RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON GOOD CLINICAL PRACTICES (GCP) IN RWANDA

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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 its article 8, paragraph 7 and 12, the Authority is mandated to regulate and inspect clinical trials. Reference to the provisions of the technical regulation N° CBD/TRG/015 Rev_1 governing the conduct of clinical trials especially in its article 32, the Authority Issues Guidelines N° DIS/GDL/044 on Good Clinical Practices (GCP) in Rwanda.

The objective of these Guidelines is to ensure that clinical trials in Rwanda are conducted in accordance with National and International ethical and scientific standards. The guidelines provide details of the quality processes required in the conduct of clinical trials to ensure that human subjects participating in the clinical trials are protected, and clinical trials are scientifically sound. The guidelines also provide guidance on how the results of clinical trials should be collected, recorded, analyzed, audited and reported.

Strict adherence to these guidelines will facilitate the mutual acceptance of clinical data by international regulatory authorities, especially since the guidelines adopt the basic principles outlined by the International Committee on Harmonization of Good Clinical Practice (ICH-GCP) notwithstanding some modifications to suit the local requirements.

I am confident that the publication of these Guidelines will mark yet another milestone in our efforts to strengthen the pharmaceutical industry in its efforts to promote meaningful clinical trials in Rwanda. The Guidelines will also pave the way for researchers to achieve excellence in clinical trials in Rwanda.

I would like to thank all stakeholders who have been involved in the development, review and validation of these Guidelines.

Dr. Charles KARANGWA
Acting Director General

ACCRONYMS AND ABBREVIATIONS

ADRs	Adverse Drug Reactions
AEs	Adverse Events
BE	Bioequivalence
CAPA	Corrective Action and Preventive Action
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiography
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical
IMP	Investigational Medicinal Product
IP	Investigational Product
IRB	Institutional Review Board
IVP	Investigational Veterinary Product
NEC	National Ethics Committee
PI	Principal Investigator
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
TMF	Trial Master File

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GLOSSARY

In these guidelines, unless the context otherwise states:
"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law Nº 003/2018 of 09/02/2018.

"Adverse Event" Any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product 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).

Research Institution" Any public or private entity, agency, medical or dental facility where clinical trials are conducted.

"**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 pharmacodynamics 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.

"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 and scientific 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.

"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.

"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.

Sponsor" An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a trial. This excludes an individual company, institution or organization which has been requested to provide money for a trial and does not benefit in any way from the results of the trial

"Investigator" An individual who conducts a clinical investigation.

"Sub-investigator" Any member of a clinical trial team, supervised by the investigator at a trial site and allowed to perform critical trial-related procedures

"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.

"Placebo" A medication with no active ingredients or a procedure without any therapeutic effect.

"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).

Trial Master File & Essential Documents

The Trial Master File (TMF) and evidence trail (also referred to as the audit trail or document trail) must be maintained in a format which is accessible. A good evidence trail will include documentation which helps 'tell the story of the trial e.g., documents which describe the handling and decision making associated with notable issues, disagreements etc. These documents are often very helpful for day-to-day management of the trial and handover as well as demonstrating that the organization was acting appropriately at the time; a convincing evidence trail of regulatory compliance will not be able to be pulled together once an inspection notice has been received.

"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, 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 principal 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.

"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.

"***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.

"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.

1.0 INTRODUCTION

Clinical trials are essential for research and development(R&D) in the area of drug discovery, vaccine development and other medical products. Current knowledge about the safety and efficacy of specific medical products and treatments, came from randomized controlled clinical trials that are a crucial part of clinical research designed to answer important scientific and health care questions. Randomized controlled trials form the foundation for "evidence-based medicine", but such research can be relied upon only if it is conducted according to principles and standards collectively referred to as "Good Clinical Practice" (GCP).

Rwanda recognizes the widely accepted consensus that all research participants are entitled to maximum guarantees that are transnational and non-negotiable**.** These prerogatives can be realized in a clinical trial environment, practice and structures that promote good clinical practice. An important component of these systems and structures are National ethics guidelines for good clinical practice that complement the provisions of clinical trials regulations in place.

The purpose of these guidelines is to equip the clinical trial environments with clearly articulated standards of good clinical practice in research that are relevant to local context and settings. They ensure that clinical trials on human participants are well designed and conducted according to sound scientific and ethical standards within the framework of good clinical practices.

Compliance with these standards provides the Authority, Researchers, Academia, CROs and the general public with assurance that the rights, safety and wellbeing of trial participants are protected and that clinical trial data are credible.

1.1 Scope

These guidelines apply to the conduct and management of clinical trials on medicines, vaccines, biological products, herbal medicines, medical devices and in Vitro Diagnostics (IVDs) on human participants.

1.2. General GCP principles

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki in 1964, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society.
3. A trial should be initiated and continued only if the anticipated benefits outweigh the risks.
4. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society.

5. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
6. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
7. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
8. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified healthcare provider.
9. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
10. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
11. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
12. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
13. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
14. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

1.3. Clinical Trial Submission Process

An applicant who is interested to conduct clinical trial in Rwanda shall submit to the Authority a Clinical Trial Application (CTA) compiled according to the regulatory requirements set out in the guidelines for clinical trial application. However, a pre-submission meeting may be necessary to discuss pertinent issues prior to formal Clinical trial submission.

The application shall include a valid ethical clearance from Rwanda National Ethics Committee (RNEC). The Sponsor or Principal investigator may also seek a collaboration note from Rwanda Biomedical Centre (RBC) in the event that the trial involves the public health programs such as HIV, Malaria, TB, Expended program for Immunization, Mental Health, Reproductive Health etc.

In all cases, the Authority shall accept parallel submission to Rwanda National Ethics Committee (RNEC) in order to reduce any unnecessary delays. However, the clinical trial approval certificate of the Authority cannot be granted without a valid ethical clearance from Rwanda National Ethics Committee.

Applicant are encouraged to visit the Authority website (www.rwandafda.gov.rw) in order to get information regarding regulations, guidelines and applicable forms to compile the application referring to the instructions on how to register a Clinical Trial. After review of the trial application, the Authority shall produce and deliver the Clinical Trial Approval Certificate

(CTAC) and conduct the GCP inspection at the clinical trial sites. The flowchart for clinical trial application process is attached as in the **ANNEXURE-I**

2.0 ROLES & RESPONSIBILITIES

2.1 Rwanda National Ethics Committee /Institutional Review Board

The main responsibility of the Independent Ethics Committee (IEC) /Institutional Review Board (IRB) is to safeguard the rights, safety and wellbeing, of trial participants.
In the execution of its roles and responsibilities, the IEC/ IRB:

a) Reviews the ethical aspects of research protocols and protocol amendments to ensure that research will be conducted in accordance with Good Clinical Practices (GCP).
b) Ensures that the compensation package planned in the trial is consistent with existing requirements.
c) Ensures that informed consent is obtained from all trial participants before enrolment
d) Grants the Ethical clearance in the instances where research proposals and protocols meet ethical standards.

2.2 Roles and responsibilities of Rwanda FDA

The conduct of Clinical trials shall be reviewed and get approval from the Authority before they are initiated. The Authority has the mandate to regulate and inspect clinical trials conducted in Rwanda. To achieve this, the Authority fulfils the following responsibilities:

1) Issuance of regulations, guidelines and forms for clinical trial oversight
2) Grant of Clinical Trial Approval Certificate
3) Approval manufacturing or import license of the investigational importation including placebos
4) Inspection of ongoing Clinical trials in Rwanda
5) Ensure proper coordination and engagment of stakeholders in clinical trials
6) Suspending, stopping or terminating the non-compliant clinical trials if necessary
7) Publish register of approved, suspended and rejected clinical trials

The Clinical trial unit within the division of Pharmacovigilance and Safety Monitoring shall assume clinical trial oversight related activities. The roles and responsibilities shall be but not limited to the following:

1) Drafting regulations and development of appropriate guidance documents such as guidelines standards operating procedures, forms and formats necessary for implementation of clinical trial oversight activities;
2) Coordinating pre-submission/client orientation meetings to discuss issues related to Applications or any related issues regarding conduct of clinical trials in Rwanda
3) Receiving of Clinical Trial Applications
4) Planning, scheduling and coordinating the review of clinical trial applications and amendments
5) Processing of Clinical Trial Approval certificates for recommended trials
6) Ensuring effective communications among stakeholders

7) Reviewing of all reports for clinical trials (safety reports, quarterly reports, close-out reports, serious adverse event reports and final clinical trial reports)
8) Updating and maintaining register of clinical trial in Rwanda
9) Receiving, acknowledgment and analysing of Safety reports such as Serious Adverse Event (SAE) and SUSARs reports
10) Planning and coordinating GCP inspections for on-going approved clinical trials in Rwanda
11) Conducting and follow up GCP inspections at trial sites
12) Preparation of stakeholder's meetings
13) Preparation of needs for capacity building in clinical trials
14) Implementing the internal tracking system to monitor timelines for clinical trial applications and amendments
15) Conducting periodic Performance review and approval timelines

In the execution of its roles and responsibilities, the Authority shall ensure that clinical trials are conducted in accordance with ethical principles and regulatory requirements established by the Authority.

2.3 Role of Rwanda Biomedical Centre (RBC)

Rwanda Biomedical Centre (RBC) shall be but not limited to the following:

a) provide a collaborative note for the clinical trial involving public health program products such as HIV, Malaria, TB, Expended program for Immunization, Mental Health, Reproductive Health etc.
b) Contribute to the preparation and clinical trial sites readiness
c) Use scientific data from clinical trial to improve clinical services delivery

2.4 The Sponsor

The sponsor is an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs, to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). In addition, the sponsor shall ensure the following:

- ✓ clinical trial is being conducted under qualified and experienced investigator(s)
- ✓ clinical trial application(s) and amendment(s) to the Authority are prepared and submitted,
- ✓ proper monitoring of the clinical trial
- ✓ all the necessary ethic review(s) and regulatory approval(s) are obtained
- ✓ any reviewing ethics board and regulatory Authority are promptly informed of any significant new information in a clinical study
- ✓ compliance with labelling, reporting and record-keeping requirements of IP,
- ✓ clinical trial is conducted in accordance with GCP

- ✓ timely delivery of investigational product(s) to the investigator(s)
- ✓ appropriate procedures for management and maintaining records that document shipment, receipt, storage and storage conditions, return, and safe disposal of the investigational product(s) are in place,
- ✓ storage conditions of investigational products are maintained as specified by the manufacturer.

The agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as annex of the protocol or in a separate agreement.

