RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON GOOD CLINICAL PRACTICES (GCP) IN RWANDA

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GUIDELINES DEVELOPMENT HISTORY

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ADOPTION BY RWANDA FDA	
STAKEHOLDERS CONSULTATION	
ADOPTION OF STAKEHOLDERS' COMMENTS	
DATE FOR COMING INTO EFFECT	

FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018, specifically in its article 8, paragraph 7 and 12, the Authority is mandated to regulate and inspect clinical trials. Reference to the provisions of the technical regulation Nº CBD/TRG/015 Rev_0 governing the conduct of clinical trials especially in its article 32, the Authority Issues *Guidelines Nº DIS/GDL/033* on Good Clinical Practices (GCP) in Rwanda.

Guidelines for Good Clinical Practice (GCP) comes in the right very timely and necessary in the wake of a greater demand by the pharmaceutical industry to conduct clinical trials in Rwanda. The objective of these Guidelines is to ensure that clinical trials in Rwanda are conducted in accordance with National and International ethical and scientific standards.

These guidelines provide details of the quality processes required in the conduct of clinical trials to ensure that human subjects participating in the clinical trials are protected and that trials conducted are based on science and well-designed. They also provide a guidance on the results of clinical trials are 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 with some modifications to suit the local requirements.

GCP is an accepted requirement internationally prior to product registration. All parties involved in the conduct of clinical trials should therefore share the responsibility of adhering to the Guidelines and to ensure acceptability of data and findings worldwide.

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

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

Dr. Charles KARANGWA
Acting Director General

ACCRONYMES AND ABBREVIATIONS

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

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GLOSSARY

In these guidelines, unless the context otherwise states:

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

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

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

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

"Assent" A process by which a child, who is capable of understanding voluntarily, confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the child's decision to participate. Assent is documented by means of a written, signed and dated assent form from the child. As part of the assent process, parents and guardians must give informed consent.

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

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

"**Child**" A person who is below eighteen (18) years of age or the definition of child as defined in the laws currently enforced in Rwanda.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

"Placebo" A medication with no active ingredients or a procedure without any medical benefit

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

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

Trial Master File & Essential Documents

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

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

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

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

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

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

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

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

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

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

PART ONE: INTRODUCTION AND SCOPE

1.0 introduction

Clinical trials are essential for research and development(R&D) in the area of drug discovery, vaccine development and other medical products. Based on current knowledge about the safety and efficacy of specific medical products and treatments has come from randomized controlled clinical trials that are crucial part of clinical research designed to answer important scientific and health care questions. Randomized controlled trials form the foundation for "evidence-based medicine", but such research can be relied upon only if it is conducted according to principles and standards collectively referred to as "Good Clinical Practice" (GCP)[1]

Rwanda recognizes the widely accepted consensus that all research participants are entitled to minimum guarantees that are transnational and non-negotiable.[2], [3] These prerogatives can be realized in clinical trial environment, practice and structures that promote good clinical practice. An important component of these systems and structures are National ethics guidelines for good clinical practice that complement the provisions of clinical trials regulations in place.

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

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

1.1 SCOPE

These guidelines apply to the conduct and management of clinical trials on medicines,vaccines,biological products, herbal medicines,medical devices and In Vitro Diagnostics (IVDs) on human participants.It has been developed and customized after reviewing different guidelines including the International Conference on Harmonisation ICH E6 document [4]. Rwanda food and Drug Authority recognise that Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with ICH, GCP and the applicable regulatory requirements. The available international guidelines [5]–[12] have been reviewed to customize with national context and has come with the following clear guidance showcasing how clinical trials in Rwanda should be scientifically sound, and described in a clear, detailed protocol with consistent information and detailed plan as follow.

1.2. General GCP Principles

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki in 1964, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society.
3. A trial should be initiated and continued only if the anticipated benefits outweigh the risks.
4. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
5. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
6. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

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

2.Clinical trial protocol and amendments.

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

2.1. General Information.

This shall include:

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

ii. Name and address of the Sponsor and monitor (if other than the Sponsor)

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

iv. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial

v. Name and title of the Principal Investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

vi. Name, title, address, and telephone number(s) of the other investigators designated by the PI to be responsible for some aspects of the study.

vii. Name(s) and address (es) of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

viii. A clear statement on compensation and benefits package for clinical trial participants.

ix. Publication policy.

2.2. Background Information

This shall include:

i. Name and description of the investigational product(s).

ii. A summary of findings from nonclinical studies that potentially have significance to the clinical trial.

iii. Summary of findings from completed clinical studies/trials that are relevant to the trial.

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

v. Summary of the local background rates with respect to the condition for which the intervention is proposed.

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

vii. Description of the population to be studied.

