GUIDELINES FOR APPLICATIONS TO CONDUCT

CLINICAL TRIALS IN KENYA

PREPARED BY

EXPERT COMMITTEE ON CLINICAL TRIALS

_Revised version 2014_
Foreword

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

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

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

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

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

Signed
Dr. C. Muraguri
Director of Medical Services
Ministry of Health
Acknowledgements

The Pharmacy and Poisons Board acknowledges the contribution of the following in the research and compilation of these guidelines:
   The Ministry of Health
   Our stakeholders, partners and clients

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

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

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LIST OF CONTRIBUTORS

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

The ECCT members

1. Dr. Kipkerich Koskei
2. Dr. Fred Siyoi
3. Prof. Gilbert Kokwaro
4. Prof. Walter Jaoko
5. Dr. Rashid Aman
6. Dr. Monique Wasunna
7. Dr. Bernhards Ogutu
8. Dr. George Osanjo

The ECCT Secretariat

1. Mr. George Muthuri
2. Dr. Edward Abwao
3. Ms Mary Njeri
6.2.8. Assessment of Efficacy
6.2.9. Assessment of Safety
6.2.10. Statistics
6.2.12. Direct Access to Source Data/Documents
6.2.13. Quality Control and Quality Assurance

7. RESEARCH INVOLVING CHILDREN
   7.11.1. Non clinical safety data
   7.11.2. Pharmaceutical properties
   7.11.3. Pharmacokinetics
   7.11.4. Pharmacodynamics
   7.12. Specific and General
   7.13. Practical considerations to facilitate pharmacokinetic studies
   7.14. Efficacy
   7.15. Safety
   7.16. Postmarketing information
   7.17. Ethics

8. INSURANCE COVER

9. PUBLICATION POLICY

10. REQUIREMENTS CONCERNING INFORMED CONSENT

11. THE INVESTIGATOR’S BROCHURE

12. INVESTIGATIONAL NEW DRUG (IND) DOSSIER

13. PHASE ONE CLINICAL TRIALS
   13.1. Non-clinical aspects
   13.2. Pharmacodynamics
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.3. Pharmacokinetics</td>
<td>40</td>
</tr>
<tr>
<td>13.4. Safety Pharmacology</td>
<td>40</td>
</tr>
<tr>
<td>13.5. Toxicology</td>
<td>40</td>
</tr>
<tr>
<td>13.6. Estimation of the First Dose in Human</td>
<td>40</td>
</tr>
<tr>
<td>13.7. Investigator Site Facilities and Personnel</td>
<td>41</td>
</tr>
<tr>
<td>13.8. Mode of Action</td>
<td>42</td>
</tr>
<tr>
<td>13.9. Quality aspects</td>
<td>42</td>
</tr>
<tr>
<td>13.10. Reliability of very small doses</td>
<td>43</td>
</tr>
<tr>
<td>13.11. Clinical aspects</td>
<td>44</td>
</tr>
<tr>
<td>13.11.1. General aspects</td>
<td>44</td>
</tr>
<tr>
<td>13.12. Monitoring and communication of adverse events/reactions</td>
<td>44</td>
</tr>
<tr>
<td><strong>14. LABELING:</strong></td>
<td>45</td>
</tr>
<tr>
<td>14.2. Re-labeling</td>
<td>45</td>
</tr>
<tr>
<td>14.3. Sponsor responsibilities:</td>
<td>46</td>
</tr>
<tr>
<td>14.4. Product Accountability and Disposal:</td>
<td>47</td>
</tr>
<tr>
<td><strong>15. SAFETY REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)</strong></td>
<td>47</td>
</tr>
<tr>
<td><strong>16. REQUIREMENTS CONCERNING DATA AND SAFETY MONITORING BOARD (DSMB)/DATA MONITORING COMMITTEE (DMC)</strong></td>
<td>48</td>
</tr>
<tr>
<td>17. PROTOCOL AMENDMENTS</td>
<td>48</td>
</tr>
<tr>
<td>18. INFORMATION ON ONGOING TRIALS</td>
<td>49</td>
</tr>
<tr>
<td>19. POST TRIAL INFORMATION</td>
<td>49</td>
</tr>
<tr>
<td>20. INSPECTIONS</td>
<td>50</td>
</tr>
</tbody>
</table>
21. TERMINATION OF CLINICAL TRIAL  50

22. ARCHIVING  51

23. CONDITIONS FOR CLINICAL TRIAL IMPORT LICENCE  51

24. KENYA CLINICAL TRIALS REGISTRY  52

HERBAL PRODUCTS  53

1. CHEMISTRY- MANUFACTURING- CONTROL (CMC) CONSIDERATIONS FOR HERBAL PRODUCTS  53

Information on the herbal product proposed for phase 3 studies  54

16. PRE-CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS  55

Information needed to support a clinical trial for a herbal product  55

2. CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS  56

ANNEXES  59

Annex 3  67

Declaration by applicant:  67

Annex 4  68

Declaration of Financial Disclosure/Conflict Of Interest  68
**Abbreviations and Definition of Terms**