2.5 Contract Research Organizations (CROs)

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing. The CRO should implement quality assurance systems**.**

2.6 The Principal Investigator (PI)

The principal investigator has a sole or joint responsibility for the design, conduct, delegation of trial responsibilities, analysis and reporting of the trial. The principal investigator is accountable to the sponsor and the Authority. If the principal investigator is not a resident of Rwanda, a resident shall be appointed to assume full responsibilities of Principal investigator for all local trial sites.

The PI shall be knowledgeable and have an understanding of the investigational product. In the case of a multi-centre trial there must be a local principal investigator (PI) attached to each site. The principal investigator shall also ensure:

a) a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties is maintained;
b) research team are adequately trained about the protocol, the investigational product, and their trial-related duties and functions
c) adequate medical care is provided to a study participant for any adverse events, including clinically significant laboratory values,
d) Investigational products are well handled and managed at trial site
e) The effective monitoring and reporting of adverse reactions and events according the timelines set out in regulations and guidelines
f) may assign all duties for investigational product accountability at the trial site to an appropriate pharmacist, medical doctor or another qualified individual who shall be under the supervision of the investigator.

2.7 The Monitor

The monitor is appointed by and reports to the sponsor. The monitor is responsible for overseeing the progress of a clinical trial and ensuring that it is conducted, recorded and reported

in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Pharmacy Practice (GPP).

Monitors should be:

a) appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately and qualifications should be documented.
b) thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to trial participants, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

The monitor shall fulfil the following responsibilities:

a) To verify that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with approved protocol and/or amendments.
b) To act as the main line of communication between the sponsor and the investigator.
c) To verify that the investigator has adequate qualifications and resources (adequate laboratories, equipment, and staff),
d) To verify the proper use of investigational products.
e) To verify that written informed consent was obtained before each subject's participation in the trial.
f) To ensure that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies,
g) To verify that the investigator and the investigator's trial staff are adequately informed about the trial.
h) To control that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
i) To verify that the investigator is enrolling only eligible trial participants.
j) To report the trial participant recruitment rate.
k) To verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
l) To monitor that the investigator provides all the required reports, notifications, applications, and submissions timely.
m) To check the accuracy and completeness of the CRF entries, source documents and other trial-related records

2.7.1 The Auditor

The auditors are independent individuals appointed by sponsors, local and other regulatory authorities to conduct a systematic and in-depth examination of trial conduct and compliance with the protocol, SOPs, GCP, GLP, GPP and the applicable regulatory requirements. An audit is separate from routine monitoring or quality control functions.

2.7.2 The Inspector

The inspector is a qualified employee of local and international regulatory authority whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites/sponsors/CROs/bioequivalence facilities. The inspection of clinical trials is conducted as per Authority guidelines of clinical trial inspection.

2.8 Clinical Trial Approvals in Rwanda

The following steps must be undertaken before a clinical trial can be conducted in Rwanda:

a) **Research Ethics Committee Clearance**: All clinical trials to be conducted in Rwanda must apply for and receive ethical clearance from Rwanda National Ethics Committee (RNEC) or Institutional Review Board (IRB).
b) **Competent Regulatory Authority Approval**: A sponsor/principal investigator (PI) must apply to the Rwanda Food and Drugs Authority for approval to conduct a clinical trial in Rwanda.

3.0 CLINICAL TRIAL PROTOCOL AND AMENDMENTS.

The contents of a trial protocol should include the following topics. However, site specific information may be provided on a separate protocol page or addressed in separate agreements. Some information listed below may be contained in other protocol influenced documents such as the investigator's brochure.

3.1. Trial General Information.

The trial general information shall include:

a) Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
b) Name and address of the Sponsor and monitor (if other than the Sponsor)
c) Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor.
d) Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial
e) 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).
f) Name, title, address, and telephone number(s) of the other investigators designated by the PI to be responsible for some aspects of the study.
g) 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.
h) A clear statement on compensation and benefits package for clinical trial participants.
i) Publication policy.

3.2. Trial background Information

The background shall include:

a) Name and description of the investigational product(s).
b) A summary of findings from nonclinical studies that potentially have significance to the clinical trial.
c) Summary of findings from completed clinical studies/trials that are relevant to the trial.
d) Summary of the known and potential risks and benefits, if any, to human participants.
e) Summary of the local background rates with respect to the condition for which the intervention is proposed.
f) Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
g) Description of the population to be studied.
h) References to literature and data that are relevant to the trial and that provide background for the trial.
i) Justification for the trial is being conducted in Rwanda.

3.3 Trial Objective and Purpose

This section should provide the details and well clear explanations (reason of execution) of the trial being conducted in Rwanda and not in the host country of the applicant. A detailed description of the objectives including general and specific objective as well as purpose of the trial will be provided under this section. Primary and secondary outcomes as well as variables to deal with (dependent, independent and intermediaries) will be addressed in this section.

3.4 Trial design

The Authority acknowledges that scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. Therefore, a description of the trial design should include the following:

a) specific statement of the primary endpoints and the secondary endpoints
b) details justification of the variables to deal with
c) expected trial outcomes in the short- and long-term.
d) description of the trial design to be conducted, such as double- blind, placebo-controlled, parallel design
e) schematic diagram of trial design, procedures and stages.
f) description of the measures taken to minimize and avoid bias including randomization process and blinding;
g) description of the trial treatment(s) dose and dosage regimen of the investigational product(s)
h) description of dosage form, packaging, and labelling of the investigational product(s) and sample of label to be used.
i) planned duration of trial participant, sequence and duration of all trial periods, including follow-up, if any,
j) quantities and source of investigational products or comparators will also be provided

k) detailed description of the "stopping rules" or "discontinuation criteria" for trial participants. parts of trial and entire trial.
l) Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s) in case of premature termination.

3.5 Trial participant eligibility criteria

A brief description of specific characteristics of the trial participants (e.g. disease/ stage/ indication/ conditions/ treatment etc.) as applicable shall be provided. The trial participant inclusion and exclusion criteria shall be clearly defined under this section.

The premature withdrawal criteria such as terminating investigational product treatment/trial treatment and procedures specifying:

a) all withdrawal criteria including voluntary withdrawal by trial participants without prejudice to future treatment by the physician.
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.

3.6 Treatment of trial participants

a) The treatment(s) to be administered to the trial participant shall specify the name(s) of all the investigation product(s), the dose(s), the dosing schedule(s), the route or mode(s) of administration, treatment period and duration(s), including the follow-up period(s) for trial participant for each investigational product treatment/trial treatment arm.
b) Other medication or treatment(s) permitted (including rescue medication) and not permitted before and or during the trial will also be included here.
c) Procedures for monitoring trial participant compliance,
d) Description of treatment applied to control group(s) and/or control period(s), placebo, and other therapy and any other treatment that may be given concomitantly including measures to be implemented to ensure effective safe handling of the products.
e) detailed description of diagnostic devices or kits applied to be used in the clinical trial.
f) Description of special analyses and/or tests or procedures to be carried out.

3.7 Assessment of efficacy

Under this the section of the protocol, the applicant will provide following:

a) the specification of efficacy parameters.
b) methods and timing for assessing, recording, and analysing of efficacy parameters
c) clear procedures for interim assessment of trial

3.8 Assessment of safety

Under this the section of the protocol, the applicant will provide following:

a) The specification of safety parameters.
b) The methods and timing for assessing, recording, and analysing of safety parameters

c) procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.
d) the type and duration of the follow-up of trial participants after adverse events.
e) Provision of dealing with adverse events
f) List of Adverse Event of Special Interest (AESI) and/or Expected Adverse Events information which include whether the event is related to intervention or not, rational for listing each event, expected rate or frequency of each event and laboratory limit if applicable.
g) A copy form that will be used to report adverse events

3.9 Trial statistics

This section shall contain the following:

a) A description of the statistical methods to be employed, including timing of any planned interim analysis.
b) The number of participants planned to be enrolled. In multicenter trials, the numbers of enrolled participants projected for each trial site should be specified.
c) Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
d) The level of significance to be used.
e) Criteria for the termination of the trial
f) Methods for data analyses and evaluation of results.
g) Procedure for accounting for missing, unused, and spurious data.
h) 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).
i) The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

3.10 Ethical Considerations

A clinical trial protocol must include a statement of the ethical considerations involved in the proposed trial and informed consent form or otherwise shall be obtained for each to the trial participants before enrollment. The following bodies are involved in CT review processes in Rwanda:

a) The Rwanda National Ethics committee (RNEC) a central independent body and Local Institutional Review Boards (IRBs.)
b) All clinical trials conducted in Rwanda must undergo ethical review by Rwanda National Ethics Committee.

A valid ethical Clearance Approval shall be provided before the Authority issues an authorization for clinical trial conduction in Rwanda.

3.11 Data Handling and Record Keeping

Research record keeping is not just simply storing the data or notes after publication. It also includes careful recording, clear documentation and proper management of records during and after the research activities. This include but not limited to:

a) 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.
b) 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.
c) 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.

3.12 Publication of clinical trial report

The principal investigator or sponsor has a duty and right to publish trial results. The publication policy, if not addressed in a separate agreement, including a plan for the dissemination of the results (publishing plan) shall be provided as an annex to the trial protocol. Prior to publication, sponsor or principal investigator is required to convene a dissemination meeting among stakeholders and all parties involved.

During the publication of the trial results, the investigators are obliged to preserve the accuracy of the results. For collaborative studies and multi-centre trials, publication conditions need to be clearly outlined in the protocol and authorized by the relevant regulatory authorities

3.13 Protocol Amendment

Any major 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. 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.

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. A list of substantial amendments is attached as **ANNEXURE-XI.**

4.0 TRIAL MASTER FILE & ESSENTIAL DOCUMENTS

The Trial Master File (TMF) refers to a repository of documents that collectively can be used by monitors, auditors, assessors and sponsors to demonstrate that a clinical trial is being or has been conducted in compliance with Good Clinical Practice (GCP) and the approved protocol

The TMF must be updated, maintained and accessible upon request as per the defined SOPs. It is the responsibility of the PI to ensure that the TMF includes all relevant essential documents, and is stored at trial site in a secure location, with restricted access. Ideally, the documents included in the TMF are following:

a) Trial documents (protocol, investigator's brochure, participant information documents, SOPs, instructions, manuals, guidelines, etc.)
b) Documents related to the Investigational Product (certificates of analysis, shipment records, storage records, etc.)
c) Training documentation for trial team (training of site staff, Certificates, training log, etc)
d) Details of the laboratories, if applicable.
e) Contracts, agreements, budgets, etc.
f) Monitoring visit reports (for each site visit onsite or central)
g) Documents related to the safety reporting
h) Regulatory documents (approvals from Authority and Ethics, notifications, reports, etc.)
i) Site specific documents (list of site staff and their CVs, investigator's declarations, site preparedness documents, etc.)
j) Audit related documents, if available (if an audit/inspection was conducted).
k) Significant communications (correspondences with different authorities,
l) Others (routine records such staff meeting minutes, handover documents etc)

If the TMF are kept by different collaborating organizations, they will ensure that there is a clearly documentation process to describe how each section of the TMF is updated.

