RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON GOOD CLINICAL PRACTICES IN RWANDA

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by 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. The Authority issues these guidelines No DD/PIL/GDL/013 on Good Clinical Practices (GCP) in Rwanda in reference is also made to the provisions of the technical regulations Governing the Conduct and Inspection of Clinical Trials in Rwanda especially in its article 32.

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 and in strict compliance with the law relating to research on human beings. The guidelines provide details of the quality processes required in the conduct of clinical trials to ensure that human participants 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 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 contributed to the development, review, and validation of these guidelines.

Prof. Emile BIENVENU
Director General

DOCUMENT DEVELOPMENT HISTORY

First issue date	10/05/2021
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Document Revision History

Revision number	Changes made and/or reasons for revision
0	First issue
1	1. The reference number was changed from DIS/GDL/044 to No FDISM/PVSM/GDL/010 Rev_1 as per the current SOP on document control; 2. Criteria for designing, conducting, recording, and reporting clinical trials in line with ICH GCP guidelines included; 3. Frequency of trial monitoring Trials based on risk and the complexity of clinical trial included; 4. Considerations for inspection of multicentre trials wereincluded; 5. Include necessary editorial changes in line with SOP on document control.
2	1. Adoption of new Rwanda FDA organogram for GCP activities from PVCT to PIL Division; 2. Necessary editorial changes in line with updated SOPs and SOP on document control were included.

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ACCRONYMS AND ABBREVIATIONS

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

GLOSSARY/Definitions

In these Guidelines, unless the context otherwise states:

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

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

"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.
"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.

"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.

"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.

"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 Research 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 assure 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 using 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 humans 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.

"Investigator's Brochure" A compilation of the clinical and non-clinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human study participants.
"Investigator" An individual who conducts a clinical investigation.

"**Law on research of human beings**" means Law N° 015/2022 of 29/06/2022 Relating to Research on Human Being.

"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).

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

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

"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.

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

"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-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.

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

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

"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.

"**Substantial amendment**": means a change to the terms of the protocol or any other trial-supporting documentation that is likely to have a 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 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 that is accessible. A good evidence trail will include documentation that helps 'tell the story of the trial e.g., documents that 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.

"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 conducted.

1. INTRODUCTION

Any research on a human being to be conducted in Rwanda must respect international principles and the provisions of the Law on research of human beings. 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 healthcare 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 provide clinical trial environments with clearly articulated standards of good clinical practice in research that are relevant to local contexts 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 well-being of trial participants are protected and that clinical trial data are credible.

1.1 Scope

These guidelines are based on GCP principles in the conduct and inspection of clinical trials on pharmaceuticals, biological products (e.g. vaccines), radiopharmaceuticals, herbal medicines, and medical devices in Rwanda. These guidelines encourage the implementation of improved and more efficient approaches for clinical trial design, conduct, oversight, recording, and reporting as per the latest version of ICH GCP guidelines.

1.2 GCP Principles in the Rwandan Context

(a) All clinical trials, including Bioavailability and Bioequivalence studies, shall be designed, conducted, recorded, monitored, and reported in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the latest version of ICH GCP guidelines and the provisions of laws and regulations enforced in Rwanda.
(b) Before a trial is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual trial participant, and society. A trial shall be initiated and continued only if the anticipated benefits outweigh the risks.
(c) The rights, safety, and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.
(d) The available non-clinical and clinical information on an investigational product should be

adequate to support the proposed clinical trial.

(e) Clinical trials shall be scientifically sound and described in a clear and detailed protocol.

(f) A trial shall be conducted in compliance with the protocol that has received prior ethical clearance from the Rwanda National Ethics Committee in accordance with the relevant law governing research on human beings and the Approval from the Authority.

(g) The medical care given to, and medical decisions made on behalf of the trial participants shall always be the responsibility of a qualified physician, dentist, or pharmacist when appropriate.

(h) Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her respective task(s).

(i) Freely given informed consent shall be obtained from every trial participant prior to clinical trial participation.

(j) All clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records irrespective of the type of media used.

(k) The confidentiality of records that could identify trial participants shall be protected, respecting the privacy and confidentiality rules in accordance with the applicable laws.

(l) Investigational products shall be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practices (GMP). They shall be used in accordance with the approved protocol.

(m) Systems with procedures that assure the quality of every aspect of the trial shall be implemented. Those systems shall focus on the aspects that are essential to ensure trial participant protection and the reliability of trial results.

(n) Systems with procedures that assure the quality of every aspect of the trial shall be implemented. Those systems shall focus on the aspects that are essential to ensure trial participant protection and the reliability of trial results.

1.3 Conduct of Clinical Trial in Rwanda

Clinical trials in Rwanda shall be conducted in a manner that ensures the safety and well-being of participants and produces reliable and valid results as per the latest version of ICH GCP guidelines. The sponsor or principal investigator who is interested in conducting clinical trial in Rwanda shall submit to the Authority a Clinical Trial Application (CTA) according to the format and content of 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 as in the Guidelines for clinical trial application.

The sponsors or principal investigators are encouraged to visit the Authority's website www.rwandafda.gov.rw to get information regarding regulations, guidelines, and application forms to compile a clinical trial application for review and approval by the Authority. They should also register the clinical trial in at least one of the publicly accessible registries accepting international clinical trial information and which is recognized by the World Health Organization.

The approved clinical trial shall receive the Clinical Trial Approval Certificate (CTAC) and be subjected to GCP inspection at the clinical trial sites to ensure that clinical trials are conducted in accordance with ethical, scientific, and Rwanda FDA regulatory requirements. The GCP inspection criteria for designing, conducting, recording, and reporting clinical trials are stated in the latest version

of the ICH GCP Guidelines.

