technical content of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The Pharmacy and Poisons Board (PPB) adopts the relevant and current ICH, World Health Organization (WHO)-Good Clinical Practice (GCP) ,PIC/S and Good Clinical Laboratory Practice (GCLP) standardsto promote consistency, completeness, and uniformity in clinical trial submissions, thereby facilitating efficient scientific assessment and transparent regulatory decision-making.

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Ag. CHIEF EXECUTIVE OFFICER

1.0 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 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 Fourth edition.

Some of the additions in this edition are;

1. Additional / revised Definitions
2. Edits to comply with QMS and ICH requirements
3. Revised review process and approval flow charts Alignment with the Pharmacy and Poisons (Conduct of Clinical Trials) Rules, 2022
4. New application process/requirements regarding multi-site clinical trials

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 practice around the world.

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

1.1 Legal Framework

The regulation for the conduct of clinical trials is governed under the provisions of Section 25A of the Pharmacy and Poisons Act, Cap 244 Laws of Kenya (hereinafter referred to as the “Act”) and the Subsidiary Legislation thereunder.

The Board, under Section 3A of the Act, is empowered to grant or withdraw authorization for conducting clinical trials of medical products; investigate conduct related to the manufacture, import, export, storage, distribution, sale and use of medical products; constitute technical and expert advisory committees and institute administrative, civil and criminal proceedings.

In performing its functions in regulation of health products and technologies, the Board, under Section 3B(2)(o) and (p) of the Act, approves and regulates clinical trials including approving the use of unregistered medicinal substances for purposes of clinical trials and compassionate use.

Section 25A of the Act gives an elaborate outline on regulation of clinical trials which includes approval of the relevant ERC. In regulation, the Board is mandated under Section 3B (2)(r) of the Act to collaborate with other national, regional and international institutions. Therefore, the Board recognizes the role played by the National Commission for Science, Technology and Innovation (NACOSTI) established under the Science, Technology and Innovation Act, 2013 (STI Act) which is mandated to accredit research institutes and approve all scientific research in Kenya. The Science Technology and Innovation (Relevance and Quality Assurance in Research) Regulations, 2014 under rule 7 makes it a requirement for the establishment of an institutional scientific and ethical review committee accredited by the Commission, which are then recognized by the Board before approval of a clinical trial.

In addition to the foregoing, it is a requirement for every practicing registered pharmacist and enrolled pharmaceutical technologist, practicing in their private capacity, government, faith-based institutions, non-governmental organizations, training institutions, research organizations or any other institution, to have a valid practicing license under the provisions of Section 9C (3) of the Act.

This guideline shall consistently reference the most current versions of ICH GCP, WHO GCP, PIC/S, and other internationally recognized regulatory standards.

1.2 Scope

The guideline for Conduct of Clinical Trials in Kenya is applicable to all stakeholders in clinical research, to provide guidance into clinical trial application submission, review, approval and monitoring in Kenya

1.3 Vision

To be a global leader in promoting and protecting public health

1.4 Mission

To protect and promote the health of the public by regulating the profession of pharmacy and ensuring access to quality, safe, efficacious and affordable medical products and health technologies

1.5 Corporate Values and Principles

The board seeks to cultivate a conducive and responsive organizational culture for both internal and external stakeholders and enhance service delivery by embracing the following core values;

1. Commitment to public health
2. Professionalism
3. Accountability and transparency
4. Integrity and respect
5. Quality
6. Diversity and Inclusion

1.6 Core Functions

1. Ensure the quality, safety and efficacy of medical products and health technologies.
2. Regulation of training and practice of pharmacy.
3. Advising the government on any matter relating to the regulation of medical products, health technologies and pharmaceutical services.

2.0 APPLICATION REQUIREMENTS

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

- 2.1.1 Unregistered medical products, vaccines or medical devices
- 2.1.2 Registered medical products or medical devices where the proposed clinical trials are outside the conditions of approval for marketing authorization. These may include changes to:
  - 2.1.2.1 Indications and clinical use
  - 2.1.2.2 Target patient population(s)
  - 2.1.2.3 Routes of administration
  - 2.1.2.4 Dosage regimens
- 2.1.3 Comparative bioavailability trials
- 2.1.4 Studies intended to generate data on a product that is registered in Kenya based on foreign-generated data.
- 2.1.5 Studies to establish bioequivalence for registration of generic products
- 2.1.6 Studies to identify any adverse reactions to one or more medical products
- 2.1.7 Studies to generate information on the absorption distribution, metabolism and excretion of one or more medical products;
- 2.1.8 Or any study that is going to use an investigational product on human beings.
- 2.1.9 Post- Marketing clinical trials (Phase IV) of registered medicines including the efficacy studies monitoring resistance

2.2 Exemptions**;**

- 2.2.1 Exempt status may not be determined by the researcher (Investigators may not self-exempt).
- 2.2.2 This guideline does not cover randomized controlled trials relating to behavioral interventions.
- 2.2.3 Research in adults involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey

procedures, interview procedures, or observation of public behavior, unless:

2.2.3.1 Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

2.2.3.2 Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. Note: This exemption does not apply to research in the pediatric population.

2.2.4 Research involving the collection or study of existing data, documents, or pathological or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

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

2.4 For a multi-site clinical trial conducted in Kenya, a single parent application shall be submitted by the Sponsor or the Sponsor's authorized representative. The parent application shall designate a Coordinating Principal Investigator who will have overall responsibility for coordination and oversight of the trial across all participating sites.

2.5 In addition, the parent application shall include site-specific sub-applications, each comprising a site-specific addendum that provides detailed information for the respective trial site. Such information shall include, but not be limited to, site infrastructure, available facilities, equipment, and the qualifications and capacity of the study staff to conduct the trial.

2.6 An application must be made by completing the appropriate online application form (Annex 1; FOM015/CTR/SOP/003) on https://ctr.pharmacyboardkenya.org/users/login 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 guidelines can be downloaded from the PPB website: https://pharmacyboardkenya.org/clinical-trials

2.7 An application to conduct a clinical trial shall include all the documents as indicated in Annex 2 (***FOM010/CTR/SOP/003***)

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

3.0 PROCEDURES FOR ACCEPTANCE, REVIEW, AND APPROVAL OF APPLICATIONS

Application

3.1 All applications to conduct a clinical trial will be received online at https://ctr.pharmacyboardkenya.org by the Clinical trials division of the Product Safety Department of the Pharmacy and Poisons Board.

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

Application Reference Number

3.3 When an application for a Clinical trial is accepted, an automatic system generated reference number will be issued for each application. This ECCT reference number must be quoted in all correspondence concerning the application in the future. This will be communicated through email of the applicant or through the clinical trials online system.

Review

3.4 The Pharmacy and Poisons Board (PPB) shall conduct scientific and regulatory evaluation of submitted clinical trial applications.

3.5 The PPB has an Expert Committee on Clinical Trials (ECCT) drawn from a pool of external experts to provide independent scientific advice and support the review process.

3.6 All individuals involved in the review of clinical trial applications, , shall declare any actual, potential, or perceived conflict of interest prior to participating in the evaluation process. Reviewers shall not have financial, professional, or personal interests that could compromise, or be perceived to compromise, their impartiality and objectivity.

3.7 Confidentiality will be maintained at all times during review.

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

3.9 The decision of the PPB (approval, request for additional information or rejection) will be communicated in writing to the applicant within 50 working days of the receipt of a complete and valid application

3.10 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.

3.11 The review shall consider among other things;

3.11.1 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 randomization, comparator and endpoints;

3.11.2 Compliance with the requirements concerning the manufacturing and import of investigational products and auxiliary medical product,

3.11.3 Compliance with the labelling requirements;

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

3.12 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.

3.13 Approval for importation of investigational products and comparator will be dependent on approval to conduct the clinical trial. The quantities approved for import shall be justifiable in relation to the study and timelines.

3.14 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.

3.15 A list of the approved/ rejected clinical trials will be updated bi-annually and can be accessed from the website; www.pharmacyboardkenya.org

3.16 The review process for applications will be within timelines specified in this guideline, and the same will be internally monitored. Reliance decisions for clinical trial applications shall be as per the Board’s guidelines on reliance mechanisms.

4.0 INVESTIGATOR

4.1 Categories of Investigator

4.1.1 Clinical trials are conducted by Principal Investigators who have entered into an agreement with a Sponsor to conduct a clinical trial. The investigator is responsible for the conduct of the clinical trial at the trial site(s).

4.1.2 In the case of a multi-centre/multi-site trial, each site must have a Kenyan resident Principal Investigator (PI) and at least one sub-investigator (Sub-I) who are registered with Kenya Medical Practitioners and Dentists Council (KMPDC).

4.1.3 The PI must be a Kenya-based clinician and must have actively participated in at least two clinical trials as a co-investigator. The local PI has sole or joint responsibility for the conduct of trial and delegation of trial responsibilities of the trial.

4.1.4 A Sub-I must be a Kenya-based member of the clinical team designated and supervised by the PI at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

4.1.5 A Co-PI may be a qualified non-clinician scientist; e.g. a laboratory/medical scientist, biostatistician, epidemiologist, public health specialist, veterinarian or equivalent qualified and experienced person who can provide trial oversight management. At least one Co-PI must be a clinician and qualified to provide medical oversight.

4.1.6 The role of each Co-PI must be clearly described for the trial, and their complementary responsibilities carefully detailed so that all responsibilities of the PI, as defined, are covered.

4.1.7 For multi-site clinical trials conducted a Coordinating Principal Investigator (CPI) should be designated to coordinate the implementation of the approved protocol across all participating sites.

4.2 Investigator Qualifications

4.2.1 The Principal Investigator must:

- 4.2.1.1 Be appropriately qualified to conduct the study, with relevant training, and experience within the professional area;
- 4.2.1.2 Have a degree in medicine, pharmacy, pharmacology, toxicology, biochemistry, dentistry, or a related discipline from a university recognized in Kenya;
- 4.2.1.3 Have a valid practice license from the relevant regulatory authority;
- 4.2.1.4 Have a valid professional indemnity cover;
- 4.2.1.5 Have had formal training in GCP that was undertaken at least two years before the date of an application for the trial;
- 4.2.1.6 Have previous experience as co-investigator in at least two clinical trials;
- 4.2.1.7 Is a citizen of Kenya or is permanently resident in Kenya.
- 4.2.1.8 Permit monitoring and auditing of the trial and inspection by PPB or appointed representatives.
- 4.2.1.9 Keep a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties

4.2.2 Investigators shall satisfy the following:

- 4.2.2.1 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.
- 4.2.2.2 Have a current practice license from the relevant regulatory authority.
- 4.2.2.3 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.

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

4.2.2.5 Had formal training in Good Clinical Practice (GCP) within the last two 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.

4.3 Adequate resources

The Investigator must:

4.3.1 Demonstrate (e.g. based on retrospective data) the potential to recruit the required number of suitable participants within the agreed recruitment period.

4.3.2 Have sufficient time and funds to properly conduct and complete the trial within the agreed trial period.

4.3.3 Have available an adequate number of appropriately qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.3.4 Ensure that all persons assisting with the trial are adequately informed about the protocol, the IP and their trial-related duties and functions.

4.3.5 Be responsible for supervising any individual or party to whom the Investigator delegates study tasks conducted at the trial site.

4.3.6 Ensure that any party retained to perform study tasks is qualified to perform those study tasks.

4.4 Medical care of trial participants

4.4.1 A qualified medical practitioner, who may be the PI, Co-PI or, if appropriate, a Sub-I, should be responsible for all trial-related medical decisions.

4.4.2 The medical care given to, and medical decisions made on behalf of the participants must always be the responsibility of a qualified medical practitioner or when appropriate a qualified dentist registered with the Kenya Medical Practitioners and Dentists Council

4.4.3 In addition, they must have current annual Practice License at the time of submission of application to PPB.

4.4.4 During and after a participant's involvement in a clinical trial, the investigator shall ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory abnormalities, that are related to the trial.