5.0 QUALITY MANAGEMENT SYSTEM

A formalised system for documenting procedures, processes and responsibilities for ensuring quality and compliance with the Clinical Trials Regulations is implemented. Different quality assurance processes for monitoring compliance with regulatory requirements and SOPs will be available across clinical trial sites. Evidence of activities carried out at clinical trial sites should be included in the Trial Master File to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement.

The research team shall ensure that quality check, audit and monitoring actions are dealt with in a timely manner and corrective actions and preventive actions are implemented in accordance with timelines agreed with the Authority.

6.0 CLINICAL TRIAL SITE OPERATIONS

The clinical trial operations are activities related to the clinical trial conduct at a given site from the start up to the close out. The site operational structure should be composed with a multidisciplinary team to ensure proper planning, conduct, patient safety, and data quality, while fostering good communication between study site team, PI and sponsor.

The activities at clinical trial sites may be coordinated by PI or appointed trial site manager depending on the organizational structure. The approved site organizational structure shall be posted at the entrance of the trial site and shall be verified during the monitoring, or audit/inspection of clinical trials.

7.0 PARTICIPANT INFORMATION /INFORMED CONSENT FORM

7.1 Participant Information

Before enrolling in a clinical trial, the following information must be given to each trial participant in non-ambiguous languages:

a) Title of trial to be conducted
b) A statement explaining the purposes of the trial
c) The expected length of time for participation.
d) A description of all the procedures that will be completed during enrollment on the clinical trial.
e) Any possible benefits that may be expected from the research.
f) A description of any predictable risks.
g) Information about any alternative procedures or treatment (if any) that might benefit the trial participant
h) A statement describing the confidentiality of information collected during the clinical trial, how records that identify trial participant will be kept
i) A statement if any compensation or medical treatments are available if injury occurs,
j) Statement that the participation is voluntary
k) Statement that participant have the right to refuse treatment and will not losing any benefits for which they are entitled
l) A statement on contact information related

The information must be given in at least one of the official languages used in Rwanda that is understandable to the trial participant. The translation in Kinyarwanda shall reflect the original information in other languages (English or French). Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the trial participant or participant legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.

After providing detailed information about the trial, the research team member will evaluate the level of understanding of the study participant using a structured questionnaire. The potential participant to be recruited should score at least 75% of the given tests. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally

acceptable representative. The template of the participant information sheet is provided to guide sponsors or PI when preparing the application (**ANNEXURE-II**).

7.2 Informed Consent Form

The Informed Consent Form (ICF) is an essential component of ethical research. Prior to participation in the trial, a written informed consent form should be signed and personally dated by the trial participant or by the trial participant legally acceptable representative, and by the person who conducted the informed consent discussion. The following information. The ICF to be signed should have the information that the trial participant had:

a) opportunity and adequate time to discuss the study objectives and have had questions well answered.
b) Understood and has rights to drop out at any time
c) Understood and accept to receive investigational product
d) Understood possible benefits and harms
e) agreed to meet the requirements of a trial participant
f) understood that confidentiality will be respected.
g) agreed to the future use of samples taken in this study as explained in the information Sheet.
h) Confirmed voluntary participation in the trial.

1. 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.
2. If a trial participant is unable to read, or is a child, or is in unconsciousness, or is a mentally disabled, a legally acceptable representative should sign the informed consent on behalf of the trial participant.
3. If a trial participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The template of participant Informed Consent Form (ICF) is provided to guide sponsors or PI when preparing the application (**ANNEXURE-III**)

8.0 INVESTIGATIONAL BROCHURE

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/ interval, methods of administration and safety monitoring procedures. The IB shall d have a statement of confidentiality and if new data are generated, the investigational brochures must be updated.

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

a) data on Chemical, physical and pharmaceutical properties and formulations,
b) Preclinical data that includes non-clinical pharmacology, pharmacokinetics and product metabolism in animals, and toxicological data,
c) Human pharmacology that includes pharmacokinetics and metabolism in human, safety and efficacy data
d) Marketing experience in countries where the investigational product is being marketed or approved.
e) Summary of data and guidance for investigators.

The table of content of an investigation brochure is provided on this document for the clear guidance (**ANNEXURE-IV)**

9.0 DATA SAFETY MONITORING BOARD (DSMB)

An independent data-monitoring committee or data core may be established by the Sponsor to assess at intervals the progress of a clinical trial, the safety data, the critical efficacy endpoints, and to recommend to the Sponsor whether to continue, modify, or stop a trial. DSMB shall have terms of reference and appointed qualified and competent members relevant to the clinical trial being conducted. There are always members with clinical and statistical experience, and members with expertise in ethics and the specific disease area. The size and composition of the DSMB depends on the trial.

The Sponsor shall provide a charter of work, membership and curriculum vitae of all the DSMB members as applicable. All members of the DSMB shall sign the charter which should include:

a) Terms of Reference
b) Membership and their CVs
c) Proof of Independence of the Committee
d) Scope of work for DSMB Members
e) Meeting schedules
f) Standard Operating Procedures of the Committee
g) It is recommended that at least one member of the DSMB is a Rwandese

10.0 MATERIAL 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. All the concerns about material transfer agreement will have to be addressed in the agreement and will comply with the template as provided on the attachment of this document (**ANNEXURE-V)**

11.0. REPORTING IN CLINICAL TRIALS

In line with regulations governing clinical trials in Rwanda, the PI shall submit to the Authority the safety reports and other reports such as progress reports, site close out report and final reports according to the timelines set out in relevant guidelines

11.1. Safety Monitoring and Reporting of Adverse Events

11.1.1 Safety Monitoring of Adverse Events

a) The principal investigator or sponsor should ensure that the trial is adequately monitored for the protection of the rights, safety and well-being of trial participants and for the collection and analysis of high-quality data.

b) The principal investigator should monitor on regular basis the safety of study participants
c) The principal investigator should make close follow up of the participant that reported any serious event
d) In blinded trials eg double blind studies, when a serious adverse event is judged reportable on an expedited basis, the blind may only be broken for that specific trial participant by the sponsor even if the investigator has not broken the blind.
e) Data Safety Committee or Data Safety Monitoring Board will carry interim analysis for the safety reports and formulate appropriate recommendations
f) The sponsor shall also ensure that the report of interim safety data analysis from Data Safety Committee or Data Safety Monitoring Board are submitted to Rwanda within fifteen (15) calendar days
g) The overall safety evaluation of the test drug(s)/investigational product(s) should be reviewed, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths.
h) Any patients or patient groups at increased risk should be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of drug metabolism or excretion etc.
i) The Authority should closely monitor the frequency, severity and seriousness of reported adverse event and conduct investigation where necessary.

11.1.2 Reporting of Serious Adverse Events (SAEs)

In line with regulations governing clinical trial in Rwanda, the Principal investigator (PI) will:

a) report to the sponsor all serious adverse events (SAEs), both expected or unexpected, as soon as possible but no later than seventy-two (72) hours upon receiving notice of such an event.
b) 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.
c) report adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations
d) submit autopsy reports and terminal medical reports in case the SAEs resulted in death of trial participants.
e) Submit causal relationship between SAEs and the Investigational product that is established, evaluated, and clarified for further assessment;

11.1.3 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

In line with regulations governing clinical trial in Rwanda, the Principal investigator (PI) will:

a) report to the sponsor all Suspected Unexpected Serious Adverse Reactions (SUSARs) as soon as possible but no later than seventy-two (72) hours upon receiving notice of such an event
b) Report 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;
c) report adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations
d) submit autopsy reports and terminal medical reports in case the SUSARs resulted in death of trial participants.
e) Submit causal relationship between SUSARs and the Investigational product that is established, evaluated, and clarified for further assessment.

11.1.4 Management of Safety Reports

All safety reports shall be reported using the ADR/AEFIs reporting forms as **ANNEXURE-VI** and completed forms are sent to *pv_sm@rwandafda.gov.rw* or using online reporting portal of PharmacoVigilance information Monitoring System (PViMS): https://pvims.rwandafda.gov.rw/security/landing

The Authority records and analyses received safety reports and provides feedback. The Authority may require additional information in case the event reported resulted in death of a trial participant or conduct an investigational inspection at the site.

The causality assessment of safety reports shall be done by the internal committee established by the Authority. The PI shall continue the follow up on the outcome of the reported SAEs and SUSARs and report to the Authority in the progress or final report as required.

11.2. Progress reports

In line with regulations governing clinical trials in Rwanda, the PI shall submit to the Authority the following reports:

a) Monthly progress report for study not exceeding six (6) months,
b) Quarterly progress report for studies with more than seven (7) months and less or equal to eleven (11) months,
c) Six (6) months progress report for one-year study and above;

The progress report shall be submit using the format provided as **ANNEXURE-VII** to these guidelines.

11.3 Site Close out report

The PI shall submit to the Authority within thirty (30) calendar days from the day of last enrollment of trial participant the close out report to document that all activities required for trial are completed, and copies of essential documents are held in the appropriate files. The content and format of close out report will comply with the close out reporting format attached as **ANNEXURE-VIII**. In this report, the management of remaining investigational medicinal products (IMP) will be highlighted and copy (ies) of disposal certificate should be provided as annexes to the report.

11.4 Trial Final Report

The 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 (Guideline's structure and content of clinical study report). The content and format of Final Trial Report will comply with final trial report format attached as **ANNEXURE-IX**. 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.

The Authority will record and analyze all received progress, close out and final reports from approved clinical trials and provide feedback. After completion of analysis of the final report, the Authority updates the registry for clinical trials in Rwanda. The analysis will be done in accordance with pre-established procedures described in standards operating procedures.

12.0 SUSPENSION OR TERMINATION OF A CLINICAL TRIAL

In line with regulations governing clinical trial conduct in Rwanda, the Authority may:

1. suspend or terminate the authorization to conduct clinical trial due to non-compliance with existing laws, regulations and guidelines by a notice in writing to the holder of clinical trial authorization;
2. 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. 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
4. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants, ensure appropriate therapy and follow-up for the trial participants, and inform the Authority.