During the inspection, Rwanda FDA will verify compliance with the following criteria:

(a) **Rwanda FDA clinical trial regulatory requirements:** All clinical trials should have obtained Clinical trial Authorization to conduct the trial and be conducted in compliance with the latest version of ICH GCP guidelines;

(b) **Approved Protocol and its supplementary documents**: The Authority shall verify that the approved protocol is being followed at the trial sites to meet the trial objectives;

(c) **Ethical considerations:** Rwanda FDA shall verify that the trial is conducted in accordance with ethical principles, including obtaining informed consent from participants, ensuring their privacy and confidentiality, and protecting vulnerable populations;

(d) **Investigator qualifications**: Rwanda FDA shall verify that the site's investigators have the appropriate qualifications, training, and experience to conduct the trial;

(e) **Trial site organization**: Rwanda FDA shall verify that the site has adequate setting including working space, consultation area, laboratories, pharmacy, and equipment to ensure safe, consistent, and proper conduct of the trial;

(f) **Management of investigational product(s):** Rwanda FDA shall verify at the site that the conditions for investigational products are acceptable and that the investigational product(s) is supplied only to the eligible trial participants as per specified dose(s) in the approved protocol. The inspectors shall verify and ensure that the receipt, use, return, and disposal of the investigational product(s) at the trial sites are controlled and documented adequately in line with Rwanda FDA regulatory requirement(s);

(g) **Trial Monitoring**: Rwanda FDA shall verify that the trial is monitored to ensure that it is being conducted in compliance with the protocol and that the safety and well-being of participants are being protected;

(h) **Documentation and record keeping**: Rwanda FDA shall verify that the trial-related data and documentation to ensure that they are accurately recorded and properly stored to ensure data integrity;

(i) **Safety reporting:** Any adverse events that occur during the trial should be reported to Rwanda FDA and Rwanda National Research Ethics Committee**;**

(j) **Data analysis**: Rwanda FDA shall verify that the trial data are analyzed using appropriate statistical methods;

(k) **Reporting in clinical trials:** Rwanda FDA shall verify that the results of the trial are reported clearly and concisely and in accordance with Rwanda FDA regulatory requirements;

(l) **Quality assurance and quality control systems:** Rwanda FDA shall ensure that written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the approved protocol, GCP guidelines, and Rwanda FDA regulatory requirements.

2. ROLES AND RESPONSIBILITIES

2.1 Rwanda National Research Ethics Committee (RNEC)

The main responsibility of the RNEC is to safeguard the rights, safety, and well-being, of trial participants in Rwanda. Specific and general responsibilities are provided for under articles 4 and 5 of Ministerial Order No. 002/MoH/2023 of 21/03/2023 relating to Rwanda National Research Ethics Committee on a human being.

In the execution of its roles and responsibilities, RNEC is responsible to:

(a) safeguard the rights, safety, and well-being of all trial participants with special attention paid to the trials involving vulnerable participants;
(b) grant or withdraw ethical clearance approval on clinical trial;
(c) Consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation deemed necessary;
(d) conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human participants;
(e) request more information that would add value to the protection of the rights, safety, and/or well-being of the participants;
(f) determine if the clinical trial proposed protocol and its supplementary documents adequately address relevant ethical concerns and meet applicable regulatory requirements;
(g) determine if the proposed protocol and its supplementary documents adequately address relevant ethical concerns in case the prior consent of the trial participant or the participant's legally acceptable representative is not possible (i.e., in emergencies);
(h) review both the amount and method of payment for participants to ensure that neither present problems of coercion or undue influence on the trial participants;
(i) ensure that information regarding payment to participants, including the methods, amounts, and schedule of payment to trial participants, is outlined in the written informed consent form and any other written information to be provided to the trial participants;
(j) request the sponsor and/or principal investigator to seek final approval from the Authority before initiating the clinical trial;
(k) communicate the list of clinical trials that have obtained favorable/unfavorable ethical decisions to the Authority through the Joint Institutional Collaboration Framework between RNEC and the Authority.

2.2 Roles and Responsibilities of the Authority

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 shall fulfil the following responsibilities:

(a) Issuance of regulations, guidelines, and forms for clinical trial oversight;
(b) Grant of Clinical Trial Approval Certificate for new applications and amendments;
(c) Approval of manufacturing or import license of the investigational importation including placebos;
(d) Inspection of Clinical trials in Rwanda;
(e) Ensure proper coordination and engagement of stakeholders in clinical trials;
(f) Suspending, stopping, or terminating the non-compliant clinical trials if necessary;
(g) Publish register of approved, suspended, and rejected clinical trials.

Moreover, the Clinical trial unit within the divisions of Pharmacovigilance and Clinical Trial in collaboration with Pharmaceutical and Inspections Licensing shall assume responsibilities of clinical trial oversight. The requirements, guidelines, procedures, and forms are developed according to the laws and regulations in Rwanda as well as international clinical trial guidance aiming at protecting the safety and rights of human participants and ensuring that trials are adequately designed to meet scientifically sound objectives, and preventing any potential fraud and falsification of data. The

matters pertaining to clinical trial oversight in Rwanda, roles and responsibilities of the Authority shall be but not limited to:

(a) Review of all reports for clinical trials (safety reports, DSMB reports, quarterly reports, close-out reports, serious adverse event reports, and final clinical trial reports);
(b) Update and maintain the register of clinical trials in Rwanda;
(c) Develop the training needs for capacity building in clinical trials;
(d) Implement the internal tracking system to monitor timelines for clinical trial applications and amendments and GCP inspections (**APPENDIX-V**);
(e) Conduct periodic performance reviews and approval timelines.

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

The Authority shall review clinical trial applications and amendment applications and shall issue the regulatory decision within the timelines described in the guidelines for review and approval of clinical trial applications. After approval, the GCP inspection may be conducted using a risk-based approach. The trial may be inspected at initial, ongoing, and after the trial completion depending on the complexity and risk involved as per the guidelines on GCP inspections.