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

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

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

4.4.8 Proper protection procedures or treatments should be administered to trial participants SAEs or SUSARs.

4.4.9 The investigator shall ensure that he/she has adequate Professional Indemnity insurance cover before engaging in clinical trials activities

4.5 Communication with ERC and/or PPB

4.5.1 Before initiating a trial, the PI should have the written and dated approval from PPB and other relevant bodies.

4.5.2 During the clinical trial, the Investigator must provide PPB and/or ERC all updated documents, including but not limited to, updated IB, additional safety data, updated informed consent and protocol amendments.

4.6 Compliance with the protocol

4.6.1 The investigator should conduct the trial according to the approved protocol, PPB legal requirements and internationally recognized regulatory standards.

4.6.2 The sponsor and all Principal investigator/s shall sign and date the protocol of the trial to confirm the agreement.

4.6.3 The investigator shall not implement any major deviation from or changes to the protocol and Informed Consent Form (ICF) without prior review and approval of the PPB and ERC except when the changes involve only logistical or administrative aspects of the trial

4.6.4 For exceptional implemented deviation or changes, for instance immediate safety of participants already recruited into the trial, the reasons for it and, if appropriate, the proposed protocol amendment(s) should be documented and submitted to PPB and ERC as well as documented appropriately.

4.6.5 The investigator should implement procedures to ensure the integrity of performance of the study tasks performed and any data generated.

4.6.6 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.

4.7 Investigational Product(s)

4.7.1 Responsibility for IP(s) accountability at a trial site rests with the Investigator.

4.7.2 The Investigator may assign his/her duties for IP(s) accountability at a trial site to an appropriately qualified pharmacist.

4.7.3 The investigator and study pharmacist shall establish SOPs for handling of the IP(s).

4.7.4 A designated pharmacist shall be responsible for the custody and control of the IP(s).

4.7.5 The pharmacist shall maintain complete and accurate records of receipt, storage, handling, dispensing, and return or disposal of the IP, and shall ensure that the product is processed, handled, and stored in accordance with the approved protocol, manufacturer's instructions, and applicable storage conditions.

4.7.6 The pharmacist or designated personnel shall maintain an up-to-date inventory and accountability log for the IP(s) at the trial site. These records shall ensure full traceability of the IP, including quantities received, dispensed to each participant, returned by participants, and returned to the sponsor or otherwise disposed of. All discrepancies shall be documented, investigated, and resolved in accordance with established procedures.

4.7.7 The investigator should ensure that the IP(s) are used only in accordance with the approved protocol.

4.7.8 The IP(s) shall be imported into Kenya only after approval of the protocol by PPB.

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

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

4.8 Randomization Procedures and Unblinding

4.8.1 The Investigator must follow the trial's randomization procedures, if any.

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

4.8.3 Any premature unblinding of the IP(s) for whatever reason (e.g.

accidental unblinding or due to an SAE) should be documented and promptly communicated to the Sponsor.

4.9 Informed Consent for Clinical Trial Participants

4.9.1 The Investigator is responsible for ensuring that an adequate information package, in an acceptable format appropriate for the Kenya context, is available for use in the process of seeking informed consent from (ICF) participants to participate in the clinical trial

4.9.2 If the trial is a multi-site and/or multi-country trial, the site PI must ensure that informed consent procedures take cognizance of the characteristics of the site participants and tailor the ICF and procedures accordingly.

4.9.3 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 Informed Consent forms should be submitted to PPB and ERC.

4.9.4 In obtaining and documenting informed consent, the investigator should comply with the NACOSTI accredited ERC 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.

4.9.5 The written ICF 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 ICF, and written information should receive ERC favorable opinion. Communication of the new information to participants must be documented and signed.

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

4.9.7 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 (LAR) to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.9.8 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 LAR, of all pertinent aspects of the trial including the written information and ERC and PPB approval.

4.9.9 The language used in the oral and written information about the trial, including the written ICF, should be as non-technical as practical and should be understandable to the participant or the participant's LAR and the impartial witness, where applicable.

4.9.10 The informed consent document should be provided in a participant’s preferred written language.

4.9.11 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the participant or the participant's LAR 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 LAR.

4.9.12 Prior to participation in the trial, the written ICF should be signed or thumb printed and personally dated by the participant or by the participant's LAR, and by the person who conducted the informed consent discussion.

4.9.13 If a participant is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to participant, is read and explained to the participant or the participant’s LAR, and after the participant or the participant’s LAR has orally consented to participate in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form.

4.9.14 The witness signs to affirm that the participant or participant’s LAR willingly consented to participate.

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

a) That the trial involves research;
b) The purpose of the trial;
c) Why the potential participant has been approached;
d) That participation is voluntary; that refusal to participate, or withdrawal from the trial at any time, will not prejudice the ongoing care of the person in any way;
e) The trial treatment(s) and the probability for random assignment to each treatment;
f) The trial procedures to be followed, including all invasive procedures;
g) The participant's responsibilities;
h) Those aspects of the trial that are experimental;
i) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
j) The probability and magnitude of the foreseeable risks of harm;
k) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this (e.g. Phase I Clinical Trial);

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

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

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

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

p) The planned reimbursements, if any, for time, inconvenience and expenses;

q) 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 LAR is authorizing such access.

r) 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.

s) ERC contact details for information and concerns regarding the rights of trial participants;

t) That the participant or the participant's LAR 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.

u) 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.

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

w) The expected duration of participating in the trial.

x) The approximate number of participants locally and globally (if applicable) involved in the trial;

4.9.16 The Investigator, or an appropriate designee, should obtain the participant's consent to participate in the trial in accordance with the principles outlined in the Declaration of Helsinki and other guidelines.

4.9.17 Prior to participation in the trial, the participant or the participant's LAR should receive a copy of the signed and dated (same day as that signed for approval to participants) written ICF and any other written information provided to the participants. During participation in the trial, the participant or the participant’s LAR 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.

4.9.18 When a clinical trial includes participants who can only be enrolled in the trial with the consent of the participant’s LAR (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 ICF.

4.9.19 In emergency situations, when prior consent of the participant is not possible, the consent of the participant's LAR, if present, should be requested. When prior consent of the participant is not possible, and the participant’s LAR 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 ERC and PPB requirements.

4.9.20 Once informed consent has been obtained, the original signed informed consent document must be kept with the trial records, and a copy of the signed informed consent document must be offered to the participant. A further copy of the signed informed consent document must be in the participant's source documents or medical records.

4.10 Records and Reports

4.10.1 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 regulatory authorities.

4.10.2 Agreements made by the Sponsor with the PI and any other parties involved with the clinical trial should be in writing, as part of the protocol or in a separate agreement.

4.10.3 The Investigator shall be responsible for the collection, verification, accurate recording, maintenance, security, and retrieval of source data generated during the clinical study, ensuring data integrity and confidentiality at all times.

4.10.4 The investigator shall submit all relevant trial data to PPB in a timely manner.

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

4.10.6 Source documents should adhere to the ALCOA+ principles (attributable, legible, contemporaneous, original, accurate, complete, secure and reliable).

4.10.7 The source document(s) must be signed and dated and stored securely.

4.10.8 Changes to source data must be traceable, must not obscure or delete the original entry, and must be explained if necessary (via an audit trail).

4.10.9 The Investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor by means of Case Report Forms (CRF). The design of the CRF should facilitate observation of the participant and be consistent with the study protocol.

4.10.9.1 The protocol should specify which data will be entered directly into the CRF and will not be supported by other source data.

4.10.9.2 Corrections to CRFs may be made only by the Investigator or an appropriate designee.

4.10.9.3 Changes to CRFs must be traceable, must not obscure or delete the original entry, and must be explained if necessary

4.10.10 Data collected by direct entry on a computer should be entered by the Investigator and/or an appropriate designee.

4.10.10.1 The computer system must be protected, access-restricted and must record a data trail of all changes made to CRFs.

4.10.10.2 The system should be designed so that data changes are documented automatically, and so that no deletion of entered data can occur in order to maintain, audit and edit the data trail.

4.10.11 The Investigator should maintain the trial documents as specified in the Essential Documents for the Conduct of a Clinical Trial. The Investigator must take measures to prevent accidental and/or premature destruction of these documents.

4.10.12 Essential documents must be retained for at least 10 years after final closure of clinical trial or for at least two years after formal discontinuation of clinical development of the IP(s).

4.10.13 The Sponsor must inform the Investigator in writing of the need for record retention and must notify the Investigator in writing when the trial-related records are no longer needed.

4.10.14 Any transfer of ownership of the data must be reported to PPB

4.10.15 A clinical trial agreement (CTA) must be signed by the Sponsor/Applicant and the Investigator.

4.10.15.1 Financial aspects of the clinical trial must be documented in the CTA.

4.10.15.2 The CTA must also describe in detail the responsibilities of the Sponsor/Applicant and Investigator.

4.11 Progress reports

4.11.1 The Investigator must provide regular progress reports (at least six-monthly) or more frequently as requested.

4.11.2 This information should include, but not be limited to:

4.11.2.1 Progress to date, or the outcome in the case of completed research;

4.11.2.2 Current enrolment status (numbers, active or closed);

4.11.2.3 Whether participant follow-up is still active or has been completed;

4.11.2.4 Evidence of non-compliance with the approved protocol or any conditions of approval;

4.11.2.5 Relevant safety data.

4.12 Premature Termination or Suspension of a Clinical Trial

4.12.1 If a trial is prematurely terminated or suspended for any reason, the Investigator must promptly inform the trial participants, and must ensure appropriate therapy and follow-up for them.

4.12.2 If the Investigator terminates or suspends a trial without the prior agreement of the Sponsor, the Investigator must promptly inform the Institution (where applicable), the Sponsor/Applicant, PPB and the ERC, and must provide a detailed written explanation for the termination or suspension.

4.12.3 If the Sponsor terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), Applicant, PPB and the ERC, and must provide a detailed written explanation for the termination or suspension.

4.12.4 If the ERC terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), Applicant, PPB and the Sponsor, and must provide a detailed written explanation for the termination or suspension.

4.12.5 If PPB and/or other regulatory authority terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), Applicant, ERC, and must provide a detailed written explanation for the termination or suspension

5.0 SPONSOR

A Sponsor can be a pharmaceutical company, the PI, a funding body, or an individual or organization designated by the funding body or academic institution. An Applicant can be an individual, company, institution, or organization that acts on behalf of the Sponsor to initiate and manage the trial as its local representative. In the case of an international Sponsor, a local Applicant designated by the Sponsor is responsible for initiation and management of the trial in the local context. The Sponsor may delegate some of its responsibilities to a Contract Research Organization (CRO), which should be clearly documented. The Sponsor and Applicant remain responsible for oversight of the conduct and monitoring of the trial.

5.1 Responsibilities of the Sponsor

5.1.1 Trial design:

5.1.1.1 The Sponsor should utilise qualified individuals (e.g. physicians, medical officers, pharmacists, clinical pharmacologists, biostatisticians, etc) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.1.1.2 If the trial is a multicenter and/or multi-country trial, any differences in trial procedures between the Kenya and other sites, must be clearly documented and explained in the trial protocol and/or related documents.

5.1.2 Investigator selection:

5.1.2.1 Sponsors should only select investigator(s) who are:

a) Qualified by training and experience, and
b) Have adequate resources to conduct the proposed clinical trial.

5.1.2.2 The Sponsor should obtain the Investigator's agreement:

a) To conduct the trial in compliance with these Guidelines, ICH GCP, the requirements of the PPB regulatory authority and with the approved protocol

b) To comply with procedures for data recording and reporting;

c) To permit monitoring, auditing and inspection; and

d) To retain the trial-related essential documents until the Sponsor informs the Investigator/Institution that these documents are no longer needed.

5.1.2.3 The Sponsor and the Investigator must sign the protocol, or an alternative document, to confirm this agreement.

5.1.3 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.

5.2 The Sponsor shall be responsible for the provision of insurance for all trial participants and ensure that the clinical trial institution, CRO and researchers have sufficient insurance cover for the clinical trial.

5.2.1 The financial aspects of the trial should be documented in a CTA between the Sponsor and the Investigator/Institution. A signed declaration must be provided by the Sponsor which states that there are sufficient funds available to complete the trial.

5.2.2 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.

5.2.3 Computerized systems

5.2.3.1 The Sponsor shall ensure that all computerized systems used for the capture, processing, reporting, and storage of clinical trial data are developed, validated, and maintained in a manner that ensures the validity, integrity, confidentiality, and security of the data.