13.0 MANAGEMENT OF INVESTIGATIONAL PRODUCTS

13.1 Manufacturing, importing, packaging, labelling, and Coding of IP(s)

1) The investigational product(s) (including active comparator(s) and placebo, if applicable) should be characterized as appropriate at the stage of development manufactured in accordance with current GMP principles.
2) The IP should be coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with labelling requirement(s);
3) The import permit of investigational products and trial products shall be obtained from the Authority. The requirements for importing IP are detailed in the guidelines for importation of medical products. However, the valid clinical trial approval certificate is a prerequisite to obtain an import permit of IPs;
4) The quantities of investigational products to be imported should correlate with number of trial participants to be enrolled;
5) The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations;
6) The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage;
7) In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding;
8) If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

13.2 Supplying and handling of investigational Product(s)

1) The investigational product(s) should be stable over the period of use. In case of shelf-life extension, the authorization should be obtained from the Authority.
2) Quantities of the investigational product(s) supplied on the site should correlate with trial participants and trial protocol.
3) SOPs for management of investigational products (IP) at the site should be in place;
4) The pharmacist shall ensure the good storage, distribution and dispensing of the IP;
5) The pharmacist should maintain an inventory of the IP at the site, those used by trial participants, return to sponsor or alternative disposal of unused investigational product(s);
6) The Investigational product(s) should be used only on the trial participants in accordance with the approved protocol;
7) If there is blinding, there should be criteria for breaking of the code;
8) The pharmacist should explain the correct use of the IP and check at appropriate intervals during the trial, that each trial participant is following the instructions.

13.3 Randomisation Procedures and blinding

In the case of randomization of participants, the procedure must be documented. In a blinded, randomized study it is usually necessary to supply and keep the treatment code for each individual participant at both the study site and with the sponsor.

The investigator should follow the trial's randomisation procedures and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

The date, reasons for, and name of the individual breaking the study code must be documented. Before the treatment code is broken for statistical analysis, the code for each participant must be returned to the sponsor with a documented explanation for each episode where the code was broken. Any master code supplied (e.g. to the pharmacy) must be returned to the sponsor. No copies of the code should be taken by any person involved in the study. Copies of the treatment code will be available to the investigator at the end of the study after the database is locked.

14.0 COMPENSATION AND INSURANCE COVER

The sponsor should ensure all trial participants are satisfactorily insured against possible injuries that might arise during the conduct of the clinical trial. A valid insurance certificate covering the duration of the study must be provided prior to study initiation. The Authority reserves the right, after review and analysis of the design and interventions, to exempt trial participant insurance if the study does not compromise the safety of the trial participants.

An insurance certificate shall contain at least the following:

a) Insurance company

b) Policy number
c) Initial Date
d) Expiry Date
e) Insured (Policy Holder/Sponsor)
f) Description of activity (purpose of the policy)
g) Information concerning the trial: Title of insured protocol &protocol number (if available), number of trial sites, number of participants (planned number of patients who are expected to take part in the clinical trial)
h) list of 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)

15. **FINANCIAL DECLARATION**

The financial aspects of the trial should be documented in an agreement between the Sponsor and the Principal Investigator/Contracted Research Organization/Institution. 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.

16 TRANSPARENCY &CONFLICT OF INTEREST MANAGEMENT

The clinical trial oversight activities will be conducted in a transparent manner in accordance with provisions of regulations, guidelines and standards operations procedures for clinical trials. A Clinical Trial Registry (CTR) that includes authorized, ongoing, suspended, terminated and/or completed clinical trials will be publicly accessible. The rights of trial participants in terms of privacy and confidentiality must be protected and maintained at all cost.

Institutions including organizations sponsored to conduct clinical trials and research ethics committees must have clearly formulated policies regarding conflicts of interest to ensure high ethical standards in clinical trials. Any financial compensation received from trial sponsors must be commensurate with the efforts of the research team. Financial compensation should be at fair market value, and the rate of compensation per trial participant should not vary according to the volume of trial participant enrolled by the research and should meet other existing legal requirements. Furthermore, it is unethical for the research team to accept payment solely for referring participants to the trial site. A declaration of any potential conflicts of interest (s) should be provided for all investigators.

17.0 CLINICAL TRIAL CONDUCT IN SPECIAL POPULATION

The special populations include but not limited to children, pregnant women, prisoners, unconscious, disabled individuals, elderly people, ethnic minorities, patients with incurable

diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

The special population whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention.

The PI or Sponsor shall justify the involvement of the special population and ensure appropriate evaluation procedures for ascertaining participants' ability to give informed consent. If the trial participants are deemed unable to understand and to make a choice, then an appropriate legal representative may consent on their behalf.

18.0 MULTI-CENTRE CLINICAL TRIALS

A multi-Centre clinical trial shall be conducted by several investigators in several sites in accordance with a single trial protocol. Trial sites may be located in one or several countries:

a) If a multi-centre clinical trial is being conducted and all research centres are located in Rwanda, the IRB/IEC shall issue a single opinion regarding such clinical trials.
b) If a multi-centre clinical trial is conducted in more than one country simultaneously, the IRB/IEC shall provide a single opinion regarding the clinical trial site (s) in Rwanda
c) If a multi-centre clinical trial is conducted and all research centres are located in Rwanda, the Authority shall take a single decision regarding such clinical trials.
d) If a multi-centre clinical trial is conducted in more than one country simultaneously, the Authority shall take a single decision regarding the clinical trial in Rwanda

The multi-country trials conducted in Rwanda shall comply with applicable laws, regulations, guidelines governing clinical trial conduct and other relevant documents such as standard treatment guidelines used in Rwanda.

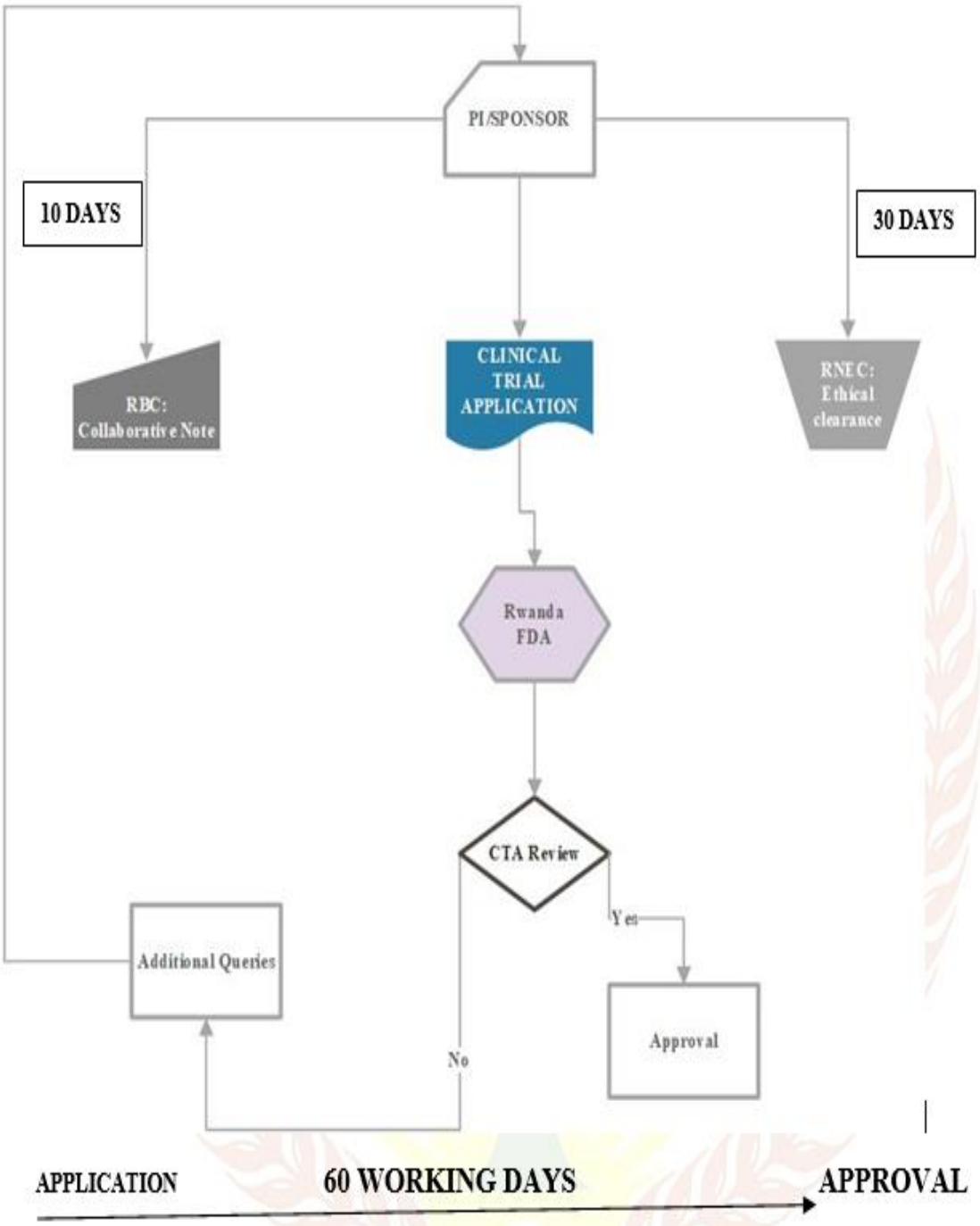
19.0 SANCTION AND PENALTIES

Any person who contravenes these Guidelines or sections is liable to regulatory sanctions and penalties which shall be imposed by the Authority. These sanctions may include but not limited to any of the under listed, Suspension of an on-going clinical trial, Revocation of a clinical trial approval issued (stopping of a trial/recall of all investigational products).

20.0 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	22/07/2021	22/07/2021	23/07/2021

ANNEXURE-I. FLOWCHART OF APPLICATION PROCESS



ANNEXURE-II. FORMAT FOR PARTICIPANT INFORMATION SHEET

Study Title:
Study Centre:
Principal Investigator:
Sponsor:
Language: English/French/Kinyarwanda

INTRODUCTION.

1. What does my participation involve?

The purpose of this section is to state the reason the participant is being invited to take part in the research project and to explain the purpose of the form and the nature of informed consent.

Examples of statement:

You are invited to take part in this research project, which is called [*Name of research project*]. You have been invited because [*Explain reason for invitation*]. Your contact details were obtained by/from [*provide details]*.
This Participant Information Sheet/Consent Form tells you about the research project. It explains the processes involved with taking part. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local health worker. Participation in this research is voluntary. If you don't wish to take part, you don't have to. If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- ✓ Understand what you have read
- ✓ Consent to take part in the research project
- ✓ Consent to be involved in the research described
- ✓ Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep. You will be given a copy of this Participant Information Sheet to keep.