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

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Drug Reaction</td>
<td>ADR</td>
<td>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.</td>
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<tr>
<td>Adverse Event</td>
<td>AE</td>
<td>Any untoward medical occurrence in a patient or clinical investigation study participant administered a study or intervention product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.</td>
</tr>
<tr>
<td>Applicant</td>
<td></td>
<td>An institution applying to conduct a clinical trial – Sponsor/sponsor representative</td>
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<tr>
<td>Assent</td>
<td></td>
<td>A child’s affirmative agreement to participate in research, where the child is below the age of the majority but old enough to understand the proposed research in general, its expected risks and possible benefits and the activities expected of them as subjects.</td>
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<td>Abbreviation</td>
<td>Meaning</td>
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<tr>
<td>Audit</td>
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<td>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.</td>
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<td>Audit Certificate</td>
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<td>A declaration of confirmation by the auditor that an audit has taken place.</td>
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<td>Audit Report</td>
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<td>A written evaluation by the sponsor’s auditor of the results of the audit.</td>
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<tr>
<td>Blinding/Masking</td>
<td></td>
<td>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).</td>
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<tr>
<td>Case Report Form</td>
<td>CRF</td>
<td>A form used to record data on each trial subject during the trial, as defined by the study protocol.</td>
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<tr>
<td>Clinical Trial</td>
<td>CT</td>
<td>Clinical trials are systematic studies aimed at determining the safety and efficacy of drugs or devices. Clinical trials are generally classified into Phases I to IV.</td>
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<tr>
<td>Clinical Trial Report</td>
<td></td>
<td>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.</td>
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<tr>
<td>Comparator</td>
<td></td>
<td>A medicinal or marketed product (Active or placebo) used as a reference in a clinical trial.</td>
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<td>Term</td>
<td>Abbreviation</td>
<td>Meaning</td>
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<td>--------------</td>
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<td>Confidentiality</td>
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<td>Maintenance of the privacy of trial participants including their personal identity and all personal medical information.</td>
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<td>Contract Research Organization</td>
<td>CRO</td>
<td>An individual or organization contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board or may also be called a Independent Data Monitoring Committee (IDMC) or an Independent Data Monitoring Board (IDMB)</td>
<td>DSMB</td>
<td>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.</td>
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<tr>
<td>Division of Medicines Information and Pharmacovigilance</td>
<td></td>
<td>The Division at the PPB at the time being responsible for the issues of pharmacovigilance and clinical trials.</td>
</tr>
<tr>
<td>Documentation</td>
<td></td>
<td>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.</td>
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<tr>
<td>Drug</td>
<td></td>
<td>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.</td>
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<td>Abbreviation</td>
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<tr>
<td><strong>Emancipated Minors</strong></td>
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<td>A child who has been granted the status of adulthood by a court order or other formal arrangement.</td>
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<tr>
<td><strong>Essential Documents</strong></td>
<td></td>
<td>Documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced.</td>
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<tr>
<td><strong>Ethical Clearance</strong></td>
<td></td>
<td>An authorization issued by an NCST accredited ethics committee to conduct a clinical trial in Kenya.</td>
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<tr>
<td><strong>Good Clinical Practice</strong></td>
<td>GCP</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Good Manufacturing Practice</strong></td>
<td>GMP</td>
<td>That part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.</td>
</tr>
<tr>
<td><strong>Impartial Witness</strong></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Independent Ethics Committee</strong></td>
<td>IEC</td>
<td>A committee that has been formally designated to approve, monitor, and review biomedical and behavioural research involving humans with the aim to protect the integrity, rights, safety and welfare of the research subjects.</td>
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<td>Abbreviation</td>
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<tr>
<td><strong>Informed Consent</strong></td>
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<td>A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.</td>
</tr>
<tr>
<td><strong>Audit</strong></td>
<td></td>
<td>The act of conducting an official review of documents, facilities, records, and any other resources deemed to be related to the clinical trial and that may be located at the trial site, at the sponsor's and/or CRO's facilities. It is conducted by a sponsor, institution, IRB or regulatory authority.</td>
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<tr>
<td><strong>Interim Clinical Trial/Study Report</strong></td>
<td></td>
<td>A report of intermediate results and their evaluation based on analyses performed during the course of a trial.</td>
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<tr>
<td><strong>Investigational New Drug</strong></td>
<td>IND</td>
<td>A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.</td>
</tr>
<tr>
<td><strong>Investigator's Brochure</strong></td>
<td>IB</td>
<td>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.</td>
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<tr>
<td><strong>Legally Acceptable Representative</strong></td>
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<td>An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial.</td>
</tr>
<tr>
<td><strong>Material Transfer Agreement</strong></td>
<td>MTA</td>
<td>A written agreement entered into by a <em>provider</em> and a <em>recipient</em> of research material, aimed at protecting the intellectual and other property rights of the provider while permitting research with the material to proceed.</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td>All individuals from the ages of birth until the legal age of adulthood which is 18 years in Kenya.</td>
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<tr>
<td><strong>Monitor</strong></td>
<td></td>
<td>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.</td>
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<tr>
<td><strong>Monitoring Report</strong></td>
<td></td>
<td>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.</td>
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<tr>
<td><strong>Multi-centre Trial</strong></td>
<td></td>
<td>A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one Principal Investigator.</td>
</tr>
<tr>
<td><strong>Participant/study Participant</strong></td>
<td></td>
<td>An individual who participates in a clinical trial, either as a recipient of the investigational product or as a control.</td>
</tr>
<tr>
<td><strong>Phase I Clinical Trial</strong></td>
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<td>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.</td>
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<tr>
<td><strong>Phase II Clinical Trial</strong></td>
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<td>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.</td>
</tr>
<tr>
<td><strong>Phase III Clinical Trial</strong></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Phase IV Clinical Trial</strong></td>
<td></td>
<td>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.</td>
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<tr>
<td>Pre-clinical Studies</td>
<td></td>
<td>Non Human studies of product development.</td>
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<tr>
<td>Pharmacy and Poisons Board</td>
<td>PPB</td>
<td>The National legal Drug Regulatory Authority established by Cap 244 laws of Kenya.</td>
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<tr>
<td>Protocol</td>
<td></td>
<td>A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor.</td>
</tr>
<tr>
<td>Protocol Amendment</td>
<td></td>
<td>A written description of change(s) to or a formal clarification of a study protocol.</td>
</tr>
<tr>
<td>Periodic Safety Update Report</td>
<td>PSUR</td>
<td>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.</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>PI</td>
<td>An appropriately qualified person responsible for the conduct of the clinical trial. If there is more than one trial site in Kenya, there shall be a Coordinator who will be responsible for all the sites in Kenya. For clinical trials conducted in Kenya the site PI must be resident in the country. The Principal Investigator is the leader of the team and can delegate responsibilities to sub-investigators.</td>
</tr>
<tr>
<td>Quality Assurance</td>
<td>QA</td>
<td>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).</td>
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<tr>
<td><strong>Quality Control</strong></td>
<td>QC</td>
<td>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.</td>
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<tr>
<td><strong>Randomization</strong></td>
<td></td>
<td>The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.</td>
</tr>
<tr>
<td><strong>Serious Adverse Event</strong></td>
<td>SAE</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Source Data</strong></td>
<td></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Source Documents</strong></td>
<td></td>
<td>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).</td>
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<tr>
<td>Sponsor</td>
<td></td>
<td>An individual, company, institution or organization which takes legal responsibility for the initiation, management and/or financing of a clinical trial.</td>
</tr>
<tr>
<td>Sub-Investigator</td>
<td></td>
<td>Any individual member of the clinical trial team designated and supervised by the principal investigator at a trial site to perform critical trial-related procedures and/or make important trial-related decisions.</td>
</tr>
<tr>
<td>Suspected Unexpected Serious Adverse Reaction</td>
<td>SUSAR</td>
<td>A serious adverse reaction that is not Identified in practice, severity or frequency by the reference safety information.</td>
</tr>
<tr>
<td>Trial Site</td>
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<td>A facility with appropriate infrastructure to support the conduct of a specific clinical trial.</td>
</tr>
<tr>
<td>Vulnerable Study Participants</td>
<td></td>
<td>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.</td>
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INTRODUCTION