5.2.3.2 The Sponsor shall ensure that, prior to use, all computerized systems are subjected to an appropriate level of validation to demonstrate that the systems are fit for their intended purpose and capable of producing reliable and reproducible data.

5.2.3.3 The Sponsor shall ensure that the scope of validation is commensurate with the level of functionality utilized. Validation shall be conducted in accordance with a documented plan. All key aspects of the validation process shall be documented, and upon completion, the results shall be assessed by a suitably qualified individual.

5.2.3.4 Where a computerized system is deemed fit for use, the Sponsor shall ensure that the decision is documented and authorized by appropriate management or a designated representative. Any system limitations shall be clearly described in relevant procedures.

5.2.3.5 The Sponsor shall ensure that, for each computerized system, all components (e.g., hardware and software) are clearly defined and documented, including within the associated validation package.

5.2.3.6 Where additional functionality is introduced beyond the scope of the original validation, the Sponsor shall assess the need for further validation and ensure that additional validation is performed where required.

5.2.3.7 Where additional computerized systems are interfaced with an existing laboratory information management system (LIMS) or other trial-related systems, the Sponsor shall ensure that the impact of the new systems on overall functionality, data integrity, and performance is assessed.

5.2.3.8 The Sponsor shall ensure that all records associated with the validation of computerized systems are securely retained and archived in accordance with applicable record retention requirements.

5.2.3.9 The Sponsor shall ensure that computerized systems are located in secure and appropriate environments and that environmental conditions and external factors that may adversely affect system performance, data integrity, or security are identified, assessed, and controlled.

5.2.3.10 The Sponsor shall ensure that disaster recovery and business continuity procedures are established and maintained for all computerized systems.

5.2.3.11 The Sponsor shall ensure that access to computerized systems is controlled. The identity and access rights of authorized users shall be documented and subjected to periodic review to ensure that access permissions remain current and appropriate.

5.3 Quality management and control

5.3.1 Quality Management

5.3.1.1 The Sponsor should implement a quality management system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.

5.3.1.2 The Sponsor should focus on trial activities that promote human participant protection and reliability of trial results. These include:

a) Utilization of qualified individuals, as appropriate, throughout all stages of the trial process, from designing the protocol and CRF to analysing and preparing the clinical trial reports.

b) Designating appropriately qualified medical personnel to be available to advise on trial-related medical challenges.

c) Ensuring that all aspects of the trial are operationally feasible and avoiding unnecessary complexity, procedures and data collection.

5.3.1.3 Different quality management systems may be used and should be proportionate to the risks inherent in the trial. Regardless of the system used, a risk-based approach should be adopted which focuses on:

a) Identification of processes and data that are critical to assure human participant protection and reliability of trial results. This should occur during the development of the protocol.

b) Identification of potential risks to critical trial processes and data. Such risks should include systems and clinical trial processes.

c) Risk evaluation, including the likelihood of errors occurring given existing risk controls, the potential impact of such error on human participant protection and reliability of trial results, and the extent to which such errors would be detectable.

d) Risk control: Sponsors should incorporate risk mitigation activities in the protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to protocols and SOPs, and adequate training in processes and procedures.

e) Periodical risk review to ascertain whether the quality management activities remain effective and relevant.

5.3.2 Quality Assurance and Quality Control

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

5.3.2.2 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.

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

5.3.2.4 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.

5.4 Contract Research Organization (CRO)

5.4.1 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.

5.4.2 Although the CRO must implement quality assurance and quality control, the Sponsor is responsible for:

5.4.2.1 Ensuring oversight of any trial-related duties and functions carried out on its behalf;

5.4.2.2 Ensuring that the CRO has the required skills, experience and competencies to conduct clinical trials.

5.4.3 Trial-related duties and functions that is transferred to the CRO must be specified in writing. Any duties and functions not specifically transferred to the CRO remains with the Sponsor.

5.4.4 Any reference to the Sponsor in this guideline shall be understood to include a CRO where the CRO has been delegated and has assumed the Sponsor’s trial-related duties and responsibilities.

5.5 Safety Reporting

5.5.1 Sponsor responsibilities

5.5.1.1 The Sponsor shall be responsible for the ongoing safety evaluation of the IP(s). The Sponsor’s commitment to provide safety information shall be documented in the CTA between the Sponsor and the Investigator.

5.5.1.2 The Sponsor shall promptly notify the Investigator and PPB of any findings that may adversely affect the safety of trial participants or impact the conduct of the clinical trial.

5.5.1.3 The Sponsor shall ensure expedited reporting of all Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) to PPB and the relevant ERC. Immediate and appropriate measures, including medical treatment where required, shall be taken to safeguard the safety and well-being of trial participants.

5.5.1.4 The Sponsor shall report to the PPB all SAEs and SUSARs occurring in clinical trials conducted in Kenya, as well as those occurring in the same clinical trial at sites outside Kenya.

5.5.1.5 The Sponsor shall report to the PPB all SAEs and SUSARs related to the same active substance, regardless of pharmaceutical form, strength, or indication under investigation, arising from clinical trials conducted outside Kenya.

5.5.2 Local safety reporting timelines

5.5.2.1 Fatal or life-threatening SAEs and SUSARs should be reported by the sponsor as soon as possible and in any case no later than seven (7) days after being made aware of the case. If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor is to submit a completed report based on the initial information within an additional eight (8) days.

5.5.2.2 SAEs and SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

5.5.2.3 In addition to expedited safety reporting requirements, the Sponsor shall submit an annual safety report to the PPB, starting from the date of authorization and continuing throughout the duration of the clinical trial, or upon request. The annual safety report shall summarize all new safety information received during the reporting period and provide an assessment of the safety of participants enrolled in the trial(s).

5.5.2.4 As part of the annual renewal submission, the Sponsor shall provide a line listing of adverse events, including SAEs and SUSARs, recorded during the reporting period.

5.5.3 Foreign safety reporting timelines

5.5.3.1 Fatal or life-threatening SUSARs shall be reported within 7 calendar days of first knowledge, with follow-up information submitted within 8 additional days.

5.5.3.2 SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

5.5.3.3 Foreign SAEs shall be submitted quarterly in line listings or safety summaries, unless otherwise requested by the Board.

5.5.4 Reporting system or pathway

5.5.4.1 SUSAR and SAE reports shall be submitted to PPB through the clinical trials portal online system. The reports shall be entered directly into the prescribed reporting form on the portal or uploaded under the CIOMS tab, as applicable.

5.5.5 Safety reporting parameters

5.5.5.1 Patient ID

    - 5.5.5.2 Age
    - 5.5.5.3 Date of recruitment into the study
    - 5.5.5.4 Type of SAE/SUSAR
    - 5.5.5.5 Start date of the SAE/SUSAR
    - 5.5.5.6 End date of the SAE/SUSAR
    - 5.5.5.7 Reason for reporting the event as a SAE/SUSAR
    - 5.5.5.8 Relation to IP
    - 5.5.5.9 Outcome of the SAE/SUSAR

5.5.6 For multi-centre/multi-regional clinical trials, the sponsor shall notify all the investigators involved in ongoing clinical trials of all SAEs or SUSARs within 15 calendar days

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

5.5.8 All fatal cases shall be accompanied by a formal autopsy report e.g. copies of diagnostic test results, laboratory reports, or medical record progress notes where available. In exceptional circumstances where a formal autopsy is not practicable, provision of a verbal autopsy report shall be submitted.

5.5.9 Foreign regulatory decisions that affect the safety or use of the product under study shall be reported to PPB within seven (7) days through a detailed report.

5.5.10 Literature reports that affect the safety of the product under study shall be submitted within fifteen (15) days thorough a detailed report and a copy of the publication.

5.5.11 New information or notification of change in nature, severity or frequency of risk factors for the product under study or conduct of trial shall be submitted within fifteen (15) days.

5.5.12 Notwithstanding the above, the Board may require more frequent reporting of the safety reports depending on the nature of the clinical trial being implemented. This if required, shall be communicated to the PI and or sponsor in writing.

5.6 Investigational Product(s) Management

5.6.1 When planning trials, a Sponsor should ensure that sufficient safety and efficacy data from pre-clinical studies and/or clinical trials are available to support human exposure using the proposed route, dosages, duration and in the trial population to be studied.

5.6.2 The Sponsor must update the Investigators Brochure (IB) as new information becomes available.

5.6.3 The Sponsor must ensure that the IP(s) (including active comparator and placebo, if applicable) is characterized as appropriate for the stage of development of the product, is manufactured in accordance with any applicable GMP standards, and is coded and labelled in a manner that protects blinding, if applicable. Labelling must comply with PPB regulatory requirements.

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

5.6.5 The IP must be packaged to prevent contamination and deterioration during transport and storage.

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

5.6.7 If significant formulation changes are made to the IP or comparator product during the course of clinical development, the results of any additional studies of the formulated product (e.g. stability, dissolution rate, bioavailability) necessary to assess whether the pharmacokinetic profile of the product is significantly altered must be available before use of the new formulation in clinical trials.

5.6.8 The Sponsor is responsible for supplying a sufficient quantity of IP(s).

5.6.9 The Sponsor must not supply an Investigator with IP(s) until the Sponsor obtains all required documentation (e.g. ERC and PPB approval and other regulatory documentation).

5.6.10 The Sponsor must ensure that written procedures include instructions and relevant documents for the Investigator to follow for handling and storage of IP for the trial. The procedures must address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused IP to the Sponsor (or alternative disposition if authorised by the Sponsor and in compliance with the PPB-approved protocol).

5.6.11 The Sponsor must:

a) Ensure timely delivery of IP to the Investigator.

b) Maintain records that document shipment, receipt, disposition, return and destruction of the IP.

c) Maintain a system for retrieving IP and documenting such retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

d) Maintain a system for disposal of unused IP and for its documentation. Disposal must be done according to PPB regulations.

e) Take steps to ensure that IP(s) is stable over the period of use.

f) Maintain sufficient quantities of IP used in the trials to reconfirm specifications, if necessary, and maintain records of batch sample analyses and characteristics. To the extent that IP stability permits, samples should be retained until analyses of trial data are complete or as required by the applicable regulatory requirement(s), whichever is longer.

g) The sponsor must provide and maintain a system for retrieving and disposal of trial-related waste (e.g. syringes and needles).

5.7 Monitoring

5.7.1 The purpose of trial monitoring is to verify that:

5.7.1.1 The rights and well-being of human participants are protected;

5.7.1.2 Reported trial data are accurate, complete and verifiable from source documents;

5.7.1.3 The trial is conducted in compliance with the currently approved protocol and with PPB requirements.

5.7.2 Selection and Qualifications of Monitors

Monitors should be:

5.7.2.1 Appointed by the Sponsor.

5.7.2.2 Appropriately trained, with the scientific and/or clinical knowledge necessary to monitor the trial adequately. A monitor's qualifications should be documented.

5.7.2.3 Thoroughly familiar with the IP, the protocol, the informed consent documents and other written information to be provided to participants, the Sponsor's SOPs and PPB requirements.

5.7.3 Extent and Nature of Monitoring:

5.7.3.1 The Sponsor must ensure that trials are adequately monitored in accordance with PPB requirements. The Sponsor should determine the appropriate extent and nature of monitoring based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial.

5.7.3.2 The Sponsor must develop a systematic, prioritized, risk-based approach to monitoring clinical trials. Flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy.

5.7.4 Monitor's Responsibilities:

The Monitor must ensure that the trial is conducted and documented properly by carrying out activities in accordance with sponsor requirements when relevant and necessary to the trial and the trial site:

5.7.4.1 Act as the main line of communication between the Sponsor and the Investigator;

5.7.4.2 Verify that the Investigator has adequate qualifications and adequate resources, and that facilities are adequate to safely and properly conduct the trial;

5.7.4.3 Verify, handling and management of the IP(s):

a) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial;
b) That IP is supplied only to trial participants who are eligible to receive it and at the protocol specified doses.
c) That participants are provided with the necessary instructions on properly using, handling, storing and returning IP(s);
d) That receipt, use and return of IP(s) at the trial sites are controlled and documented adequately;
e) That disposal of unused IP(s) at the trial sites complies with applicable regulatory requirements.

