RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR CLINICAL TRIAL APPLICATION IN RWANDA

FEBRUARY, 2021

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GUIDELINES DEVELOPMENT HISTORY

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018, specifically in article 8, paragraph 7 and 12 to regulate and inspect clinical trials.

Reference to the provisions of the technical regulation N^{o} CBD/TRG/015 Rev_0 governing the conduct of clinical trials, the Authority Issues *Guidelines N^{o} DIS/GDL/033* on clinical trial application.

These guidelines have been developed to provide guidance to the applicants and the Authority in preparation and managing applications for clinical trials. These guidelines were developed in reference to the existing guidelines of World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Good Clinical Practices (ICH E6) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

Dr. Charles KARANGWA
Ag. Director General

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ACCRONYMES AND ABBREVIATIONS

AE:	Adverse Event
API:	Active pharmaceutical Product
AVAREF:	African Vaccine Regulatory Forum
CIOMS:	Council of International Organization for Medical Science
CRO:	Contract Research Organization
CRF:	Case report form
CTA:	Clinical Trial Application
CTA-A:	Clinical Trial Application for Amendment
DSMB:	Data Safety and Monitoring Board
EUAL:	Emergency Use Assessment and Listing Procedure
FPP:	Finished pharmaceutical Product
GCP:	Good Clinical Practice
GLP:	Good laboratory Practice
GMP:	Good Manufacturing Practice
IB:	Investigator's Brochure
ICH:	International Conference on Harmonization
ICFs:	Informed Consent Forms
IRB:	Institutional Review Board
IP:	Investigational Product
MTA:	Material Transfer Agreement
NDA:	New Drug Application
QOS:	Quality Overall Summary
PI:	Principal Investigator
RNEC:	Rwanda National Ethics Committee
Rwanda FDA	Rwanda Food and Drugs Authority
SAE:	Serious Adverse Event
SmPC:	Summary of product characteristics
SUSARs:	Suspected Unexpected Serious Adverse
VICH:	Veterinary International Conference for Harmonization
WHO:	World Health Organisation

1.0. GLOSSARY

In these guidelines, unless the context otherwise states:

''An applicant'' means the Sponsor or Principal Investigator who was issued a Clinical Trial Certificate. The applicant shall therefore be responsible for signing the application form.

"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law N^{o} 003/2018 of 09/02/2018.

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

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

"Applicable Regulatory Requirement(s)" Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

"Assent" A process by which a child, who is capable of understanding 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 child's decision to participate. Assent is documented by means of a written, signed and dated assent form from the child. As part of the assent process, parents and guardians must give informed consent.

"Audit" A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol and applicable standard operating procedures (SOPs), the Authority and ICH-GCP requirement(s).

"Blinding/Masking" A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware; and double-blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).
"Child" A person who is below eighteen (18) years of age or the definition of child as defined in the laws currently enforced in Rwanda.

"Case Report Form" A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each study participant.

"Clinical Trial/ Study" Any investigation in human study participants 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.

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

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

"Data and Safety Monitoring Board" An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints and to recommend to the sponsor whether to continue, modify, or stop a trial.

"Documentation" All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

"Drug/Medicine" includes:

1. A substance or mixture of substances prepared, sold or represented for use in:
   i. Restoring, correcting or modifying organic functions in man, and
   ii. The diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it, in man, or
2. Nutritional supplements
   Concentrated sources of nutrients or other substances produced in a pharmaceutical dosage form such as tablets, gelatine capsules (soft or hard), sachets, syrups and powders. Dietary components include herbs, vitamins and minerals (with concentration less than the recommended daily allowance), natural oils, royal jelly, pollen and bee propolis. All these ingredients can be included in dietary supplements on the condition that their sole function is supplementation and improvement of body function.

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

"Ethical Clearance" An authorization to conduct a clinical trial issued by the Rwanda National Ethics Committee (RNEC) or Institutional Review Boards (IRB) based on ethical issues related to trials involving human participants in Rwanda.

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

"Good Manufacturing Practice (GMP)" The part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorization.

"Impartial witness" A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the Informed Consent Form and any other written information supplied to the participant.

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

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

"Institutional Review Board/Independent Ethics Committee (IRB/IEC)" An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of trial participants.

''Investigational medicinal Product" A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

"Investigational Veterinary Product" Any biological or pharmaceutical form of, or any animal feed containing one or more active substances being evaluated in a clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

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

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

"Legal representative" The name given to describe the executor, administrator or the person who looks after another person's affairs.

"Materials Transfer Agreement" An MTA is a written contract that governs the transfer of tangible research materials or biological samples between parties.

"Monitor" The person responsible for ensuring that the study is performed at the agreed progression and that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, GLP and the Authority requirement(s).

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

''Non-substantial amendment" means changes to the details of a trial study which have no significant implications for the study participants, conduct, management and scientific value of the research

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

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

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

"Phase IV studies" Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing

authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

"***pharmaceutical product***" any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions.

"Placebo" An inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure.

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

"Principal Investigator" A person responsible for the conduct of the clinical trial at a trial site who is a physician, dentist or other qualified person, resident in Rwanda and a member of good standing of a professional body. If a trial is conducted by a team of individuals at a trial site, the principle investigator is the responsible leader of the team. See also Sub-investigator.

"Protocol" A document that describes the objective(s), design, methodology, statistical considerations and organization of a trial. The protocol usually also gives the background and rationale for the trial but these could be provided in other protocol referenced documents.

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

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

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

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

"Sponsor-Investigator" An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a study participant. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

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

"***Substantial amendment***": means change to the terms of the protocol or any other trial supporting documentation that is likely to have significant impact and affect the safety and integrity of trial participants, the scientific value of the research, the conduct or management of the research, and the quality or safety of any investigational medicinal product used in research.

"The Law" means Law No. 003/2018 of 09/02/2018 establish Rwanda Food and Drugs Authority and Determining its Mission, Organization and Function.

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

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

2.0. INTRODUCTION

Clinical trials are planned scientific investigations conducted in humans and animals to gather information on the safety and efficacy of medical products and health technologies. Such experiments involve the administration of investigational products in patients, healthy volunteers or animal species to generate data which can later on be used for marketing authorization of a product. The regulatory authority mandated to regulate the conduct of clinical trials in Rwanda is Rwanda Food and Drugs Authority (Rwanda FDA).

These guidelines highlight requirements that need to be followed by Investigators and Sponsors when submitting their applications for approval to conduct clinical trials in Rwanda. Good Clinical Practice (GCP) principles and other ethical considerations are also detailed with the aim of ensuring that trial participants are protected and safeguarded against any harm that might arise as a result of participating in clinical trials.

The guidelines are arranged in a modular format as adopted from the ICH guidelines to allow consistent and uniform documentation of submissions. These will in-turn pave-a-way for speedy assessment of applications by the Authority and ultimately decisions on approval/non-approval based on clear and transparent criteria.

These guidelines have been developed to assist applicants to prepare applications for authorization of their clinical trials in Rwanda. The document is divided into different modules as follows:

- **Module 1: Administrative and General Information**
- **Module 2: Overview and Summaries**
- **Module 3: Data on Quality**
- **Module 4: Non-Clinical Study Reports**
- **Module 5: Clinical Study Reports**
- **Module 6: Veterinary Clinical Trials**
- **Module 7: Medical Devices and Diagnostics Clinical Trials**

Applicants should submit their applications as per the Modules and the Common Technical Document (CTD) highlighted in these guidelines. Information in these Modules should be presented in relevant sections. The overall organization of the CTD format should not be modified.

3.0. SCOPE

These Guidelines are addressed to investigators, the pharmaceutical industry, Clinical Research Organizations (CROs) and sponsors of clinical trials, whether for academic purposes or for generation of data, intended for inclusion in the regulatory submissions for investigational products. They will be applicable to all clinical trials applications which have been applied to the Authority for approval before the initiation of any clinical trial. However, a new application for clinical trial conduct in Rwanda is required for the following categories of products/ circumstances:

1. New Medicines, Vaccines and other biological products, herbal medicines, cosmetics, medical devices and diagnostics for which safety/efficacy profile has not been determined;
2. A clinical investigation of a non-CE-marked (Certificate of European) medical device in the following circumstances:
3. The introduction of a completely new concept of device into clinical practice where components features and/or methods of action, are previously unknown;
    a) Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body, in which case compatibility and biological safety will need to be considered;
    b) Where a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function;
    c) Where in vitro and/or animal testing of the device cannot mimic the clinical situation
4. Registered medicines, vaccines and other biological products, herbal medicines, cosmetics, medical devices and diagnostics where the proposed clinical trials are outside the conditions of approval. These may include changes to:
    a) Indications and clinical use
    b) Target patient or animal population(s) e.g. Age group and race.
    c) Routes of administration
    d) New dosage scheme/regimen.
    e) The intended use of a device(s)
    f) New combination drug products
    g) New drug delivery/release system
5. Academic clinical trials: clinical trial not funded by pharmaceutical or biotechnology company for commercial ends but by public-good agencies (usually universities or medical trusts) to advance medicine.

MODULE I: ADMINISTRATIVE AND GENERAL INFORMATION

This section describes administrative and application procedures. Applicants are therefore advised to read carefully this section before compiling dossiers and assemble applications ready for submission to the Authority. Module I should contain all administrative documents (for example, application forms and certifications), labelling, general correspondences) as needed.

All applications and supporting documents shall be in one of the official languages used in Rwanda. Participants' information sheets and Informed Consent Forms (ICFs) shall be in Kinyarwanda, English and French.

Data shall be presented in both A4 papers and in electronic format in Compact Discs (CDs). The Paper documents shall be arranged in spring file folders while electronic documents should be in word format, Times New Times, font 12. Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced.
The information/data must be compiled in accordance with these guidelines. Where information is required in the application forms its location shall be cross referenced in the submission.

1.1 CLINICAL TRIAL APPLICATION PROCESS AND REQUIREMENTS

1.1.1 Pre-Clinical Trial Application (CTA) Meeting

a) An application for a pre-CTA consultation meeting should be made by the sponsor or Principal investigator and submitted to the Authority prior to the documents submission;
b) The pre-CTA meeting creates an opportunity for the Sponsor and the Authority to deliberate on the potential study plan, address areas of conflict if any, clarification of the Clinical trial requirements prior to submission of the clinical trial application.
c) The application should include proposed date and time for the meeting, list of proposed attendees and a brief synopsis as per **Annex-6** (hard and electronic copies) of the proposed study listing questions (if any) to be addressed by the Authority, during the meeting;
d) A confirmation of the date, venue and time of meeting shall be duly conveyed to the Sponsor within thirty (30) calendar days after the receipt of meeting request.

1.1.2 Clinical Trial Application (CTA) requirements

A Clinical Trial Application made to the Authority shall be accompanied by the following:

1. Signed and dated application Letter
2. A duly filled, dated and signed clinical trial application form obtained from the Authority 's website (**Annex 1**)
3. General investigational plan

4. A Clinical Trial Protocol (detailed content as per **Annex 2**)
5. Investigator's Brochure (IB)
6. Capacity building plan including training and updating of staff involved in the trial.
7. Ethical Clearance Certificate
8. Participant Information Leaflet (PIL).
9. Informed Consent Forms (English, French and Kinyarwanda) and /or Assent Forms (if applicable).
10. Curriculum vitae (CVs) of Principal investigator and Co- investigator(s)
11. Joint declaration by Sponsor & Principal Investigator in prescribed format (**Annex-3**)
12. Evidence of accreditation of the designated Laboratories or other evidence of Good Laboratory Practice (GLP) and assay validation.
13. Letters of Access (if applicable) authorizing Authority to access related files (Drug master Files, Site Reference Files) must be submitted.
14. Investigational Product (IP) Dossier. (**Annex-4**)
15. Declarations by Principal investigator and/or Co- investigators (**Annex-5**)
16. Evidence of agreement between the Sponsor and the Principal Investigator.
17. Case Report Forms (CRFs), (hard copy or electronic)
18. Serious Adverse Events report form
19. Good Manufacturing Practice (GMP) Certificate or ISO Certificate where applicable
20. Valid Local Insurance Policy Covering trial participants
21. Signed and dated Financial Declaration
22. DSMB Membership and signed Charter
23. Signed and dated Sponsor/PI Contractual Agreement
24. Trial product labels for other trial medicines
25. Trial product package Insert/s for other trial medicines/product
26. Mock up labels for the Investigational product(s).
27. Materials Transfer Agreement (if applicable)
28. Trial site agreement (if applicable)
29. Evidence of payment of prescribed fees

1.2 DETAILS ON CLINICAL TRIAL APPLICATION REQUIREMENTS

1.2.1 Application Letter

The application letter shall be signed, dated and addressed to the following address:

The Director General
Rwanda Food and Drugs Authority
Email : info@rwandafda.gov.rw
Kigali, Rwanda.

1.2.2 Application Fees

An application shall be accompanied by a non-refundable application fee as prescribed in the Regulations N^{o} CBD/TRG/004 related to regulatory service tariff/fees and fines.
The application fees should be paid on the Rwanda FDA accounts:

- National Bank of Rwanda (BNR): **1000047658** entitled ‘’ Rwanda FDA’’ in Frw
- National Bank of Rwanda (BNR): **1000047666** entitled ‘’ Rwanda FDA’’ in USD
- Bank of Kigali (BK): **000400697209363** entitled "Rwanda Food and Drugs Authority" in Frw
- Bank of Kigali (BK): **000400697209464** entitled "Rwanda Food and Drugs Authority" in USD

The authority is not reliable for transfer charges.

1.2.3 Application Form for Clinical Trial

The application shall be submitted in duplicates and forms dated and signed by all principal investigators as per **Annex 1.**

1.2.4 Clinical Trial Protocol and Protocol Amendments

A. Clinical Trial Protocol

1.2.4.1 General Information

This shall include:

i. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
ii. Name and address of the Sponsor and monitor (if other than the Sponsor)
iii. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor.
iv. Name, title, address, and telephone number(s) of the Sponsor's medical expert (or dentist when appropriate) for the trial.
v. Name and title of the Principal Investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
vi. Name, title, address, and telephone number(s) of the other investigators designated by the PI to be responsible for some aspects of the study.
vii. 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.
viii. A clear statement on compensation and benefits package for clinical trial participants.
ix. Publication policy.