2. What is the purpose of this research?

Briefly describe the following aspects of your project in simple terms and in only a couple of sentences for each point:

- ✓ Aim of the project and its significance
- ✓ How the project is intended to fill any gap in knowledge
- ✓ How it may contribute to care or education or research in the future

- ✓ Any relevant background including what is already known
- ✓ Whether the research is for the purpose of obtaining a degree or other educational qualification, is funded by a grant, or has sponsorship of some kind.

3. What does participation in this research involve?

Include information and clear explanation of the following:

- ✓ *Consent form will be signed prior to any study assessments being performed*
- ✓ *Initial steps: Screening for eligibility, Randomisation and/or the use of a control group Where a control group or similar methodology is to be used in your research, you should include a statement that participants may be allocated to either a control or experimental group, and that they may not be told which of these groups they are in.*
- ✓ *Procedures and Activities: all procedures and activities, nature, number, timing and time commitment of procedures and activities, visits, questionnaires, interviews, focus groups, etc:*
  - *a) Nature of follow-up*
  - *b) Duration of participant's involvement (including follow-up)*
  - *c) Duration of the research project (if this is different from their involvement)*
- ✓ *Reimbursement and costs (if applicable)*
- ✓ *How the research will be monitored*
- ✓ *The commitment required by the participant*
- ✓ *Access to personal records that may be required*
- ✓ *Whether any part of the research project will be recorded (video/audio). Information that should be included: They will be taped or photographed (they should also be reminded of this before data is collected).*
  The tape or a certified transcript of the tape is raw data and will be securely retained for five years.
  Their identity can be masked if they request this.
  If another organisation or person has rights of access to the data collected on tape.
- ✓ *Details on the use of interpreters in the consent and/or data collection process*
- ✓ *Venue details and a statement whether participants may choose the venue*

Explain any other relevant information including:

- ✓ *How many people will be taking part in the project overall and at this site*
- ✓ *Whether there are different groups e.g. case/control groups, different types of focus groups*
- ✓ *The size or scope of a project e.g. number of schools or hospitals or countries involved*
- ✓ *Whether the project involves researchers from a number of organizations working in collaboration*
- ✓ *Whether this is a follow-on study/sub-study/extension study. If so, state the relationship to the previous research and specify if data may be used for future research*

Email or internet distribution

If you will use email or the internet to distribute questionnaires and receive responses, you should include the following statement in the information provided to participants:

The researcher will take every care to remove any identifying material from the responses you provide as early as possible. Likewise, individuals' responses will be kept confidential by the researcher and will (or participants will) not be identified in the reporting of the research. However, the researcher cannot guarantee the confidentiality or anonymity of material transferred by email or the internet.

Examples of statement:

If you decide to take part in the research project, you will first be given a questionnaire asking about [provide details]; this will determine if you are eligible to take part. Completing the questionnaire will take approximately [*specify expected time*].
If the screening questionnaire shows that you meet the requirements, then you will be able to start the research project. If the screening questionnaire shows that you cannot be in the research project, the research coordinator will discuss other options with you.
This research project has been designed to make sure the researchers interpret the results in a fair a There are no costs associated with participating in this research project, nor will you be paid.
However, you may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visit and appropriate way and avoids study doctors or participants jumping to conclusions.

4. Other relevant information about the research project?

Explain any other relevant information including:

- ✓ *How many people will be taking part in the project overall and at this site*
- ✓ *Whether there are different groups e.g. case/control groups, different types of focus groups*
- ✓ *The size or scope of a project e.g. number of schools or hospitals or countries involved*
- ✓ *Whether the project involves researchers from a number of organisations working in collaboration*
- ✓ *Whether this is a follow-on study/sub-study/extension study. If so, state the relationship to the previous research*

5. Information of Investigational Products

In addition to the usual information, participant information sheets for protocols involving drug therapy must include:

- ✓ *Name of drug (generic preferred, trade name if necessary to the study design)*
- ✓ *any conditions in which the drug should not be taken (for example during pregnancy)*
- ✓ *whether the drug is meant to treat the disease or to relieve symptoms, and therefore how important it is to take the drug*
- ✓ *how to tell if the drug is working and what to do if it appears not to be working*
- ✓ *when and how to take the drug (for example before or after meals)*

- ✓ *what to do if a dose is missed and the implications of not taking the drug for any length of time*
- ✓ *any interactions with alcohol or other drugs (generic and trade names)*
- ✓ *storage and disposal of the drug*
- ✓ *risks, side effects, discomforts, inconveniences, restrictions, or other negative effects which might occur as a result of taking the drug*
- ✓ *the probability of adverse effects from the test drug compared with other procedures (or drugs) used for the same purpose*
- ✓ *any category of participant to be excluded from the research*
- ✓ *an explanation that randomisation and/or placebos may be used (where relevant)*

6. Radiation

In addition to the usual information, participant information sheets for protocols involving radiation must include the following statement
In this project you will be exposed to radiation at a level considered safe for you as long as you have not also been exposed to radiation in other research projects or as a part of investigation (X-Rays) or treatment (Radiotherapy) in the past year. Please advise the researcher if you have had any exposure to radiation for any reason in the last year.

7. Do I have to take part in this research project?

Explain that taking part in the research is entirely voluntary.

Examples of statement:

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine care, your relationship with professional staff or your relationship with [*Institution*].

8. What are the possible benefits of taking part?

Do not attempt to build up participant hope in this section. Reference to the potential benefit to others in the future may be appropriate, but should not be exaggerated. You should give potential participants an idea of what they should expect if they agree to take part. It is important that you consider their perspective and likely view of any impacts on them, their lives and those close to them. Potential participants need to know what they are being asked to give consent to, so make it clear what elements are additional to standard care, and/or what elements of standard care they may not receive if they agree to take part. There will be specific issues pertinent to your particular study and the types of participants you intend to recruit which must

be considered here (e.g. adults not able to consent for themselves or children / young people). Specific issues may include:

Examples of statement:

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include [*describe any likely benefits to participants or other people in the future*].

9. What are the possible risks and disadvantages of taking part?

Provide information on the possible risks with taking part in this research project and strategies the researchers will use to manage and/or minimize the risks. Please include details of all significant risks of harm, risks to confidentiality and psychological risk. Some specific issues you should consider include:

- ✓ *Impact on possible pregnancy and breast feeding, including young people and pregnancy*
- ✓ *Side effects of treatments / therapies in trials*
- ✓ *Discovering health related findings*
- ✓ *Impact on insurance*

Try to describe the likelihood of adverse things happening, as well as severity in language all potential participants are likely to understand All group participants will be asked to maintain the confidentiality of group discussions and identity of participants.

Finally, you should provide potential participants with more details of what is involved so that you can fully support them in making an appropriate decision. Some of the issues that might be appropriate here include:

- ✓ *What if something goes wrong?*
- ✓ *What will happen if I don't want to carry on with the study?*
- ✓ *How will my information be kept confidential?*
- ✓ *What will happen to the results of this study?*
- ✓ *Who is organizing and funding this study?*
- ✓ *How have patients and the public been involved in this study?*
- ✓ *Who has reviewed this study?*
- ✓ *Further information and contact details*
- ✓ *What to expect during the consent process?*
- ✓ *What if relevant new information becomes available?*
- ✓ *Informing General Practitioner / other healthcare practitioner*
- ✓ *What will happen to the samples I give?*

Examples of statement:

You may feel that some of the questions we ask are stressful or upsetting. If you do not wish to answer a question, you may skip it and go to the next question, or you may stop immediately. If you become upset or distressed as a result of your participation in the research project, the

research team will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research team. This counselling will be provided free of charge

10. What if I withdraw from this research project?

Provide information regarding how participants withdraw and implication for them if they do so. Include information on the use and submission of the withdrawal of consent form. Where appropriate, explain that if a participant withdraws part-way through a research project that data collected to that point may not be able to be deleted.

Examples of statement

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. A member of the research team will inform you if there are any special requirements linked to withdrawing. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

11. Could this research project be stopped unexpectedly?

The participant should be advised of the potential for the project to be terminated before completion and the reasons that might make termination necessary.

Examples of statement

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as [*provide details of possible reasons*].

12. What will happen to information about me?

Information should be provided regarding the following:

- ✓ *Whether the data collected or used is individually identifiable, re-identifiable (coded) or non-identifiable*
- ✓ *Where the data will be kept and who will have access to it*
- ✓ *How long it will be stored and what will happen to the data at the end of the storage period (Refer to your institution's policy on retention of study data)*

- ✓ *Whether the participant is being asked to provide consent for the use of their data for this project only, or for extended (related research) or unspecified (any future research) use of their data*

Examples of statement

By signing the consent form, you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. [*Explain how it will be confidential and, if it is identifiable, where it will be kept and who will have access to it*]. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

The personal information that the research team collect and use is [*types of information, e.g. information from questionnaires*].

13. What about compensation and complaints?

You should inform participants how complaints will be handled and what redress may be available. Clarify whether there is a procedure in place for this and, if so, what the procedure is. You will need to distinguish between complaints from participants regarding their treatment by members of staff/the research team and something serious happening during or following their participation in the research project.

Examples of statement:

You will not be paid to take part in the study; however, we will make sure that you don't bear additional costs from your participation. All diagnostic tests will be free of charge, as well as the treatment you may need during your participation. If you suffer any distress or psychological injury as a result of this research project, you should contact the research team as soon as possible. You will be assisted with arranging appropriate treatment and support.

14. Who is organising and funding the research?

Organising and funding research. Where commercial sponsorship is available, provide the international sponsor (if applicable)

Examples of statement:

This research project is being conducted by [*Name of person*].

This research is being conducted by [*name of international sponsor*].

It is being funded by [*Name of funding organisation and address*].

15. Who has reviewed the research project?

All research in Rwanda involving humans is reviewed by an independent Ethics Committee and approved on the competent Authority (Rwanda FDA) in case they involve regulated products

Examples of statement:

The ethical aspects of this research project have been ethically cleared by [*RNEC/IRB of institution*] and approved by Rwanda FDA. This project will be carried out according to the principles of Good Clinical Practices and other regulatory requirements which has been developed to protect the interests of people who agree to participate in human research studies.

16. Further information and who to contact

List the names and contact phone numbers of other appropriate persons involved in the project including researchers and study coordinators.