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

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

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

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

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

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

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

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

Signed

Dr. K. C. Koskei OGW

Registrar, Pharmacy and Poisons Board
SECTION ONE

1. Application Requirements

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

1.1.1. Unregistered medicines, vaccines or medical devices

1.1.2. Registered medicines where the proposed clinical trials are outside the conditions of approval for registration. These may include changes to:
   1.1.2.1.1. Clinical indications
   1.1.2.1.2. Target population(s)
   1.1.2.1.3. Routes of administration
   1.1.2.1.4. Dosage

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

1.1.4. Studies to establish Bioequivalence for registration of generic products

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

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

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

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

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

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

1.6. Applications shall be submitted to the following address:

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

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

NB Any application that does not meet the listed requirements will not be accepted or reviewed.
2. Procedures for Acceptance, Review and Approval of Applications

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

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

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

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

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

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

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

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

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

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

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

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

3. Qualifications and Responsibilities of Investigators, Sponsors and Monitors

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

3.2. For multi site studies in Kenya, the coordinating investigator, should be a Kenyan resident and should assume full responsibility for the trial.
3.3. The medical doctor in the study team responsible for the clinical care of patients in a trial should be duly registered by Kenya Medical and Dentists Practitioners Board.

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

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

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

4. Investigator

4.1. Investigators shall satisfy the following:

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

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

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

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

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

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

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

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

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

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

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

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

4.5. Medical Care of Trial Subjects

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

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

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

4.5.4. The subject should be informed when medical care is needed for intercurrent illness for which the investigator becomes aware.

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

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

4.5.7. The investigator shall not implement any deviation from or changes to the protocol and Informed Consent Form without prior review and approval of the PPB and ERC except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes or is based on issues relating to the immediate safety of subjects already recruited into the trial.

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

4.5.9.1. The IP(s) should be kept by a Pharmacist who shall maintain records of the delivery process and who ensures that the product is processed and stored correctly.
4.5.9.2. The Pharmacist should maintain an inventory of the IP at the site, those used by each subject and the return to sponsor or alternative disposition of unused product(s).

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

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

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

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

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

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

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

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

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

5. Sponsor

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

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

5.3. 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.

5.4. 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.

5.5. 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.

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

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

5.8. The Sponsor shall obtain the investigator’s/institutions’ agreement on the following items:

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

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

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

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

5.11. The Sponsor shall ensure that the IP’s (including active comparator(s) and placebo) is manufactured in accordance with Good Manufacturing Practices and are adequately packed and labelled in a manner that protects the blinding if applicable. In addition the labelling should comply with the regulatory requirements.

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

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

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

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

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

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

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

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

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

5.21. When the trial is completed, the sponsor should submit a preliminary report to PPB within 30 (thirty) days and final report within 90 (ninety) days.

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

5.23. Capacity building may include, but is not limited to, the following activities:
   5.23.1. Developing technologies appropriate to health-care and biomedical research,
   5.23.2. Training of research and health-care staff,
   5.23.3. Educating the community from which research subjects will be drawn.

5.24. External sponsors are ethically obliged to ensure the availability of:
   5.24.1. health-care services that are essential to the safe conduct of the research treatment of subjects who suffer injury as a consequence of
5.24.2. Services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned

6. Clinical Trial Protocol

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

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

6.2.1. General Information

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

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

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

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

6.2.1.5. 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.

6.2.1.6. 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).

6.2.1.7. 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.

6.2.2. Background Information

6.2.2.1. Justification and need for the study.

6.2.2.2. Name and description of the investigational product(s), including;
6.2.2.3. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

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

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

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

6.2.2.7. Description of the population to be studied.

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

6.2.3. **Trial Objectives and Purpose**

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

6.2.4. **Trial Design**

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

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

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

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

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

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

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

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

6.2.4.9. 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.

6.2.5. **Selection and withdrawal of study participants**

6.2.6. This will include:
6.2.6.1. Inclusion criteria.

6.2.6.2. Exclusion criteria.

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

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

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

6.2.6.6. Whether and how participants are to be replaced.

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

6.2.7. Treatment of study participants

6.2.7.1. 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.

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

6.2.7.3. 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).

6.2.7.4. Procedures for monitoring participant’s compliance.

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

6.2.8. Assessment of Efficacy

6.2.8.1. This will include:


   6.2.8.1.2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.
6.2.9. **Assessment of Safety**

6.2.9.1. This will include:

6.2.9.1.1. Specification of safety parameters.
6.2.9.1.2. The methods and timing for assessing, recording, and analyzing safety parameters.
6.2.9.1.3. Procedures for eliciting reports of and for recording and reporting adverse events and co-occurring illnesses.
6.2.9.1.4. The type and duration of the follow-up of subjects after adverse events.
6.2.9.1.5. A clear description of study procedures and quantities of any body fluids to be collected for study analysis.

6.2.10. **Statistics**

6.2.11. This will include:

6.2.11.1. Frequency of DSMB or SMC meetings if applicable.
6.2.11.2. A description of the statistical methods to be employed, including timing of any planned interim analysis (es).
6.2.11.3. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.
6.2.11.4. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
6.2.11.5. The level of significance to be used.
6.2.11.6. Criteria for the termination of the trial.
6.2.11.7. Procedure for accounting for missing, unused, and spurious data.
6.2.11.8. 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).
6.2.11.9. Procedures for reporting any protocol violations.
6.2.11.1.10. The selection of study participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

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

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

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

6.2.11.1.14. The level of significance to be used.

6.2.11.1.15. Criteria for the termination of the trial.

6.2.11.1.16. Methods for data analyses and evaluation of results.

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

6.2.11.1.18. 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).

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

6.2.12. Direct Access to Source Data/Documents

6.2.12.1. 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.

6.2.13. Quality Control and Quality Assurance

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

6.2.13.2. 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.

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

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

6.2.13.5. Choice of investigators

6.2.13.6. Monitors and monitoring plan
7. Research Involving Children

7.1. Before undertaking research involving children, the investigator must ensure that:
7.1.1. The research might not equally well be carried out with adults;
7.1.2. The purpose of the research is to obtain knowledge relevant to the health needs of children;
7.1.3. A parent or legal representative of each child has given permission;
7.1.4. The agreement (assent) of each child has been obtained to the extent of the child’s capabilities; and,
7.1.5. A child’s refusal to participate or continue in the research will be respected.
7.1.6. Pediatric patients should be given medicines that have been appropriately evaluated for their use.