1.2.4.2 Background Information and Rationale

This shall include:

i. Name and description of the investigational product(s).
ii. A summary of findings from nonclinical studies that potentially have significance to the clinical trial
iii. Summary of findings from clinical studies/trials that are relevant to the trial.
iv. Summary of the known and potential risks and benefits, if any, to human participants.
v. Summary of the local background rates with respect to the condition for which the intervention is proposed.
vi. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
vii. Description of the population to be studied.
viii. A statement that the trial shall be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
ix. References to literature and data that are relevant to the trial and that provide background for the trial.
x. Signed declaration by the applicant and all investigators that they are familiar with and understand the protocol and shall comply with principles of Good Clinical Practice (GCP) as determined by the Authority in the conduct of the trial.
xi. Justification for the trial is being conducted in Rwanda.

1.2.4.3 Trial Purpose and Objectives

i. Aim of the trial and reason for its execution.
ii. A detailed description of the objectives and the purpose of the trial

1.2.4.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

i. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
ii. If markers are being used as endpoints, they should be validated.
iii. 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.
iv. Number of participants to be involved in the trial and the statistical justification.
v. A description of the measures taken to minimize/avoid bias, including: Randomization and Blinding.
vi. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).

vii. Description of the dosage form, packaging, and labeling of the investigational product(s) and sample of label to be used for investigational product.
viii. The expected duration of participant participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
ix. Quantities and sources of all investigational medicines and/or comparators (whether to be imported or purchased locally).
x. A detailed description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.
xi. Accountability procedures for the investigational product(s).
xii. Maintenance of trial treatment randomization codes and procedures for breaking codes.
xiii. 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.
xiv. Specifications and instructions for anticipated deviations from the protocol.

1.2.4.5 Trial Endpoints

A description of the trial design should include the primary endpoint and important secondary endpoints.

1.2.4.6 Selection and withdrawal of participants

This section shall include eligibility and withdrawal criteria of study participants:

i. Participant inclusion criteria.
ii. Participant exclusion criteria.
iii. Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
    a. When and how to withdraw participants from the trial/investigational product treatment.
    b. The type and timing of the data to be collected for withdrawn participants.
    c. Whether and how participants are to be replaced.
    d. The follow-up for participants withdrawn from investigational product treatment/trial treatment.

1.2.4.7 Treatment of Trial Participants

i. 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.
ii. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
iii. Procedures for monitoring participant compliance.

iv. Description of treatment applied to control group(s) or control period(s), placebo, and other therapy and any other treatment that may be given concomitantly including measures to be implemented to ensure the safe handling of the products.
v. Description of diagnostic devices or kits applied to be used in the clinical trial.
vi. Description of special analyses and/or tests or procedure to be carried out.

1.2.4.8 Assessment of Efficacy

i. Specification of the efficacy parameters.
ii. Methods and timing for assessing, recording, and analyzing of efficacy parameters.
iii. Clear procedures for interim assessment of trial.

1.2.4.9 Assessment of Safety

i. Specification of safety parameters.
ii. The methods and timing for assessing, recording, and analyzing safety parameters.
iii. Procedures for eliciting reports of and for recording and reporting adverse event and inter current illnesses.
iv. List of adverse events of special interest (AESI) and/or expected adverse events – information shall include:
    a. Whether event is related to the intervention or not.
    b. Rationale for listing each event
    c. Expected rate or frequency of each event
    d. Laboratory limits (if applicable)
v. The type and duration of the follow-up of participants after adverse events.
vi. Provision for dealing with all adverse events.
vii. Copy of form to be used to report adverse event.

1.2.4.10 Statistics

i. A description of the statistical methods to be employed, including timing of any planned interim analysis.
ii. The number of participants planned to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified.
iii. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
iv. The level of significance to be used.
v. Criteria for the termination of the trial
vi. Methods for data analyses and evaluation of results.
vii. Procedure for accounting for missing, unused, and spurious data.

viii. 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).

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

1.2.4.11 Ethical Consideration

General ethical consideration relating to the clinical trial and informed consent sheet or form or otherwise shall be given to the trial participants before starting any clinical trial. A valid ethical Clearance certificate shall be provided before the authority issue an authorization for clinical trial conduction in Rwanda.

1.2.4.12 Data Handling and Record Keeping

i. Procedure for keeping a list of participants and detailed records indicated on the case report form (CRF) for each individual taking part in the trial.
ii. All clinical and experimental data (electronic or paper) shall be kept in a secured place for a period of twenty (20) years for New Drug Application (NDA) after completion of the trial and be made readily available for review upon request by the Authority.
iii. The protocol, documents, case report forms, Informed Consent Forms and other trial related documents should be retained for at least ten (10) years by the sponsor; and the trial subject's documents should be retained for at least ten (10) years by the medical institution. The subject identification codes should be retained by the investigator and the sponsor for at least ten (10) years.

1.2.4.13 Publication of clinical trial report

i. Publication policy, if not addressed in a separate agreement.
ii. Publication policy, including a plan for the dissemination of the results (publishing plan)

B. Clinical Trial Protocol Amendment

1. Any amendment to an already approved trial protocol, trial arrangements and investigational product shall be submitted to the Authority for approval before such amendments are carried out. The application form for amendment (Annex-7) shall be submitted together with other supporting documents.
2. If such amendments are necessary to protect the life of participants, an urgent amendment may be carried out but the investigator shall inform the ethics committee and the Authority of such amendments with an immediate phone call, followed by a written report within forty-eight (48) hours.
3. All amendments shall be accompanied by a proof of payment of prescribed fees as per regulations N^{o} CBD/TRG/004 related to regulatory service tariff/fees and fines;
4. The sponsor may make amendments to the protocol after the commencement of the clinical trial. If those amendments are substantial and are likely to have an impact on the safety of the trial participants or to change the interpretation of the scientific documents in

support of the conduct of the trial, the sponsor shall notify the Authority of the reasons for, and content of, these amendments.

5. To the notion of "amendment" The following changes do not count as an 'amendment':
   i. A change to the documentation submitted to the Authority during the ongoing assessment of the request for authorization by the Authority, and
   ii. A change to the documentation submitted to RNEC during the ongoing assessment of the request for authorization by the Ethics Committee.
   iii. Safety Report (SR) is not considered as an amendment and thus does not have to be notified as a substantial amendment to the Authority.
   iv. A change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as an amendment, if the sponsor and legal representative remain identical. However, the sponsor should ensure that the Authority is aware of this change as soon as possible, in order to allow the Authority to exercise its supervisory function.
6. The notion of "**substantial**":
   i. Amendments to the trial are regarded as 'substantial' where they are likely to have a significant impact on:
      a) the safety, physical or mental integrity of the clinical trial participants, or
      b) the scientific value of the trial
   ii. In all cases, an amendment is only to be regarded as 'substantial' when one or both of the above criteria are met.
   iii. The responsibility of assessing whether an amendment is regarded as substantial or not lies with the sponsor.
   iv. The Authority shall however recommend a reassessment of a Sponsor's classification of an amendment when necessary.
   v. The annual update of the investigational brochure is not considered as substantial amendment. However, the sponsor has to verify whether the update relates to changes which are to be considered as substantial. In that case, the rules for notification of substantial amendments apply to the change.
   vi. The sponsor should assess also whether the combination of substantial amendments lead to changes of the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would then be subject to a new authorization procedure.
   vii. Substantial amendments may relate to information relevant for assessment by the Authority, Ethics Committee, or both.
   viii. Without prejudice to the above points, the Authority reserves the right to direct for an amendment to the protocol.
7. Format and content of notification

   The notification of a substantial amendment should include the following:
   i. A signed cover letter, including a highlighted indication of any special issues related to the amendment and indication where the relevant information or text is in the original application dossier.

ii. A description of the amendment:
   a. an extract from the amended documents showing previous and new wording in track changes, as well as the extract only showing the new wording;
   b. Notwithstanding the previous point, if the changes are so widespread or far reaching that they justify an entire new version of the document, a new version of the entire document. In this case, an additional table should list the amendments to the documents. In this list, identical changes can be grouped.
   c. The new version should be identified with the date and an updated version number.

iii. Supporting information including, where applicable:
   a. summaries of data,
   b. an updated overall risk/benefit assessment,
   c. possible consequences for participants already included in the trial, possible consequences for the evaluation of the results

1.2.5 Investigator's Brochure

Investigators Brochure containing information on the following but not limited to:

1. Chemical, physical and pharmaceutical properties and formulation
2. Preclinical studies, pharmacological and toxicological data,
3. Human pharmacological and clinical data with the substance concerned and any other supporting documentation sufficient to establish quality, safety and efficacy where applicable.
4. Marketing experience in countries where the investigational product is being marketed or approved. Where appropriate there should be discussions of published reports.
5. Sample of label to be used for the investigational products.
6. Clear instructions on storage and handling of investigational products.
7. An updated investigator's brochure should be submitted at least once a year, or whenever it is updated within this period. Additional information and any changes that have been incorporated in the updated investigator's brochure should be highlighted for ease of review and evaluation.
8. Good Manufacturing Practice (GMP) certificate/statement from the country of manufacture for the product/ placebo and ISO certificates issued by the competent Authority.
9. The Investigational Brochure should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the Investigational product (IP) in the trial and be presented in the form of summaries.
10. The approved summary of product characteristics (SmPC) may be used in place of the Investigational Brochure (IB) if the IP is authorized in Rwanda and is used according to the terms of the marketing authorization. If the conditions of use in the clinical trial differ from those authorized, the SmPC should be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IP in the clinical trial. Where the IP is identified in the protocol only by its active substance, the sponsor should

elect one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

1.2.6 Investigational Product (IP) Dossier

The IP dossier (IPD) gives information related to the quality of any IP (i.e. including reference product and placebo), manufacture and control of the IP, and data from non-clinical studies and from its clinical use. However, in many cases where the IP has a marketing authorization, an IPD is not required.

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but:

i. used or assembled (formulated or packaged) in a way different from the authorized form, or
ii. when used for an unauthorized indication, or
iii. when used to gain further information about the authorized form

1.2.7 Good Manufacturing Practices (GMP) Certificate

A valid GMP certificate and/or ISO Certificate from the competent Authority of the country of origin shall be required when the IP has no marketing authorization in Rwanda or has Marketing Authorization but its original indication is modified for the purpose of the trial.

1.2.8 Ethical Clearance

a) A valid Ethical Clearance certificate for all phases of clinical trials in humans shall be required to be submitted from the facility(ies)/institution(s) being used in the conduct of the study.
b) Ethical Clearance from the RNEC/IRB shall be required.
c) Submissions of the application to the Authority may be parallel to other review boards or committees in case of emergency. The Authority shall give its position after applicant has submitted ethical clearance.
d) In case of parallel submission, the applicant shall submit any change made to the protocol by RNEC or IRB.
e) In the case of multi-Centre or multi-country studies, an approval from each institution's or country review Authority shall be required.

1.2.9 Insurance Cover

a) All trial participants must be satisfactorily insured against possible injuries that must arise during the conduct of clinical trials.

b) Sponsors and Principal Investigators shall ensure appropriate insurance cover for clinical trial participants and shall submit as evidence a local certificate of insurance cover for participants prior to the study initiation to the Authority.

c) An insurance certificate shall contain at least the following:
   1) Insurance company
   2) Policy number
   3) Initial Date
   4) Expiry Date
   5) Insured (Policy Holder/Sponsor)
   6) Description of activity (purpose of the policy)

d) Information concerning the trial:
   1) Title of insured protocol and protocol number (if available)
   2) Number of trial sites
   3) Number of participants (planned number of patients who are expected to take part in the clinical trial)

e) Insured (list all events that are covered by the insurance policy e.g. deaths, permanent and temporary impairment of health conditions, relevant financial consequential losses which are the direct, consequence of the trial and which can be traced to the liability of all people operating for the performance of the trial). Exclusions (if provided for that specific protocol, please list all exclusions)

1.2.10 Financial Declaration

a) The financial aspects of the trial should be documented in an agreement between the Sponsor and the Principal Investigator/Contracted Research Organization/Institution.
b) A declaration must be signed by both the Sponsor and the Principal Investigator which states that there are sufficient funds available to complete the study.

1.2.11 Data and Safety Monitoring Board/Committee (DSMB/C)

1) An Independent Data Monitoring committee 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.
2) The Sponsor shall include charter of work, membership and curriculum vitae of all the DSMB members when applicable.
3) All members of the DSMB shall sign the charter
4) A DSMB Charter shall include
   a) Terms of Reference
   b) Membership and their CVs
   c) Proof of Independence of the Committee

d) Scope of work for Members/responsibilities of the Committee which is to assess the progress of a clinical trial including safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial.
e) Meeting schedules
f) Standard Operating Procedures of the Committee
g) It is recommended that at least one member of the DSMB is Rwandese.

1.2.12 Sponsor/ Principal Investigator Contractual Agreement

The Sponsor/ PI Contractual Agreement shall indicate;

a) The study title
b) Protocol version and date
c) Trial site
d) Investigational Product
e) Definitions of all terms
f) Effective date of agreement
g) Outline of the Sponsor's responsibilities which shall include
h) General management of the trial
i) Provision of adequate funding, resources/logistics and Investigational Products for the study
j) Insurance for the study participants

Outline of the PI's responsibilities which shall include

a) conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor;
b) comply with procedures for data recording/reporting
c) permit monitoring, auditing and inspection
d) retain all trial related essential documents until the sponsor informs the PI these documents are no longer needed

Term (period of study duration) and Termination of agreement (conditions for this)
Confidentiality. The Sponsor and the PI shall sign this agreement and the protocol.