However, during public health emergencies, the Authority may perform GCP inspections remotely. If a remote inspection reveals issues that require on-site inspection, or the inspection objectives cannot be met remotely, the site shall be physically inspected in accordance with the guidelines on GCP inspection.

2.3 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 approved protocol, the latest version of ICH GCP guidelines, and provisions of laws and regulations enforced in Rwanda. The sponsor ensures that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The roles and responsibilities of the sponsor shall include but not limited to:

(a) ensure that clinical trials is being conducted under qualified and experienced investigator(s);
(b) ensure that clinical trial application(s) and amendment(s) to the Authority are prepared and submitted;
(c) monitor properly the conduct of the clinical trial;
(d) obtain all the necessary ethic review(s) and regulatory approval(s);
(e) promptly inform the Authority and RNEC of any significant new information in the clinical study;
(f) ensure compliance with labeling, reporting and record-keeping requirements of IP;
(g) timely deliver investigational product(s) to the investigator(s);
(h) ensure 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;

(i) ensure that 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.

2.4 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 must implement quality assurance systems.

2.5 The Principal Investigator (PI)

The principal investigator has sole or joint responsibility for the design, conduct, delegation of trial responsibilities, analysis, and reporting of the trial. The PI 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 investigator (s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. They should meet all the qualifications specified in these guidelines and provide evidence of such qualifications through up-to-date curriculum vitae, valid GCP training certificates, and/or other relevant documentation requested by the Authority and/or RNEC according to the requirement set out in the latest version of ICH GCP guidelines.

The PI shall be knowledgeable and have an understanding of the protocol and its supplementary documents as well as the investigational product to be used. In the case of a multi-centre trial, there must be a local PI attached to each site.

The PI shall have different roles and responsibilities including but not limited to ensuring:

(a) A list of appropriately qualified persons to whom he/she has delegated significant trial-related duties is maintained;
(b) the research team is adequately trained about the protocol, the investigational product, and their trial-related duties and functions; adequate medical care is provided to a study participant for any adverse events, including clinically significant laboratory values;
(c) Investigational products are well handled and managed at the trial site;
(d) the effective monitoring and reporting of adverse reactions and events according to the timelines set out in regulations and guidelines;
(e) 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;
(f) any individual or party to whom the investigator delegates trial-related duties and functions

conducted at the trial site;

(g) individual or party involved in the trial is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

2.6 The Monitors

The purposes of trial monitoring are to verify that the rights and well-being of human participants are protected and, that reported data are accurate, complete, and verifiable from trial source documents. The monitor ensures that the conduct of the trial complies with the currently approved protocol/amendment(s), with the latest version of ICH GCP guidelines, and with the provisions of laws and regulations enforced in Rwanda.

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).

The monitors should be appropriately qualified and trained, with documented sound scientific and/or clinical knowledge needed to adequately monitor the trial. He/she should be thoroughly familiar with the investigational product(s), the protocol, the written informed consent form and any other written information to be provided to trial participants, the sponsor's SOPs, ICH GCP guidelines, and the applicable regulatory requirement(s) in Rwanda.

The roles and responsibilities of monitors include but not limited to:

(a) 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) act as the main line of communication between the sponsor and the investigator;
(c) Verify that the investigator has adequate qualifications and resources (adequate laboratories, equipment, and staff);
(d) verify the proper use of investigational products;
(e) verify that written informed consent was obtained before each participant participated in the trial;
(f) ensure that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies;
(g) verify that the investigator and the investigator's trial staff are adequately informed about the trial;
(h) 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) verify that the investigator is enrolling only eligible trial participants;
(j) report the trial participant recruitment rate;
(k) verify that source documents and other trial records are accurate, complete, kept up-to-date, and maintained;
(l) monitor that the investigator provides all the required reports, notifications, applications, and submissions timely;

(m) check the accuracy and completeness of the CRF entries, source documents, and other trial-related records.

2.7 The Auditor

The auditors are independent individuals appointed by sponsors, and 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.

2.8 The GCP Inspector

The inspector is a qualified employee of local and international regulatory authorities whose responsibility is to conduct announced or unannounced inspections at clinical trial sites/sponsors/CROs/bioequivalence facilities. The inspection of the clinical trial site is conducted according to provisions of guidelines on GCP inspections issued by the Authority.

3. CLINICAL TRIAL AUTHORIZATION IN RWANDA

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

(a) **RNEC Clearance**: All clinical trials to be conducted in Rwanda must apply for and receive ethical clearance RNEC. Any person who conducts research on a human being in Rwanda without prior approval by RNEC is likely to be sanctioned by RNEC with administrative sanctions and fines according to the law relating to research on human beings.

(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.

3.1 Clinical Trial Protocol and Amendments

The content of a trial protocol should include the information as per the latest version of ICH GCP Guidelines and the Authority's guidelines for clinical trial application. However, site-specific information may be provided on a separate protocol page or addressed in separate agreements. Some information may be provided in other protocol's supplementary documents such as the investigator's brochure.

3.2 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.

3.3 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 concerning 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.

3.4 Trial Objective

This section should provide the details and well clear explanations (reason for 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 objectives as well as the 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.

3.5 Trial design

The Authority acknowledges that the scientific integrity of the trial and the credibility of the data from the trial depends 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 labeling of the investigational product(s) and a sample of label to be used;
(i) the planned duration of trial participants, sequence and duration of all trial periods, including follow-up, if any;
(j) quantities and sources of investigational products or comparators will also be provided;
(k) a detailed description of the "stopping rules" or "discontinuation criteria" for trial participants. parts of the trial and the entire trial;
(l) accountability procedures for the investigational product(s), including the placebo(s) and comparator(s) in case of premature termination.