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

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

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

7.5. The decision to proceed with a pediatric development program for a medicinal product should be determined by:
7.5.1. the prevalence of the condition to be treated in the pediatric population
7.5.2. the seriousness of the condition to be treated
7.5.3. the availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments
7.5.4. whether the medicinal product is novel or one of a class of compounds with known properties
7.5.5. whether there are unique pediatric indications for the medicinal product
7.5.6. the need for the development of pediatric-specific endpoints
7.5.7. the age ranges of pediatric patients likely to be treated with the medicinal product
7.5.8. unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues
7.5.9. potential need for pediatric formulation development

7.6. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.
7.7. Pharmacokinetic studies should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

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

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

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

7.11. In addition to the other requirements, the application should also include:

7.11.1. Non clinical safety data
   7.11.1.1. Genotoxicity
   7.11.1.2. Reprotoxicity (fertility, pre and post natal development)
   7.11.1.3. Carcinogenicity (if required)
   7.11.1.4. Juvenile animal studies (in some cases, e.g. neonatal use)

7.11.2. Pharmaceutical properties

7.11.3. Pharmacokinetics
   7.11.3.1. Absorption
   7.11.3.2. Distribution
   7.11.3.3. Metabolism
   7.11.3.4. Excretion

7.11.4. Pharmacodynamics

7.12. Specific and General

7.12.1. In addition, the following will also be important
   7.12.1.1. The trial will provide useful answers
   7.12.1.2. The medicine fulfils a need of the population in which it is studied (“is relevant”)
   7.12.1.3. Children are adequately monitored and protected
   7.12.1.4. There is direct benefit for the child, or if no direct benefit, there is no more than minimal risk
   7.12.1.5. The trial results will be published
   7.12.1.6. There are provisions for end-of-trial treatment

7.13. Practical considerations to facilitate pharmacokinetic studies
7.13.1. The volume of blood withdrawn should be minimized in pediatric studies. Blood volumes should be justified in protocols.

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

7.13.3. Use of laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies (blood counts, clinical chemistry).

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

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

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

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

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

7.14. Efficacy

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

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

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

7.14.4. In pediatric 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.

7.15. Safety

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

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

7.15.3. Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in pediatric patients.
7.15.4. 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.

7.16. **Postmarketing information**

7.16.1. Normally the pediatric database is limited at the time of approval. Therefore, postmarketing 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 pediatric patients.

7.16.2. Postmarketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the pediatric population or additional information for the entire pediatric population.

7.17. **Ethics**

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

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

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

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

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

7.17.1.5. Insurance and indemnity measures

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

7.17.1.7. Identification of the provider and recipient

7.17.1.8. Identification of the material and the volume of material

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

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

7.17.1.11. Indemnification and warranties (where applicable)

8. **Insurance Cover**

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

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

8.3. Sponsors and Principal Investigators shall ensure insurance cover for clinical trial participants and shall submit as evidence a certificate of insurance cover for participants.
8.4. The certificate of insurance certificate must be duly executed by the insurance company under a valid insurance policy which makes explicit reference to the proposed study.

8.5. The insurance policy shall grant cover for compensation of study participants for injury which 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 which may be attributed to negligence.

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

9. Publication Policy

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

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

9.3. All publication relating to the study should be shared with PPB two weeks before going public.

10. Requirements Concerning Informed Consent

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

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

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

10.4. The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant’s consent. Any revised written informed consent form, and written information should receive ERC favourable opinion and lodged with PPB in advance of use.

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

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

10.7. The investigator, or a person designated by the investigator, should fully inform the participant or, if the participant is unable to provide informed
consent, the participant’s legally acceptable representative, of all pertinent aspects of the trial including the written information and ethics and PPB approval.

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

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

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

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

10.12. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant’s legally acceptable representative, and that informed consent was freely given by the participant or the participant’s legally acceptable representative.

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

10.13.1. That the trial involves research.
10.13.2. The purpose of the trial.
10.13.3. The trial treatment(s) and the probability for random assignment to each treatment.
10.13.4. The trial procedures to be followed, including all invasive procedures.
10.13.5. The participant’s responsibilities.
10.13.6. Those aspects of the trial that are experimental.
10.13.7. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
10.13.8. The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
10.13.9. The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
10.13.10. The compensation and/or treatment available to the participant in the event of trial-related injury.
10.13.11. The anticipated prorated payment, if any, to the participant for participating in the trial.
10.13.12. The anticipated expenses, if any, to the participant for participating in the trial.
10.14. That the participation in the trial is voluntarily and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.
10.15. That the PPB will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by PPB and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.
10.16. That records identifying the participant will be kept confidential and will not be made publicly available. If the results of the trial are published, the participant’s identity will remain confidential.
10.17. That the participant or the participant’s legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participating in the trial.
10.18. The person(s) to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.
10.19. The foreseeable circumstances and/or reasons under which the participation in the trial may be terminated.
10.20. The expected duration of participating in the trial.
10.21. The approximate number of participants involved in the trial.

10.22. Prior to participation in the trial, the participant or the participant’s legally acceptable representative should receive a copy of the signed and dated (same day as that signed for approval to participants) written informed consent form and any other written information provided to the participants. During participation in the trial, the participant or the participant’s legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants.
10.23. When a clinical trial includes participants who can only be enrolled in the trial with the consent of the participant’s legally acceptable representative (e.g., minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the participant’s understanding and, if capable, the participant should sign and personally date the written informed consent.
10.24. In emergency situations, when prior consent of the participant is not possible, the consent of the participant’s legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant’s legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented PPB approval to protect the
rights, safety and well-being of the participant and to ensure compliance with NEC and PPB requirements. The participant or the participant’s legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested. The age of ascent will be greater than 12 years but less than 18 years. Those parents less than 18 years can consent for their children to participate in clinical trials as emancipated minors.

11. The Investigator’s Brochure
11.1. The investigator's brochure must contain at least the following information in respect to the investigational medicinal product:
   11.1.1. The physical, chemical and pharmaceutical properties
   11.1.2. The pharmacological aspects including its metabolites in all animal species tested
   11.1.3. The pharmacokinetics and metabolism including its biological transformation in all animal species tested
   11.1.4. Toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study
   11.1.5. Results of clinical pharmacokinetic studies
   11.1.6. Information regarding safety, pharmacodynamics, efficacy and dose responses that were obtained from previous clinical trials in humans.
   11.1.7. More details are provided in ICH-GCP guidelines and may be followed when compiling information on this part.