1.2.13 Informed Consent and Assent

- The informed consent discussion and the written informed consent form and any other written information to be provided to trial participants shall include explanations of the following:
  1) The trial involves research
  2) The purpose of the trial
  3) The trial treatment(s) and the probability for random assignment to each treatment

4) The trial procedures to be followed, including all invasive procedures.
5) The participant's responsibilities.
6) Those aspects of the trial that is experimental, etc.
7) Signature and date of participant, participant's legal representative impartial witness (where applicable) and person administering Informed Consent

- In trials involving minors, parents/guardians of a minor shall be required to sign an Informed Consent form as above. In addition, an assent form similar to the Informed Consent Form shall also be signed and dated by a minor who is capable of understanding as a confirmation of 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 minor's decision to participate.
- The language used in the ICF shall be in English, French and Kinyarwanda

1.2.14 Materials Transfer Agreement (MTA)

Where applicable, an appropriate MTA which defines the rights, obligations and restrictions for the provider (PI) and recipient(s) (External Laboratory) with respect to the materials and any derivatives to be Transferred, as well as any confidential information exchanged with the material shall be provided.
The MTA shall specify;

a) The type of materials to be transferred
b) The local laboratory or institution from which the samples shall be transferred
c) The destination of the samples (intermediary and final destination)
d) The type of analyses to be carried out by the recipient(s)
e) Competence of the recipient(s) of the materials for the listed analyses to be carried out

The MTA shall be duly signed and dated by the Sponsor, PI and the recipient(s) of the materials at external laboratory.

1.3 CLINICAL TRIAL APPLICATION REVIEW PROCESS

1.3.1 Review of New Clinical Trial Application

The Authority's clinical trial procedure for review of new application is detailed as follows:

1) After receiving the Clinical trial application from the applicant, the Authority shall assign the Clinical trial application reference number to the application which will be communicated with applicant for future correspondences.
2) The Authority shall screen the application for completeness and compliance with the requirements
3) After screening, the Authority shall communicate to the applicant the missing documents (if any) as per clinical trial requirements stipulated in these guidelines

4) The applicant shall gather the missing requirements and submit them to the Authority within thirty (30) calendar days unless she/he requests for extension before deadline. If the applicant fails to submit the missing requirements within specified period, the application shall be considered as withdrawn by the applicant.
5) The Authority shall reviews/assess the complete application as per clinical trial assessment guidelines
6) The Authority shall send a list of queries or request for clarifications (if any) to the applicant.
7) The applicant shall submit the query responses/clarification within thirty (30) calendar days unless she/he requests for extension before deadline.
8) The Authority shall review the query responses/clarifications and if provided information is satisfactory, the authority shall proceed with the approval process of the application.
9) When the applicant repeatedly provides unsatisfactorily query responses, the Authority shall convene a face to face meeting with applicant to discuss on Authority's decision and close the application file.

1.3.2 Clinical Trial Application Review Timelines

The Authority will implement the following timelines in processing applications for clinical trials applications:

a) The review process of a new clinical trial application shall not exceed sixty (60) working days upon compliance with all requirements from the date of receipt of the completed application.
b) The review process of substantial amendment for an approved clinical trial shall be made with thirty (30) working days.

Note that the regulatory decision shall be communicated to the applicant in writing. The timelines for clinical trial review shall not include the time taken by the applicant to respond to any requests for additional information from the Authority. A stop-clock mechanism shall thus apply each time the Authority requests for additional information.

The Approval for importation of trial related medicines will be dependent on the award of the clinical trial certificate for the conduct of the clinical trial in Rwanda

1.3.3 Expedited Clinical trial evaluation

In case of public health emergencies of the international concern, the Authority shall expedite the review of products listed on Emergency Use Assessment and Listing Procedure (EUAL) and African Vaccine Regulatory Forum (AVAREF) readiness plan.

1.4 VALIDITY OF CLINICAL TRIAL AUTHORIZATION

A clinical trial approval certificate shall be valid for one (1) year period for clinical trial of less than or equal to one (1) year. In case the applicant fails to complete the trial within the planned period, she/he shall apply for renew of clinical trial approval. In case of clinical trial that goes beyond one (1) year, the clinical trial approval certificate shall be valid for one (1) year renewable.

1.5 REFUSAL OF CLINICAL TRIAL AUTHORIZATION

The Authority shall not authorize a clinical trial when it is satisfied that: -

1) The information and documents as set out in the guidelines have not been provided;
2) The application contains false or misleading information;
3) The information provided is insufficient to enable the Authority assess the safety and risks of the investigational product;
4) Queries raised by the Authority in relation to the application made to it were not adequately responded to;
5) The applicant has not submitted an ethical clearance
6) The use of the drug, medical device or herbal drug for the purposes of the clinical trial endangers the health of a clinical trial participant or any other person;
7) The objectives of the clinical trial will not be achieved;
8) It is not in the public interest to authorize the clinical trial; and
9) Any other reasonable grounds as may be determined by the Authority.

1.6 INVESTIGATION PRODUCT

1.6.1 Importation and exportation of Investigational Products

Applicants shall be required to obtain an import permit for importation of Investigational products after authorization of the trial. In case of exportation of the Investigational Products, the applicant should obtain export permit from the Authority

1.6.2 Manufacture

All investigational products (IPs), including active comparators and placebos, shall be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and evidence of this shall be submitted with the clinical trial application. In case the IP contains a narcotic or psychotropic substance, applicants must possess the necessary approval for the controlled substances.

1.6.3 Labelling of Investigational Products

The following information shall be labelled on the carton, inner label and the blisters or strips of the investigational drug product for a clinical trial:

Parameters	**Unit carton or subject kit**	**Inner Labels**	**Blister/Strips/ Vials**
Clinical Trial Protocol Number	√	√ *	√
No, of Subjects or Initial of subject	√**	√**	√**
Investigational Drug Product name or code	√	√	√
Dosage form	√	√*	√**
Name of Active substance	√	√	√
List of expients	√	√*	√*
Strength	√	√	√
Instructions for use	√**	√ **	√**
Lot number	√**	√	√
Batch number	√	√**	√**
Manufacturing date	√	√**	√
Expiry date	√	√	√
For clinical Trial use only/Cautionary statement	√	√*	√
Name and address of Manufacturer	√***	√***	√***
Route of administration	√	√	√
Storage condition	√	√	√
Pack size (Unit/Vol)	√	√	√

NA Not Applicable

* Exempted for small label such as ampoule and vial.

** Where applicable

*** With letter of authorization where it applies

If the product is supplied without an outer carton, the information that is required on the outer carton should be stated on the inner carton.

1.6.4 Use of the Investigational Products

a) The investigational product shall only be supplied to the investigator(s) at the trial site(s) for which a clinical trial approval has been issued for the purpose and use as stated in the protocol.

b) The holder of the Clinical Trial Approval shall ensure that adequate precautions are taken for all study medication(s), such as storage as per the manufacturer's prescribed storage conditions in a secure and access-controlled location, to prevent theft, misuse, accidental or

illegal distribution. Temperature and where prescribed, humidity monitoring shall be done for all areas where the IPs are stored.

1.7 SAFETY REPORTING IN CLINICAL TRIAL

1.7.1 Reporting of Serious Adverse Events (SAEs)

In line with regulations governing clinical trial in Rwanda:

1) the Principal investigator (PI) shall report to the Authority all serious adverse events (SAEs), both expected or unexpected, as soon as possible but no later than seven (7) calendar days upon receiving notice of such an event. A detailed written report on the event within a further eight (8) calendar days.
2) The Authority may require additional information in case the event reported consists of, or results in the death of a trial participant;
3) Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should also be reported
4) For reported deaths, additional information (e.g., autopsy reports and terminal medical reports) should be submitted;
5) The relationship between SUSARs and the Investigational product must be established, evaluated, clarified and submitted to the Authority for further assessment;
6) The expedited reporting is applicable for clinical trials of investigational products, comparator products and for products used in bioavailability (BA) and bioequivalence (BE) studies

1.7.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

In line with regulations governing clinical trial in Rwanda:

1. Fatal or life threatening SUSARs should be submitted not later than seven (7) calendar days after the sponsor has information that the case reported fulfils the criteria for a fatal or life-threatening SUSAR, with any follow up information to be reported within a further eight (8) calendar days;
2. The Authority may require additional information in case the event reported consists of, or results in the death of a participant;
3. For reported deaths, additional information (e.g., autopsy reports and terminal medical reports) should be submitted;
4. The relationship between SUSARs and the Investigational product must be established, evaluated, clarified and submitted to the Authority for further assessment;
5. The expedited reporting is applicable for clinical trials of investigational products, comparator products and for products used in bioavailability (BA) and bioequivalence (BE) studies.

1.8 PROGESS AND FINAL REPORT OF CLINICAL TRAL

In line with regulation governing clinical trial in Rwanda, the Principal investigator shall submit the following reports:

1. A progress report shall be submitted to the Authority during the conduct of the Clinical trial:
   c) on monthly basis for study not exceeding six (6) months,
   d) on quarterly basis for studies from seven (7) months to eleven (11) months
   e) on a six (6) months basis for one-year study and above;
2) Final Report of the Clinical Trial shall be submitted to the Authority within ninety (90) calendar days of the completion or termination of the clinical trial using the standard format as per ICH E3 (Guidelines structure and content of clinical study report);
3) Any unexpected safety issue that changes the risks-benefit analysis and is likely to have an impact on trial participants should be reported together with proposed actions to be taken.

1.9 DISCONTINUATION OF CLINICAL TRIAL

In case of clinical trial discontinuation by a sponsor or principal investigator (PI) in its entirety or at a clinical trial site, the sponsor or PI shall:

1) cause the information to reach the Authority not later than fifteen (15) calendar days after the date of the discontinuation;
2) provide the Authority with the reason for the discontinuation and its impact on the proposed or ongoing clinical trials in respect of the investigational product including issues related to accountability and disposal of investigational product;
3) inform all investigators of the discontinuation and of the reasons for the discontinuation, and advise them in writing of any potential risks to the health of clinical trial participants or other persons as soon as possible; and
4) Stop the use or importation of the investigational product as from the date of the discontinuation and take all reasonable measures to ensure the recovery of all unused quantities of the investigational product in respect of each discontinued clinical trial site.

1.10 SUSPENSION OR TERMINATION OF A CLINICAL TRIAL

In line with regulations governing clinical trial conduct in Rwanda:

1. The Authority may, by a notice in writing to the holder of authorization, suspend or terminate the authorization due to non-compliance with existing laws, regulations and guidelines;
2. The Authority may disqualify or blacklist an investigator if the Authority has information indicating that an investigator (including a sponsor-investigator) has failed to comply with laws, regulations and guidelines, or has submitted to the Authority or to the sponsor false information in any required report.
3. The Authority may suspend, terminate or withdraw authorization of a clinical trial at any

time if the conditions of authorization of a trial have been violated or if there is an information raising doubts about the safety or scientific validity of the trial, or the conduct of the trial at a particular trial site

1.11 PUBLICATION OF CLINICAL TRIAL RESULTS

The sponsor/Principal Investigator may publish the results of a clinical trial after completion. The publication may be done in peer reviewed journals, books or any other materials to allow for a wider community including study participants, to access the data/evidence generated from the trial.

Sponsors and principal Investigators may publish trial outcomes as they were originally registered in the Registry. A copy of the publication must be submitted to the Authority.

1.12 DISPOSAL OF INVESTIGATIONAL PRODUCTS

1. The Sponsor or PI is responsible for the destruction of unused and/or returned investigational products. Investigational products should therefore not be destroyed without prior written authorization by the Authority.
2. The delivered, used and recovered quantities of Investigational product should be recorded, reconciled and verified by or on behalf of the sponsor or PI for each trial site and each trial period.
2. Destruction of unused investigational products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.
3. Request to dispose investigational products shall be made to the Authority as prescribed in the Regulations for Recall, Handling & Disposal of Unfit Medicines & Cosmetics.

1.13 CLINICAL TRIAL INVOLVING SPECIAL POPULATIONS

Some for clinical trial may involve special populations. In this case the requirement may be different.

1.13.1 Vulnerable Persons and Groups

These are groups and individuals that "may have an increased likelihood of being wronged or of incurring additional harm" during clinical trials. This includes for example persons who are illiterate, marginalized by virtue of their social status or behavior, or living in an authoritarian environment, may have multiple factors that make them vulnerable. Vulnerable groups include Individuals in hierarchical relationships, Institutionalized persons, poor people and the unemployed, some ethnic and racial minorities, homeless persons, refugees or displaced persons, people living with disabilities, people with incurable or stigmatized conditions or diseases and

people faced with physical frailty. Declaration of Helsinki and CIOMS guidelines should be considered when conducting clinical trials in vulnerable groups or individuals.

1.13.2 Women

Clinical trials should enroll subjects that are representative of the population(s) expected to use the therapeutic product. Specifically:

1) It is recommended that a representative number of women be included in clinical trials for therapeutic products that are intended to be used specifically by women or by heterogeneous populations that include women.
2) It is recommended that women, including those of child-bearing potential and postmenopausal women, be included at the earliest possible stages of clinical trial research; so that potential sex-related differences are identified and taken into consideration when planning Phase III pivotal trials.
3) Although it may be reasonable to exclude certain potential subjects at early stages due to characteristics that may render evaluation of therapy more difficult (e.g. women and/or men on concomitant therapies), inclusion of such subjects is encouraged as early as possible in phases of clinical development so that therapeutic product interactions (e.g. drug-drug; natural health product-drug; natural health product- natural health product and product-disease) can be identified and assessed.
4) ICH M3 guidelines should be followed when women are to be included in clinical trials.

1.13.3 Paediatric population

Data on the appropriate use of Investigational products in the paediatric population should be generated unless the use of a specific Investigational product in paediatric patients is clearly inappropriate. The pediatric development programme should not delay completion of adult studies and availability of products for adults. The decision to proceed with a paediatric development programme for an Investigational product, and the nature of that programme, involve consideration of many factors.

In case of trials involving pediatric populations, ICH-E11 guidelines for Clinical investigations trials in pediatric population should be followed.

1.13.4 Geriatric population

Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug. The ICH guidelines for studies in support of special populations: geriatrics E7 should be followed for clinical trials that involve;

- New Investigational products that are likely to have significant use in the elderly, either because the disease intended to be treated is characteristically a disease of aging (e.g.,

Alzheimer's disease) or because the population to be treated is known to include substantial numbers of geriatric patients (e.g., hypertension).