3.6 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.

3.7 Treatment of trial participants

The rights of every participant recruited in a clinical trial must be protected during and after the trial. The PI and sponsor of a given clinical trial must observe the following steps:
(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 the 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.

3.8 Assessment of efficacy

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

a. The specification of efficacy parameters;
b. Methods and timing for assessing, recording, and analyzing efficacy parameters;
c. Clear procedures for interim assessment of trial.

3.9 Assessment of safety

Under this section of the protocol, the applicant will provide the following:
(a) The specification of safety parameters;
(b) The methods and timing for assessing, recording, and analyzing 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; Provision of dealing with adverse events;
(e) Provision of dealing with adverse events;
(f) List of Adverse Events of Special Interest (AESI) and/or Expected Adverse Events information which includes whether the event is related to intervention or not, the rationale 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.

3.10 Trial Statistics

This section shall contain the following:
(a) A description of the statistical methods to be employed, including the timing of any planned interim analysis;
(b) The number of participants planned to be enrolled. In multicenter trials, the number 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).

3.11 Ethical Considerations

A clinical trial protocol must include a statement of the ethical considerations involved in the proposed trial and an informed consent form or otherwise shall be obtained for each of the trial participants before enrolment. The following bodies are involved in CT review processes in Rwanda. All clinical trials conducted in Rwanda must undergo ethical review by RNEC, which is a national independent. A valid ethical Clearance Approval shall be provided before the Authority issues an authorization for clinical trial conduction in Rwanda.

3.12 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 includes, but not limited to:

(a) Procedure for keeping a list of participants and detailed records indicated on the 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 twenty (20) years for market authorization 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 participant's documents should be retained for at least ten (10) years by the medical institution. The participant identification codes should be retained by the investigator and the sponsor for at least ten (10) years.

3.13 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. Before publication, the 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.

3.14 Protocol Amendment

Amendments relating to the conduct, design, methodology, investigational product, or the investigator or site(s) of the clinical trial and which may have a substantial impact on the safety or rights of the participant or the reliability and robustness of the data generated in the clinical trial, shall be subject to approval by the Authority. 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 in a written report within forty-eight (48) hours.
In case of changes not affecting the aforementioned circumstances, the Authority should be notified of reasons for, and description (s) of the changes. A list of amendment(s) and changes is attached as **APPENDIX-VII**.
Note that, if the sponsor may change or add the investigational product after the commencement of the clinical trial, he/she shall submit a new application to the Authority with justification and all application requirements as per the guidelines on Clinical application in Rwanda.

4. 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 the latest version of ICH GCP Guidelines 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 the trial site in a secure location, with restricted access. Ideally, depending on the stage of the trial, the documents included in the TMF are the 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 the 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 as staff meeting minutes, handover documents, etc.).

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

5. QUALITY MANAGEMENT SYSTEM

The sponsor should implement a system to manage quality throughout all stages of the trial as per the latest version of the ICH GCP guidelines. Those systems should focus on trial activities essential to ensuring human participants' protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision-making.

A formalized 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 requirements.
The research team shall ensure that quality check, audit, and monitoring actions are dealt with on time and corrective actions and preventive actions are implemented following timelines agreed with the Authority.

6. CLINICAL TRIAL SITE OPERATIONS

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

between the study site team, PI, and sponsor.

The activities at clinical trial sites may be coordinated by the 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. 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 enrolment 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 participants 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 participants have the right to refuse treatment and will not lose any benefits to 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 (**APPENDIX-I**).

7.2 Informed Consent Form

The Informed Consent Form (ICF) is an essential component of ethical research. Before participation in the trial, a written informed consent form should be signed and personally dated by the trial participant

or by the trial participant's acceptable representative, and by the person who conducted the informed consent discussion.

The ICF to be signed should have the following 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 rights to drop out at any time;
(c) understood and accepted 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.

Notes: 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.

If a trial participant is unable to read, is a child, is unconscious, or is mentally disabled, a legally acceptable representative should sign the informed consent on behalf of the trial participant.

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 the Participant Informed Consent Form (ICF) is provided to guide sponsors or PI when preparing the application (**APPENDIX-II**).

8. 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 participants. 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 IBs must be updated.

The IB must contain 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 humans, 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 contents of an IB is provided in this document for clear guidance (**APPENDIX-III**).

9. 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, and 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 appoint 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 depend 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; and
(g) it is recommended that at least one member of the DSMB is a Rwandese.

10. MATERIAL TRANSFER AGREEMENT (MTA)

Where applicable, an appropriate MTA that defines the rights, obligations, and restrictions for the provider (PI) and the 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 the external laboratory. All the concerns about the material transfer agreement will have to be addressed in the agreement and will comply with the template as provided in the attachment of this document (**APPENDIX-IV**).

11. REPORTING IN CLINICAL TRIALS

In line with regulations governing the conduct and inspection of clinical trials in Rwanda, the PI shall submit to the Authority the safety reports and other reports such as progress reports, site close-out reports and final reports according to the timelines and requirements 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 the collection and analysis of high-quality data;
(b) The principal investigator should make close follow-up of the participant who reported any serious event;
(c) In blinded trials e.g. 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.

11.1.2 Reporting of Serious Adverse Events

In line with regulations governing the conduct and inspection of clinical trials 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 follow-up medical reports on the SAEs' evolution or outcome and action taken;
(e) Submit autopsy reports and terminal medical reports in case the SAEs resulted in the death of trial participants;
(f) Submit a 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

In line with regulations governing the conduct and inspection of clinical trials 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 follow-up medical reports on the SUSARs evolution or outcome and action taken;
(e) submit autopsy reports and terminal medical reports in case the SUSARs resulted in the death of trial participants;
(f) submit causal relationship between SUSARs and the Investigational product that is established, evaluated, and clarified for further assessment;
(g) in case of multi-countries trials including Rwanda, the sponsor shall submit a line list of all SUSARs occurring in other sites with action taken by the respective regulatory bodies.