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

12. Investigational New Drug (IND) Dossier
12.1. Clinical trial investigational new drug must be manufactured in accordance with Good Manufacturing Practices (GMP). This implies that the manufacture of the investigational medicinal product may be subject to GMP inspection by PPB in the same way as the case of marketed drug products.
12.2. Chemistry and manufacturing information for IND(s) which have not been registered by PPB should be presented in a concise manner and should include the following:
   12.2.1. Required details on Active Pharmaceutical Ingredient (API)
   12.2.2. Nomenclature
   12.2.3. Name and address of the manufacturer
   12.2.4. Physicochemical properties
   12.2.5. Route of synthesis and summary of manufacturing process
   12.2.6. Documented evidence of structure and stereochemistry
   12.2.7. Characterization of impurities
   12.2.8. Specifications and their justifications
   12.2.9. Batch analyses
12.2.10. Validation of analytical procedures
12.2.11. Container closure system
12.2.12. Stability studies
12.3. Required details on Investigational Medicinal Product (IMP)
12.4. Name, strength and dosage form
12.5. Description and composition
12.6. Name and address of the manufacturer
12.7. Pharmaceutical development
12.8. Description of manufacturing process including flow diagram and Controls of Critical Steps and Intermediates
12.10. Specifications and their justifications (including excipients)
12.11. Batch analyses
12.12. Validation of analytical procedures
12.13. Characterization of impurities
12.14. Certificates of analysis (CoAs) of the clinical batches of the test product, placebo and modified comparator.
12.15. Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathy (TSE) certificates for excipients of human or animal origin
12.16. Stability studies
12.17. Container closure system
12.18. If the pharmaceutical properties of the IMP have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified.
12.19. Pharmaceutical alterations in the IMP that are used in an ongoing clinical trial and that may affect the quality, safety and/or efficacy of the IMP must immediately be reported and justified to PPB.
12.20. In cases where an extension of shelf life for the IMP is desired, an application for this must be submitted to PPB. In such cases stability data must be submitted.
12.21. In case of IMP(s) which have been registered by PPB, a cross reference to the part of the dossier containing chemistry and manufacturing information should be declared.

13. Phase One Clinical Trials

13.1. Non-clinical aspects
13.1.1. Demonstration of relevance of the animal model
13.1.2. Qualitative and quantitative differences may exist in biological responses in animals compared to humans. For example, differences in affinity for molecular targets, tissue distribution of the molecular target, cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.
13.1.3. Where there is evidence of species-specificity of action from in vitro studies with human cells compared with cells from a test species, the value of the in vivo response of the test species may be significantly reduced in terms of predicting the in vivo human response. It should be
noted that a similar response in human and animal cells in vitro is not necessarily a guarantee that the in vivo response will be similar.

13.1.4. Animal studies with highly species-specific medicinal products therefore, may:
13.1.4.1. not reproduce the intended pharmacological effect in humans;
13.1.4.2. give rise to misinterpretation of pharmacokinetic and pharmacodynamic results;
13.1.4.3. not identify relevant toxic effects.

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

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

13.1.7. The demonstration of relevance of the animal model(s) may include comparison with humans of:
13.1.7.1. Target expression, distribution and primary structure.
13.1.7.2. Pharmacodynamics
13.1.7.3. Binding and occupancy, functional consequences, including cell signaling if relevant.
13.1.7.4. Data on the functionality of additional functional domains in animals, if applicable,
13.1.7.5. Metabolism and other pharmacokinetic aspects
13.1.7.6. Cross-reactivity studies using human and animal tissues (e.g. monoclonal antibodies).

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

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

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

13.2. Pharmacodynamics

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

13.2.2. A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps in order to increase the likelihood to detect significant pharmacological effects with low doses and to identify active substances with U-shaped or bell-shaped dose-response curves.
13.2.3. Since a low dose is to be administered to humans in the first-in-human trial, this is of high importance.

13.3. Pharmacokinetics

13.3.1. Standard pharmacokinetic and toxicokinetic data should be available in all species used for safety studies before going into human trials.

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

13.4. Safety Pharmacology

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

13.4.2. 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.

13.5. Toxicology

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

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

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

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

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

13.6. Estimation of the First Dose in Human

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

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

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

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

13.6.5. In order to further limit the potential for adverse reactions in humans, a safety factor may be applied in the calculation of the first dose in human. This should take into account criteria of risks such as the novelty of the active substance, its biological potency and its mode of action, the degree of species specificity, and the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL. The safety factors used should be justified.

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

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

13.7. Investigator Site Facilities and Personnel

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

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

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

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

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

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

13.7.7. 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.
13.8. **Mode of Action**

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

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

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

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

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

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

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

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

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

13.8.3. 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.

13.9. **Quality aspects**

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

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

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

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

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

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

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

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

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

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

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

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

13.10. Reliability of very small doses

13.10.1. 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.
13.11. Clinical aspects

13.11.1. General aspects

13.11.1.1. The safety of participants in first-in-human clinical trials can be enhanced by identification and planned mitigation of factors associated with risk.

13.11.1.2. Key aspects of the trial should be designed to mitigate those risk factors, including:
13.11.1.2.1. study population;
13.11.1.2.2. trial sites;
13.11.1.2.3. first dose;
13.11.1.2.4. route and rate of administration;
13.11.1.2.5. number of subjects per dose increment (cohort);
13.11.1.2.6. sequence and interval between dosing of subjects within the same cohort;
13.11.1.2.7. dose escalation increments;
13.11.1.2.8. transition to next dose cohort;
13.11.1.2.9. stopping rules;
13.11.1.2.10. allocation of responsibilities for decisions with respect to subject dosing and dose escalation.

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

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

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

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

13.12. Monitoring and communication of adverse events/reactions

13.12.1. The trial design should provide a specific plan for monitoring for adverse events or adverse reactions.

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

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

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

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

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

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

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

14. Labeling:

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

14.1.1. Statement indicating that the product is for “clinical trial purpose only”

14.1.2. Name, number or identifying mark

14.1.3. Recommended storage conditions

14.1.4. Name and address of the sponsor

14.1.5. Protocol code or identification

14.1.6. The expiry date

14.1.7. The writing “Keep out of reach of children”

14.2. Re-labeling

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

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

14.2.3. Any re-labelling of Investigational Product requires the prior approval of PPB. In general it is recommended that wherever possible investigational product is not relabelled. It is however accepted that in certain cases it is necessary to re-label and as such we will, review applications for the extension of expiry dates based on sufficient evidence being provided by the applicant that an extended expiry date is
14.2.4. It is required that re-labelling be performed in accordance with the GMP requirements “In case of use date extension, an additional label should be affixed to the investigational medicinal product. This additional label should include the new use date and repeat the batch number. It may be superposed on the old use date, but, for quality control reasons not on the original batch number. This operation may be performed on site by the clinical trial monitor(s) or the clinical trial site pharmacist, in accordance with specific and standard operating procedures and under contract if applicable. The operation should be checked by a second person. Documented evidence of this additional labelling should be available in the trial documentation and in the batch records.”