Examples of statement:

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the principal investigator on [*insert Names, Positions, Phone number, e-mail Adress*] or any of the following Research contact persons and Research site manager [*insert Names, Positions, Phone number, e-mail Adress*]*:*

ANNEXURE-III: PARTICIPANT INFORMED CONSENT FORM(ICF)

Title: [*Insert the Project Title***]**
Short Title: [*Short Project Title if Any***]**
Protocol Number: [*Insert the Protocol Number*]
Project Sponsor: [*Insert the names of Project Sponsor*]
Principal Investigator: [*Insert the names of Principal Investigator/*
Research Site: [*Location where the research will be conducted*]

I [*insert the names of participant*] have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received**.**

I understand that research team, representatives from the sponsor, members of the National Ethics Committee or Rwanda FDA overseeing this study and will be given access to my medical records so they can verify what was done and look at the data. In signing this, I authorize access to my medical records.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without penalty and any loss of medical care

I understand that I will be given a signed copy of this document to keep.

I voluntarily agree to participate in this study.

[Insert the Names of Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

Declaration by Researcher

I have given a verbal explanation of the research project [Insert the name of research]; its procedures and risks and I believe that the participant has understood that explanation.

[Insert the Names of Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

INFORMED CONSENT FORM(ICF) FOR LITERATE PARTICIPANT

Title: [*Insert the Project Title***]**
Short Title: [*Short Project Title if Any***]**
Protocol Number: [*Insert the Protocol Number*]
Project Sponsor: [*Insert the names of Project Sponsor*]
Principal Investigator: [*Insert the names of Principal Investigator/*
Research Site: [*Location where the research will be conducted*]

I [*insert the names of participant*] have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I have read the patient information sheet, or it has been read to me, and I have understood the purpose of the study, the procedure to be conducted, and the risks and benefits related to my participation. I have had the opportunity to ask questions and all have been answered to my satisfaction.

I understand that study staff, representatives from the sponsor, members of the ethics committee overseeing this study and the regulatory authority will be given access to my medical records so they can verify what was done and look at the data. In signing this, I authorize access to my medical records.

I understand that I may drop out of this study at any time, for any reason, without penalty and without any loss of medical care.

I voluntarily agree to participate in this study.

[Insert the Names of Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

Witness (if participant is illiterate):

I have witnessed the accurate reading of the consent form to the participant. I confirm that the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

[Insert the Witness Names of Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

INFORMED CONSENT FORM(ICF) FOR LITERATE PARENT

Literate Participant

Title: [*Insert the Project Title***]**
Short Title: [*Short Project Title if Any***]**
Protocol Number: [*Insert the Protocol Number*]
Project Sponsor: [*Insert the names of Project Sponsor*]
Principal Investigator: [*Insert the names of Principal Investigator/*
Research Site: [*Location where the research will be conducted*]

Declaration by literate parents or guardians of participants aged 5 to 17 years (children)

I [*insert the names of participant*] have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I have read the patient information sheet, or it has been read to me, and I have understood the purpose of the study, the procedure to be conducted, and the risks and benefits related to my child's participation. I have had the opportunity to ask questions and all have been answered to my satisfaction.

I understand that study staff, representatives from the sponsor, members of the ethics committee overseeing this study and the regulatory authority will be given access to my child's medical records so they can verify what was done and look at the data. In signing this, I authorize access to my child's medical records.

I understand that my child may drop out of this study at any time, for any reason, without penalty and without any loss of medical care.

I voluntarily agree for my child to participate in this study.

[Insert the Names of Child Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

[Insert the Names of Witness Parent/Legal Guadian (please print)]

Relationship with the participant: Mother /Father /Other legal guardian, specify……

Signature **Date:** (DD/MM/YYYY)

INFORMED CONSENT FORM(ICF) FOR ILLITERATE PARENT

Literate Participant

Title: [*Insert the Project Title***]**
Short Title: [*Short Project Title if Any***]**
Protocol Number: [*Insert the Protocol Number*]
Project Sponsor: [*Insert the names of Project Sponsor*]
Principal Investigator: [*Insert the names of Principal Investigator/*
Research Site: [*Location where the research will be conducted*]

For witnesses of illiterate parents or guardians of participants aged 5 to 17 years (children)

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Consenting parents/guardians who are illiterate should include their thumb print.

I have witnessed the accurate reading of the consent form to the parent/guardian of the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

[Insert the Names of Child literate Participant (please print)]

Signature **Date:** (DD/MM/YYYY)

[Insert the Names of Witness Parent/Legal Guadian (please print)]

Relationship with the participant: Mother/ Father /Other legal guardian, specify:……

Signature **Date:** (DD/MM/YYYY)

Investigator (or designee):

I, the undersigned, have defined and explained to the participant in a language he/she understands, the procedures of this study, its aims and the risks and benefits associated with his/her participation. I have informed the participant that confidentiality will be preserved, that he/she is free to withdraw from the trial without affecting the care he/she will receive at the hospital. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this ICF has been provided to the participant.

[Insert the Names of Investigator/Designee (please print)]

Signature **Date:** (DD/MM/YYYY)

ANNEXURE-IV. FOMAR OF INVESTIGATIONAL BROCHURE

a. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. 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. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guidance provides the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. 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. 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. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

b. General Considerations

The IB should include:

2.1 Title

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

3.1 Table of Contents

3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in

humans. The information provided may include the following, as appropriate, if known/available:

- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Species tested
Number and sex of animals in each group
Unit dose (e.g., milligram/kilogram (mg/kg))
Dose interval
Route of administration
Duration of dosing
Information on systemic distribution
Duration of post-exposure follow-up
Results, including the following aspects:

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans.

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related product.

A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product

4 APPENDIX 1:

TITLE PAGE (Example)
SPONSOR'S NAME
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)
INVESTIGATOR'S BROCHURE
Edition Number:
Release Date:
Replaces Previous Edition Number:
Date:

5 APPENDIX 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

NB: References on 1. Publications
2. Reports
These references should be found at the end of each chapter
Appendices (if any)
Single dose
Repeated dose

Carcinogenicity
Special studies (e.g. irritancy and sensitisation)
Reproductive toxicity
Genotoxicity (mutagenicity)

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

ANNEXURE-V. FORMAT MATERIAL TRANSFER AGREEMENT

Material transfer agreement
Parties (Sender and receiver of CT materials)
The sender:
P.O. Box
Tel
Fax:
Email)
and
[*Insert other party's details including ABN and address*] (Recipient)

Background

The sender proposes to provide, or as at the date of this agreement has provided, the recipient with the Materials (as defined below) and any related Confidential Information for the purpose of [*to insert accurate description of the purpose for which the material is being provided to Recipient – if there is a detailed project, then the protocol number should be referenced here*]

Purpose.

The Recipient has agreed to use the Material and to keep confidential all Confidential Information of the subject to the following terms and conditions of this agreement

Description of the Materials

The Materials being provided by …….. to the Recipient include: [*description of the materials being provided by Supplier – If the Material is data, indicate the type (de-identified, re-identifiable, identifiable), description and format being shared); If the Material is bio specimen, Rwanda FDA or… to ensure compliance with the Policy to Store and Access Samples Stored Offsite accessible on our intranet*]

Defined terms

In this document:

Confidential Information of the sender includes the following, whether or not in material form:
all information that is confidential to the sender and that is disclosed (whether before or after the execution of this agreement) by t the Recipient including but not limited to all information relating to the Material and any confidential know-how, data, results, models, samples, intellectual property, technology, trade secrets, drawings, processes, formulae, product development plans,
but excludes the following information, being information that:
is public knowledge or is lawfully known to or in the possession or control of the Recipient, other than as a result of a breach of confidentiality or this agreement;
is independently developed by the Recipient without the use of the Rwanda FDA confidential information and/or Materials; or
is required by law to be disclosed.
Intellectual Property Rights means all intellectual property rights subsisting anywhere in the world, including the following rights:

patents, copyright (including future copyright and software), rights in circuit layouts, designs, trade and service marks (including goodwill in those marks), domain names and trade names, confidential information and any right to have confidential information kept confidential whether or not such rights are registered or capable of being registered; and to the extent available any application or right to apply for registration of any of the rights referred to in paragraph (a).

Conditions for provision of Material

Use generally

The Recipient:

May only use the Material for the Purpose;

Must not use the Material or any products containing any part of the Material or resulting from the use of the Material, for any commercial purpose without the prior written consent of the sender

Must comply with any applicable laws in relation to the importation, transportation, use, maintenance or disposal of the Material;

must keep the Material secure and protected from unauthorised access, misuse, damage, destruction, unauthorised disclosure or modification, or theft and must immediately report to sender if it suspects the Material has been dealt with contrary to this clause;

must not distribute or release the Material (nor any unmodified derivatives or genetically engineered modifications which are based on the Material) to any person other than the employees of the Recipient, and must make sure that no one is allowed to take or send the Material to any location other than a location under the control of the Recipient without prior written permission from the sender.

The Recipient must not disclose the Material to any third party in any form in or from which an individual's identity is apparent or may reasonably be ascertained without the consent of the sender.

Publication

The Recipient has the right to publish its findings and results from the research with the Material, provided that:

The sender is either named as a co-author or given the opportunity to contribute to the publication, the sender is acknowledged (in a form to be agreed prior to publication) as the source of the Material.

Intellectual Property Rights in Materials and Results

The sender retains all ownership and Intellectual Property Rights in the Material and derivatives of the Material and grants the Recipient a non-exclusive, royalty-free licence to use, adapt, reproduce and exploit the Material for the Purpose;

In consideration of sender supplying the Materials to the Recipient, the Recipient will, as soon as practicable, inform the sender in writing of any and all findings and research results produced by or on behalf of the Recipient related to the use of the Material (Results) and of any new Intellectual Property Rights developed from its use of the Materials. The Recipient and the sender will enter into negotiations to discuss their respective ownership rights in relation to any new Intellectual Property Rights in the Results.

Recipient acknowledgements

The Recipient acknowledges and agrees that:

The Material is made available for investigational use only;
It will not obtain or attempt to obtain any patent protection in relation to:
Any part of the Material (or any modification or use of any part of the Material); or
Any materials that could not have been made but for having access to the Materials,
Without the written consent of the Head of the sender or its legal representative. .

Use and disclosure of Confidential Information

The Recipient agrees to use all Confidential Information solely for the Purpose and to keep it confidential. The Recipient may only disclose Confidential Information to those of its employees and officers who have a need to know and are aware that the Confidential Information must be kept confidential.

The Recipient must establish and maintain effective security measures to safeguard the Confidential Information from access or use not authorised by this agreement and must keep the Confidential Information under its control.

Agreement end and return or destruction of Material and any Confidential Information after agreement ends

Unless otherwise agreed, this agreement ends on the date the associated clinical trial (for which the Materials have been obtained) ends.