- New formulations and new combinations of established medicinal products when there is specific reason to expect that conditions common in the elderly (e.g., renal or hepatic impairment, impaired cardiac function, concomitant illnesses or concomitant medications) are likely to be encountered and are not already dealt with in current labelling.
- New formulation or new combination is likely to alter the geriatric patient's response (with regard to safety/ tolerability or efficacy) compared with that of the non-geriatric patient in a way different from previous formulations.
- New uses that have significant potential applicability to the elderly.

1.14 CONDUCT OF CLINICAL TRIALS

Clinical trials should be conducted according to the clinical trials control regulations issued by the Authority, ICH-Good Clinical Practice guidelines. The study design, statistical considerations, choice of control groups, reporting of data and conduct of the trial should be as detailed in ICH guidelines E3-E16. Analysis of samples at the clinical laboratory shall follow WHO-Good Clinical Laboratory Practice guidelines.

1.15 ADVERTISEMENT OF CLINICAL TRIALS

Clinical trials may be advertised in order to promote the trial to the public and recruit participants.

Advertisements may be done using Information education and communication materials such as brochures, posters, banners or through televisions, radio programs, newspapers and any other media. Before such advertisements are made public, approval must be obtained from the Authority and ethics committees and must follow existing local rules and regulations.

MODULE II: SUMMARIES OF NON-CLINICAL, CLINICAL AND QUALITY DATA

This Module is applicable to phase I, II and III clinical trials that involve new Investigational Products. Clinical trials using well established Investigational products that have been registered and marketed in Rwanda are exempted to submit details on this part. Updated Investigator's brochure and prescribing information will suffice. The summaries shall be submitted in both hard and electronic formats. Note that the electronic copies must be submitted on CD-ROM, in either **MS Word** format (PDF format of the QOS is not acceptable). The organization of these summaries is described in ICH Guidelines for M4Q, M4S, and M4E.

Module 2 should contain 7 sections in the following order:

(i) CTD Table of Contents
(ii) CTD Introduction
(iii) Quality Overall Summary
(iv) Nonclinical Overview
(v) Clinical Overview
(vi) Nonclinical Written and Tabulated Summaries
(vii) Clinical Summary

2.1 CTD Table of contents

A listing of the contents of module 3 and 4

2.2 CTD Introduction

This sub-section is not applicable to Clinical Trials Applications (CTAs). This section is reserved for use during the preparation of application at later stages of development of the New Investigational Product (e.g., New Applications) and maintained to ensure consistent numbering of subsequent sections.

2.3 Investigational Product Quality Overall Summary

The documentation on Investigational Product Quality Overall Summary (IP-QOS) must be submitted in both hard copy and electronic format. Note that electronic copies must be submitted on CD-ROM, in either MS Word or Word Perfect format (PDF format of the QOS is not acceptable). This document in electronic files should be placed at the beginning of **Module 3**.

The applicant shall fill in the summary of the quality of the Investigational product in the IP Quality Overall Summary template **(Annex 4)** as well as additional Quality information as outlined in the template, should be completed as stipulated in the guidelines. The template shall

be used for clinical trials involving human and veterinary medicinal products, biologicals, medical devices and diagnostics.

For placebo-controlled studies, a qualitative list of the ingredients in the placebo should be submitted.

2.4 Non-Clinical overview

The Non clinical overall Summary overview as prescribed shall be submitted. This document must be submitted in both hard copy and electronic format. This document in electronic files should be placed at the beginning of **Module 4**.

The non-clinical overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed 30 pages. The non-clinical overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

Studies conducted to establish the pharmacodynamics effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise. The integrated overview and conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking into account the pharmacology, pharmacokinetics, and toxicology results, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling).

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

2.5 Clinical overview

This section is generally applicable to clinical trials that are in late phase of development. Available data and details will mainly be on safety studies conducted for the same Investigational product in other populations. First in human (FIH) clinical trials with no data on the effect of the Investigational product in humans are exempted to submit details on this part.

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data

provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information. The clinical Overview should be presented in the following sequence

- Product Development Rationale
- Overview of Biopharmaceutics (If applicable)
- Overview of Clinical Pharmacology
- Overview of Efficacy (If applicable)
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

2.6 Nonclinical Written and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

This section is applicable to phase I, II and III clinical trials that involve new Investigational Products. Clinical trials using well established Investigational products marketed in Rwanda are exempted to submit details on this part. Clinical trials that were conducted in Rwanda in previous phases are also exempted on this part. Updated Investigator's brochure will be enough.

2.7 Clinical Summary

This is a summary of the Investigational product experience in humans. The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which

full reports have been included in Module 5. This section is not applicable for first in human (FIH) clinical trials whose Investigational products have not been tested in humans.

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy for guidance on the content of this section.

MODULE III: QUALITY OF THE INVESTIGATIONAL PRODUCTS

3.1 Introduction to the module

This module shall describe details regarding the chemistry, manufacturing and control of the Investigational Product. Data to demonstrate quality of the investigational product including relevant batch analyses results should be attached. The data should be presented as provided in the following sections.
If a comparator medicinal product is used, the proprietary name of the medicinal product, non-proprietary name or common name of the Active Pharmaceutical Ingredient, company name, country from which the clinical supplies were obtained (as well as the market status in that country), dosage form(s) and strength(s) should be listed. Preferably, the comparator product should be obtained from the market with stringent authorities. For comparator FPPs not obtained from the market with stringent authorities, where the results of the clinical trial are intended to be used in support of a new investigational application for market authorization, the applicant should be aware that additional information may be requested at the registration stage (e.g., comparative in vivo or in vitro studies).

If the comparator medicinal product is modified in any way in order to blind the trial (e.g., grinding of tablets, encapsulation of tablets), results of an *in vitro* study (e.g., comparative dissolution profiles for solid dosage forms) comparing the unchanged and the modified product should be submitted. For sterile products that are repackaged for blinding purposes, it should be demonstrated that sterility is maintained.

3.2 Table of contents of Module 3

A Table of Contents should be provided that lists all of the reports and gives the location of each study report in the Common Technical Document.

3.2.S Active Pharmaceutical Ingredient

Some of the information included under the "S Active Pharmaceutical Ingredient" section may not be available to the applicant of the Clinical Trial Application. If such is the case, the manufacturer of the Active Pharmaceutical Ingredient can file an Active Pharmaceutical ingredient (APIMF) directly to the Authority. The API manufacturer would then be considered the APIMF Holder. This APIMF will be held in strict confidence and will be used in support of the application only upon receipt of written authorization from the supplier/ APIMF Holder of the Active Pharmaceutical Ingredient (i.e., via a Letter of Access).

The sponsor should be able to provide most of the information on the Active Pharmaceutical Ingredient, except possibly the proprietary information found in the closed part of the APIMF

(e.g. sections S.2.2, S.2.4 and S.2.6 (see below)). It is the responsibility of the sponsor to obtain all other information from the supplier of the Active Pharmaceutical Ingredient and include this in the application. The information from the Open part of the APIMF should be included in the Quality Overall Summary.

Regardless of the information provided by the supplier of the Active Pharmaceutical Ingredient, the manufacturer of the dosage form is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the Active Pharmaceutical Ingredient are developed by the manufacturer's facilities and for providing the results of batch analyses performed at the manufacturer's facilities.

For further information on the requirements for APIMFs, see Rwanda FDA's Guidelines on submission of documentation for registration of human medicinal products.

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Information on the nomenclature of the Active Pharmaceutical Ingredient should be provided. For example:

(a) Recommended International Non-proprietary Name (INN);
(b) Compendial name, if relevant;
(c) Chemical name(s);
(d) Company or laboratory code;
(e) Other non-proprietary name(s) (e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN)); and
(f) Chemical Abstracts Service (CAS) registry number.

3.2.S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section S 1.1. For Active Pharmaceutical Ingredients existing as salts, the molecular mass of the free base should also be provided.

3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the Active Pharmaceutical Ingredient. Give the physical and chemical properties of the Active Pharmaceutical Ingredient such as the physical description, solubility's (e.g. aqueous/non aqueous solubility profile, pH-dependent solubility profile), polymorphism, particle size distribution, pH and pKa values. Other characteristics could include UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition

coefficient, etc. This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

***Physical Description**:*

The description should include appearance, color, and physical state.

***Solubility**:*

The solubility should be provided in a number of common solvents (e.g. water, alcohols, etc.) as well as the solubility's over the physiological pH range (pH 1.2 to 6.8) in at least 3 buffered media (1.2,4.5 and 6.8). Phrases such as "sparingly soluble" or "freely soluble" should be quantitatively defined or a literature reference can be provided (e.g., "as per USP"). If this information is not readily available, it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

$$\text{Dose/solubility volume} = \frac{\text{Largest dosage strength (mg)}}{\text{Minimum concentration of the drug (mg/ml)*}}$$

Corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

As per the Biopharmaceutic Classification System (BCS), *highly soluble (or highly water-soluble)* APIs are those with a dose/solubility volume of less than or equal to 250 ml.

Polymorphism

The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;

The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

Particle size distribution

Studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1

3.2.S.2 Manufacture

If API manufacturer has to submit APIMF to Authority, the following information should be included:

3.2.S.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.S.2.2 Description of Manufacturing Process and Process controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the synthetic process of the Active Pharmaceutical Ingredient. Active Pharmaceutical Ingredients which are milled/micronized should be indicated as such. A summary of the expectations at each phase is provided below.

For Active Pharmaceutical Ingredients which are manufactured as sterile substances, a complete description of the method of sterilization should be provided. Controls in place to maintain sterility during transportation and storage should also be summarized.

Phase I Clinical Trial Applications

A flow diagram of the synthetic process(es) should be provided that includes chemical structures and configurations of starting materials, intermediates and the Active Pharmaceutical Ingredient. In addition, all reagents (including chemical formulae), solvents and catalysts should be specified in the flow diagram.

Phase II Clinical Trial Applications

In addition to the flow chart, a stepwise narrative description of the Active Pharmaceutical Ingredient manufacturing process should be provided. The use of all reagents, solvents, catalysts and auxiliary materials should be summarized in the manufacturing process description. Relevant process controls should be indicated where critical steps in the synthesis have been identified.
The description of the manufacturing process at Phase II should be sufficiently detailed to address quality and safety concerns without being overly restrictive to process optimization.
For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description, addressing critical process controls and safety concerns, should be provided at Phase II.

Phase III Clinical Trial Applications

A detailed flow chart and narrative process description should be provided. The detailed description provided at Phase III should include critical steps identified in the process and relevant process controls (e.g. reaction times, pH, temperatures, etc.), including all purification steps.

In addition to the above information, the data provided for an Active Pharmaceutical Ingredient produced by fermentation should include:

- Source and type of micro-organism used; composition of media;
- precursors;
- additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and
- Name and composition of preservatives.

For Active Pharmaceutical Ingredients of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for residues resulting from such treatments in the Active Pharmaceutical Ingredient specification. Absence of toxic metals and radioactivity may also have to be confirmed.

3.2.S.2.3 Control of Materials

Active Pharmaceutical Ingredients or materials used in the synthesis which are of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and an attestation confirming this should be provided either as an Attachment or directly within the QOS, if applicable.

Phase II and Phase III Clinical Trial Applications

Sponsors should provide details of the starting materials for the synthesis of the Active Pharmaceutical Ingredient. The level of detail expected concerning controls on starting materials for synthesis increases as synthetic steps get closer to the final Active Pharmaceutical Ingredient. Generally, the "starting material for synthesis" is:

- A synthetic precursor one or more synthetic steps prior to the final intermediate;
- A well-characterized, isolated and purified substance with the structure fully elucidated;
- controlled by well-defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities

Acids, bases, salts and esters (or similar derivatives) of the Active Pharmaceutical Ingredient, and the racemate of a single enantiomeric Active Pharmaceutical Ingredient, are not considered final intermediates.

For starting materials which are commercially purchased, the source and a copy of the provisional specifications is typically considered acceptable. For "starting materials for synthesis" which are manufactured in-house, a copy of the flow chart and provisional specifications for the starting material should be provided.

3.2.S.2.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications] Phase III Clinical Trial Applications

Provide a summary of critical steps identified in the synthesis and the tests and tentative acceptance criteria for their control. In-process controls or provisional specifications for isolated intermediates may be summarized here.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and other Characteristics

For all Clinical Trial Applications

Confirmation of structure based on synthetic route and spectral analyses should be provided. Copies of the actual spectra are not required for Clinical Trial Applications, but should be available upon request.

The Quality Overall Summary should include a list of the studies performed and a conclusion from the studies (e.g., if the results support the proposed structure, spectral interpretations).

The studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally includes elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), X-ray diffraction (XRD) and Mass Spectra (MS) studies.

When an Active Pharmaceutical Ingredient is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical studies.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the Active Pharmaceutical Ingredient specification should include a test to ensure isomeric identity and purity.

If the Active Pharmaceutical Ingredient is a single isomer or a fixed ratio of isomers, provide the rationale for this decision. For existing drugs (e.g., generics), include a summary of any comparative studies performed.

For Active Pharmaceutical Ingredients that contain an asymmetric centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, a summary of results of a study should be submitted demonstrating that the material exists as a racemic mixture (e.g., specific optical rotation).

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be

placed on the purification and the specification for the Active Pharmaceutical Ingredient. If a Active Pharmaceutical Ingredient consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

If, based on the structure of the Active Pharmaceutical Ingredient, there is not a potential for isomerism, it may be sufficient to include a statement to this effect.

Polymorphism:

If the potential for polymorphism is a concern, sponsors are expected to provide a summary of investigations of the Active Pharmaceutical Ingredient, recrystallized from several solvents, to determine if the active Pharmaceutical Ingredient exists in more than one crystalline form. If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, criteria should be incorporated into the Active Pharmaceutical Ingredient specification to ensure that the desired polymorph is the one obtained.

Particle size distribution:

For poorly soluble Active Pharmaceutical Ingredients, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behavior of the FPP. Particle size can also be important in dosage form performance (such as inhalation products), achieving uniformity of content in low-dose tablets, desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size is deemed relevant to the performance of the FPP, results from several development batches should be provided, and appropriate controls on particle size distribution included in the specifications.