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

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

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

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

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

14.3. Sponsor responsibilities:

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

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

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

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

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

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

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

14.3.1.7. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and
characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

14.3.1.8. After the end of the trial, submit an executive summary report of the study within 30 days and submit a copy of the Clinical Study Report within 60 days. The report should conform at least to the consolidated system of reporting trials (CONSORT) unless otherwise specified in the conditions specified in the approval letter

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

14.4. **Product Accountability and Disposal:**
14.4.1. A product Accountability/Disposal report shall be submitted to PPB within 3 months from the Last Patient Out date. The report should include:
   14.4.1.1. Date(s) and quantity received for each product
   14.4.1.2. Balance of the study medication(s)
   14.4.1.3. Drug Destruction Certificate, and/or written evidence return to the used/unused drug supplies to country of origin (whichever applicable).
   14.4.1.4. PPB should be provided with a report of shipment to the sponsor of destruction of the remaining test articles

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

14.4.3. All study products will be destroyed with a written permission from the board

15. **Safety Reporting Of Suspected Unexpected Serious Adverse Reactions (SUSARS)**
15.1. Initial reports of SUSARs should be provided by the Sponsor to PPB as soon as possible but within seven calendar days of the notification of the SUSARs with follow up reports being provided within a further eight calendar days.

15.2. The SUSAR reports can be submitted to the Board through the online system at [www.pv.pharmacyboardkenya.org](http://www.pv.pharmacyboardkenya.org)

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

15.4. The SAE Log should include:
   a. Patient ID
   b. Age
   c. Type of SAE
   d. Start date of the SAE
   e. End date of the SAE
   f. Reason for reporting the event as an SAE
   g. Relation to investigational drug
   h. Outcome of the SAE

15.5. Serious / fatal reactions local are reported within seven days
15.6. Non-serious local reports are reported should be provided in the fifteen days.

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

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

15.9. All fatal cases shall be accompanied by a formal autopsy report.

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

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

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

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

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

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

15.15.1. At least 6 monthly after authorization and until the placing on the market

15.15.2. At least 6 monthly for the first two years after being placed on the market

15.15.3. Annually for the subsequent two years

15.15.4. Thereafter at three-yearly intervals

15.15.5. Immediately upon request

16. Requirements Concerning Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

16.1. The Pharmacy and Poisons Board recommends the formation of a Data Safety and Monitoring Board (DSMB) to monitor trials, the following issues related to DSMB must be submitted to PPB:

16.1.1. Composition of DSMB or SMC

16.1.2. Copy of the DSMB/SMC Charter

16.1.3. DSMB or SMC reports which should be submitted to PPB within two weeks of the deliberations.

17. Protocol Amendments

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

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

17.3. PPB acknowledgment must be obtained for all amendments especially
the following:
17.3.1. Changes that affect patient selection and monitoring
17.3.2. Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
17.3.3. Changes that affect patient discontinuation
17.3.4. Addition/removal of an investigational site
17.3.5. Change of Principal Investigator
17.3.6. Changes that result in the extension of duration of a trial

18. Information on Ongoing Trials

18.1. The sponsor and/or PI must submit progress reports to PPB on an annual basis from the date of initiation of the clinical trial. The progress report should contain:
18.1.1. Copy of the progress report that should contain among others; the current status of the study, summary of the patients screened, failed screening, enrolled, withdrawn, lost to follow-up, and challenges
18.1.2. Summary of protocol violations and protocol violations
18.1.3. Updated IB of the investigational product
18.1.4. Number of trial subjects enrolled.
18.1.5. Copy of the latest DSMB report
18.1.6. Copy of favourable opinion from the IEC of record.
18.1.7. SAE Log that should include
   18.1.7.1. Patient ID
   18.1.7.2. Age
   18.1.7.3. Type of SAE
   18.1.7.4. Start date of the SAE
   18.1.7.5. End date of the SAE
   18.1.7.6. Reason for reporting the event as an SAE
   18.1.7.7. Relation to investigational drug
   18.1.7.8. Outcome of the SAE
18.2. The request for annual approval must be submitted at least six weeks before the expiry of the granted approval.
18.3. The applicant must receive an acknowledgement of this submission before proceeding with the study. These documents must be submitted to PPB at least six weeks before the expiry of the previous approval.
18.4. In addition, for multi site trials in Kenya, the Sponsor must submit a summarised report for all the sites that should contains the above.

19. Post Trial Information

19.1. A Final Report shall be submitted to the PPB at the end of the trial.
19.2. 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 120 days of the study closure.
19.3. The Board shall be informed of any results that will be publicly released at least 14 days before this information is publicly released
19.4. PPB shall conduct a review that shall include scrutiny of Interim
20. **Inspections**

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

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

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

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

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

20.6. 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.

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

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

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

20.7.3. All amendments to the Protocol have been approved.

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

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

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

21. **Termination of Clinical Trial**

21.1. **Premature termination:**

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

21.1.2. 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

21.1.2.1. As soon as possible, inform all co-investigators of the termination and of the reasons for the termination and advice them in writing of potential risks to the health of clinical study participants or other
persons including ensuring that patients continue to receive medical care.

21.1.2.2. 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.

21.2. Withdrawal of PPB approval:

21.2.1. 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.

21.3. End of trial (Study closeout):

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

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

21.3.3. The structure and content of the final study report should be as provided in the ICH guidelines.

22. Archiving

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

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

22.3. 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.

22.4. The study documents shall be archived for a minimum of seven years from the end of the study.

23. Conditions for Clinical Trial Import Licence

23.1. Endorsement of Clinical Trial Import License

23.1.1. 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.

23.1.2. 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.

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

23.1.4. 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.

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

23.1.6. Change of Information

23.1.7. 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.