5.7.4.4 Verify that the Investigator follows the approved protocol and all approved amendments, if any.

5.7.4.5 Verify that written informed consent was obtained before each trial participant's participation in the trial.

5.7.4.6 Ensure that the Investigator receives the current IB, all documents and all trial supplies needed to conduct the trial safely and properly in compliance with PPB requirements.

5.7.4.7 Ensure that the Investigator and the Investigator's staff are adequately informed about the trial.

5.7.4.8 Verify that the Investigator and the Investigator's staff are performing specified trial functions in accordance with the protocol and any other written agreement.

5.7.4.9 Verify that the Investigator enrols only eligible participants.

5.7.4.10 Report the participant recruitment rate.

5.7.4.11 Verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

5.7.4.12 Verify that the Investigator provides all required reports, notifications, applications and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial.

5.7.4.13 Check the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.

5.7.4.14 Inform the Investigator of any CRF entry error, omission or illegibility. The Monitor must ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary) and initialed by the Investigator or by an authorised member;

5.7.4.15 Determine whether AEs, SAEs and SUSARs are appropriately reported within time periods required by GCP, the protocol, the ERC, the sponsor and PPB;

5.7.4.16 Determine whether the Investigator maintains the essential documents;

5.7.4.17 Communicate deviations from the protocol, SOPs, GCP and PPB requirements to the investigator and take appropriate action designed to prevent recurrence of the detected deviations.

5.7.5 The Monitor must follow the Sponsor's written SOPs as well as those procedures specified by the Sponsor for monitoring a specific trial.

5.7.6 Monitoring Report:

5.7.6.1 The Monitor must submit a written report to the Sponsor and the Investigator after each site visit or trial-related communication;

5.7.6.2 Reports must include the date, site, name of the Monitor and name of the Investigator or designated individual(s) contacted;

5.7.6.3 Reports must include a summary of what the Monitor reviewed and the Monitor's statements concerning significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance;

5.7.6.4 Review and follow-up of the Monitoring Report with the Sponsor must be documented by the Sponsor's designated representative;

5.7.6.5 Monitoring results must be provided to the Sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities must be documented in sufficient detail to allow verification of compliance with the monitoring plan.

5.7.7 Monitoring Plan:

5.7.7.1 The Sponsor must develop a monitoring plan tailored to specific human participant protection and data integrity risks of the trial.

5.7.7.2 The plan must:

a) Describe the monitoring strategy, the responsibilities of all the parties, monitoring methods to be used and the rationale for their use;
b) Draw attention to the monitoring of critical data and processes;
c) Reference the applicable policies.

5.8 Audits

5.8.1 The purpose of a Sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements. The Sponsor must perform audits as part of implementing quality assurance.

5.8.2 Selection and Qualification of Auditors:

5.8.2.1 The Sponsor must appoint individuals who are independent of the clinical trials to conduct the audits.

5.8.2.2 The Sponsor must ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor’s qualifications should be documented.

5.8.3 Auditing Procedures:

5.8.3.1 The Sponsor must ensure that the audit is conducted in accordance with the Sponsor's written procedures.

5.8.3.2 The Sponsor's audit plan and procedures for a trial audit must be guided by the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants, and any identified problem(s).

Observations and findings of the auditors must be documented.

5.8.3.3 When required by applicable law or regulation, the

Sponsor must provide an audit certificate.

5.9 Procedures to manage non-compliance

5.9.1 The Sponsor is required to inform the appropriate ERC and PPB of possible instances of serious contravention of GCP during the course of a clinical trial that affect participant's safety, the credibility of data and/or the ethics of the trial.

5.9.2 When significant non-compliance is discovered, the Sponsor must perform a root cause analysis and implement appropriate corrective and preventive actions.

5.10 Premature termination or suspension of a trial

If a trial is prematurely terminated or suspended, the Sponsor must inform the Investigator/Institution, ERC and PPB promptly of the termination or suspension and the reason

5.11 Reporting and release of trial results

5.11.1 The Sponsor must ensure that trial results and outcomes are reported to the Investigators and PPB via the PPBCTR.

5.11.2 The Sponsor and the PI are responsible for appropriate dissemination of the trial findings.

5.11.3 Results should be disclosed within one year of completion of analysis of the trial results.

5.12 Publication of trial results

5.12.1 The Investigator has a duty and a right to publish trial results, and must negotiate accordingly with the Sponsor.

5.12.2 For collaborative studies and multi-centre trials, publication conditions must be clearly described in the protocol, and approved by the relevant regulatory authorities.

6.0 CLINICAL TRIAL PROTOCOL

A Clinical trial protocol is a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial as defined in the ICH GCP guidelines Chapter 6. The clinical trials protocol should comply to the SPIRIT (Standard Protocol Items; Recommendation for Interventional Trials) Checklist

6.1 General Information

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

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

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

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

6.1.5 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.

6.1.6 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).

6.1.7 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.

6.1.8 If it is a global trial, the information for sections 7.1.5 to 7.1.7 above shall be included in the site-specific addendum

6.2 Background Information

6.2.1 Justification and need for the study.

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

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

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

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

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

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

6.2.2.6 Description of the population to be studied.

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

6.3 Trial Objectives and Purpose

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

6.4 Trial Design

A description of the clinical trial design should include:

6.4.1 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.

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

6.4.3 A description of the measures taken to minimize/avoid bias, including randomization and blinding.

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

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

6.4.6 Accountability procedures for the IP(s), including the placebo(s) and comparator(s), if any.

6.4.7 If use of a placebo is proposed, this must be properly justified in terms of the Declaration of Helsinki and contextualised for local circumstances.

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

6.4.9 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.

6.5 Selection and withdrawal of study participants

This will include:

6.5.1 Inclusion and exclusion criteria

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

6.5.2.1 When and how to withdraw participants from the trial/ IP treatment;

6.5.2.2 The type and timing of the data to be collected for withdrawn participants;

6.5.3 Whether and how participants are to be replaced;

6.5.4 The follow-up for participants withdrawn from IP treatment/ trial treatment.

6.6 Treatment of study participants

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

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

6.6.3 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).

6.6.4 Procedures for monitoring participant's compliance.

6.7 Ethical Consideration

Description of all the possible ethical concerns in the study and how these will be managed

6.8 Post-Trial Access Program

The Sponsor shall put in place measures to ensure that the study participants have access to successful investigational products for their disease condition before the products have received a marketing authorization in Kenya, especially so for the Phase III clinical trials.

6.9 Assessment of Efficacy

This will include:

6.9.1 Specification of the efficacy parameters.

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

6.10 Assessment of Safety

This will include:

6.10.1 Specification of safety parameters.

6.10.2 The methods and timing for assessing, recording, and analysing safety parameters.

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

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

6.10.5 A clear description of study procedures and quantities of any biological samples to be collected for study analysis.

6.11 Statistics

This will include:

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

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

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

6.11.4 The level of significance to be used.

6.11.5 Criteria for the termination of the trial.

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

6.11.7 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).

6.11.8 Procedures for reporting any protocol violations.

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

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

6.11.11 The number of participants planned to be enrolled. In multicentre trials, the numbers of enrolled participant s projected for each trial site should be specified.

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

6.11.13 The level of significance to be used.

6.11.14 Criteria for the termination of the trial.

6.11.15 Methods for data analyses and evaluation of results.

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

6.11.17 A statistician should:

a) Write and sign off on the analysis plans before the trial data is available and before any analysis has started
b) 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 participants to be included in the analyses
c) Put sample tables and listings in the SAP, to show how data will be presented
d) Include any planned interim analyses in the SAP
e) Describe and justify in the trial report any deviations from the SAP
f) 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.

6.12 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit inspections from PPB providing direct access to source data/documents and copies of the source documents will be made if needed by PPB inspectors.

Research Involving Children

6.13 The sponsor should briefly summarize available information on the

6.13.1 Pathophysiology of the disease,

6.13.2 Methods of diagnosis, and

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

6.14 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.

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

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

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

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

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

6.16.4 No incentives or financial inducements are given to the participant 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;

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

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

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

6.16.8 The informed consent forms, assent forms and the patient information sheets should be in a language that the parent or legal representative clearly understand.

6.17 Pediatric patients should be given interventions that have been appropriately evaluated for their use.

6.18 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.

6.19 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.

6.20 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.

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

6.21.1 The prevalence of the condition to be treated in the pediatric population

6.21.2 The seriousness of the condition to be treated

6.21.3 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

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

6.21.5 Whether there are unique pediatric indications for the medicinal product

6.21.6 The need for the development of pediatric-specific endpoints

  - 6.21.7 The age ranges of pediatric patients likely to be treated with the medicinal product
  - 6.21.8 Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues
  - 6.21.9 Potential need for pediatric formulation development

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

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

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

6.25 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.

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

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

  - 6.27.1 Non clinical safety data
  - 6.27.2 Genotoxicity
  - 6.27.3 Reprotoxicity (fertility, pre and post-natal development)
  - 6.27.4 Carcinogenicity (if required)
  - 6.27.5 Juvenile animal studies (in some cases, e.g. neonatal use)
  - 6.27.6 Pharmaceutical properties
    - 6.27.7 Pharmacokinetics
    - 6.27.8 Absorption
    - 6.27.9 Distribution
    - 6.27.10 Metabolism

6.27.11 Excretion

6.27.12 Pharmacodynamics

Specific and General

6.28 In addition, the following will also be important

6.28.1 The trial will provide useful answers to the study population

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

6.28.3 Children are adequately monitored and protected

6.28.4 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)

6.28.5 The trial results will be published

6.28.6 There are provisions for end-of-trial treatment

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

6.29.1 Preterm new-born infants

6.29.2 Term new-born infants (0 to 28 days)

6.29.3 Infants and toddlers (29days to 11 months)

6.29.4 Toddlers (12-59 months)

6.29.5 Children (6 to 12 years)

6.29.6 Adolescents (12 to 18years)

Practical considerations to facilitate pharmacokinetic studies

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

6.31 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 maneuver) should not exceed

3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time.

6.32 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.

6.33 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.

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

6.35 Use of laboratories experienced in handling small volumes of blood for pharmacokinetic

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

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

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

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

6.40 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"

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

Efficacy

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

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

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

6.45 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

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

6.47 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.

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

6.49 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, behavioral, cognitive, sexual, and immune maturation and development.

Post marketing information

6.50 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.

6.51 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 Review Committee (ERC)

6.52 Since the protocol has already been reviewed by ERC by the time it is being submitted to the board, PPB will review this section to confirm that these areas are adequately covered.

6.53 Description of all the possible ethical concerns in the study and the plans to address each of the issues.

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

- 6.54.1 Patient Information leaflets (PIL) and Informed Consent Forms (ICF) for any proposed archiving of biological specimens for later research or for genetics research.
- 6.54.2 Treatment and/or management of participants and their disease condition(s) after completion of trial
- 6.54.3 Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and PPB requirements
- 6.54.4 Any arrangement for the follow-up of trial study participants after the conclusion of the trial.
- 6.54.5 Insurance and indemnity measures
- 6.54.6 In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:
  - 6.54.6.1 Identification of the provider and recipient
  - 6.54.6.2 Definition of the trial and how the material will and will not be used
  - 6.54.6.3 Maintenance of confidentiality of background or supporting data or information, if any

Insurance Cover

6.55 All clinical trial participants must be adequately and satisfactorily insured against possible injuries that might arise during the conduct of the clinical trials

6.56 The insurance cover shall be provided by an insurer that is registered by Insurance Regulatory Authority of Kenya not unless there is a justifiable reason why this should not be the case.

6.57 For all sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provide prior to study initiation

6.58 Sponsors and Principal Investigators shall ensure that there is valid and adequate insurance cover for clinical trial participants throughout the study and shall submit as evidence a certificate of insurance cover for participants to the board.

6.59 The insurance certificate must be duly executed by the insurance company under a valid insurance policy which makes explicit reference to the proposed study.

6.60 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.

6.61 Self-insurance of clinical trial participants such as by the NHIF will not be sufficient.

6.62 In addition, the study investigators and pharmacists shall be required to have a valid Professional Indemnity insurance cover for the period of the trial

6.63 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;

Pre-Submission meetings

6.64 Sponsors or applicants can request for pre-submission meetings to discuss pertinent issues prior to formal submissions.