3.2.S.3.2 Impurities

The tables in the Quality Overall Summary template can be used to summarize the names, structures, and origin of the impurities. The origin refers to how the impurity was introduced (e.g., "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis", etc.). It should also be indicated if the impurity is a metabolite of the Active Pharmaceutical Ingredient.

Results of the impurity investigation should be provided. For quantitative tests, it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

For Phase I Clinical Trial Applications

The structure (or other identifier, if not structurally characterized) as well as the origin should be included in the Active Pharmaceutical Ingredient impurity table.

For Phase II and III Clinical Trial Applications

The impurity name (or identifier), structure (if characterized) and origin should be provided in the table for all specified impurities.

Impurity levels for previously manufactured nonclinical and clinical batches may also be summarized within this section.

3.2.S.4 Control of API

3.2.S.4.1 Specification

[Information in this section not required for Phase I Clinical Trial Applications]
A summary of the specification for the Active Pharmaceutical Ingredient should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the Active Pharmaceutical Ingredient.

The specification can be summarized according to the table in the Quality Overall Summary template including the Tests, Method Types (including Source), and Acceptance Criteria. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.) and Source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.).
Phase II Clinical Trial Applications
Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (refer to Section S.4.5 - *Justification of Specification*).
Phase III Clinical Trial Applications
Specifications are expected to be re-assessed prior to the Phase III application and reflect those intended for the marketing application, based on additional manufacturing experience and stability information.

3.2.S.4.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]
For Phase II and III Clinical Trial Applications the applicant is required to submit information
A brief description of the analytical methods used for the Active Pharmaceutical Ingredient should be provided for all tests included in the Active Pharmaceutical Ingredient specifications (e.g. method type, column size, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, but should be available upon request.

3.2.S.4.3 Validations of Analytical Procedures

[Information in this section not required for Phase I Clinical Trial Applications] Phase II and III Clinical Trial Applications

The suitability of the analytical methods and a tabulated summary of the validation carried out should be provided (e.g. results or values for specificity, linearity, range, accuracy, precision, intermediate precision, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be provided for Clinical Trial Applications.

3.2.S.4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total impurity tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". When reporting the analytical results, it is important that the method used for each test be identified (including Type and Source).

Batch analysis results for the Active Pharmaceutical Ingredient may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. The batch number, batch sizes, and dates and sites of production should be stated for all batches.

For Phase I Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

For Phase II Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of Active Pharmaceutical Ingredient may be provided as supporting data, with a commitment that the batch analysis for the specific lot to be used in that protocol will be submitted prior to dosing.

For Phase III Clinical Trial Applications

Analytical results from the batch (es) to be used in the proposed clinical trial, or batches representative thereof, should be provided.

Note: For the purpose of this guidance document, a "representative batch" is defined as a batch of Active Pharmaceutical Ingredient or FPP that is manufactured using the same formulation (for the FPP), method of manufacture and equipment, specifications and the same container closure system as the proposed clinical batch, with a similar batch size. All subsequent references in this guidance document to "representative batch" should be interpreted per this definition.

3.2.S.4.5 Justification of Specification

[Information in this section is not required for Phase I Clinical Trial Applications]

The sponsor should ensure the specification includes all the tests and acceptance criteria appropriate for the Active Pharmaceutical Ingredient, and that reasonable limits for impurities and residual solvents have been established. Acceptance criteria should be based on manufacturing experience, stability data and safety considerations.

3.2.S.6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized.
The tables in the Quality Overall Summary template can be used to summarize the information on the batches used in the stability studies. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples or representative batches will be monitored according to the stability protocol until the re-test period has been established.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".
Available long-term and accelerated stability data for the Active Pharmaceutical Ingredient should be provided at each stage of development to support its storage (conditions and re-test period) and use in the manufacture of the FPP.

The proposed storage conditions and re-test period (or shelf life, as appropriate) for the Active Pharmaceutical Ingredient should be reported.

Stress testing:

Stress testing of the Active Pharmaceutical Ingredient can help identify the likely degradation products, which can in turn help establish the degradation pathways, the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual Active Pharmaceutical Ingredient and the type of FPP being developed.

3.2.S.7.2 Stability Protocol and Stability Commitment

If full long-term stability data supporting the re-test period is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or batches considered representative thereof, will be monitored according to the stability protocol. A summary of the stability protocol (in tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.S.7.3 Stability Data

Results of the stability studies (e.g., long-term studies, accelerated studies, stress conditions, etc.) should be presented in an appropriate format.

The actual stability results (i.e., raw data) used to support the clinical trial should be provided as a separate Attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

For Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not summarized in 2.3.S.4, a brief description of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Sections S.4.2 and S.4.3.

3.2.P FINISHED PHARMACEUTICAL PRODUCT (FPP)

3.2.P.1 Description and Composition of the FPP

A description of the FPP and its composition should be provided. The information provided should include:

(a) Description of the dosage form;

The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics (e.g., "The proposed FPP is available as oval, round, immediate-release, aqueous film- coated tablet in three strengths (5 mg, 10 mg, and 20 mg).").

(b) Composition, i.e., list of all components of the dosage form, their amount on a per unit basis (including overages, if any) and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications);

The composition should express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per mL, mg per vial, etc.) and percentage basis including a statement of the total weight or measure of the dosage unit. This should include all components used in the manufacturing process, regardless if they appear in the final FPP. If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 2% overage of the active pharmaceutical ingredient to compensate for manufacturing losses.").

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)"). The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.) should also be stated.

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, coloring blends, imprinting inks, etc.).

(c)**Description of reconstitution diluent(s),** if applicable;

List all reconstitution solvents/diluents to be used in the proposed clinical study.

If the reconstitution solvent/diluent is manufactured in-house, a separate FPP section (e.g. Sections P.1-P.8) should be completed for the chemistry and manufacturing information for the reconstitution solvent/diluent.

(d) Type of container closure system used for accompanying reconstitution diluent, if applicable:

A brief description of the container closure system(s) used for the accompanying reconstitution diluent should be provided, if applicable (for commercially-purchased diluents, provide information only if the primary packaging has been changed);

(e) Qualitative list of the components of the placebo samples used in the clinical trials, if different from the components listed in P.1 (b)

3.2.P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that may influence batch reproducibility, product performance and FPP quality.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all potential diluents over the range of dilution. These studies, including tests for purity, potency, sub-visible particulate matter, pH, etc., should preferably be conducted on aged samples. Where the type of container is not specified, compatibility should be demonstrated in suitable containers. If one or more containers are identified, compatibility of admixtures should be demonstrated only in the specified containers.

For Phase I Clinical Trial Applications

This section should only be completed for sterile products. Summaries of compatibility studies with diluents and containers should be included in this section.

For Phase II and III Clinical Trial Applications

To the extent possible, information pertaining to the following aspects of pharmaceutical development should be submitted:

a) The compatibility of the Active Pharmaceutical Ingredient with excipients listed in P.1 should be discussed. For combination products, a summary of investigations of the compatibility of the Active Pharmaceutical Ingredients with each other should be provided.

b) A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between earlier clinical formulations and the formulation (i.e., composition) described in P.1 should be discussed, if applicable.

c) The selection of the manufacturing process described in P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

d) The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of Active Pharmaceutical Ingredient in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for labelling.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the FPP for the batches used in the clinical studies. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative office(s).

An attestation should be provided in the Quality Overall Summary or as an Attachment confirming that the FPP to be used in the Local study was manufactured according to Good Manufacturing Practices.

3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.
The batch formula should express the quantity of each component on a per batch basis including a statement of the total weight or measure of the batch. This should include all components used in the manufacturing process, regardless if they appear in the final FPP. If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g., "Contains 5 kg overage of the active pharmaceutical ingredient to compensate for manufacturing losses."). Batch formula tables should be representative of the lots intended for use in the proposed clinical trial.

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., "Microcrystalline Cellulose NF (PH 102)").

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the manufacturing process of the FPP. The level of detail expected at each phase of Clinical Trial Application is outlined below.

For sterile products, a complete narrative description of the manufacturing process should also be submitted *regardless of the clinical trial phase*. Furthermore, details of sterilization and lyophilization (if applicable) procedures should be provided for all Clinical Trial Applications.
For Phase I Clinical Trial Applications
A flow chart of the manufacturing process should be provided clearly indicating the order of addition of components and a summary of unit operations (e.g. blending, screening, etc.).
For Phase II Clinical Trial Applications
A flow chart and narrative description of the manufacturing process should be provided. Detailed summaries of process controls (e.g. blending times, end-points for drying operations, etc.) are not required, with the exception of the sieve/screen size for immediate-release solid oral dosage forms.

The description of the manufacturing process at Phase II should be sufficient to fully describe the process without being restrictive to continuing process development and optimization.

For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description which addresses critical process controls, and safety and bioavailability concerns, should be provided at Phase II.

For Phase III Clinical Trial Applications

A flow chart and a detailed narrative description of the process should be provided. A summary of in-process controls and process parameters (e.g. mixing/blending time, temperature, pH for preparations of solutions) should be provided. The critical steps, process controls, intermediate tests and final product controls should be identified and described in additional detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

3.2.P.3.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications] Phase III Clinical Trial Applications

To the extent possible at the time of submission, sponsors should provide information on the following:

Critical Steps: Tests and tentative acceptance criteria for controls on the critical steps in the FPP manufacturing process, where identified.

Intermediates: Information on the quality and provisional controls on intermediates isolated during the process, where relevant.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

This includes the specifications for all excipients, including those that do not appear in the final FPP (e.g., solvents). If the standard claimed for an excipient is a Schedule B compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the compendial monograph.

Confirmation should be provided that none of the excipients which appear in the FPP are prohibited for use in drugs.

3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data).

This information should include biological source, country of origin, manufacturer, and a brief description of the suitability of use based on the proposed controls.

For gelatin for use in pharmaceuticals, supporting data should be provided which confirms that the gelatin is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE). Supporting information for excipients of human or animal origin should be provided as a separate Attachment.

3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a FPP or by a new route of administration, full details of manufacture, characterization and controls should be provided, with cross-references to supporting safety data (nonclinical and/or clinical) using the relevant sections of the Quality Overall Summary according to the Active Pharmaceutical Ingredient and/or FPP format.

3.2.P.5 Control of FPP

3.2.P.5.1 Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications]
A summary of the specification(s) for the FPP should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the dosage form.

The specification(s) can be summarized according to Authority's Quality Overall Summary template including the Tests, Method Types, Sources, and Acceptance Criteria. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.) and the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.).

For phase II Clinical Trial Applications
Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (Please refer to Section P.5.6 - *Justification of Specification*).

For phase III Clinical Trial Applications
Specifications are expected to be re-assessed prior to the Phase III submission and reflect those intended for the marketing application, based on additional manufacturing experience and stability information.

3.2.P.5.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications] For Phase II and III Clinical Trial Applications
A brief description of the analytical methods used for the FPP should be provided for all tests included in the FPP specifications (e.g. reverse-phase HPLC, GC, etc.). Detailed descriptions of

the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, although this information should be available upon request.

3.2.P.5.3 Validation of Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications] For Phase II and III Clinical Trial Applications
Suitability of the analytical methods and a tabulated summary of the validation information should be provided (i.e. results or values for specificity, linearity, range, accuracy, precision, robustness, limit of detection and limit of quantitation, where applicable).

Complete validation reports should not be submitted for Clinical Trial Applications, although this information should be available upon request. For substances which comply with a Schedule B monograph, reference to the monograph will be considered sufficient for all Clinical Trial Applications.

3.2.P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications".
This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms". When reporting the analytical results, it is important that the method used be identified (including Type and Source).

Batch analysis results for the FPP may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. In all cases, the batch numbers, batch sizes, dates and sites of production, and input Active Pharmaceutical Ingredient batches should be provided.

For Phase I Clinical Trial Applications
Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

For Phase II Clinical Trial Applications
Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of FPP may be provided as supporting data with a commitment that the batch analysis for the specific lot(s) to be used in that protocol will be submitted prior to dosing.

For Phase III Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial, or batch(es) considered representative thereof, should be provided.

3.2.P.5.5 Characterization of Impurities

Information on the characterization of impurities should be provided, if not previously summarized in Section S.3.2 - *Impurities.*

This information includes degradation products (e.g., from interaction of the Active Pharmaceutical Ingredient with excipients or the container closure system), solvents in the manufacturing process for the FPP, etc. The tables in the Quality Overall Summary template in section S.3.2 can be used to summarize this information.

This section may also be used to report any new impurities found in the FPP during stress testing (e.g. photostability testing).

3.2. P.5.6 Justification of Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications.]

The sponsor should ensure the specification(s) includes all the tests and acceptance criteria appropriate for the FPP, and that reasonable limits for degradation products have been established. Acceptance criteria should be based on manufacturing experience, stability data, and safety considerations. For impurities/degradation products which are unique to the FPP, acceptance criteria should be supported by appropriate toxicology and safety studies.

3.2.P.7 Container Closure System

A description of the container closure system(s) to be used in the clinical trial should be provided, including the materials of construction for each packaging component. This includes packaging components that:

a) are product contact surfaces

b) are used as a protective barrier to help ensure stability or sterility c) are used for drug delivery

d) are necessary to ensure FPP quality during transportation

For sterile products, details of the washing, sterilization and depyrogenation should be submitted in this section.

For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), additional detail may be required.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The tables in the Quality Overall Summary template can be used to summarize the information on the batches used in the stability studies.
Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples (or representative batches) will be monitored according to the stability protocol until the shelf-life of the FPP has been established with confidence.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

For sterile products, sterility should be reported at the beginning and end of shelf life. During development it is expected that sterility will be monitored on a routine basis (e.g. annual basis) until the shelf life has been determined with confidence. For parenteral products, sub-visible particulate matter should be reported at every test interval until a shelf life has been established. Bacterial endotoxins need only be reported at the initial test interval.