23.2. Discontinuation of Trial

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

24. Kenya Clinical Trials Registry

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

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

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

25. Sanctions

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

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

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

25.1.3. Black listing non-compliant Sponsor or Principal Investigator

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

25.1.5. Refusal to issue import permit of the study medications

25.1.6. Suspension of the study

25.1.7. Stopping of the study

25.1.8. Fining
SECTION TWO

HERBAL PRODUCTS

1. Chemistry-Manufacturing-Control (CMC) Considerations for Herbal Products

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

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

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

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

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

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

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

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

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

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

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

**HERBAL SUBSTANCE:**

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

**HERBAL PRODUCT:**

1. Amount of active ingredient
2. List of excipients
3. Type of product (tablet, capsule, etc.) and its method of manufacture
4. Analysis of putative active ingredient(s) via chemical or biological parameters
5. Analysis of a sizeable chemical constituent (analytical marker compound)

**Information on the herbal product proposed for phase 3 studies**

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

**HERBAL SUBSTANCE:**

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

**HERBAL PRODUCT:**

1. As above for phase 1/2 trials.
16. Pre-Clinical Considerations for Herbal Products

Introduction: Information needed for a conventional drug

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

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

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

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

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

Information needed to support a clinical trial for a herbal product

Efficacy

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

Toxicology

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

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

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

**Pharmacokinetics**

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

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**2. Clinical Considerations for Herbal Products**

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

**Introduction: Information needed for a standard intervention**

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

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

**Important note on Phase I, Phase II and Phase III Trials**

Development of safe and effective herbal products requires subjecting all such product to the different phases of clinical investigation of a new investigational product. The purpose of a clinical trial is to evaluate an intervention for a clinical condition. Positive (or negative) data can lead to a recommendation to use (or not to use) the treatment. Use of a suboptimal dose that is safe but ineffective does not serve the needs of the community. Although the trial indicates only if the particular tested dose of the intervention was ineffective, the community may conclude that all doses of the intervention are ineffective and patients will be denied possible benefits from the intervention. The inappropriate rejection of an intervention, “because phase 2 studies did not precede a phase 3 trial, and a suboptimal dose was used in the phase 3 trial”, is common for herbal medicines. For some herbal products, there may exist previous research that has determined the optimum dose for a treatment. For others, dose-ranging phase 2 studies will need to be performed prior to beginning more extensive phase 3 studies. Therefore, if the scientific literature does not contain scientifically valid dose-ranging data, the investigator should first perform phase 2 trials to generate these data.

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

**Information needed to support phase 2 trials**

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

Examples of safety parameters are:

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Safety parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>lack of neurologic symptoms</td>
</tr>
<tr>
<td>Skin</td>
<td>clinical evidence of lack of allergic reactions</td>
</tr>
</tbody>
</table>
Musculoskeletal: lack of arthritis or myalgias, normal values of CPK

Gastrointestinal: clinical evidence of tolerability

Liver: normal values of SGOT or SGPT, alkaline phosphatase, Total bilirubin,

Kidney: normal values of BUN or creatinine

Endocrine system normal values of albumin or total protein, uric acid, glucose, cholesterol, amylase or lipase, sodium/potassium, calcium

Cardiovascular: normal EKG and blood pressure

Hematopoietic: normal values of complete blood count

Additionally: more intensive investigation of any organ system likely to be particularly affected by the product

**Information needed to support phase 3 trials**

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

- Preliminary efficacy data from phase 2 trials.

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

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

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

To be completed by the Sponsor or Sponsor's representative.  
(To be submitted along with the necessary protocol as indicated in the GUIDELINES FOR APPLICATIONS TO CONDUCT CLINICAL TRIALS IN KENYA.)

<table>
<thead>
<tr>
<th>Study Title:</th>
</tr>
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<tbody>
<tr>
<td>Public Title:</td>
</tr>
<tr>
<td>Protocol No:</td>
</tr>
<tr>
<td>Version No:</td>
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<tr>
<td>Date of Protocol:</td>
</tr>
<tr>
<td>Study Drug:</td>
</tr>
<tr>
<td>ECCT Ref number (if applicable):</td>
</tr>
<tr>
<td>Sponsor:</td>
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<tr>
<td>Contact Person:</td>
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<tr>
<td>Address:</td>
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<tr>
<td>Telephone Number:</td>
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<td>Fax Number:</td>
</tr>
</tbody>
</table>

## TICK AND PROVIDE NECESSARY DETAILS AS APPROPRIATE

### 2. NUMBER OF SITES

- **Single site in Kenya:**  
  - yes □ no □  
  - If yes, name of site:  
  - If yes, list the sites:

- **Multiple sites in Kenya:**  
  - yes □ no □  
  - Number of sites anticipated in Kenya ( )  
  - If yes, list the sites:

- **Multiple countries:**  
  - yes □ no □  
  - Number of countries anticipated in the trial ( )  
  - If yes, list the countries:

- **Does this trial have a data monitoring committee?**  
  - yes □ no □
3. PARTICIPANTS (SUBJECTS)

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

4.0 AGE SPAN

Less than 18 years
   If yes specify:
      In Utero
      Preterm Newborn Infants (up to gestational age < 37 weeks)
      Newborn (0-28 days)
      Infant and toddler (29 days - 23 months)
      Children (2-12 years)
      Adolescent (13-17 years)

18 years and over
   Adult (18-65 years)
   Elderly (> 65 years)

5.0 DESIGN OF THE TRIAL

Controlled
   If yes, specify:
      Randomised
      Open :
      Single blind :
      Double blind:
      Parallel group:
      Cross over :
         Other :

If yes to other specify:

If controlled, specify the comparator:

Other medicinal product(s)
Placebo
Other

If yes to other, specify:

6.0 GROUP OF TRIAL SUBJECTS
Healthy volunteers | yes □ no □
Patients        | yes □ no □

**Specific vulnerable populations**

Women of child bearing potential | yes □ no □
Women of child bearing potential using contraception | yes □ no □
Pregnant women | yes □ no □
Nursing women | yes □ no □
Emergency situation | yes □ no □
Subjects incapable of giving consent personally | yes □ no □
If yes, specify:
Others: | yes □ no □

If yes, specify

### 7.0 GENDER

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<tr>
<td>Female</td>
<td>□</td>
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<tr>
<td>Male</td>
<td>□</td>
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</table>

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

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

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

- Given name
- Middle name, if applicable
- Family name
- Qualification
- Professional address
10.0 ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED TRIAL RELATED DUTIES AND FUNCTIONS (repeat as needed for multiple organisations)

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

Repeat as necessary for multiple organisations:
Organisation:
Name of contact person:
Address:
Telephone number:
All tasks of the sponsor  yes □  no □
Monitoring  yes □  no □
Regulatory (e.g. preparation of applications to PPB & ethics committee)  yes □  no □
Investigator recruitment  yes □  no □
IVRS – treatment randomisation  yes □  no □