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

ix. Justification for the trial is being conducted in Rwanda.

Rwanda Food and Drug Authority recommend that this section addressed in the Clinical trial protocol include - Name and description of the investigational product(s), A clear summary of findings from nonclinical studies that possibly have clinical implication to the trial, Summary of findings from clinical trials that are pertinent to the trial, Summary of the known and potential risks and benefits, if any, to human subjects, Description, explanation and justification for the route of administration, dose , dosage regimen, and treatment period(s). A statement that the trial shall be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s) within Rwanda, Description of the population under study. References to the available literature and data that are relevant to the trial and that provide background for the trial, signed declaration by the applicant and all investigators that they are very well familiar with and understand the protocol and shall comply with principles of Good Clinical Practice (GCP) as determined by the Rwanda Food and Drugs Authority in the conduct of the trials in Rwanda.

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

Rwanda Food and Drug Authority acknowledge that scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. Therefore, a description of the trial design should include: specific statement of the primary endpoints and the secondary endpoints as well details justification of the variables to deal with and expected trail outcomes in the short- and long-term A description of the type/design of trial to be conducted, be a double- blind, placebo-controlled, parallel design and a schematic diagram of trial design, procedures and stages as well.

This section would also contain the description of the measures taken to minimize and avoid bias, including: well clear Randomization Process and Blinding. A description of the trial treatment(s) dose and dosage regimen of the investigational product(s). it will provide the

description of dosage form, packaging, and labelling of the investigational product(s) and sample of label to be used for investigational product. The planed duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any, quantities of investigational medicines and comparators will be also provided here.

This section will also provide a detailed description of the "**stopping rules**" or "**discontinuation criteria**" for individual subjects, parts of trial and entire trial. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any

This section shall include about subject inclusion and exclusion criteria, withdrawal criteria such as terminating investigational product treatment/trial treatment and procedures specifying: When and how to withdraw subjects from the trial/investigational product treatment.

This section is supposed to provide the details on the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route or mode(s) of administration, and the treatment period and duration(s), it will also include the follow-up period(s) for subjects for each investigational product treatment/trial treatment arm of the trial. Other medication or treatment(s) permitted (including rescue medication) and not

permitted before and or during the trial will also be included here. Procedures for monitoring subject compliance, Description of treatment applied to control group(s) or control period(s), placebo, and other therapy and any other treatment that may be given concomitantly including measures to be implemented to ensure effective safe handling of the products. The section shall also provide the detail description of diagnostic devices or kits applied to be used in the clinical trial. Description of special analyses and/or tests or procedure to be carried out.

This section will provide methods and timing for assessing, recording, and analysing of efficacy parameters and clear procedures for interim assessment of trial subjects.

Rwanda FDA expect to see in this section the details about specification of safety parameters including the methods and timing for assessing, recording, and analysing safety parameters, procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses, the type and duration of the follow-up of subjects after adverse events, provision for dealing with all adverse events. Copy of form to be used to report adverse event

should appear among list of appendices as well as the follow up plan to monitor the outcomes of the events

This section contains the description of the statistical methods to be employed, including timing of any planned interim analysis. The number of subjects planned to be enrolled. In case of multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Adscription of the statistical methods to be employed should be provided.

The reason for choice of sample size, including reflections on or calculations of the power of the trial and clinical justification. It will also include the level of significance to be used, Methods for data analyses and evaluation of results. Procedure for accounting and dealing for missing, unused, and spurious data, procedures and schedule 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 in the final report as appropriate. The section will also provide the selection of subjects to be included in the analyses including but not limited to all randomized subjects.

Maintenance and record of trial treatment randomization codes and procedures for breaking codes. The identification of any data to be recorded directly on the CRFs. Number of human subjects to be involved in the trial and the statistical justification. Specifications and instructions for anticipated deviations from the protocol. This section may also contain the description about emergency unblinding call centre (24/7) ?????

Part 2 - CTU CULTURE AND PRACTICE

This part describes different sections that are very crucial for every CTU as far as GCP is concerned and it is critically important to ensure staff remain aware of basic standards of good practice to ensure ongoing regulatory compliance which can be demonstrated at inspection. Rwanda FDA, remains with mandate to ensure the following items are properly maintained and properly in use.

The Trial Master File (TMF) and evidence trail (also referred to as the audit trail or document trail) must be maintained at an accessible place upon request [13]. A good evidence trail will include documentation which helps '**tell the story'** of the trial, this includes documents which describe the handling and decision making associated with notable issues, disagreements, evidence on communication among stakeholders. These documents are often very helpful for day-to-day management of the trial and handover as well as demonstrating that the collaborators are acting appropriately.