For FPPs which are reconstituted or diluted prior to administration, stability and compatibility studies covering the entire in-use period should be provided. Furthermore, for products which are diluted or reconstituted into a secondary container closure system (i.e., infusion kit), compatibility data should be submitted to support in-use conditions in that specific container closure. Available long-term and accelerated stability data should be provided for the FPP at each stage of development to support its storage conditions and shelf-life.
Stress testing:

For certain FPPs, stress testing of dosage forms may be appropriate to assess the potential for changes in physical and/or chemical properties of the FPP. The nature of the stress testing will depend on the type of FPP being developed.
Proposed storage conditions and shelf life:
The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and shelf life for the FPP should be provided. Alternative storage conditions may be acceptable with supporting scientific data.
Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Do not refrigerate", "Protect from light", "Protect from moisture").

3.2.P.8.2 Stability Protocol and Stability Commitment

If full long term stability data supporting the proposed shelf life is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or samples considered representative of the clinical batches, will be monitored throughout the duration of the clinical trial.

A summary of the stability protocol (e.g. tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.P.8.3 Stability Data

Results of the stability studies (e.g. long-term and accelerated studies) should be presented in an appropriate format. The actual stability results (i.e., raw data) used to support the clinical trial should be provided as an Attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as "within limits" or "conforms".

For Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not previously summarized, details of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Section P.5.2 and P.5.3. A list of Attachments should be provided (e.g., actual stability results (raw data), specifications for excipients, letters of access to Drug Master Files, letters of attestation of BSE/TSE-free material, etc.).

MODULE IV: NON CLINICAL STUDY REPORTS

The goals of the pre-clinical /nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. The information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

The data should be organised as follows:
Table of Contents of Module 4
Study Reports

- Pharmacology
  - Primary Pharmacodynamics
  - Secondary Pharmacodynamics
  - Safety Pharmacology
  - Pharmacodynamic Drug Interactions
- Pharmacokinetics
  - Analytical Methods and Validation Reports (if separate reports are available)
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - Pharmacokinetic Drug Interactions (nonclinical)
  - Other Pharmacokinetic Studies
  - Toxicology
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Local tolerance
- Other Toxicity Studies

Literature References

4.1 Applicants are required to conduct pre-clinical studies according to the ICH guidance document M3 (R2): *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *guidelines of the Organisation for Economic Cooperation and Development (OECD).* For biotechnology-derived products the applicants should follow ICH S6. The Nonclinical Study Reports should be presented in the order described in the guidance M4S.

4.2 The data that is submitted to the Authority on non-clinical safety studies should have originated in studies that have been conducted in compliance with the Principles of GLP. Laboratories that perform safety pharmacology and toxicology studies are required to have worked under the conditions of GLP.

4.3 The applicant shall be required to submit evidence of GLP via a declaration letter signed by the director of the research facility testifying to have conducted the studies as per GLP compliance for each study, and the quality assurance (QA) statement must list all QA activities and confirm that the study report reflects the raw data.

4.4 The test facility itself should be part of a national compliance monitoring programme at the country of origin and be listed as a compliant facility. If this latter prerequisite cannot be complied with because of lack of a national compliance monitoring programme then Authority at its own discretion might arrange for the inspections to confirm GLP compliance.

4.5 This module is applicable to new Investigational products only. For product that have already been established an updated investigator's brochure is sufficient.

4.6 Investigator's Brochure (IB)

4.7 The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

4.8 The contents of the IB should be approved by the disciplines that generated the described data and medically qualified person should generally participate in the editing of an IB.

4.9 If the investigational product is locally marketed and its pharmacology is well established and widely understood by medical practitioners, an extensive IB may not be necessary a current Summary of Product Characteristics may be submitted as an alternative.

4.10 If a marketed product is being studied for a new use (i.e., a new indication) an IB specific to that new use should be prepared.

4.11 The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.

MODULE V: CLINICAL STUDY REPORTS

This document provides guidance on the organization of these study reports, other clinical data, and references within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.
The clinical study reports will be required for clinical studies that are not first in humans (FIH). The reports provide details on clinical experience in humans regarding the investigational product.

This module is applicable to new Investigational products only. For product that have already been established an updated investigator's brochure is sufficient.
The data shall be organized as shown below.

5.1 Table of Contents of Module 5

The table of content should list all documents included in Module 5.

5.2 Tabular Listing of All Clinical Studies

If applicable, if data is available or have been requested it should be presented in a tabular format to facilitate the understanding and evaluation of the results.

5.3 Clinical Study Reports

Efficacy of the product as well as information on the safety of use should be addressed in this section. Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the content of this section

Refer ICH guidelines for the structure and content of clinical study report (E3).

a) Reports of Biopharmaceutical Studies
b) Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials where applicable,
   (i) Plasma Protein Binding Study Reports
   (ii) Reports of Hepatic Metabolism and Drug Interaction Studies
   (iii) Reports of Studies Using Other Human Biomaterials
c) Reports of Human Pharmacokinetic (PK) Studies where applicable,
   (i) Healthy Subject PK and Initial Tolerability Study Reports
   (ii) Patient PK and Initial Tolerability Study Reports
   (iii) Intrinsic Factor PK Study Reports
   (iv) Extrinsic Factor PK Study Reports
   (v) Population PK Study Reports
d) Reports of Human Pharmacodynamic (PD) Studies
   (i) Healthy Subject PD and PK/PD Study Reports
   (ii) Patient PD and PK/PD Study Reports
e) Reports of Efficacy and Safety Studies

(i) Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
(ii) Study Reports of Uncontrolled Clinical Studies
(iii) Reports of Analyses of Data from More Than One Study
(iv) Other Clinical Study Reports

f) Reports of Post-Marketing Experience if available
g) Case Report Forms and Individual Patient Listings. Refer ICH Guidelines on clinical trial studies

5.4 Literature References

A list of cited references should be provided. References that have not been provided should be available upon request.

MODULE VI: VETERINARY CLINICAL TRIALS

This module intends to provide guidance on authorization of clinical trials involving veterinary Investigational products. It provides guidance on the design and conduct of all clinical studies of veterinary products in the target species.

6.1 All trials involving unregistered veterinary medicines for the purpose of generating data to support a marketing authorization or for other purposes shall not be conducted without prior authorization from the Authority.

6.2 Unless otherwise justified, clinical trials shall be carried out with control animals trolled clinical trials. The effect obtained should be compared with a placebo or with absence of treatment and/or with the effect of an authorized medicinal product known to be of therapeutic value.

6.3 The clinical trials application procedures, application form, protocol, pre-clinical and clinical summaries should be as presented in the Module 1-5 of these guidelines.

6.4 The design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species should be conducted and documented in accordance with the principles of Good Clinical Practice (GCP) for veterinary clinical studies. The latter should be conducted in consideration of the welfare of the study animals, the effects on the environment and the study personnel, and to residues in the edible products derived from food-producing study animals.

6.5 Applicants are therefore required to follow requirements as outlined in these guidelines as well as those of current VICH guideline for Good Clinical Practices (VICH GL9).

6.6 The Authority shall grant approval after Ethical clearance from relevant competent Authority.

MODULE VII: MEDICAL DEVICES AND DIAGNOSTICS TRIALS

The guidance is intended to assist researchers, medical device manufacturers, members of research ethics committees, investigators and sponsors in understanding arrangements for clinical trial application of clinical trial of medical devices in Rwanda.

7.1 **Clinical trials involving investigational medical devices** including diagnostics must have an approval from the Authority before being conducted. Clinical investigations are subject to different levels of regulation, depending on the level of risk. An investigational device should be classified as a serious risk device if its studies pose life-threatening harm, could cause permanent physical damage or impairment, or would require medical intervention to prevent such damage.

7.2 **Sponsors or Manufacturers** should submit an application to conduct clinical investigation of unregistered Class B, C, and D devices in clinical trials and in vitro diagnostic devices.

7.3 **Ethical clearance from Ethics committee** should always be sought for a clinical investigation of a non-CE marked medical device, a performance evaluation of an in vitro diagnostic device, or other research involving a medical device.

7.4 **Approvals** are not required for post market surveillance of "non-interventional" post-market surveillance studies of a CE Marked product, which are considered to be service evaluations. These non-interventional studies of CE marked product are classified as follows;

7.5 The product is used within its intended purpose.

7.6 The assignment of any patient involved in the study to a particular therapeutic strategy or diagnostic procedure is not decided in advance by a protocol but falls within current clinical practice.

7.7 The decision to use the product is clearly separated from the decision to include the patient in the study.

7.8 No diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of current clinical practice.

7.9 Epidemiological methods are to be used for the analysis of the data arising from the study.

However, a post-market surveillance study should be submitted to the Authority to review if it does not meet the criteria for non-interventional studies of CE marked products. In particular, the following should always be treated as interventional studies and should be reviewed by the Authority:

- Randomized controlled trials;
- Case series studies involving additional research procedures, e.g. additional blood samples or radiography, or investigations outside those that would normally be employed in the routine management of the patient.

It should be noted that all post-market surveillance studies require a protocol and an informed consent to obtain access to medical information and processing of identifiable patient data.

7.10 Application procedure

An application to authorize a clinical trial involving a medical devices or diagnostics shall be made in accordance with provisions provided in module 1 of these guidelines. In addition, the following documentation will be required;

7.10.1 Device Description, design and materials including User manual of the device.
7.10.2 Marketing history
7.10.3 Risk assessment and standard list
7.10.4 Toxicology and biological safety
7.10.5 Sterilization validation
7.10.6 Electrical safety
7.10.7 Safety and usefulness of medical device
7.10.8 Safety and appropriateness of use of tissues of animal origin
7.10.9 Signed and approved protocol with data compiled as prescribed in Annex 3 and current ISO standards.
7.10.10 Certificate of ISO/ Quality audit (ISO 13485) for manufacture of the device if applicable.
7.10.11 The Investigational product dossier with data compiled in a common submission template as prescribed in Guidelines on submission of documentation of registration of medical devices issued by the Authority.

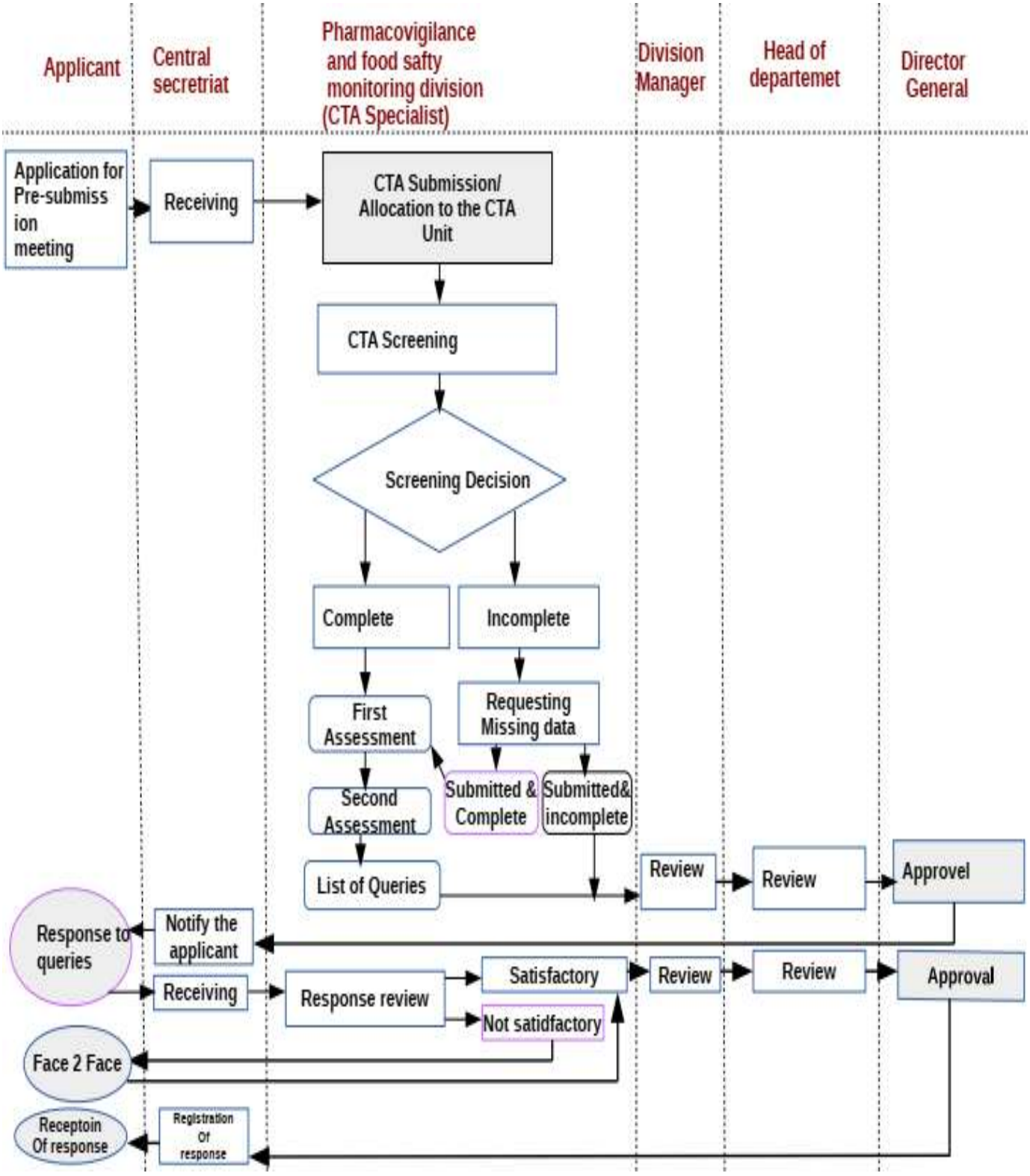
7.11 Conduct of clinical trials involving medical devices and diagnostics

The design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices should be as prescribed in the ISO 14155-2011 (en) Clinical investigation of medical devices for human subjects – Good Clinical Practice and ISO14971: 2007 Medical devices – application of risk management to medical devices guidelines.

7.12 Importation of investigational device and diagnostics

Devices must be labelled “for investigational use only”. Rwanda FDA guidelines for importation and exportation of medical products should be followed prior to importation.