6.65 During the request for the pre-submission meeting, the applicant will be required to submit the following information

6.65.1 Background information on the disease to be treated
6.65.2 Background information on the product
6.65.3 Quality development
6.65.4 Non-clinical development
6.65.5 Clinical development
6.65.6 Regulatory status
6.65.7 Rationale for seeking advice
6.65.8 Proposed Questions and Applicant's positions

6.66 The request for a pre-submission meeting shall be made through an official letter addressed to the Chief Executive Officer, Pharmacy and Poisons Board and sent to admin@pharmacyboardkenya.org, copied to cta@pharmacyboardkenya.org

6.67 The request for a meeting should propose two different dates for the meeting with the proposed dates being at least three weeks away.

Publication Policy

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

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

The Investigator's Brochure

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

6.70.1 The physical, chemical and pharmaceutical properties
6.70.2 The pharmacological aspects including its metabolites in all animal species tested

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

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

6.70.5 Results of clinical pharmacokinetic studies

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

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

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

Investigational Medicinal Product/ Drug Dossier (IMPD)

6.72 The sponsor shall submit the IMPD directly to PPB or may submit it through the PI

6.73 The investigational Medicinal Product Dossier shall be prepared as per the ICH guidelines

6.74 Clinical trial investigational new drug must be manufactured in accordance with current 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.

6.75 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:

6.75.1 Required details on Active Pharmaceutical Ingredient (API)

6.75.2 Nomenclature

6.75.3 Name and address of the manufacturer

6.75.4 Physicochemical properties

6.75.5 Route of synthesis and summary of manufacturing process

6.75.6 Documented evidence of structure and stereochemistry

- 6.75.7 Characterization of impurities
- 6.75.8 Specifications and their justifications
- 6.75.9 Batch analyses
- 6.75.10 Validation of analytical procedures
- 6.75.11 Container closure system
- 6.75.12 Stability studies

6.76 Required details on Investigational Medicinal Product (IMP)

6.77 Name, strength and dosage form

6.78 Description and composition

6.79 Name and address of the manufacturer

6.80 Pharmaceutical development

6.81 Description of manufacturing process including flow diagram and Controls of Critical Steps and Intermediates

6.82 Control of materials

6.83 Manufacturing information for novel excipients and manufacturing process development.

6.84 Specifications and their justifications (including excipients)

6.85 Elucidation of structure and other characteristics of the API

6.86 Control of drug substance

6.87 Batch analyses

6.88 Analytical procedure for testing the drug substance and validation of analytical procedures

6.89 Characterization of impurities

6.90 Certificates of analysis (CoAs) of the clinical batches of the test product, placebo and modified comparator.

6.91 Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathy (TSE) certificates for excipients of human or animal origin

6.92 Stability studies

6.93 Container closure system

6.94 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.

6.95 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.

6.96 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.

6.97 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.

Phase One Clinical Trials

Non-clinical aspects

6.98 The application should demonstrate the relevance of the animal model used

6.99 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.

there 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.

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

6.100.1 Not reproduce the intended pharmacological effect in humans;

6.100.2 Give rise to misinterpretation of pharmacokinetic and pharmacodynamics results;

6.100.3 Not identify relevant toxic effects.

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

6.102 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.

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

6.103.1 Target expression, distribution and primary structure.

6.103.2 Pharmacodynamics

6.103.3 Binding and occupancy, functional consequences, including cell signaling if relevant.

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

6.103.5 Metabolism and other pharmacokinetic aspects

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

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

6.105 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.

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

Pharmacodynamics

6.107 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.

6.108 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.

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

Pharmacokinetics

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

6.111 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

6.112 Standard core battery data should be available beforethe first administration in humans

6.113 The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous and respiratory systems, should generally be conducted before human exposure, in accordance with ICH S7A and S7B

6.114 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

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

6.116 In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies should generally be evaluated before initiating human clinical trials.

6.117 More information on pharmacokinetics (PK) (e.g., absorption, distribution, metabolism and excretion), in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration. These data can be used to compare human and animal metabolites and for determining if any additional testing is warranted.

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

6.119 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.

6.120 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.

6.121 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

6.122 The estimation of the first dose in human is an important element to safeguard the safety of participants 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.

6.123 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.

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

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

6.126 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 Minimum Anticipated Biological Effect Level (MABEL). The safety factors used should be justified.

6.127 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.

6.128 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

6.129 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.

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

6.131 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.

6.132 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.

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

6.134 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.

6.135 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

6.136 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.

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

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

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

6.137.3 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.

6.137.4 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:

6.137.4.1 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 participant s and patients.

6.137.4.2 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.

6.137.4.3 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.

6.138 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

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

6.140 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.

6.141 Specific points to be considered are:

6.141.1 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.

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

6.141.3 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.

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

6.143 A characterization 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 characterize the active substance and drug product.

6.144 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 characterization studies but can affect biological properties and could have clinical consequences.

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

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

6.146.1 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.

6.146.2 Where there are differences in the manufacturing process and the limitations of product characterization, 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

6.147 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

6.148 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

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

6.149.1 Study population;
6.149.2 Trial sites;
6.149.3 First dose;
6.149.4 Route and rate of administration;
6.149.5 Number of participant s per dose increment (cohort);
6.149.6 Sequence and interval between dosing of participant s within the same cohort;
6.149.7 Dose escalation increments;
6.149.8 Transition to next dose cohort;
6.149.9 Stopping rules;
6.149.10 Allocation of responsibilities for decisions with respect to participant dosing and dose escalation.

6.150 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.

6.151 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.

6.152 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 participant s that might have received either placebo or the active medicinal product. There should always be rapid access to the treatment allocation codes when relevant.

6.153 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

6.154 The reporting of the adverse events will be as indicated under the section on Safety Reporting below.

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

6.156 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.

6.157 All clinical staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions.

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

6.159 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.

6.160 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.

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

6.162 Communication of SAEs and SUSARs is particularly important. Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SAEs/SUSARs to PPB.

Labelling:

6.163 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:

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

6.163.2 Recommended storage conditions

6.163.3 Protocol code or identification

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

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

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

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

6.163.8 The trial participant identification number/treatment number and, where relevant, the visit number

6.163.9 The name of the investigator (if not included above)

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

6.163.11 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

6.163.12 The complete physical address of the manufacturing site

Re-labelling

6.164 In general, it is recommended that wherever possible investigational product is not relabeled. 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.

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

6.166 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.

6.167 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 testing protocol and stability report, certificates of analysis (COAs) from reanalysis of the relevant batches must be submitted to PPB.**

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

6.169 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.”*

6.170 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 relabeled and that, where appropriate, re-labelling seals are used to re-seal opened packaging.

6.171 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.

6.172 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.

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

7.0 REQUIREMENTS CONCERNING DATA AND SAFETY MONITORING BOARD

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

- 7.1.1 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;
- 7.1.2 There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- 7.1.3 There is prior information suggesting the possibility of serious toxicity with the study treatment;
- 7.1.4 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;
- 7.1.5 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;
- 7.1.6 The study is large, of long duration, and multi-center.

7.2 The following issues related to DSMB shall be submitted to PPB:

- 7.2.1 Composition of DSMB or SMC
- 7.2.2 Copy of the DSMB/SMC Charter
- 7.2.3 DSMB or SMC reports which should be submitted to PPB within two weeks of the deliberations and in the request for annual approval.

7.3 Factors that may be considered when appointing members to DSMB include;

- 7.3.1 Relevant expertise,
- 7.3.2 Experience in clinical trials and
- 7.3.3 Serving on other DSMBs, and

7.3.4 Absence of serious conflicts of interest

7.4 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.

7.5 Composition may include

7.5.1 Clinicians with expertise in relevant clinical specialties

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

7.5.3 Toxicologists,

7.5.4 Epidemiologists, and

7.5.5 Clinical pharmacologists,

7.5.6 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.

7.5.7 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.

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

7.6 We recommend that sponsors establish procedures to:

7.6.1 Assess potential conflicts of interest of proposed DSMB members;

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

7.6.3 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;

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

8.0 MANUFACTURING AND IMPORT OF INVESTIGATIONAL PRODUCTS

8.1 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 participant and the reliability of data generated in the clinical trial (‘good manufacturing practice’).

8.2 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, and a certificate of GMP be issued by a competent authority from the country of manufacture provided. At the minimum, the GMP certificate should include the Competent authority name and contact details, address of the manufacturing site, date of inspection and validity period. This implies that the manufacture of the investigational product may be subject to control and inspection in the same way as the case of marketed medicinal products.

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

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

8.4.1 Drug Substance:

8.4.1.1 Names and Source

8.4.1.2 Method of Manufacture

8.4.1.3 Physicochemical Properties and Structure Elucidation

8.4.1.4 Impurities

8.4.1.5 Specifications and Test Methods and Batch Analyses

8.4.1.6 Stability and Packaging

8.4.2 Dosage Form:

8.4.2.1 Source

8.4.2.2 Developmental Pharmaceutics

8.4.2.3 Formulation and Method of Manufacture and Packaging

8.4.2.4 Specifications and Test Methods and Batch Analyses

8.4.2.5 Stability

8.5 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.

8.6 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.

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

8.8 The manufacturing process and manufacturing facility of the investigational product may be subject to GMP inspection by PPB

8.9 Approval for importation of investigational products and comparator will be dependent on approval to conduct the clinical trial. The quantities approved for import shall be justifiable in relation to the study and timelines.

Pharmacy

8.10 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.

8.11 The pharmacy should have;

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

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

8.11.3 Thermometers, hygrometers, weighing balances, etc. that are regularly calibrated and with calibration records kept and these may be subject to inspection by the board

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

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

8.11.6 Procedures to comply with GMP

8.11.7 A rigorous quality management system

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

8.13 Storage areas should:

8.13.1 Have adequate space for different study products to be stored apart

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

8.13.3 Be protected from direct sunlight

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

8.13.5 Be secure

8.13.6 Be accessible only to authorized staff

8.13.7 Have records for logging study products in and out

Pharmacy Staff

8.14 Each study shall have a Study Pharmacist who shall be suitably qualified and experienced to handle the IMP.

8.15 The Pharmacist shall be resident in Kenya and must be duly registered by the Board.

8.16 The pharmacy staff must be sufficient in number for the type and amount of work that the pharmacy undertakes in the study.

8.17 The Pharmacist shall have a valid Professional Indemnity Insurance Cover throughout the study

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

8.19 A pharmacist should have overall responsibility for investigational products and marketed medicines, including emergency medicines used in the study. This should be a delegated function from the Principal Investigator of the study.

8.20 The Pharmacy staff handling IMP should receive GCP training and periodic refresher training at a minimum of once every two years.

Product Handling, Accountability and Disposal:

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

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

- 8.22.1 To safeguard participants and health care professionals by ensuring that IMPs are appropriate for use and are procured, handled, stored and used safely and correctly.
- 8.22.2 To ensure that IMPs are managed and dispensed to patients in accordance with the protocol.
- 8.22.3 To ensure that all pharmacy clinical trials procedures comply with relevant guidelines and regulations.
- 8.22.4 Perform the IMP duties and responsibilities as delegated to him/her by the principal investigator.
- 8.22.5 All pharmacy teams involved in the setting up of clinical trials and dispensing of trial medication must adhere to GCP which ensures
  - 8.22.5.1 The protection of participants involved in trials and
  - 8.22.5.2 The credibility of the data generated in the trial.

8.23 The Pharmacy staff handling the investigational products shall be adequately trained on how to handle and dispense the IMP.