11.1.4 Management of Safety Reports

All safety reports shall be reported using the CIOMS form and completed forms are sent to info@rwandafda.gov.rw using the 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 the death of a trial participant or conduct an investigational inspection at the site.

The causality assessment of safety reports shall be submitted to the internal clinical trial technical committee established by the Authority for review and recommendation. 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.

11.1.5 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; Six (6) months progress report for one-year study and above.

The progress report shall be submitted using the format provided on the Rwanda FDA Website.

11.1.6 Site Close-out report

The PI shall submit to the Authority within thirty (30) calendar days from the day of the last enrollment of the trial participant the close-out report to document that all activities required for the trial are completed, and copies of essential documents are held in the appropriate files. The content and format of the close-out report will comply with the close-out reporting format attached as **APPENDIX-IV** in the Guidelines for GCP Inspection of Clinical Trials in Rwanda. In this report, the management of

remaining investigational medicinal products (IMP) will be highlighted and a copy (ies) of the disposal certificate should be provided as annexes to the report.

11.1.7 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 the Final Trial Report will comply with the final trial report format attached on the Rwanda FDA website. Any unexpected safety issue that changes the risk-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 the 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 standard operating procedures.

12. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

12.1 Manufacturing of investigational product

It is the responsibility of the sponsor or principal investigator to supply an IP produced in compliance with the principles of GMP for IPs. The Authority shall verify the Good Manufacturing Practices (GMP) compliance for the manufacture of the investigational product including placebo according to the procedures in the relevant guidelines.

The GMP certificate for imported investigational products should be issued by the national competent authority of the country of origin of the IP. For locally manufactured investigational products, the content and format of the GMP certificate shall comply with the guidelines on Good Manufacturing Practices issued by the Authority.

To accept evidence of GMP compliance issued by other regulatory authorities to support the quality of the investigational product (s), the Authority shall rely on different criteria. These include but not limited to the GMP certificate, confirmation, or GMP inspection report issued by:

(a) Stringent Regulatory Authorities/WHO listed authorities;
(b) Competent Authority of countries that are standing PIC/s members;
(c) World Health Organization (WHO) prequalification program;
(d) Authorities operating at maturity level 3(ML3) or maturity level 4 (ML4);
(e) Competent Authority that has a recognition agreement with the Authority;
(f) EAC Joint GMP inspection procedure.

However, if the investigational product is manufactured in a country whose GMP control system is not recognized by the Authority, in addition to the valid evidence of GMP compliance issued by the regulatory authority of the country of origin, a GMP certificate or GMP confirmation document that satisfies conditions stated in sections a, b, c, d, e, and f is compulsory.

12.2 Importing, packaging, labelling, and coding of investigational product(s)

(a) 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);
(b) The import permit for investigational products and trial products shall be obtained from the Authority. The requirements for importing IP are detailed in the guidelines for the importation of medical products. However, the valid clinical trial approval certificate is a prerequisite to obtaining an import permit for IPs;
(c) The quantities of investigational products to be imported should correlate with the number of trial participants to be enrolled;
(d) 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;
(e) The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage;
(f) 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;
(g) If significant formulation changes are made in the investigational or comparator product(s) during 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 before the use of the new formulation in clinical trials;
(h) The Authority shall verify the Good Manufacturing Practices (GMP) compliance for the manufacture of the investigational product including placebo according to the procedures set out in the relevant guidelines.

In the case of a locally manufactured investigational product, the content and format of the GMP certificate shall comply with guidelines on Good Manufacturing Practices issued by the Authority. In the event of an imported investigational product, the Authority shall rely on the evidence of GMP compliance issued by the competent Authority of the country of origin.

12.3 Supplying and handling of investigational product(s)

(a) The investigational product(s) should be stable throughout use. In case of shelf-life extension, authorization should be obtained from the Authority.
(b) Quantities of the investigational product(s) supplied on the site should correlate with trial participants and trial protocol.
(c) SOPs for management of investigational products (IP) at the site should be in place;
(d) The pharmacist shall ensure the good storage, distribution, and dispensing of the IP;
(e) The pharmacist should maintain an inventory of the IP at the site, those used by trial participants return to the sponsor or alternative disposal of unused investigational product(s);
(f) The Investigational product(s) should be used only on the trial participants in accordance with the approved protocol;

(g) If there is blinding, there should be criteria for breaking of the code;
(h) 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.

12.4 Randomization 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 participant at both the study site and with the sponsor.

The investigator should follow the trial's randomization 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.

13. COMPENSATION AND INSURANCE COVERAGE

A clinical trial that necessitates insurance coverage for participants must be clearly defined, and the insurer must be a recognized entity in Rwanda. The sponsor is responsible for ensuring that all trial participants are adequately insured against potential injuries that may occur during the clinical trial. A valid insurance certificate, covering the duration of the study, must be submitted before the initiation of the trial. The Authority reserves the right, upon review and analysis of the study design and interventions, to exempt trial participant insurance if it is determined that the safety of the participants is not compromised.
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.

14. 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.

15. TRANSPARENCY AND CONFLICT OF INTEREST MANAGEMENT

The clinical trial oversight activities will be conducted transparently in accordance with provisions of regulations, guidelines, and standard operations procedures for clinical trials. A Clinical Trial Register (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 costs. The Law relating to research on human beings provides key rights of a research participant or trial participant as well as other internationally recognized principles.

Institutions including organizations sponsored to conduct clinical trials must have formulated policies regarding the avoidance of conflicts of interest to ensure high ethical standards in the management of 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 participants enrolled in 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.