APPENDIX I: Clinical Trial Application Process Flow chart



APPENDIX II: Phases of Clinical Trials

Phase I

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

Phase II

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

Phase III

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

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

ENDORSEMENT OF THE GUIDELINES

	Author	Authorized by	Approved by
Title	Division Manager of Pharmacovigilance & Food Safety Monitoring	Head of Food & Drugs Inspections & Safety Monitoring Department	Director General
Names	**NTIRENGANYA Lazare**	**GISAGARA Alex**	**Dr Charles KARANGWA**
Signature			
Date	**02/02/2021**	**02/02/2021**	**02/02/2021**

ANNEXES

Annex 1: Clinical Trial Application Form (CTA)

(This application should be completed and signed by sponsor or Principal investigator)

Clinical Trial Application Form (CTA)		
1.	Title of the Study:	
2.	Protocol Number :	
3.	Protocol version number	
4.	Protocol date:	
5.	Clinical trial Phase	
6.	Trial objectives	
7.	Trial Design:	
8.	Investigational product's name, number or identifying mark	
9.	Indications	
10.	Comparator product (if applicable	
11.	Concomitant medications (if applicable	
12.	Number of Participants	
13.	Trial Site (s)	
14.	Duration of the trial	
15.	Amount paid for this application	
16.	Sponsor's names	Names: Institution E-mail address: Phone number (with country code):

Annex 1: Clinical Trial Application Form (CTA)

17.	Principal Investigator's names	Names: Institution E-mail address: Phone number (with country code):
18.	Contact Person names and Full address	Names: Institution E-mail address: Phone number (with country code):

DECLARATION BY THE APPLICANT

19.

I, (*Insert the names of Sponsor or PI*) the undersigned, hereby declare that I have submitted all required documentations, and have disclosed all information which may influence the approval of this application

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

I, agree and ensure that once the above said clinical trial is approved, will be conducted according to the submitted protocol, legal, ethical and regulatory requirements of Rwanda FDA

20.	**Names of applicant**	**Signature**	**Date**

ANNEX 2: Clinical Trial Protocol Format

*(This template should be filled in and submitted in **Microsoft word format** with times new roman style font size 12 black ink)*

1. GENERAL INFORMATION	
Title of Study	
Protocol Identification Number/code	
Protocol Version Number (where applicable)	
Date of Protocol	
Rwanda FDA Application Number	
Ethical Clearance Number/ Date of Approval	
Name of Investigational Product or Intervention	
Therapeutic Classification	
Dosage Form(s) and Strength(s)	
Route(s) of Administration	
Name of Comparator Product (where applicable)	
Name and address(es) of the Applicant	
Name and address(es) of the Sponsor	
Name and address(es) of the Principal Investigator (PI)	
Name and address(es) of the Study Monitor	
Name and address(es) of Study Site(s)	
Name and address of the manufacturer of investigational product	
Name and address of the manufacturer of comparator product (if applicable)	
Phase of Trial	

ANNEX 2: Clinical Trial Protocol Format

Duration of study		

2. BACKGROUND AND RATIONALE

(Insert a brief, concise introduction into the clinical problem and previous treatments and developments, i.e., pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature (citations by consecutive numbering, with list at end of this section; important or not readily available references may be included with the paper submission, if appropriate). This section should also contain information on the new drug). Provide rationale for conducting the study in Rwanda

3. OBJECTIVE OF THE TRIAL

(Insert the objectives that are the same as the objectives contained in the protocol. Include the primary objective and secondary objectives)

Primary Objective(s):

Secondary Objective(s):

4. STUDY ENDPOINTS

(Insert the endpoints that are the same as the endpoints contained in the body of the protocol. Include the primary endpoint and important secondary endpoints)

Primary Endpoint(s):

Secondary Endpoint(s):

5. STUDY DESIGN

5.1 *Insert summary description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design). Provide a simple summarized snapshot of your study design not to exceed a single page. This section should include a diagram that provides a*

ANNEX 2: Clinical Trial Protocol Format

quick to 1 page. Please present an overview of your study design in a schematic diagram and tables. The data presentation can be adapted depending on the nature of your study and can be customized according to your protocol. Example: complete the tables with study-specific information and adapt the table(s) to illustrate your study design.

Arm 1	*Sample size*	*Intervention A*
Arm 2	*Sample size*	*Intervention B*

Include instructions for progressing to next phase (if applicable):

Include a schematic diagram to show the design, procedures and stages including study arms, visits, time-points, interventions etc.

5.2 *Summary of the randomization method and procedures to allocate participants to treatment groups;*

5.3 *Blinding (methods of blinding (masking) and other bias reducing techniques to be used);*

5.4 *Summary description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), including packaging, and labeling of the investigational product(s);*

5.5 *Maintenance of trial treatment randomization codes and procedures for breaking codes;*

5.6 *Total study duration (anticipated starting/ finishing dates);*

ANNEX 2: Clinical Trial Protocol Format

5.7 *Expected duration for each subject including post treatment period etc;*

6. STUDY PARTICIPANTS

6.1 *Provide a brief description of specific characteristics of the trial participants (e.g. disease/ stage/ indication/ conditions/ treatment etc.) as applicable and of diagnostic criteria and assessment*

6.2 *State the Inclusion criteria:*

6.3 *State the Exclusion criteria*

7. PREMATURE WITHDRAWAL / DISCONTINUATION CRITERIA

7.1 ***Withdrawal criteria:***

7.1.1 *Enumeration of all conditions / criteria and management for drug/ patient's withdrawal or (premature) discontinuation, including voluntary withdrawal by subject without prejudice to future treatment by the physician. The type and timing of the data to be collected for withdrawn participants.*

7.1.2 *State whether and how participants are to be replaced.*

7.1.3 *The follow-up for participants withdrawn from investigational product treatment/trial*

7.1.4 *Treatment*

7.2 *State the stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial;*

8. INVESTIGATIONAL DRUG FORMULATION

ANNEX 2: Clinical Trial Protocol Format

8.1 *(Brief description of the study drug(s) and formulation to be used in the clinical trial. The relationship to the formulations used in the preclinical and/or other clinical trials should be delineated, as applicable. This may also include disclosure of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already performed if different formulations have been used during clinical development.)*

8.2 *Instructions for safe handling;*

8.3 *State the accountability procedures for the investigational product(s), placebos and comparator(s) and disposal;*

9. DOSAGE REGIMEN

9.1 *Rationale for dose selection*

9.2 *Provide the following regarding the treatment(s) to be administered:*

9.2.1 *The name(s) of all the product(s):*

9.2.2 *Dose(s):*

9.2.3 *The dosing schedule(s):*

9.2.4 *The route/mode(s) of administration:*

9.2.5 *The treatment period(s):*

9.2.6 *Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial:*

9.2.7 *Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial:*

ANNEX 2: Clinical Trial Protocol Format

9.2.8 *Procedures for monitoring participant's compliance:*

9.2.9 *Wash-out period (Description for pre-, during- and post-trial, as applicable)*

10. PRE-STUDY SCREENING AND BASELINE EVALUATION

(Describe in summary the process of clinical validation for participation in the clinical trial, including methodology / schedule of events.)

11. TREATMENT / ASSESSMENT VISITS

(Insert the schedule of all events / visits / procedures during the clinical trial)

12. EFFICACY VARIABLES AND ANALYSIS

12.1 *Description and validation of primary endpoint(s), i.e. responses/changes from baseline over time in relation to clinical trial events. Description and validation of related secondary changes (secondary endpoints) following from clinical trial events.*

12.2 *Provide specification of the efficacy parameters.*

12.3 *Describe the methods and timing for assessing, recording, and analyzing efficacy parameters*

13. ASSESSMENT OF SAFETY

13.1 *Specification of safety parameters:*

13.2 *The methods and timing for assessing, recording, and analyzing safety parameters:*

ANNEX 2: Clinical Trial Protocol Format

13.3 *Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.*
13.4 *The type and duration of the follow-up of subjects after adverse events*
13.5 *RISKS: (Identify potential risks and mitigation strategies (e.g. need for and risks associated with long term immunosuppression)*
13.6 *DATA and SAFETY MONITORING PLAN (DSMP):* *(Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)* 13.7 *Immune Monitoring and immunosuppression: (Describe and justify the plan for immunosuppression and immune monitoring (if applicable)*
14. ASSAYS/METHODOLOGIES
14.1 *Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies (Provide a more detailed summary of assay methods and summarize assay qualification/validation. Indicate where specialized testing will be conducted)* 14.2 *The names and contact addresses of the laboratories to be used for the study;* 14.3 *State the location of the attached draft Material Transfer Agreements (MTAs) in the submission;*

ANNEX 2: Clinical Trial Protocol Format

14.4 *State the duration for long term storage of samples and the area to be stored*
15. STATISTICAL ANALYSIS PLAN
15.1 *Specify the planned sample size to be used in the study and its justification*
15.2 *Summary of description of the statistical methodologies to be used to evaluate the effectiveness of the investigational product, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance and the statistical model to be used.* 15.3 *Analysis of trial parameters (primary/ secondary endpoints), population, demographics, as applicable.* 15.4 *Efficacy analysis methods and results of efficacy end-point analysis.* 15.5 *Safety analysis methods and results of safety end-point analysis.* 15.6 *Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/ pharmacological etc parameters, as applicable.* 15.7 *Pharmacokinetic endpoint analysis, as applicable.* 15.8 *Interim analysis and role of Data Safety Monitoring Board, as applicable*
16. OUTCOME CRITERIA
(Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives)
17. DATA MANAGEMENT
(Describe procedures for recording, processing, handling, and retaining raw data and other study documentation)
18. MONITORING PLAN
(Summary of the monitoring plan) *State the location of the detailed monitoring plan in the submission*
19. ETHICAL CONSIDERATIONS

ANNEX 2: Clinical Trial Protocol Format

19.1 *State the ethical clearance reference number and institutions that have approved the trial* *Institution review Board ethical clearance: Number and date* *NIMR ethical clearance number and Date:*
19.2 ***Insurance Details:*** 9.2.1 *Insert local Insurance Company name and address:* 9.2.2 *policy cover number:* 9.2.3 *Validity:* 9.2.4 *Expiry Date:* 9.2.5 *State the location of the Insurance cover in the submission:* 9.2.6 *Number of insured participants*
19.3 ***Participant Information sheets and Informed Consent forms:*** *(The contents should be as per ICH guidelines, these guidelines and declaration of Helsinki)* 9.3.1 *State the version number and dates for both English and Swahili versions* 9.3.2 *State the location of the Participant Information sheets and Informed Consent forms in the submission*
19.4 *State the amount to be reimbursed to the participants*
19.5 *Treatment and/or management of participants and their disease condition(s) after completion of trial*
19.6 *Follow-up of trial study participants after the conclusion of the trial*
19.7 *In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:*
19.8 *Identification of the provider and recipient*
19.9 *Identification of the material and the volume of material*

ANNEX 2: Clinical Trial Protocol Format

19.10	*Definition of the trial and how the material will and will not be used.*
19.11	*Maintenance of confidentiality of background or supporting data or information, if any*
19.12	*Indemnification and warranties (where applicable)*
19.13	*Details on post-trial access to the products*

ANNEX 3: Joint Declaration for Sufficient Funds

(This form should be completed and signed by Sponsor and National Principal Investigator concerning to Complete Study)

Title of the study:

Protocol:

Investigational Product(s):

I, <*insert full name*>, Sponsor /representing the sponsor (*delete whichever is not applicable*) and
I, <full name>, Principal Investigator/National Principal Investigator

hereby declare that sufficient funds have been made available to complete the above-mentioned study according to legal, ethical, and regulatory requirements currently enforced in Rwanda.

Done at ……

Signed by: **Date:……**

SPONSOR (or representative)
Name:
Address:
Email address:
Phone number:

Signed by: **Date:……..**

National /Principal Investigator:

Name:
Address:
E-mail address:
Phone number:

ANNEX 4: Investigational Product Quality Overall Summary Template

*This template should be filled in and submitted in **Microsoft word format** with New times roman style font size 12 black ink). Details on this summary should as inserted as prescribed in the CTD module 3.)*

Title of Study	
Protocol Identification Number/code	
Protocol Version Number (where applicable)	
Date of Protocol	
Rwanda FDA Application Number	
Name of Investigational Product or Intervention	
Therapeutic Classification	
Dosage Form(s) and Strength(s)	
Route(s) of Administration	
Clinical trial Design *(extract from the protocol)*	
Name of Comparator Product (where applicable)	
Name and address(es) of the Applicant	
Name and address(es) of the Sponsor	
Name and address(es) of the Principal Investigator (PI)	
Name and address(es) of the Study Monitor	
Name and address(es) of Study Site(s)	
Name and address of the manufacturer of investigational product	
Name and address of the manufacturer of comparator product (if applicable)	
Phase of Trial	
Proprietary (Brand) Name of FPP	
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	
Company Name	
Dosage Form(s)	
Strength(s)	
Country from which the Clinical Supplies were Obtained for the Lot to be Used in this Clinical Trial (as well as the market status in that country)	

ANNEX 4: Investigational Product Quality Overall Summary Template

2.3. S ACTIVE PHARMACEUTICAL INGREDIENT (NAME, MANUFACTURER)

2.3. S.1 General Information (name, manufacturer)

2.3. S.1.1 Nomenclature (name, manufacturer)

(a) Recommended International Non-proprietary name (INN):

(b) Compendial name, if relevant:

(c) Chemical name(s):

(d) Company or laboratory code:

(e) Other non-proprietary name(s) (e.g., national name, USAN, BAN):

(f) Chemical Abstracts Service (CAS) registry number:

Note: For Phase I Trials only (a) and (b) is required

2.3. S.1.2 Structure (name, manufacturer)

(a) Structural formula, including relative and absolute stereochemistry:

(b) Molecular formula:

(c) Molecular mass:

2.3. S.1.3 General Properties (name, manufacturer)

(a) Physical description (e.g., appearance, colour, physical state):

(b) Physical form (e.g., preferred polymorphic form, solvate, hydrate):