8.24 Each clinical trial site shall have a regularly reviewed and updated pharmacy protocol to guide on the handling and dispensing of the investigational products

8.25 All investigational products shall be under the care and responsibility of a Pharmacist validly registered and with current practice licence of the board

8.25.1 The Study Pharmacist shall maintain;

8.25.1.1 Certify QP release statement

8.25.1.2 QP declaration

8.25.1.3 IMP certificate of analysis

8.25.1.4 Viral safety studies and data (if applicable)

8.25.1.5 BSE-/TSE-free certificate(s)

8.25.1.6 Master randomization list

8.25.1.7 IMP code breaks

8.25.1.8 IMP prescription template

8.25.1.9 IMP accountability log template

8.25.1.10 IMP destruction log template

8.25.1.11 Temperature log

8.25.1.12 Temperature deviation log

8.25.1.13 IMP recall information

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

8.25.3 All clinical trial sites shall maintain;

8.25.3.1 Calibration records of all the equipment relevant to the storage and dispensing of the IMP

8.25.3.2 Local dispensing/pharmacy procedure SOPs

8.25.3.3 IMP ordering and shipping records

8.25.3.4 Acknowledgement of receipt

8.25.3.5 Completed IMP prescriptions

8.25.3.6 IMP accountability log

8.25.3.7 IMP storage records

8.25.3.8 IMP temperature storage records

8.25.4 Records of temperature and humidity control and monitoring shall be maintained and these may be subject to inspection by PPB

8.25.5 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.

8.25.6 An investigator shall administer the drug only to participants 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.

8.25.7 An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants. 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.

8.25.8 All study products will be destroyed after a written permission from the board, following a written application/ request from the Sponsor/ investigator’s team and the disposal be witnessed by a PPB inspector who shall issue a Drug Destruction Certificate.

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

   8.25.9.1 Date(s) and quantity received for each product

   8.25.9.2 Balance of the study medication(s)

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

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

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

Accountability at Trial Site

8.26 The pharmacist shall keep records of each stage of the handling and use of the investigational product, such as:

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

8.26.2 Dispensing or manufacturing it

8.26.3 Giving each participant the dose or doses specified by the protocol

8.26.4 Returning unused product to the sponsor or delegate,

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

8.26.6 Keeping an inventory

8.26.7 Reconciling the entire IMP received from the sponsor.

8.27 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 participants.

Recall

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

Retention of samples

8.27.2 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 end of the trial.

Laboratories that Perform the Analysis of Clinical Trials Samples

8.28 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.

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

8.30 All laboratory equipment used in a clinical trial should have valid maintenance and calibration certificates.

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

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

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

8.34 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.

8.35 Laboratory staff should have valid registration and practice licenses with the Kenya Medical Laboratory Technicians and Technologists Board (KMLTTB).

8.36 The Laboratories should have an External Quality Assurance (EQA) program in place for important endpoint assays e.g. hematology, biochemistry, microbiology etc.

8.37 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.

8.38 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.

8.39 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.

8.40 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 participant safety.

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

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

8.43 Laboratory staff should receive periodic GCLP refresher training every two years.

8.44 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.

8.45 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.

8.46 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.

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

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

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

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

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

8.52 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.

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

8.54 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.

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

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

8.57 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 participant s or impact on the ERC approval and/or the approval given by Pharmacy and Poisons Board

8.58 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

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

8.60 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.

8.61 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.

8.62 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.

8.63 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/participant 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.

8.64 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

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

8.66 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.

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

8.68 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.

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

Method validation

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

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

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

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

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

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

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

8.77 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.

8.78 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.

8.79 Prior to use, analytical equipment should be subjected 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).

8.80 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

8.81 All computerized 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.

8.82 Prior to use, all computerized systems should be subjected to an appropriate level of validation. The primary aim of any validation process will be to demonstrate that the computerized 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 utilized. 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 computerized system is deemed fit for use the decision should be documented and authorized by laboratory management or their designated representative. Any limitations of the system should be clearly described in laboratory procedures.

8.83 For each computerized 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.

8.84 If additional functionality is utilized 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.

8.85 If additional computerized 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.

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

8.87 Computerized 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.

8.88 Disaster recovery procedures should be considered for all computerized systems.

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

8.90 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.

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

Controlled Human Infection Studies (CHIS)

8.92 Controlled Human Infection studies are trials in which participants are intentionally challenged with a well-characterized pathogen in a controlled manner while being closely monitored.

8.93 The challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner.

8.94 The well characterized strain of an infectious agents should be administered at a controlled dose and by a specific route to carefully selected adult volunteers.

8.95 The studies require safe and accurate microbiology, good clinical facilities, careful recruitment and monitoring. Volunteers should be monitored for evidence of carriage or infection under medical supervision to anticipate or manage symptoms of disease.

8.96 The value of the information to be gained should clearly justify the risks to human subjects.

8.97 Consideration should be whether the burden of disease being studied is of sufficient importance to justify the risks associated with participant involvement, and the costs, including opportunity costs, of the effort.

8.98 The investigators should be adequately qualified, trained and experienced in the conduct of CHIM studies as well as treating patients with the infectious disease being investigated. They should be able to spend adequate time for oversight of these studies.

8.99 The study should have adequate number of qualified members and adequate infrastructure for conduct of CHIM studies.

8.100 The study team should be compliant with ICH-GCP for conduct of clinical trials.

8.101 All the study personnel should be conversant with the SOPs which are pertinent to them.

8.102 It is important to choose well characterized challenge strain for CHIM studies. The key elements for quality control include:

8.102.1 Well characterized seed material and cells with documented growth

8.102.2 Comparative virulence studies (against benchmark reference material)

8.102.3 Well-characterized and documented growth and maintenance media

8.102.4 Freedom from adventitious agents (including Transmissible Spongiform Encephalopathies)

8.102.5 Adequacy and consistency of manufacturing process including growth media, batch release tests

8.102.6 Safety testing (animal toxicity studies)

8.103 As CHIM studies require careful ethical consideration of both risk to participants, and to their contacts, the provision of robust clinical service to support the participant should an adverse event occur should be in place.

8.104 The study participants should be adequately informed about the study they are getting enrolled into. A test of their understanding of what the study is about should ideally be administered to each of the participants.

8.105 It is not appropriate to consider human challenge trials with an organism that causes disease with high case fatality rate, or where there is a long and uncertain latency period or there are no existing therapies to prevent or ameliorate disease and preclude death.

8.106 The clinical facilities to recruit and manage study participants must ensure that the infection risk is no greater than if the study was carried out elsewhere in the world.

8.107 Complete clearance/resolution of disease is required before the end of the study

8.108 CHIM models should be developed in maximally resourced settings before introduction to Kenya.

8.109 Data on the quality of the CHIM from several previous studies should be submitted for evaluation together with the study protocol.

8.110 Data Monitoring and Safety Boards (DMSB) are recommended for all CHIM studies.

8.111 The challenge trials should be undertaken in accordance with GCP, protocol and in special facilities that are designed and operated in a manner that can prevent the spread of the challenge organism to people outside the study or to the environment.

8.112 The clinical facilities should be capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given. In addition to providing immediate access to appropriate medical care and treatment, the facilities should be designed to prevent the spread of disease, particularly when the challenge organism is a genetically modified organism or an organism that is not endemic to the locality.

8.113 The study endpoints must be consistently defined, and easily identified before the onset of any significant pathology, in order to minimize the risk to participants, and to ensure that clinical or scientific outcomes are assessed.

8.114 The challenge strains should ideally be chosen and manufactured in compliance with GMP at a level similar to that required for a product to be studied in a Phase 1 clinical trial.

8.115 Implementation of a Quality Assurance (QA) of inocula from manufacture, that may require Good Manufacturing Practice certification, through to a regulated delivery pathway to the volunteer is required.

8.116 A no-fault insurance cover should be obtained for all of these clinical trials.

8.117 Chemistry Manufacturing and Control considerations for challenge strains, should generally be similar to those for biologic products.

8.118 Before initiating a challenge study in humans, enough consideration should be given to selection of the challenge strain(s). If candidate challenge strains differ in virulence, the least virulent strain that will serve the goals of the challenge study should be used.

8.119 If the original source of a pathogen is a patient, any information about the clinical presentation of that patient and any other aspects of the clinical context should be recorded.

8.120 Passage history of the challenge strain should be documented, including identification of the growth medium and other raw materials used in its isolation and passage, or in some cases, relevant information about animals used for propagation.

8.121 The presence of specific virulence factors and the range of antimicrobial susceptibility should be well-documented.

8.122 Genotypic characterization, full genomic DNA sequencing, of the challenge strain should be provided.

8.123 For microbial purity; it is important to establish that other contaminating pathogens are not being administered through contamination of the challenge agent.

8.124 Potency testing; Administration of hyper-potent doses of challenge inocula could lead to significant unanticipated morbidity. Conversely, the consequence of administering a sub-potent challenge may be that no useful information is derivable from the challenge study and that volunteers will have been placed at risk without justification. In all cases the selected target dose should balance safety of the volunteers with an "attack" rate based on clinical response to the challenge inocula that will support the objectives of the proposed challenge study.

8.125 Stability should be determined by assessment of potency and purity over time. A stability program should include purity and potency testing at specified intervals. In cases where the challenge inoculum is prepared fresh after growth from an aliquot of a cell or virus bank, or harvested after growth in live animals, a demonstration that the challenge inoculum maintains its potency during the period between its preparation and its administration is required.

8.126 In both cases of pre-prepared and freshly prepared challenges, a potency determination of the inoculum at the time of administration is desirable and will serve to verify the actual dose delivered.

8.127 The CMC should include periodic testing of purity and potency of the cell or virus banks, if applicable. For challenge strains that have been genetically modified, demonstration of the integrity of the modifications should be integrated into the stability and pre-challenge testing program.

8.128 CHIM studies should be conducted under the provisions of GCP

8.129 Safety evaluation of the controlled human infection model; Careful assessment of the expected risks associated with exposure to the challenge organism is a critical component of preclinical evaluation of a CHIM. Sponsors should provide adequate information to assess risks to subjects in the proposed studies.

8.130 For controlled human infection studies, sponsors should provide a description of possible risks to be anticipated based on clinical manifestations associated with natural infection and data from prior clinical studies con- ducted with the challenge strain, if available.

8.131 When a challenge strain has been attenuated, data from preclinical studies in relevant animal models may provide additional information regarding risks and the potential for severe or serious outcomes and this information should be provided.

8.132 Sponsors should provide data to justify the selection of the starting dose of the challenge inoculum. Staggered escalation of the challenge dose, with safety review between dosing cohorts, can enhance the safe conduct of the study.

8.133 Eligibility criteria for human challenge studies should exclude persons at increased risk for complications following challenge. In certain cases, development of appropriate eligibility criteria may require recognition and management of pathogen-specific risks.

8.134 The study protocol should clearly specify stopping rules and management of withdrawal of study participants at different stages of the study.

8.135 The investigator should inform the subject during consent, that in case of withdrawal (either voluntary or at investigator's discretion), the subject may have to undergo confinement for a quarantine period.

8.136 Dose limited toxicity should be defined in the context of various severity of infection that the challenge produces.

8.137 The major direct risk to the participants in CHIM studies is the occurrence of symptomatic infection and its possible consequences such as severe disease, complications, and death. Other foreseeable direct risks to participants like immediate reactions to challenge strain, delayed immune-mediated reactions, and possibility of a dormant infection/carriage, and indirect risks such as stress associated with stay at an isolation facility and loss of wages should be considered.

8.138 Occurrence of SAEs in CHIM studies should be monitored adequately.

8.139 Risk mitigation and risk management plan for each study should be outlined in advance after a careful evaluation of information available pertinent to the study material and study processes.

8.140 The plan for risk mitigation should consider minimization of risks during several stages of the study design and conduct.

8.141 Controlled human infection studies in females of reproductive potential; In the absence of a compelling rationale and justification, pregnant women, lactating women and women actively trying to become pregnant should be excluded from controlled human infection studies.

8.142 Managing the risk of environmental transmission; Infectious pathogens may have the potential to be transmitted to others such as household members, study staff, the community, and to the environment. The specific precautions to mitigate these possible transmission risks should clearly be presented.

8.143 CHIM studies should be undertaken in accordance with a protocol, and in special facilities that are designed and operated in a manner that prevents the spread of the challenge organism outside the study or to the environment.

8.144 The clinical facilities should be capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given.

8.145 Safety monitoring systems for the studies should be established, and the safety monitoring and risk minimization and management plan to be submitted for approval.

9.0 PROTOCOL AMENDMENT

9.1 For an amendment to an approved protocol;

9.1.1 Any new information which affects the conduct/management of the trial, safety of the participants 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 for review and approval

9.1.2 Arrangements must be in place for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects.

9.1.3 The safety measures, such as temporarily halting the trial, may be taken without prior authorization from the PPB but must be reported to the Board.