Recipient liability

Except to the extent prohibited by law, the Recipient assumes all liability for damages which may arise from its use, storage or disposal of the Material. The sender will not be liable to the Recipient for any loss, claim or demand made by the Recipient, or made against the Recipient by any other party, due to or arising from the use of the Material by the Recipient, except to the extent permitted by law when caused by the gross negligence or wilful misconduct of the sender.

Termination

The sender may terminate this agreement at any time with immediate effect by giving written notice to the Recipient.

Any obligations in relation to confidentiality and privacy under this agreement continue to apply to the parties to this agreement after termination.

Termination of this agreement does not affect any accrued rights or remedies the sender may have.

Miscellaneous

This agreement may be executed in any number of counterparts. All counterparts will constitute one instrument. The parties agree that facsimile or email signatures will be accepted as originals.

A party must not assign or otherwise transfer any or all of its rights arising out of this agreement without the written consent of the other party. This agreement constitutes the entire agreement between the parties with respect to the transfer of Material to the Recipient. This agreement may be amended only by written agreement of both parties.

EXECUTED AS AN AGREEMENT

Signed for …… Head of the sender Institution or by its authorised representative
Signature
Signed for *[insert full name of other party]*
by its authorised representative:

Names

Date of Signature[dd/mm/yyyy]

Signed for *[insert full name of other party]* by its authorised representative Signature

Signed for *[insert full name of other party]*
by its authorised representative:

Names
Date of Signature [dd/mm/yyyy]

ANNEXURE-VI SERIOUS ADVERSE EVENTS (SAE) REPORTING FORM

DIS/FOM/060

RWANDA FDA
Rwanda Food and Drugs Authority
P O. Box 1948 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

ADVERSE DRUG REACTION/ADVERSE EVENT FOLLOWING IMMUNIZATIONREPORTING FORM

Type of Report	**Seriousness of ADR/AEFI**	**Category of Suspected Product**
Initial☐ Follow up☐	Serious☐Not Serious☐	Medical product☐ Vaccine☐

I.PATIENT INFORMATION

Patient ID/initials: _____ **Gender**: Male ☐Female ☐**Weight**(kg)_____ **Height** (m): _____Pregnancy Status: **YES** ☐ **NO** ☐**Date of birth**: ____/____/____ **Patient Address:**Village _____Cell: _____ Sector: _____District: _____ Phone N° _____	**Patient's Medical History**(Provide any relevant medical history and laboratory results including dates (if done): …… …… …… …… ……

II. INFORMATION ON ADVERSE EVENT(S)

Brief description of the ADR/AEFI:

(a) Information on Onset: **Date of ADR/AEFI onset:** ____ /_____/_____(dd/mm/yyyy) **Time of onset:** _____/____/_____(hours, Min, Sec) **Date ADR/AEFI stopped:** _____/ ____/_____(dd/mm/yyyy)	**(d) Adverse Event Evolution/ Outcome:** Recovered ☐ Recovering ☐ Recovered with sequelae ☐ Not recovered ☐ Congenital abnormality ☐ Death ☐ Unknown ☐
(b)Severity of the ADR/AEFI: Mild ☐ Moderate ☐ Severe ☐ Unknown ☐ **Reason for seriousness:** Prolonged hospitalization☐Disability ☐Congenital abnormality☐Death☐Life threatening☐	**(e)Causality of the ADR/AEFI (If performed):** Certain☐Probable/Likely ☐Possible ☐Unlikely ☐Unclassifiable ☐
(c) Action Taken: Drug withdrawn ☐ Dose increased ☐ Dose reduced ☐Dose not changed ☐Substituted ☐Antidote ☐**Other**☐*(Specify):* …… …… ……	**(f) Optional information:** ☐Therapeutic Failure *(Provide information on medicine (s) or vaccine (s) that showed lack of efficacy*…… ☐Medication errors *(Provide details of medication errors)* ……

III. INFORMATION ON SUSPECTED PRODUCT

A. Details of suspected medicinal product Source/Supplier:……

Product brand name&manufacturer	**Generic name/ /Strength/ Dosage form**	**Route of Administration**	**Dose and frequency**	**Starting Date and Time**	**Stopping Date and Time**	**Batch N°. & Expiry date**	**Indications (Reason for use)**
Other medicines used at the same time and/ or in the last one month (including herbal medicines)							

B. Details of Suspected Vaccine					**Diluent (if applicable)**		
Name of vaccine	**Date of vaccination**	**Time of vaccination**	**Dose (1st, 2nd, 3rd etc.)**	**Batch/Lot N° &Expiry date**	**Name of diluent**	**Batch/Lot N°& Expiry date**	**Date & time of re-constitution**

IV. REPORTER INFORMATION

Name of reporter:		Qualification:		Phone number	
Health Facility Name:		District:		Report Reference N°	
E mail Address of Reporter:		Contact/Tel N°:		Date of report:	

Note: Reporters and patients' identity are held in strict confidentiality by Rwanda FDA and protected to the fullest extent of the Law. Once this form is completed please send it to Rwanda FDA via the following email: ***pv_sm@rwandafda.gov.rw***

ANNEXURE-VII. TEMPLATE TRIAL PROGRESS REPORT

To be filled and signed by the investigator and sent to pv_sm@rwandafda.gov.rw

ADMINISTRATIVE INFORMATION	
Reporting Period	**From:** ***dd/mm/yyyy*** **to:** ***dd/mm/yyyy***
Title of Protocol	
Protocol Reference Number	
Protocol Version Number (where applicable)	
Date and Reference Number of the Trial Approval	
Expected Date of Starting (as indicated on the certificate):	***dd/mm/yyyy***
Actual Date(s) of Start (at the Trial Centre(s):	***dd/mm/yyyy***
Names and contact of Principal Investigator	
Names and contact of Co-Investigator	
Names of Sponsor (If applicable)	
Name and address of the Contract research Organization (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted if applicable	
Phase of Trial (if applicable)	
Number of Clinical Trial Site.	
List of Clinical Trial Sites	
Duration of Clinical Trial	
Name of Investigational Product (IP) strength, and dosage form.	
IP Therapeutic indications	
IP Route of Administration	
IP Storage Information	

CURRENT TRIAL STATUS

Tick as appropriate

- ☐ Enrolment has not begun
- ☐ Actively enrolling participants
- ☐ Enrolment closed on: (insert date): participants are receiving treatment/intervention
- ☐ Enrolment closed on: (insert date): participants are in follow-up only.
- ☐ Analysing data
- ☐ Data analysis completed

INFORMATION ON PARTICIPANTS & INITIATED TRIAL ACTIVITIES

1) Number of persons consented.....
2) Number of persons screened.....
3) Number of persons consented and screened who are eligible for the trial.....
4) Quantity of imported investigational products and Placebos…….
5) Quantity of used investigational products and Placebos…….
6) Quantity of destroyed investigational products and Placebos …….

7) Number of participants to which the investigational product(s) has been so administered the first dose.....
8) Number of participants left to be enrolled into the trial.....
9) Number of participants who have discontinued the trial:
   - ✓ by Investigator:
   - ✓ voluntarily:
   - ✓ due to SAE:
   - ✓ lost-to-follow-up:
   - ✓ Death
10) Have there been any Serious Adverse Events (SAEs)? **Yes** ☐ **No** ☐
11) Total number of SAEs: ……. [*attach line list of SAEs documented for the quarter*]
12) Have these SAEs been reported to the Authority? **Yes** ☐ **No** ☐
13) If No, explain.....
14) I there been any amendment to the protocol since the Authority approved? **Yes** ☐ **No** ☐
15) If **YES**, is the amendment submitted to the Authority? **Yes** ☐ **No** ☐
16) If No, explain.....
17) Are there any other developments in the trial that you wish to report to the Authority? **Yes** ☐ **No** ☐
18) If YES, provide details.....
19) Are there any ethical or regulatory issues on which further advice is required? **Yes** ☐ **No** ☐
20) If YES, provide details.....
21) Date for the end of the trial
22) Date for the final trial report
23) Other information not listed:

SUMMARY OF TRIAL PROGRESS STATUS TO DATE

ADDITIONAL COMMENT FROM THE INVESTIGATOR

REEPORT APPROVAL

Names of Investigator	***Date***	***Signature***

ANNEXURE-VIII. TEMPLATE FOR TRIAL SITE CLOSE OUT REPORT

ADMINISTRATIVE INFORMATION		
Title of Protocol		
Protocol Reference Number		
Protocol Version Number (where applicable)		
Date and Reference Number of the Trial Approval		
Expected Date of Starting (as indicated on the certificate):	*dd/mm/yyyy*	
Actual Date(s) of Start (at the Trial Centre(s):	*dd/mm/yyyy*	
Names and contact of Principal Investigator		
Names and contact of Co-Investigator		
Names of Sponsor (If applicable)		
Name and address of the Contract research Organization (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted if applicable		
Phase of Trial (if applicable)		
Number of Clinical Trial Site.		
List of Clinical Trial Sites		
Duration of Clinical Trial		
Name of Investigational Product (IP) strength, and dosage form.		
IP Therapeutic indications		
IP Route of Administration		
IP Storage Information		
TRIAL SITE INFORMATION		
Name and address of Clinical Site		
Date of last recruitment		
Reason for closure		
Site Personnel involved in trial:		
Names	***Title***	***Contact***
	Site coordinator	
	Site Monitor	
	Pharmacist	
	Data Manager	
Are there changes to trial staff since the last		
Is the delegation log up to date?		
Are all training records up to date?		
Have all CAPA's been completed?		
Are progress report submitted according to the timelines?		
OBJECTIVES	**COMMENTS**	

All regulatory and other essential documents are up-to-date and enclosed in Trial Master of File (TMF)	*Provide list of documents on file at the site*
Notification of all relevant oversight bodies of closure of study such FDA, IEC/IRB	
Signed, informed consent is in TMF for each trial participant	*Provide list of participants (use codes/ study IDs)*
Documentation of all protocol violations/deviations and/ or appropriate note- to- files in the relevant essential document	*Provide list*
Appropriate follow- up and reporting of all SAEs to the Authority	*Provide number of SAEs reported and Summary of outcome for SAEs listed is relevant*
Completion of all Case Report forms for each participant	
All AEs and SAEs have been captured, followed, and resolved per protocol, and reported to the appropriate parties (Sponsor, IRB, and regulatory authorities, if applicable) according to protocol reporting requirements	
Source documents for the following Participant ID numbers were reviewed at this visit (add rows as needed): or NA	
Entry/ submission of all relevant data into database / to sponsor/ coordination center. If NOT complete, indicate the timeline for accomplishing this and document in the comments section	
Tentative date for submission of full Clinical Study Report	
***Investigational and Placebo accountability**:*	
Quantity of IPs received	
Quantity of IPs utilized in the study	
Quantity of IPs destroyed (Attach copy of destruction certificate (s)	
Quantity of IPs onsite/ returned to sponsor	
Status/ shipment/ analyses of all participant specimen according to protocol requirements (including plans for future shipments or period of time they will be stored on- site)	
If blinded study drug was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding	
All unused trial supplies properly disposed (on site) / returned to sponsor or manufacturer per instructions from sponsor	
Collected Laboratory Specimens (Samples)	
Confirm that all specimens have either been analyzed or stored for future use	
Ensure that specimens collected for future use have been adequately processed, labeled/de-identified, and stored	

Confirm site process for identification and disposition of future use specimens connected to subjects who withdraw consent or do not consent for their specimens to be saved	
Confirm destruction, per institutional policies, of specimens not identified for future analysis	
Confirm final disposition of study supplies and any equipment provided for the study: <insert study-specific items>	
Specimens collected for future use to be shipped elsewhere (if yes, specify if sponsor or Investigator arranges shipment, file shipping documentation in the Investigator	

CURRENT TRIAL STATUS

Number Screened: ……..