ANNEX 4: Investigational Product Quality Overall Summary Template

(c) Solubilities (e.g., aqueous/non aqueous solubility profile, tabular format, reporting in mg/mL):

(d) pH and pKa values:

(e) Other relevant information:

2.3. S.2 Manufacture (name, manufacturer)

2.3. S.2.1 Manufacturer(s) (name, manufacturer)

(a) Name, address, and responsibility of each manufacturer, including Contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:

(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3. S.2.2 Description of Manufacturing Process and Process Controls (name, Manufacturer)

(a) Flow diagram of the synthetic process(es):

Note: For Phase II & III include also the following should be submitted: -

(b) Detailed narrative description of the manufacturing process(es):

2.3.S.2.3 Control of Materials (name, manufacturer)

(a) For Active Pharmaceutical Ingredient manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), provide an attestation (with supporting documentation, if applicable) confirming that the material is free of BSE/TSE agents:

Note: For Phase II & III include also the following should be submitted:

(b) Information on starting materials

ANNEX 4: Investigational Product Quality Overall Summary Template

2.3. S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

(a) Summary of the controls performed at critical steps of the manufacturing

(b) Process and on intermediates:

2.3. S.3 Characterization (name, manufacturer)

2.3. S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and Summary of the interpretation of evidence of structure:

(b) Discussion on the potential for isomerism and identification of Stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):

(c) Summary of studies performed to identify potential polymorphic forms (including solvates):

(d) Summary of studies performed to identify the particle size distribution of the Active Pharmaceutical Ingredient:

(e) Other characteristics:

2.3. S.3.2 Impurities (name, manufacturer)

(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:

(b) List of drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products, metabolites), including chemical name, structure and origin:

ANNEX 4: Investigational Product Quality Overall Summary Template

Drug-related Impurity (chemical name or descriptor)	Structure	Origin

(c) List of process-related impurities (e.g., residual solvents, reagents, catalysts), including compound name and step used in synthesis:

(d) Actual levels of impurities (e.g., drug-related and process-related) found in Batches used in nonclinical and clinical studies:

Impurity (drug-related and process-related)	Acceptance Criteria	Results (include batch number and use) (e.g., clinical)		

2.3. S.4 Control of the Active Pharmaceutical Ingredient (name, manufacturer)

2.3. S.4.1 Specification (name, manufacturer)

(a) Specification for the Active Pharmaceutical Ingredient:

Test	Acceptance Criteria	Analytical Procedure (Type and Source)

ANNEX 4: Investigational Product Quality Overall Summary Template

2.3. S.4.2 Analytical Procedures (name, manufacturer)

(a) Summary of the analytical procedures (e.g., suitability, key method parameters, conditions):

2.3. S.4.3 Validation of Analytical Procedures (name, manufacturer)

(a) Tabulated summary of the validation information (e.g., system suitability testing, validation parameters and results):

2.3. S.4.4 Batch Analyses (name, manufacturer)

(a) Description of the batches to be used in this clinical trial (or representative batches):

Batch Number	Batch Size	Date of Manufacture and Site of Production	Use (e.g., clinical)

ANNEX 4: Investigational Product Quality Overall Summary Template

(b) Summary of results for the batches to be used in this clinical trial or Representative batches (should include tests, types of analytical procedures (type and source), and actual results):

2.3. S.4.5 Justification of Specification (name, manufacturer)

(a) Justification of the Active Pharmaceutical Ingredient specification (e.g., manufacturing experience, stability, historical batch analysis results, safety considerations):
For Phase one trial only Batch analysis report is required.

2.3. S.6 Container Closure System (name, manufacturer)

(a) Description of the container closure system(s) for the storage and shipment of the Active Pharmaceutical Ingredient:

2.3. S.7 Stability (name, manufacturer)

2.3. S.7.1 Stability Summary and Conclusions (name, manufacturer)

(a) Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, results obtained):

(b) Proposed storage conditions and re-test period (or shelf life, as appropriate):

2.3. S.7.2 Stability Protocol and Stability Commitment (name, manufacturer)

(a) If full long term stability data is not available at the time of filing, provide a summary of the stability protocol and a commitment for the continued monitoring of the Active Pharmaceutical Ingredient stability according to the protocol:

ANNEX 4: Investigational Product Quality Overall Summary Template

2.3. S.7.3 Stability Data (name, manufacturer)

(a) The actual stability results (i.e., raw data) may be found in:

(b) Summary of analytical procedures and validation information for those Procedures not previously summarized in 2.3.S.4 (e.g., analytical procedures used only for stability studies):

2.3. P FINISHED PHARMACEUTICAL PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the FPP (name, dosage form)

(a) Description of the dosage form:

(b) Composition of the dosage form:

(i) Composition, i.e., list of all components of the dosage form, and their amounts on a per unit basis (including overages, if any):

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)			
		Quantity per unit	%	Quantity per unit	%

(i) Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):-

a) Description of reconstitution diluent(s), if applicable:

ANNEX 4: Investigational Product Quality Overall Summary Template

b) Type of container closure system used for accompanying reconstitution diluent, if applicable:

c) Qualitative list of the components of the placebo samples to be used in this Clinical trial, if different from the components listed in 2.3. P.1(b):

2.3. P.2 Pharmaceutical Development (name, dosage form)

(a) Discussion on the development of the dosage form, the formulation, Manufacturing process, etc.:

(b) For sterile, reconstituted products, summary of compatibility studies with Diluents/containers:

2.3. P.3 Manufacture (name, dosage form)

2.3. P.3.1 Manufacturer(s) (name, dosage form)

(a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:

(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

(c) Attestation that the dosage form was manufactured under Good Manufacturing Practices (GMP) conditions:

2.3. P.3.2 Batch Formula (name, dosage form)

(a) List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis (including overages, if any):

Strength (label claim)	

ANNEX 4: Investigational Product Quality Overall Summary Template

Batch Size(s) (number of dosage units)	
Component and Quality Standard (and Grade, if applicable)	Quantity per batch
Total	

2.3. P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

(a) Flow diagram of the manufacturing process:

(b) Detailed narrative description of the manufacturing process, including

Equipment type and working capacity, process parameters ***(for Phase II & III trials***)

(b) For sterile products, details and conditions of sterilization and lyophilization:

2.3. P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

(a) Summary of controls performed at the critical steps of the manufacturing Process and on isolated intermediates (***for Phase II & III trials***)

2.3. P.4 Control of Excipients (name, dosage form)

2.3. P.4.1 Specifications (name, dosage form)

Specifications for non-compendial excipients and for compendial excipients

Which include supplementary tests not listed in the monograph(s) may be found in:

(a) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3. P.4.5 Excipients of Human or Animal Origin (name, dosage form)

(a) List of excipients that are of human or animal origin (including country of origin):

(b) Summary of the information (e.g., sources, specifications, description of the

ANNEX 4: Investigational Product Quality Overall Summary Template

Testing performed, viral safety data) regarding adventitious agents for excipients of human or animal origin:

For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), provide an attestation (with supporting documentation, if applicable) confirming that the material is free of BSE/TSE agents:

2.3. P.4.6 Novel Excipients (name, dosage form)

(a) Summary of the details on the manufacture, characterization, and controls,

With cross references to supporting safety data (nonclinical and/or clinical) on novel excipients (i.e., those used for the first time in a FPP or by a new route of administration):

2.3. P.5 Control of FPP (name, dosage form)

2.3. P.5.1 Specification(s) (name, dosage form)

(a) Specification(s) for the FPP:

Test	Acceptance Criteria	Analytical Procedure (Type and Source)

2.3. P.5.2 Analytical Procedures (name, dosage form)

(a) Summary of the analytical procedures (e.g., key method parameters, conditions, suitability):

2.3. P.5.3 Validation of Analytical Procedures (name, dosage form)

(a) Tabulated summary of the validation information (e.g., system suitability testing, validation parameters and results):

ANNEX 4: Investigational Product Quality Overall Summary Template

2.3. P.5.4 Batch Analyses (name, dosage form)

(a) Description of the batches to be used in this clinical trial (or representative batches):

Strength and Batch Number	Batch Size	Date of Manufacture and Site of Production	Input Drug Substance Batch	Use (e.g., clinical)

(b) Summary of results for the batches to be used in this clinical trial or Representative batches (should include tests, types of analytical procedures (type and source), and actual results):

Note: For Phase one trial only Batch analysis report is required.

2.3. P.5.5 Characterization of Impurities (name, dosage form)

(a) Information on the characterization of impurities, not previously provided in 2.3. S.3.2 (e.g., summary of actual and potential degradation products):

2.3. P.5.6 Justification of Specification(s) (name, dosage form)

(a) Justification of the Active Pharmaceutical Ingredient specification (e.g., manufacturing experience, stability, historical batch analysis results, safety considerations):

2.3.P.7 Container Closure System (name, dosage form)

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

(b) Materials of construction of each primary packaging component:

(c) For sterile products, details of washing, sterilization and depyrogenation

ANNEX 4: Investigational Product Quality Overall Summary Template

d) Procedures for container closures:

2.3. P.8 Stability (name, dosage form)

2.3. P.8.1 Stability Summary and Conclusions (name, dosage form)

(a) Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (oC, % RH, light)	Strength and Batch Number	Batch Size and Date of Manufacture	Container Closure System	Completed (and Proposed) Test Intervals

(ii) Summary and discussion of stability study results:

(b) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):

2.3. P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

(a) If full long term stability data is not available at the time of filing, provide a summary of the stability protocol and a commitment that the stability of the clinical trial samples or representative batches will be monitored throughout the duration of the clinical trial or proposed shelf life:

2.3. P.8.3 Stability Data (name, dosage form)

ANNEX 4: Investigational Product Quality Overall Summary Template

(a) The actual stability results (i.e., raw data) may be found in:

(b) Summary of analytical procedures and validation information for those Procedures not previously summarized in 2.3.P.5 (e.g., analytical procedures used only for stability studies):

5. Additional Requirements for Clinical trials for medical devices

An application to authorize a clinical trial involving a medical devices or diagnostics shall be made in accordance with provisions provided in section 2 of these guidelines. In addition, the following documentation will be required;

a) Device Description, design and materials including User manual, catalogue of IFU of the device.

b) Marketing history

c) Risk assessment and standard list

d) Toxicology and biological safety

e) Sterilization validation

f) Electrical safety

g) Safety and usefulness of medicinal substance

h) Safety and appropriateness of use of tissues of animal origin

i) Signed and approved protocol with data compiled as prescribed in Annex 3 and current ISO standards.

j) Certificate of ISO/ Quality audit (ISO 13485) for manufacturer of the device if applicable.

ANNEX 5:Declaration by Principal Investigator or Co-Investigator

(Note that all investigators should fill and sign this form)

Clinical trial protocol number.: .....…….....
Role in clinical trial:…….
Title of clinical trial: .....…….....
Clinical trial site: .....…….....
Investugational Product:…….

I, *(Insert Full names*), the **principal investigator or co-investigator *(****delete as applicable****)*** in above mentioned study, hereby DECLARE that:

1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and understand the responsibilities and obligations of the Principle Investigator (PI) within the context of this study.
2. I have notified the Rwanda FDA of any aspects of the study with which I do not/am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analyzed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol and in accordance with Rwanda FDA requirements and ICH – GCP principles.
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time.
6. I will not commence the trial before written authorization from the National Ethics Committee and Rwanda FDA has been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.

ANNEX 5:Declaration by Principal Investigator or Co-Investigator

8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions*].
10. I have*/have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with ICH-GCP (*Attach details).
11. I have*/have not (*delete as applicable*) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details).

Done at ……. on…….

Names: …….
Email address:
Phone number:
Signature:

ANNEX-6: Protocol Pre-Submission Synopsis Template

1.	Title of the Study:	
2.	Sponsor name:	
3.	Investigational Product (s)	
4.	Background and Rationale (Brief)	
5.	Indication (s)	
6.	Clinical trial Phase	
7.	Trial objectives	Primary objectives: Secondary Objectives):
8.	Trial Design	
9.	Trial End points	Primary endpoints: Secondary endpoints:
10.	Number of Participants	
11.	Eligibility criteria	Inclusion criteria: Exclusion criteria:
12.	Trial Site (s)	
13.	Duration of the trial	

ANNEXE-7: Clinical Trial Amendment Application Form (CTA-A)

(This form should be filled and signed by applicant for substantial amendment for an already approved clinical trial)

A. DETAILS OF THE APPROVED ORIGINAL PROTOCOL	
Reference Number of the approved Clinical Trial	
Date of approval of original protocol (dd/mm/yyyy)	
Clinical Trial Title	
Principal Investigator approved for the clinical trial	
Number of sites approved for the clinical trial	
Number of subjects approved for the clinical trial	
Applicant of the current amendment (Sponsor or principal investigator)	
Contact person responsible for this application	First name: Surname name: E-mail: Tel:
B. SUMMARY OF PROPOSED CHANGES	
Amendment title, number and natures supporting documentation: *List of all types of supporting documents that you will submit*	
Summary of current	**Proposed change details:**
Reason/rationale for change(s): *Please provide the rationale for each change if more*	

ANNEXE-7: Clinical Trial Amendment Application Form (CTA-A)

than one.	
Multi-centre trials: *Will this amendment apply to all approved site(s)?*	☐ **YES** ☐ **NO**
If No: Specify the sites for which the amendment will apply	

C. DOCUMENTATION CHECKLIST	
Valid ethical approval of the proposed change(s)	☐ **YES** ☐ **NO**
Proof of payment of amendment fees as per Rwanda FDA regulations	☐ **YES** ☐ **NO**
Revised Protocol with version number (if applicable)	☐ **YES** ☐ **NO**
Other relevant supporting documentation in line with the amendment	☐ **YES** ☐ **NO**
Valid ethical approval of the proposed change(s)	☐ **YES** ☐ **NO**

D. DECLARATION (by applicant)

I, (*Insert the Sponsor or PI*) the undersigned, hereby declare that I have submitted all required documentations, and have disclosed all information which may influence the approval of this application

☐ There are no changes being made other than those applied for in this submission, except for possible editorial changes. Any other changes will be applied for separately.

☐ The information submitted is true and correct.

Names:	**Signature:**	**Date:**