16. CLINICAL TRIAL CONDUCT IN VULNERABLE POPULATIONS

Article 3(11) of the Law relating to research on human beings defines a vulnerable person as "a person who cannot make consent to participate in research because of his or her age, his or her physical or social condition or obstacles based on his or her limited knowledge about the field of research in which he or she is going to participate, or such other person, as may be approved by the RNEC."

The vulnerable populations may 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 emergencies, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

The vulnerable 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 Principal Investigator 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 make a choice, then an appropriate legal representative may consent on their behalf.

17. 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. The Authority makes decisions on trial sites located in one or several countries as follows:

(a) If a multi-centre clinical trial is to be conducted and all research centres are located in Rwanda, the Authority shall issue a single opinion;
(b) If a multi-centre clinical trial is to be conducted in more than one country simultaneously, the Authority provides a single Clinical Trial Approval Certificate regarding the clinical trial site(s) in Rwanda;
(c) If a multi-centre clinical trial is conducted and all clinical trial sites are located in Rwanda, the Authority shall take a single regulatory decision regarding such clinical trial;

Note: The multi-center 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.

The multi-center trials implementing the same protocol in other countries including Rwanda shall comply with applicable laws, regulations, and guidelines governing clinical trials in respective countries; however, the Authority may rely on reports and decisions from sister regulatory bodies.

18. SUSPENSION OR TERMINATION OF A CLINICAL TRIAL

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

(a) 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;
(b) 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 the sponsor false information in any required report;
(c) 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 information raising doubts about the safety or scientific validity of the trial, or the conduct of the trial at a particular trial site;
(d) 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 trial participants, and inform the Authority.

ENDORSEMENT OF THE GUIDELINES

	Prepared by	Checked by		Approved by
Title	**Division Manager of Pharmaceutical Inspections and Licensing**	**Head of Drugs Department**	***For* QMS Division Manager**	**Director General**
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Signature				
Date	28/10/2024	28/10/2024	28/10/2024	28/10/2024

APPENDICES

APPENDIX-I: GUIDANCE ON PARTICIPANT INFORMATION SHEET

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

INTRODUCTION

20.1 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 statements:

You are invited to take part in this research project, which is called [*Name of research project*]. You have been invited because [*Explain the 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:

(a) Understand what you have read
(b) Consent to take part in the research project
(c) Consent to be involved in the research described
(d) 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.

20.2 What is the purpose of this research?

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

(a) Aim of the project and its significance
(b) How the project is intended to fill any gap in knowledge
(c) How it may contribute to care or education or research in the future
(d) Any relevant background including what is already known

(e) Whether the research is to obtain a degree or other educational qualification, is funded by a grant, or has sponsorship of some kind.

20.3 What does participation in this research involve?

Include information and a clear explanation of the following:

1) A consent form will be signed prior to any study assessments being performed
2) 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.
3) 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)
   (d) Reimbursement and costs (if applicable)
   (e)How the research will be monitored
   (f) The commitment required by the participant
   (g) Access to personal records that may be required
   (h) 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 organization or person has rights of access to the data collected on tape.

(a) Details on the use of interpreters in the consent and/or data collection process
(b) Venue details and a statement about whether participants may choose the venue

Explain any other relevant information including:

(a) How many people will be taking part in the project overall and at this site
(b) Whether there are different groups e.g. case/control groups, different types of focus groups
(c) The size or scope of a project e.g. number of schools or hospitals or countries involved
(d) Whether the project involves researchers from various organizations working in collaboration
(e) 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 statements:

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 in an appropriate way and avoid study doctors or participants jumping to conclusions.

20.4 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 several organizations working in collaboration
- ✓ Whether this is a follow-on study/sub-study/extension study. If so, state the relationship to the previous research

20.5 Information on Investigational Products

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

(a) Name of drug (generic preferred, trade name if necessary to the study design)

(b) any conditions in which the drug should not be taken (for example during pregnancy)

(c) whether the drug is meant to treat the disease or to relieve symptoms, and therefore how important it is to take the drug

(d) how to tell if the drug is working and what to do if it appears not to be working

(e) when and how to take the drug (for example before or after meals)

(f) what to do if a dose is missed and the implications of not taking the drug for any length of time

(g) any interactions with alcohol or other drugs (generic and trade names)

(h) storage and disposal of the drug

(i) risks, side effects, discomforts, inconveniences, restrictions, or other negative effects that might occur as a result of taking the drug

(j) the probability of adverse effects from the test drug compared with other procedures (or drugs) used for the same purpose

(k) any category of participant to be excluded from the research

(l) an explanation that randomization and/or placebos may be used (where relevant).

20.6 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 the 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.

20.7 Do I have to take part in this research project? Explain that taking part in the research is entirely voluntary.

Examples of statements:
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*].

20.8 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. You must 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 statements:

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*].

20.9 What are the possible risks and disadvantages of taking part?
Provide information on the possible risks of 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 risks. Some specific issues you should consider include:

20.9.1 Impact on possible pregnancy and breastfeeding, including young people and pregnancy
20.9.2 Side effects of treatments/therapies in trials
20.9.3 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 a. What if something goes wrong?

(a) What will happen if I don't want to carry on with the study?
(b) How will my information be kept confidential?
(c) What will happen to the results of this study?
(d) Who is organizing and funding this study?
(e) How have patients and the public been involved in this study?
(f) Who has reviewed this study?
(g) Further information and contact details
(h) What to expect during the consent process?
(i) What if relevant new information becomes available?
(j) Informing General Practitioner / other healthcare practitioner
(k) What will happen to the samples I give?

Examples of statements:
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

20.10 What if I withdraw from this research project?

Provide information regarding how participants withdraw and the implications 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 the 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 comply with the 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.