Number enrolled: ……..

Number of loss of follow-up: ……..

Number of Follow-up required: ……..

Number of SAE reported: ……..

Number of protocol amendments: …….

Number of death recorded

ESSENTIAL DOCUMENTS RECONCILIATION

	YES	**NO**	**NA**	**COMMENTS**
Anonymized Subject Screening & Enrolment Log				
Delegation Log				
Visit Log				
Training log				
Protocol Deviation Log				
IP Accountability/Inventory Log				
IP Approval for Transfer (if applicable)				
IP Return documentation				
IP Destruction Form				
IP Storage Temperature Log				
Maintenance Log (Device)				
Sample Inventory Log				
Sample Storage Temperature Log				
Temperature monitoring Device (LogTag) if applicable				

STATUS OF PAST OBSERVATIONS/ RECOMMENDATIONS MADE DURING MONITORING/ GCP INSPECTIONS
Have corrective measures been implemented for all observations and recommendations?), Provide summary of measures implemented for each point
OUTSTANDING ISSUES OR ACTIVITIES TO BE IMPLEMENTED
Include problems identified, if any, and recommendations/ action items for corrections
REPORT APPROVAL

Names of Investigator	***Date***	***Signature***

ANNEXURE-IX. FINAL TRIAL REPORTING TEMPLATE

ADMINISTRATIVE INFORMATION	
Title of Protocol	
Protocol Reference Number	
Protocol Version Number (where applicable)	
Date and Reference Number of the Trial Approval	
Actual Date(s) when the trial initiated of (at the Trial Centre(s):	**DD/MM/YYYY**
Meeting Date:	**DD/MM/YYYY**
Date report issued:	**DD/MM/YYYY**
Data cut-off Date:	**DD/MM/YYYY**
Date of last closing data review:	**DD/MM/YYYY**
Date report issued:	**DD/MM/YYYY**
Names and contact of Principal Investigator	
Names and contact of Co-Investigator	
Names of Sponsor (If applicable)	
Name and address of the Contract research Organization (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted if applicable	
Phase of Trial (if applicable)	
Number of Clinical Trial Site.	
List of Clinical Trial Sites	
Duration of Clinical Trial	
Name of Investigational Product (IP) strength, and dosage form.	
IP Therapeutic indications	
IP Route of Administration	
IP Storage Information	
CURRENT TRIAL STATUS	
Key Issues for Meeting Discussion	
Study Site Status	
Enrolment and Retention Status	
Status of Outcome Measures and Biospecimens	
Major Protocol Changes	
Unanticipated Problems	
Protocol Deviations	
Quality Management	
Efficacy evaluation	
Safety evaluation	
Discussion and overall conclusion	
Identified Study Challenges and Solutions	

Figures	
appendices	
ADDITIONAL COMMENT FROM THE INVESTIGATOR	
REEPORT APPROVAL	

Names of Investigator	***Date***	***Signature***

ANNEXURE-X. TIMELINES FOR PROCESSING APPLICATIONS

#	Clinical Trial Activity	Proposed Timelines
1.	Review and Approval of routine Clinical Trial applications	60 Working days
2.	Review and Approval Clinical Trial Applications during Emergencies	30 Working Days
3.	Notification of Screening outcome from Clinical Trial Applications	10 Working days
4.	Submission of Missing Requirements to the Authority	15 Working Days
5.	Submission of Query responses/additional data to the Authority	30 calendar days
6.	Processing of applications for protocol amendment	30 Working days
7.	Processing of import permits for Investigational Products	4 Working Days
8.	Notice of GCP Inspection findings	30 Calendar days
9.	Communicating GCP Inspection findings	30 Calendar days
10.	Review of final Clinical Trial reports	10 days
11.	Notification of SAEs and SUSARs from Clinical Trials	7 calendar Days
12.	Full Report of notified SAEs and SUSARs from Clinical Trials	8 calendar Days
13.	Submission of annual Progress report	Monthly = study < 6 months Quarterly= study7<11months Six months=study >1 year
14.	Submission of Close out Report	30 calendar Days from the day of last enrolment of trial participant.
15.	Submission of Trial Final Report	90 calendar Days for the enrolment of last trial participant

ANNEXURE-XI. PHASES OF CLINICAL TRIALS

PHASE I

Studies preceding this phase would have established the effect and safety of the product in animals. The purpose of this phase is to establish a preliminary evaluation of safety, tolerance and a first outline of how the drug is metabolized and excreted in humans. Phase I trials, being the first trials of a new drug in humans, shall be conducted in healthy volunteers, with their informed consent, who shall

- ✓ Be aged between 18 and 65 years and in good mental health and not pregnant or lactating.
- ✓ Not have any illness which could potentially affect the results of the trial, or which could create special conditions for unfavourable effects of the drug
- ✓ The number of volunteers participating in this phase of clinical trials shall not be less than twenty-four (24).

PHASE II

The purpose of a phase II trial is to demonstrate activity of the drug and to obtain further safety data. It also aims at the determination of effective dose ranges and regimens and provides an optimal background for the design of future therapeutic trials. This phase may be an open trial in a small number of informed consenting patients suffering from the disease or condition which the product potentially can treat. If the drug is found to be effective at this stage, and the risks considered acceptable, then it progresses to phase III trials

PHASE III

This phase consists of wider participants to further determine the therapeutic effects of the drug and possibly the short and long-term safety and efficacy balance of formulations of the drug.
The effect of treatment with the drug may be compared in this phase with established methods of treatment, if any, or with other control procedures. The design of trials in this phase shall, preferably, be randomized, double-blind or cross-over. Other designs may be acceptable for long-term safety studies. Generally, the conditions of the trial shall be as close as possible to the normal clinical setting in which the disease for which the drug is intended occurs.

PHASE IV

Phase IV trials shall be conducted on an approved product already on the market to find out more about the long-term risks, benefits, and optimal use, or to test the product in different populations of people, such as children. The trial shall include post-market surveillance

ANNEXURE-XII LIST OF SUBSTANTIAL AMENDMENTS

#	Type of substantial amendments	Scope of Substantial amendments	Required supporting documents
1.	**Amendment to Protocol and/or Informed Consent Form**	✓ Change of main study objective ✓ Change of primary or secondary endpoint which is likely to have a significant impact to: (a) the safety, or physical or mental integrity, of any subject of the trial; (b) the scientific value of the trial; (c) the conduct or management of the trial ✓ Use of a new measurement for primary endpoint ✓ New toxicological or pharmacological data or new interpretation of these data which is likely to impact the risk/benefit assessment ✓ Change in the definition of the end of the trial, even if the trial has in practice already ended ✓ Changes to inclusion/ exclusion criteria such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial or the conduct or management of the trial ✓ Addition of treatment arm (including placebo) ✓ Changes relating to the Investigational Product (e.g., change of Investigational Product, doses, mode of administration) ✓ Reduction of number of subject monitoring visits ✓ Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the trial ✓ Change in the overall sample size for the trial	1. Cover letter addressed to DG 2. Clinical Trial Protocol Amendment 3. Summary of Protocol Amendment 4. Revised Clinical Trial Protocol Amendment 5. Revised Informed Consent Form 6. Track Change Version for Informed Consent Form 7. Valid IEC/IRB clearance 8. Proof of payment of prescribed fees for Amendment

		✓ Withdrawal of an independent data monitoring board ✓ Change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment ✓ Any change in study design that fulfils the criteria for 'substantial amendment'	
2.	**Change of Local Sponsor/ Principal Investigator/ Addition of Trial Site**	✓ Change of local trial sponsor ✓ Change of principal investigator ✓ Addition of local trial site and principal investigator ✓ Change of address of local trial site	1. Cover letter addressed to DG 2. Letter from the current local sponsor indicating transfer of local sponsorship to the new local sponsor. This letter should be copied to the new local sponsor and the respective trial site PI(s) and IRB(s). 3. Curriculum Vitae of Principal Investigator 4. Signed Declarations of New PI 5. Informed Consent Form, if revised 6. Site agreement 7. Valid IEC/IRB clearance 8. Proof of payment of prescribed fees for Amendment
3.	**Change of Manufacturer of IP/Change of Chemistry, Manufacturing, Controls (CMC)/Information [if the CMC information had been submitted in the initial clinical trial application]**	✓ Importation of the medicinal product ✓ Change of name or code of IMPs ✓ Immediate packaging material ✓ Manufacturer(s) of drug substance ✓ Manufacturing process of the drug substance ✓ Specifications of active substance ✓ Manufacture of the medicinal product ✓ Specification (release or shelf-life) of the medicinal product ✓ Specification of excipients where these may affect product performance ✓ Shelf-life including after first opening and reconstitution	1. Cover letter addressed to DG 2. For change/ addition of a manufacturer: Good Manufacturing Practice (GMP) certificate; or where the GMP certificate is not available, a declaration by the manufacturer of its compliance with cGMP, and the Certificate of Analysis of the product manufactured by the new manufacturer 3. Revised CMC information 4. Track change of CMC

		✓ Major change to the formulation ✓ Storage conditions ✓ Test procedures of active substance ✓ Test procedures of the medicinal product ✓ Test procedures of non-pharmacopeial excipients	information that had been submitted in the initial clinical trial application. 5. Summary of change of the CMC information 6. Revised investigator's Brochure (IB) if applicable 7. Valid IEC/IRB clearance 8. Proof of payment of prescribed fees for Amendment

***Note**: The Substantial Amendments shall be submitted to the Authority and shall not be implemented before approval or acceptance of notification by the Authority, unless it is an urgent safety measure for trial participants*