9.2 A copy of favorable opinion letter from ERC on record shall be submitted together with the request for approval of a proposed amendment to PPB.

9.3 PPB approval must be obtained for all substantial amendments that include but not limited to amendments of the following:

Changes that may affect

9.3.1 the safety or physical or mental integrity of the participants,

9.3.2 the scientific value of the trial,

9.3.3 the conduct or management of the trial,

9.3.4 the quality or safety of any IMP used in the trial.

9.3.5 Change of main objective

9.3.6 Change of primary or secondary endpoint

9.3.7 Use of new measurements (methods) for the primary endpoint

9.3.8 Change in the definition of the end of the trial

9.3.9 Addition of a trial arm or placebo group

9.3.10 Change of in-/exclusion criteria

9.3.11 Reducing number of monitoring visits

9.3.12 Withdrawal of independent data monitoring board (DSMB)
9.3.13 Change of IMP
9.3.14 Change of dosing of IMPs
9.3.15 Change of mode of administration of IMPs
9.3.16 Change of study designs with impact on statistical analysis or the risk/benefit assessment
9.3.17 Change of sponsor or the sponsor’s legal representative
9.3.18 Revocation or suspension of the IMP’s MA
9.3.19 Changes in the manufacturing process and/or specifications of an active substance /IMP
9.3.20 Change of the reference safety information (RSI) during the conduct of a clinical trial.
9.3.21 Addition of a study site
9.3.22 Change of investigator
9.3.23 Changes to the patient information
9.3.24 Changes that affect patient selection and monitoring
9.3.25 Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc.)
9.3.26 Changes that affect patient discontinuation
9.3.27 Addition/removal of an investigational site or study arm
9.3.28 Change of Principal Investigator
9.3.29 Addition or reduction of sample size of the study
9.3.30 Changes that result in the extension of duration of a trial
9.3.31 Any changes that introduce more than minimum risk to study participants

9.4 A request for approval of an amendment shall be submitted with the following information;

9.4.1 Summary of the proposed amendments
9.4.2 Reason for the amendment
9.4.3 Impact of the amendment on the original study objectives
9.4.4 Impact of the amendments on the study endpoints and data generated.

9.4.5 Impact of the proposed amendments on the safety and wellbeing of study participants

9.5 Minor amendments or administrative changes may be implemented after getting the ERC’s approval but a record of these amendments shall be kept for possible inspection by PPB.

10.0 INFORMATION ON ON-GOING TRIALS

10.1 Research centers, researchers, sponsors, clinical research organizations (CROs) and everyone involved in the clinical trial shall comply with GCP, legal and regulatory requirements in the conduct of clinical trials.

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

10.3 Protocol violations and protocol deviations shall be reported to the board within seven days of the PI becoming aware of them. The details to be reported shall include;

10.3.1 Date of the Deviation/Violation

10.3.2 Study participant(s) affected

10.3.3 Name of the treating physician

10.3.4 Detailed description of the deviation/violation

10.3.5 Indication whether the study participants were adversely affected by the deviation/violation

10.3.6 Explanation why the deviation/violation occurred

10.3.7 Measures taken to address the deviation/violation

10.3.8 Measures taken to preclude future recurrence of the deviation/violation

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

10.4.1 Copy of the progress report that shall contain among others;

10.4.2 the current status of the study,

10.4.3 Participants flow;

10.4.3.1 summary of the patients screened,

10.4.3.2 Numbers that failed screening,

10.4.3.3 numbers enrolled,

- 10.4.3.4 numbers withdrawn and reasons for withdrawal,
- 10.4.3.5 numbers lost to follow-up,

10.4.4 challenges experienced

10.4.5 Summary of protocol deviations and protocol violations. This should include

- 10.4.5.1 Date of the Deviation/Violation
- 10.4.5.2 Study participant(s) affected
- 10.4.5.3 Name of the treating physician
- 10.4.5.4 Detailed description of the deviation/violation
- 10.4.5.5 Indicate whether the study participants were adversely affected by the deviation/violation
- 10.4.5.6 Explanation why the deviation/violation occurred
- 10.4.5.7 Measures taken to address the deviation/violation
- 10.4.5.8 Measures taken to preclude future recurrence of the deviation/violation

10.4.6 Updated IB of the investigational product

10.4.7 Drug Safety Update Report (DSUR).

10.4.8 Copy of the latest DSMB report

10.4.9 Copy of favorable opinion from the ERC of record.

10.4.10 Copy of annual practice licence for the investigators and Pharmacists

10.4.11 SUSAR and SAE Log that should include

- 10.4.11.1 Patient ID
- 10.4.11.2 Age
- 10.4.11.3 Date of enrolment into the study

10.4.11.4Type of SAE

10.4.11.5Start date of the SAE

10.4.11.6End date of the SAE

10.4.11.7Reason for reporting the event as an SAE

10.4.11.8Relation to investigational drug

10.4.11.9Outcome of the SAE

10.5 Request for annual approval shall also be accompanied by copies of annual practice licenses of the Investigators, Pharmacists and copy of valid insurance covers for study participants and valid professional indemnity cover for the investigators and study pharmacist.

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

10.7 The applicant must receive an approval of this submission before proceeding with the study.

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

10.9 All documents submitted to the board must be version referenced and dated.

10.10 These documents must be submitted to PPB at least six weeks before the expiry of the previous approval.

11.0 CLINICAL TRIAL MASTER FILE

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

11.2 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.

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

11.4 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

11.5 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.

12.0 INTEGRITY OF DATA GENERATED

12.1 All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the trial participants remains protected

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

12.3 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.

13.0 POST-TRIAL INFORMATION

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

13.2 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.

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

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

14.0 INSPECTIONS

14.1 The Board shall inspect clinical trial sites and trial sponsors to ensure that the generally accepted principles of GCP are met, in accordance with the Guidelines for The Conduct of GCP Inspections in Kenya (HPT/PDS/CTR/GUD/080).

14.2 The objectives of the inspection will be;

14.2.1 To ensure that participants in clinical trials are not subjected to undue risks and ensure their rights, safety and wellbeing,

14.2.2 To validate the quality of the data generated or

14.2.3 To investigate complaints.

14.2.4 To verify the accuracy and reliability of clinical trial data submitted to the Board in support of research or marketing applications

14.2.5 To assess compliance with the Board's guidelines and regulations governing the conduct of clinical trials.

14.2.6 To provide real-time assessment of ongoing trials

14.3 The Board may inspect clinical trial (investigator) sites, sponsor's office, data management center, contract research organization (CRO) or any other establishment related to the trial as it will be deemed appropriate by the Board to ensure compliance with the applicable regulations, GCP and clinical trial protocol.

14.4 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.

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

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

14.7 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.

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

14.9 Routine inspections will be announced at least two weeks in advance of the inspection date. This can happen due factors including but not limited to;

14.9.1 Concern about the adequacy of study participants' protection measures,

14.9.2 Issues with data integrity,

14.9.3 History of problems with the inspected site/sponsor or PI

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

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

14.12 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.

14.13 During inspections, the board shall expect records to be accessible, available and organized.

14.14 The Inspections will include but not be limited to:

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

14.14.2 Compliance with the approved Protocol, GCP and the applicable regulations

14.14.3 All amendments to the Protocol have been approved.

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

14.14.5 SUSARs/SAEs are reported as required by the Protocol

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

15.0 TERMINATION OF CLINICAL TRIAL

15.1 Premature termination:

15.1.1 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 ERC on record.

15.1.2 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

15.1.2.1 As soon as possible, inform all co-investigators of the termination and of the reasons for the termination and advise 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.

15.1.2.2 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.

15.2 Withdrawal of PPB approval:

15.2.1 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.

15.3 End of trial (Study closeout):

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

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

15.3.3 After the trial has been conducted and closed, the applicant shall submit executive summary report of the study within 30 days.

15.3.4 This should be followed by a clinical study report within 180 days of the study closure unless otherwise justified.

15.4 The structure and content of the final study report

15.5 Irrespective of the outcome of a clinical trial, the sponsor shall submit a summary of the results of the clinical trial to PPB.

15.6 The content of the reports shall be in ICH E3 format. (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf)

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

15.7.1 Clinical trial ECCT number

15.7.2 Name and contact details of the sponsor;

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

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

15.7.5 Population of participants

15.7.5.1 Age group breakdown and gender breakdown;

15.7.5.2 Inclusion and exclusion criteria);

15.7.6 Investigational medicinal products used;

15.7.7 Description of adverse reactions and their frequency;

15.7.8 Overall results of the clinical trial;

15.7.9 Comments on the outcome of the clinical trial;

16.0 ARCHIVING

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

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

16.3 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.

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

16.5 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 participant. In any other case, records must be provided within 7 days of request.

17.0 CONDITIONS FOR CLINICAL TRIAL IMPORT LICENCE

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

17.2 An import permit shall be applied for by the Sponsor of the study or the Coordinating Investigator.

17.3 The following documents should then be attached

17.3.1 The proforma Invoice or Invoice.

17.3.2 The Ethical Committee favorable opinion Letter.

17.3.3 The ECCT Approval letter from Clinical trial Division of PPB

17.4 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.

17.5 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.

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

17.7 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.

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

17.9 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.

17.10 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.

18.0 SANCTIONS

18.1 The Board shall apply the following regulatory sanctions shall be applied to the sponsor and /or Principal Investigator in the case of non-compliance with the requirements in these guidelines:

18.1.1 Notify of non-compliance and advised on how this can be remedied.

18.1.2 Issue a formal warning reminding the Sponsor or Principal Investigators of their regulatory obligations.

18.1.3 Blacklisting non-compliant Sponsor or Principal Investigator

18.1.4 Make public a list of sponsors or Principal Investigators found to be seriously or persistently non-compliant.

18.1.5 Refuse to issue import permit of the study medications

18.1.6 Suspend the study

18.1.7 Stop the study

18.1.8 Impose a fine

19.0 TRIALS DURING PUBLIC HEALTH EMERGENCIES (PHE)

19.1 Research and innovation play important roles during, after, and in anticipation of future public health emergencies.

19.2 Research undertaken during PHEs ranges from the minimally invasive (collection of data, surveillance) and strengthening of health systems, to more ‘risky’ and invasive procedures, such as the use of experimental therapeutics (unregistered, unproven or repurposed) or innovative vaccines.

19.3 research may in no way compromise the response to an outbreak or appropriate care.

19.4 There should be fair selection of participants.

19.5 studies are designed so as to yield scientifically valid results under the challenging and often rapidly evolving conditions of disasters and disease outbreaks

19.6 The research is responsive to the health needs or priorities of the disaster victims and affected communities and cannot be conducted outside a disaster situation

19.7 The participants are selected fairly and adequate justification is given when particular populations are targeted or excluded, for example health workers

19.8 The potential burdens and benefits of research participation and the possible benefits of the research are equitably distributed

19.9 The risks and potential individual benefits of experimental interventions are assessed realistically, especially when they are in the early phases of development

19.10 Communities are actively engaged in study planning in order to ensure cultural sensitivity, while recognizing and addressing the associated practical challenges

19.11 The individual informed consent of participants is obtained in Individuals capable of giving informed consent,

19.12 Research results are disseminated, data are shared, and any effective interventions developed or knowledge generated are made available to the affected communities

19.13 There shall be expedited review of application and this may also involve joint review of the application together with ERC or together with other NMRAs where a similar application has been lodged

19.14 PPB shall upon receipt of an application liaise with relevant stakeholders (including relevant ERC and other oversight bodies) to draw an appropriate plan to facilitate a holistic review of an application in a fast-track manner.

19.15 The underlisted prioritization criteria shall be applied in the selection of applications for review.

19.16 Epidemiology of the emergency. 8.3.2 Morbidity / mortality associated with the emergency and/or condition under study.

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

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

19.16.3 Risk: Benefit impact of the intervention and/or trial design.

19.17 Upon conclusion of a review the Authority shall within applicable timelines (That are internally monitored) communicate its decision on the Application to the Applicant.

19.18 The decision of the Authority may be any of the underlisted:

19.18.1 Approved

19.18.2 Deferred pending submission of further details that shall be specified.

19.18.3 Rejected;

20.0 HERBAL PRODUCTS

20.1 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.