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].

20.11What will happen to information about me?

Information should be provided regarding the following:

(a) Whether the data collected or used is individually identifiable, re-identifiable (coded), or non-identifiable;

(b) Where the data will be kept and who will have access to it;

(c) 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);

(d) Whether the participant is being asked to provide consent for the use of their data for this project only, or 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 this research project and it will only be disclosed with your permission, except as required by law. The personal information that the research team collects and uses is [types of information, e.g. information from questionnaires].

20.12 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 statements:

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.

20.13 Who is organizing and funding the research?

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

Examples of statements:

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 organization and address*].

20.14 Who has reviewed the research project?

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

Examples of statements:

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

20.15 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 statements:

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 that may be related to your involvement in the project, you can contact the principal investigator on [*insert Names, Positions, Phone number, e-mail addresses*] or any of the following Research contact persons and Research site manager [*insert Names, Positions, Phone number, e-mail address*]:

APPENDIX-II: PARTICIPANT INFORMED CONSENT FORM(ICF)

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 participants*] 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 the research team, representatives from the sponsor, members of the National Ethics Committee, or Rwanda FDA overseeing this study 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 participants*] 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 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 the 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 participants*] 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 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 /Mother /Father /Another 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 thumbprints.

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 and 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 allowed 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)

APPENDIX-III: 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 participants. 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 participants during 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 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 the 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.

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 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 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

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 unfavorable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available:

i. Nature and frequency of pharmacological or toxic effects;
ii. Severity or intensity of pharmacological or toxic effects;
iii. Time to onset of effects;
iv. Reversibility of effects;
v. Duration of effects; and
vi. Dose response.

3.6 Species tested

i. Number and sex of animals in each group;
ii. Unit dose (e.g., milligram/kilogram (mg/kg));
iii. Dose interval;
iv. Route of administration;
v. Duration of dosing;
vi. Information on systemic distribution; and
vii. 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 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:

3.7 Effects on Humans

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 the 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 several 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 based on prior experiences with the product under investigation and with related products.

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.

3.8 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 are based on previous human experience and 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 sensitization) on Reproductive toxicity
Genotoxicity (mutagenicity)
Special studies (e.g. irritancy and sensitization) on 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 a clinical trial(s).

APPENDIX-IV: 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 participant 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 biospecimen, 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:
i. 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,
ii. but excludes the following information, being information that:
   a. 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 the research agreement;
   b. is independently developed by the Recipient without the use of the Rwanda FDA confidential information and/or Materials; or
   c. is required by laws or by judicial instances to be disclosed.

Intellectual Property Rights means all intellectual property rights subsisting anywhere in the world, including 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 the Provision of Material

The Recipient:

i. May only use the Material for the Purpose;
ii. 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;
iii. Must comply with any applicable laws about the importation, transportation, use, maintenance, or disposal of the Material;
iv. Must keep the Material secure and protected from unauthorized access, misuse, damage, destruction, unauthorized disclosure or modification, or theft and must immediately report to sender if it suspects the Material has been dealt with contrary to this clause;
v. 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;
vi. 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 allowed to contribute to the publication, the sender is acknowledged (in a form to be agreed before 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 the 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 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 about 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 authorized 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 that 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 willful 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 concerning 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 authorized representative Signature
Signed for *[insert full name of other party]*

by its authorized representative:
Names

Date of Signature[dd/mm/yyyy]

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

Names **Date of Signature [dd/mm/yyyy]**

APPENDIX-V: 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 After Inspection	20 working days
10.	CAPA Response for GCP Inspection Findings	15 working days
11.	Review of final Clinical Trial reports	10 days
12.	Notification of SAEs and SUSARs from Clinical Trials	7 calendar Days
13.	Full Report of notified SAEs and SUSARs from Clinical Trials	8 calendar Days
14.	Submission of annual Progress report	Monthly = study < 6 months Quarterly= study7<11months Six months=study >1 year
15.	Submission of Close-out Report	30 calendar days from the day of last enrolment of trial participants.
16.	Submission of Trial Final Report	90 calendar days for the enrolment of the last trial participant

APPENDIX-VI: PHASES OF CLINICAL TRIALS

Phase I

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans. These trials are tested in a small group of people between 20 to 100 health volunteers.

Phase II

These trials are performed with a limited number of participants and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships to provide an optimal background for the design of extensive therapeutic trials. These trials are tested in a larger group of people generally 100–300 participants with a specific disease.

Phase III

Trials in larger (and possibly varied) patient groups to determine the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use generally in 300 to 3,000 volunteers who have the disease or condition.

Phase IV

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

APPENDIX-VII: LIST OF POSSIBLE AMENDMENTS

CHANGES RELATED TO CLINICAL PROTOCOL		
#	**Examples of changes include but are not limited to the following:**	**Type**
1	Criteria, tests, or procedures required to select or dismiss a clinical trial participant. These include changes to eligibility criteria, tests or procedures for selecting the study population, as well as tests, procedures, or criteria for dismissing clinical trial participants prematurely or at the end of the trial;	Amendment
2	Criteria, tests, or procedures required for the ongoing assessment of clinical trial participants, including assessment of safety, or evaluation of safety and efficacy. This includes protocol changes as a result of serious unexpected ADRs;	Amendment
3	Study design, study population, duration of use, objectives, or hypotheses, including adding or discontinuing a study arm that was not included as a provision in the original CTA protocol;	Amendment
4	Changes in the primary efficacy endpoint(s), important secondary efficacy endpoints (e.g., those that could be used in support of a marketing application), safety endpoints, sample size estimation, or addition of interim analyses that will affect the analysis and interpretation of the study results;	Amendment
5	Dose level, dosage schedule, or treatment duration;	Amendment
6	Changes to the post-treatment follow-up period that may affect the safety evaluation of the drug.	Amendment
7	Adding or removing a concomitant medication, which may impact on the analysis of efficacy or increase the risk to clinical trial participants;	Amendment
8	Criteria for expedited reporting of serious, unexpected adverse drug reactions;	Amendment
9	Increases in blood volume, changes in procedures, enrolling additional subjects in PK studies, or confirmatory testing in PK studies that were not specified in the original CTA protocol; and/or	Amendment
10	Aspects of the conduct of the study that may increase the risk to the health of clinical trial participants.	Amendment
11	Increasing the screening period or other administrative changes to accommodate logistical constraints in study conduct that do not affect the safety of the trial participants	Notification
12	Minor changes to the inclusion and exclusion criteria, such as laboratory chemistry cut-off values that reflect clinical practice and improve the safety of clinical trial subjects;	Notification
13	Changes to administrative information such as new contact names and numbers and ages of individuals, organizations, or other entities, involved in the conduct of the trial;	Notification
14	Updating the ICF with new safety information that does not require a protocol amendment;	Notification