12.0 PRINCIPAL EXCLUSION CRITERIA

SUSAR reporting  yes □  no □
Quality assurance auditing  yes □  no □
Statistical analysis  yes □  no □
Medical writing
   Other duties subcontracted  yes □  no □
If yes to other please specify:

11.0 PRINCIPAL INCLUSION CRITERIA

List them here;

13.0 PRIMARY END POINT(S):

List them here;

14.0 SCOPE OF THE TRIAL – Tick all boxes where applicable
### 15.0 TRIAL TYPE AND PHASE

<table>
<thead>
<tr>
<th>Type and Phase</th>
<th>□</th>
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<tbody>
<tr>
<td>Human pharmacology (Phase I)</td>
<td>□</td>
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<tr>
<td>Is it:</td>
<td></td>
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<tr>
<td>First administration to humans</td>
<td>□</td>
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<tr>
<td>Bioequivalence study</td>
<td>□</td>
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<tr>
<td>Other :</td>
<td></td>
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<tr>
<td>If other, please specify</td>
<td></td>
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<tr>
<td>Therapeutic exploratory (Phase II)</td>
<td>□</td>
</tr>
<tr>
<td>Therapeutic confirmatory (Phase III)</td>
<td>□</td>
</tr>
<tr>
<td>Therapeutic use (Phase IV)</td>
<td>□</td>
</tr>
</tbody>
</table>

### 16.0 DESIGN OF THE TRIAL
### Controlled

If yes, specify:

- **Randomised**
- **Open**
- **Single blind**
- **Double blind**
- **Parallel group**
- **Cross over**
- **Other**

If yes to other specify:

If controlled, specify the comparator:

- **Other medicinal product(s)**
  - **Placebo**
  - **Other**

If yes to other, specify:

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

- **Is there a placebo:**
- **Pharmaceutical form**:

### 18.0 Details of Site(s)
<table>
<thead>
<tr>
<th>Name of site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical address</td>
</tr>
<tr>
<td>Contact details</td>
</tr>
<tr>
<td>Contact person</td>
</tr>
</tbody>
</table>

**19.0 Capacity of Site(s):**

Number of staff, names, qualifications, experience -- including study co-ordinators, site facilities, emergency facilities, other relevant infrastructure)

**20.0 OTHER DETAILS**

20.1 If the trial is to be conducted in Kenya and not in the host country of the applicant / sponsor, provide an explanation:

20.2 Estimated duration of trial:

20.3 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application:

20.4 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country:

20.5 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection:

5.6 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities:
Annex 2

Application Requirements

The following are the requirements when submitting a clinical trial application.
1. Completed application form
2. Cover letter
3. Protocol
4. Patient Information leaflet and Informed consent form
5. Investigators Brochure/Package inserts or Investigational Medicinal Product Dossier (IMPD)
6. GMP certificate of the investigational product
7. Signed investigator(s) CV(s)
8. Evidence of recent GCP training of the core staff
9. Copy of annual practice licences of the investigators and pharmacists
10. Financial declaration by Sponsor and/or PI
11. Signed Declaration by Sponsor or Principal investigator that the study will be carried out according to protocol and applicable laws and regulations.
12. Indemnity cover for the PI and Investigators
13. Insurance Certificate for the participants
14. Copy of favourable opinion letter from the local Institutional Review Board (IRB) and Ethics committee.
15. Copy of approval letter(s) from collaborating institutions
16. A signed statement by the applicant indicating that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading.
17. Where the trial is part of an international study, sufficient information regarding the other participating countries and the scope of the study in these countries.
18. For multicentre/multi-site studies, an addendum for each of the sites should be provided that should include among other things the site’s capacity to carry out the study i.e personnel, equipment, laboratory etc
19. Upon initial application Registration at the clinical trial registry at www.ctr.pharmacyboardkenya.org
20. Payment of application fee as prescribed below

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

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

NB: All controlled documents must be referenced with Version Control and Date.
Annex 3

Declaration by applicant:

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

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

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

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

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

__________________________________________  _______________

Name, Position and Contact details  Date
(Local contact)

__________________________________________  _______________

Name and Contact details  Date
Principal Investigator  
National Co-ordinating PI
Annex 4

Declaration of Financial Disclosure/Conflict Of Interest

REPUBLIC OF KENYA
MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD

Telegrams: "MINIHEALTH", Nairobi
Phone: Nairobi 020 2716905/6, 3562107
Cellphone: 0733 – 884411/0720608811
Fax: 2713409

PHARMACY AND POISONS BOARD HOUSE
LENANA ROAD
P.O. BOX 27663-00506
NAIROBI

DECLARATION OF FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

<table>
<thead>
<tr>
<th>Protocol Title:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number:</td>
<td></td>
</tr>
<tr>
<td>Study Site(s) Identification:</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td></td>
</tr>
<tr>
<td>Name of Person Completing this form:</td>
<td></td>
</tr>
<tr>
<td>Study Role of person completing this form:</td>
<td></td>
</tr>
<tr>
<td>Study Sponsor:</td>
<td></td>
</tr>
<tr>
<td>Study Funded By:</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I hold a significant equity interest in the Sponsor or Funding Company of the applied/listed clinical trial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
$50,000.
If “True” please describe:

I am in receipt of significant payments of other sorts, the total of which exceeds USD $25,000, EXCLUDING the costs of conducting the trial or other clinical trials.

This could include, for example, payments made to the investigator or the institution to support activities (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).
If “True” please describe:

I hold a proprietary or financial interest in the test product such as a patent, trademark, copyright (including pending applications), or licensing agreement.
If “True” please describe:

I have financial arrangements whereby the value of the compensation could be influenced by the outcome of the trial.

This could include, for example, compensation that is explicitly greater for a favourable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest.
If “True” please describe:

To your knowledge, would the outcome of the study benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?
If “True” please describe:

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information (including changes to my financial interests and arrangements, or those of my spouse(s) and dependent children), I will promptly notify Pharmacy and Poisons Board and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the course of the trial or within one year after trial completion up to the publication of the final results.

Signature:  
Date:  

Full Names of Clinical Investigator:
This guidance should be followed unless it is otherwise justified in an application to the PPB.

References

5. Guidelines for Application to Conduct Drug Related Clinical Trials in Malaysia.
6. *www.clinicaltrials.gov*
7. ICH - GCP Guidelines for Clinical Trials. *http://www.ich.org*
8. EMA Note for Guidance on Clinical Investigation of Medicinal Products in The Paediatric Population (Cpmp/Ich/2711/99)
9. Guidelines for Good Clinical Practice In Ghana