20.2 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.

20.3 Information needed to support a clinical trial for a herbal product

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

20.4 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.

20.5 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)

20.6 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.

20.7 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.

20.8 Herbal Product:

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

20.9 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.

20.10 Information needed to support a clinical trial for an 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.

20.11 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.

20.12 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 participants, 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.

20.13 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.

20.14 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; e.g. vomiting, diarrhea, abdominal pain etc.
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

20.15 Information needed to support phase 3 trials

- Safety data. If the population has broader entrance characteristics compared to the populations of prior trials, the favorable 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 the fundamental ethical principles of human participation in research apply equally to herbal remedies and research involving these compounds. Consent must be obtained, participant selection must be equitable, risks and benefits must be weighed and must be favorable 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)

21.0 ANNEXES

Annex 1 Application Form (*FOM015/CTR/SOP/003*)

Registration in the online system at www.ctr.pharmacyboardkenya.org

Annex 2 (FOM010/ CTR/SOP/003)
Checklist for Submission of Request for Approval of New Application

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

Checklist for Submitting a Request for New Application

ECCT No...

Study Tittle ....

No	Item	Version No.	Date
1.	Cover letter		
2.	The Study Protocol		
3.	Patient Information leaflet and Informed consent form (English, Swahili and local languages to be used)		
4.	Investigators Brochure/Package inserts		
5.	Investigational Medicinal Product Dossier (IMPD) including stability data of the study product		
6.	Adequate data and information on previous studies and phases		
7.	GMP certificate of the investigational product from the site of manufacture and Certificate of analysis		
8.	Pictorial Sample of the investigational products. This sample should include the text of the labeling to be used		
9.	Signed investigator(s) CV(s) including that of study Pharmacist		
10.	Evidence of recent GCP training of the core study staff		
11.	DSMB Charter/draft charter including the composition and meeting schedule		

12.	Statistical Analysis Plan submitted at submission of initial application or an undertaking to submit it before end of enrolment		
13.	Detailed budget of the study		
14.	Copy of favorable opinion letter from the local Ehics Review Committee (ERC).		
15.	Indemnity cover for PI and investigators		
16.	Insurance Certificate for the study participants		
17.	Copy of current Practice Licenses for the Investigators and study Pharmacist		
18.	Copy of approval letter(s) from collaborating institutions or other regulatory authorities, if applicable		
19.	For multicenter/multi-site studies, a site specific 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.		
20.	Registration at the clinical trial registry at www.ctr. pharmacyboardkenya.org		
21.	Registration of the study at Pan African Clinical Trials Registry https://pactr.samrc.ac.za		
22.	Signed Declarations; a) Financial Disclosure/Conflict Of Interest b) Compliance with GCP, Legal and Regulatory requirements Submission of correct information		
23.	Payment of fees		
24.	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 favor 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 (FOM012/CTR/SOP/003)
Checklist for the Request for Annual Approvals of Clinical Trials

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

Checklist for Submitting a Request for Annual Approval

ECCT No………………………………………………………………………………………………

Tittle ………………………………………………………………………………………………

No.	Item	Version No.	Date
1.	Cover letter		
2.	Annual progress report		
3.	SAE and SUSAR Cumulative log		
4.	Latest Data Safety Monitoring Board (DSMB) report		
5.	Protocol Violations and Protocol Deviations log		
6.	Updated Investigators Brochure/Package inserts		
7.	The Development Safety Update Report (DSUR)		
8.	Copy of current favorable opinion letter from the local Ethics Review Committee (ERC).		
9.	Copy of the Annual Practice for the investigators and Pharmacist		
10.	Copy of the current indemnity insurance cover for the investigators		
11.	Copy of valid participants' clinical trials insurance cover		
12.	Evidence of registration of the study at at Pan African Clinical Trials Registry https://pactr.samrc.ac.za		
13.	Request for annual approval at the clinical trial registry www.ctr.pharmacyboardkenya.org		

Signed

Applicant Name………………………… Sign……………………………… Date………………

PPB Staff Name. ………………………Sign……………………………… Date……………

Annex 4a
Declaration by Applicant

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

Declaration by Applicant

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

I/We, hereby declare that all information contained therein, or referenced by, this application is complete and accurate and is not false or misleading.

I/We, the undersigned will ensure that if the above-said clinical trial is approved, it will be conducted according to the protocol submitted, and all applicable legal, GCP, ethical and regulatory requirements.

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 be conducted according to principles of GCP

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 ERC concerned within a maximum 1-year deadline after the end of the study in all countries.

_______________________________ ________________

Main Applicant Date

(Local contact)

_______________________________ ________________

Deputy (Local contact) details Date

Annex 4b
Declaration by Applicant

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

Declaration by the principal investigator

Name:
Title of the trial:
Protocol No:
Version No:
Date of the protocol: Investigational
medicinal product:
Site:

1. I have read and understood the duties and responsibilities of the investigator as outlined in the guidelines for GCP guideline ICHE6R2 or as last amended
2. I will notify the Regulatory Authority of any aspects of the above guideline with which I do not/ am unable to comply. If applicable, attach it to this declaration
3. I have thoroughly read, understood, and critically analysed the protocol and all applicable documentation, including the investigator's brochure, patient information leaflet(s)/package insert and the informed consent form(s)
4. I will conduct the trial as specified in the protocol and observe all legal requirements
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period
6. I will not commence with the trial before the relevant ERC(s) and the Regulatory Authority provide written authorization
7. I will obtain informed consent from all participants or from their legal representatives if they are not legally competent
8. I will ensure that every participant shall at all times be treated in a dignified manner and with respect including relatives

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

   *Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with GCP *attach details
11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices *attach details

12. I will submit all required reports within the stipulated timeframes

Signature:	Date:
Witness:	Date

Annex 4c
Declaration by Applicant

REPUBLIC OF KENYA

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Declaration by the monitor

Name:

Title of the trial:

Protocol No:

Version No:

Date of protocol:
Study investigational product:
Principal investigator's name:
Site:

Designation:

1. I have read and understood the duties and responsibilities of the monitor as outlined in the guidelines for GCP guideline ICHE6R2 or as last amended
2. I have notified the regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. If applicable, this may be attached to this declaration.
3. I will carry out my responsibilities as specified in the trial protocol and according to all applicable law, regulations and guidelines
4. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial [*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*
   *Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
5. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice
   *Attach details
6. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices
   *attach details
7. I will submit all required reports within the stipulated timeframes

Signature: Date:

Annex 5 (FOM014/CTR/SOP/003)

Declaration of Financial Disclosure/Conflict of Interest

REPUBLIC OF KENYA

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 honor 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
Current Workload of the Investigator

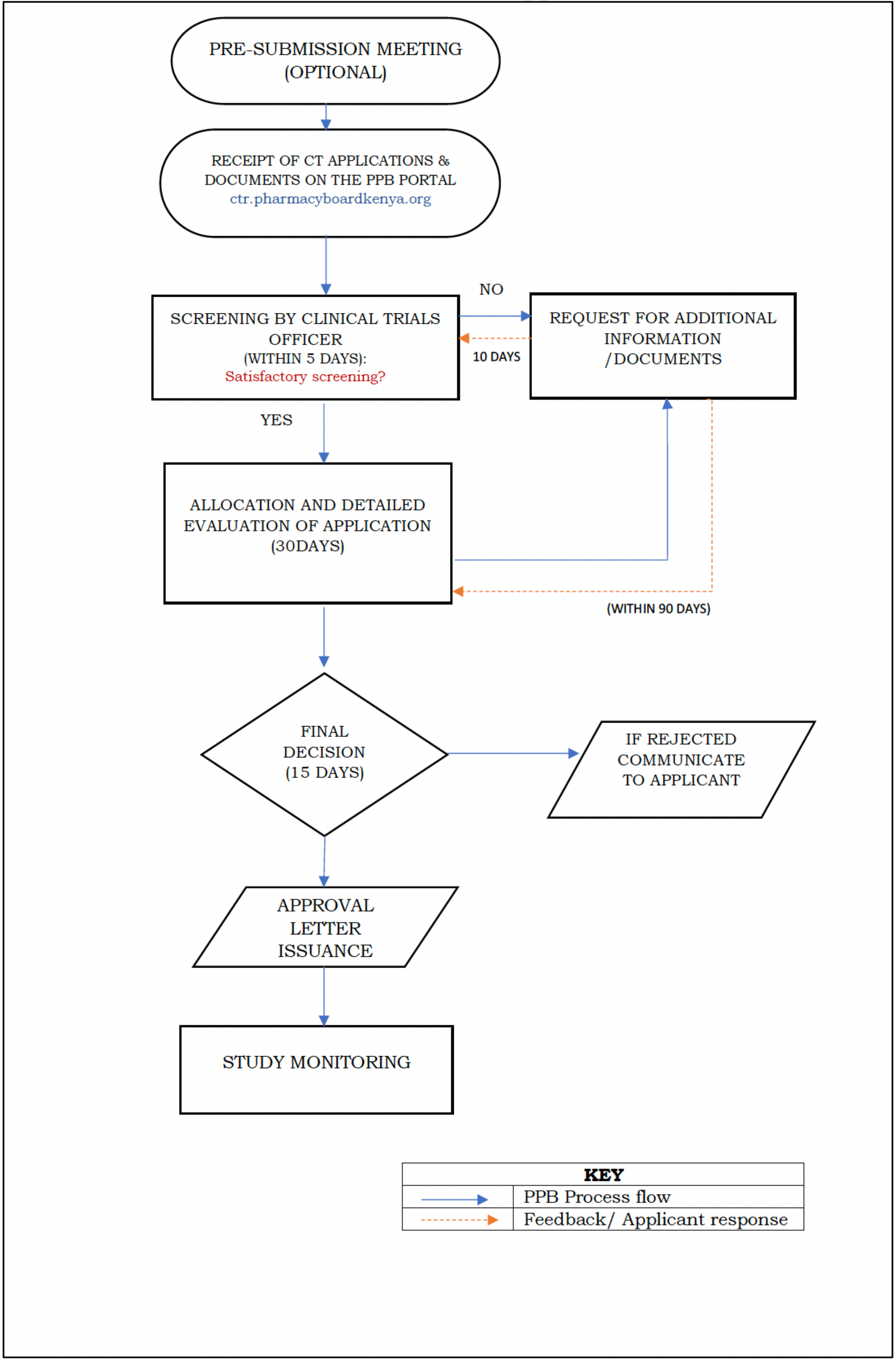
Provide the number of studies currently undertaken by the trialist(s) as principal and/or co-investigators, and the total number of patients participating in these studies. Present the commitments of the researcher(s) in relation to the work related to clinical trials and to other activities.

Recommended format for response:

Investigator (Name and designation)			
Total number of trials currently undertaken by the Investigator	Number	Date of commencement: Expected date of completion of study:	
Total number of patients/participants for which the principal investigator is responsible on specified date	Number	Date	
Estimated time per week [168 hours denominator]		**Hours**	**%**
Clinical trials	Clinical work (patient contact)		
	Administrative work		
	Clinical work		

Organization (Practice/University/employer)	Administrative work		
Teaching	Preparation/evaluation		
	Lectures/tutorials		
Writing up work for:			
Publication/presentation			
Reading /sourcing information			
Other (specify)			

Annex 7: Clinical Trials Review and Approval Flowchart



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23.0 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.

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24.0 REVISION HISTORY

Revision No.	**Date**	**Prepared**	**Sections Revised**	**Description of change**
1	10/07/2021	QAO	All	Editorial changes to comply with QMS requirements
2	13/01/2022	QAO	All	Additional / revised Definitions Editorial edits to comply with QMS requirements
3	22/09/2022	QAO	Annex 7 Section 3	Revised review and approval flowcharts Alignment with The Pharmacy and Poisons (Conduct of Clinical trials), Rules 2022
4.	28/11/2025	QAO	Glossary of terms	Update of terms
			Foreword & Legal framework	Adoption of ICH, WHO GCP guidelines
			Section 3.4	Inclusion of Procedures for multicenter trials
			Section 5	Clarification on categories and qualification of Investigators
			Section 6.5	Clarification on safety reporting
			Section 6.7	Alignment of study Monitoring requirements to ICH E6R3

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