15	Annual Investigator Brochure updates	Notification
16	Changes to the quality information that does not affect the quality or safety of the investigational product	Notification
CHANGES RELATED TO QUALITY (CMC) OF INVESTIGATIONAL PRODUCT		
	DRUG SUBSTANCE (Biologics and Radiopharmaceuticals)	
#	**Examples of changes include but are not limited to the following:**	
1	**Replacement or addition of a manufacturing site involving:**	
	(a) production of the starting material, intermediate, or drug substance	Amendment
	(b) testing (e.g., release, stability)	Notification
2	**Change in the manufacturing process for the drug substance intermediate, involving:**	
	(a) the fermentation process [for example (e.g.), scale-up, new bioreactor technology, use of new raw materials of biological origin]; or change in the route of synthesis of the radiopharmaceutical drug substance or critical component*	Amendment
	(b) the purification process (e.g. addition/removal/replacement of a purification step)	Amendment
3	**Change in the specifications for the drug substance involving:**	
	(a) deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	(b) addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
4	Change in the primary container closure system(s) for the storage and shipment of the drug substance provided the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties, and the change does not concern a sterile drug substance	Notification
5	Change in the shelf life for the drug substance, involving:	
	(a) Extension (i) if the approved shelf life is less than or equal to 18 months	Amendment
	(ii) if the approved shelf life is more than 18 months	Notification
	(b) Reduction (due to stability concerns)	Amendment
DRUG PRODUCT (Biologics and Radiopharmaceuticals)		
#	**Type of Change**	**Type**
1	**Replacement or addition of a drug product manufacturing site involving:**	
	(a) Production of a drug product (including primary packaging)	
	(b) secondary packaging	
	(c) testing [for example (e.g.), release, stability]	
2	Change in the drug product manufacturing process (e.g., scale-up, changes to the formulation process); change from manual synthesis of positron-emitting radiopharmaceutical to use of automatic synthesis unit or change in type	Amendment
3	Deletion of a drug product manufacturer/manufacturing site, primary or secondary packaging site or testing site	Notification

4	Change in the specifications for the drug product, involving:	
	a) deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	b) addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
5	**Change in the shelf life for the drug product, involving:**	
	a. Extension if the approved shelf life is less than or equal to 18 months	Amendment
	ii) if the approved shelf life is more than 18 months	Notification
	b. Reduction (due to stability concerns)	Amendment
6	Change in the storage conditions for the drug product	Amendment
7	Changes in final product dosage form (e.g., liquid to lyophilized formulation)	Amendment
8	Changes in final product strength	Amendment
9	Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution by a diluent, which is commercially available in Canada, is water for injection (WFI) or a salt solution, and after reconstitution, there is no change in the drug product specifications outside of the approved ranges.	Notification
10	Change in radiolytic protective agent or antioxidant	Amendment
DRUG SUBSTANCE (Pharmaceuticals)		
#	**Type of Change:**	**Type**
1	**Replacement or addition of a manufacturing site involving:**	
	a. production of drug substance	Amendment
	b. testing (e.g., release, stability)	Notification
2	Change in the manufacturing process for the drug substance intermediate or starting material (e.g., reaction conditions, solvents, catalysts, synthetic routes, reagents, etc.)	Amendment
3	Change in the batch size for the drug substance (no impact on quality)	Notification
4	**Change in the specification for the drug substance involving test and acceptance criteria:**	
	a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification

5	**Change in the re-test period (or shelf life) for the drug substance, involving:**	
	a. Extension	Notification
	b. Reduction (due to stability concerns)	Amendment
DRUG PRODUCT (Pharmaceuticals)		
1	Addition of a dosage form or strength	Amendment
2	Change in the composition of a dosage form	Amendment
3	Qualitative or quantitative addition, deletion or replacement of a colour or flavour with no negative impact on stability	Notification
4	Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution	Amendment
5	**Replacement or addition of a drug product manufacturer/manufacturing site involving:**	
	a. Production of an immediate-release drug product (tablet, capsule, liquids, semi-solids) within the same Manufacturer	Notification
	b. Production of an immediate-release drug product (tablet, capsule, liquids, semi-solids) to a new Manufacturer	Amendment
	c. Production of a modified release product	Amendment
	d. Production of a sterile drug product	Amendment
	e. Primary packaging (non-sterile products)	Notification
	f. Testing (e.g., release, stability)	Notification
6	Change in the drug product manufacturing process	Amendment
7	Change in the specification for the drug product tests and acceptance criteria, involving:	
	a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
8	**Change in the shelf life for the drug product, involving:**	
	a. Extension	Notification
	b. Reduction (due to stability concerns)	Amendment
9	Change in the storage conditions for the drug product	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.