Key items which support 'being ready' in this context include: Timely filing of applicable documents in the TMF ideally contemporaneously with the events being evidenced. In the scenario when CTU is using electronic source documents as part of the TMF; the site will ensure if there is a clearly documented definition of which documents are considered to be 'source' and where these documents are kept.

If the TMF are kept by different collaborating organizations, they will ensure that there is a clearly documentation process to describe how each section of the TMF is updated, by whom and when. Names and addresses of each organization involved must be kept up to date to allow the TMF sections to be pulled together in one place, and this would appear in delegation log.

Rwanda food and Drug Authority recognize that one of the risk points to stick on in any clinical trial is handover. Trials can run over several years and there are therefore likely to be staff changes during the lifetime of a trial. Considering how handover of responsibilities will be managed and documenting handover notes within the TMF can evidence how well handover risks were managed. Ensuring the archiving processes take into account timely access for audit and inspection purposes by Rwanda FDA.

Capacity development opportunities including all forms of trainings are a key feature of any quality-controlled environment, enabling staff working on clinical trials to improve their skills, knowledge and experience. Any person involved in the conduct of clinical trials must be qualified and able to demonstrate competence to perform their tasks as evidenced through qualifications and/or training [14]. On this component the CTU will provide evidence on routine staff training mechanism according to the CTU training schedule with proof of concept available in the individual staff members' training log as well as ensuring that this individual training files is up to date.

It will also appear on the provision of training for new and current staff to maintain awareness of the Clinical Trial Regulations and GCP relevant to the individuals' role.

A formalised system for documenting procedures, processes and responsibilities for ensuring quality and compliance with the Clinical Trials Regulations is a basic requirement of Registered CTU in Rwanda. Different quality assurance processes for monitoring compliance with regulatory requirements and SOPs will be available across CTUs and various examples of these processes will be available on the Rwanda FDA/ Clinical trial unity. AND/OR CTU Network website. The following activities may be considered appropriate depending upon the size and risk of the CTU's portfolio and features of the QC/QA function:

Ensuring all quality check, audit and monitoring actions are dealt with in a timely manner. Ensuring any previous inspection findings and corrective and preventative actions are actioned in a timely manner in accordance with the timelines agreed with the RFDA.

As CTUs grow and develop over time, operational structures including lines and channels of communication, reporting and accountability will need to be cleared earlier on to ensure these remain effective. Information regarding the operational structures and activities of the CTU

will form part of any inspection dossier, as such it is pertinent to consider how documentation and logs for day-to-day operational activities can be used in any later required inspection preparation.

Patient Information Sheet/Informed Consent Document template includes a statement whereby participants are notified that relevant sections of their medical records, and data collected during the study may be accessed upon request for the purpose of monitoring the safety and regulatory compliance of the trial. Failure to include this statement does not prevent the inspectors from reviewing the TMF but will impact in an inspection finding if participant consent is deemed inadequate. This sheet along with the consent form should be signed and stamped by the Ethics committee prior to enrolment and filed on the site.

I

Appropriate study designs are critical in contributing to answering scientific questions.
The study design must therefore demonstrate a high probability for providing answers to specific research questions. The investigator will provide an adequate supporting information and explanation on the study sample size and study population, the social context of a proposed

research population that creates conditions for possible exploitation or increased vulnerability among potential research participants should be assessed and addressed clearly.

The vulnerability factors and steps that will be taken to offset these should be addressed in the study design and clearly outlined in the research protocol. It is imperative that sound study designs, and use of universally accepted ethical standards are applied in both vulnerable and non-vulnerable communities. This will make a point of attention during all review process of an ethical aspect.

The design of the study should in no way prejudice the ongoing treatment and care of patients, nor should it in anyway undermine or confuse patients with respect to the best available local standard treatment practices and national policy approaches. If these are not ensured, then the design is unethical.

Publication bias among other things often serves as a barrier and can distort the body of evidence available for clinical decision making. The Rwanda Food and Drug Authority in partnership with other stake holders will start the process to establish the Rwanda National Clinical Trial Registry (RNCTR) – which is a central publicly accessible clinical trial registry of which benefits are numerous, it serves to promote collaboration among researchers, the private sector and the community through the sharing of research information; assist people to identify clinical trials they can participate in; decrease publication bias, reduce duplication of research efforts; promote best use of limited research resources, help in monitoring the implementation of National research agenda and contribute to global efforts to reduce and eliminate disease while preserving the confidentiality of commercially valuable information regarding the medicine during the development stage.

The rights of research Participants in terms of privacy must be protected at all costs. This is maintained via the use of appropriate precautions regarding participant identifiers. This will also include electronic/computerized records and access thereof of such information. Procedure for keeping a list of participating volunteer/patients and detailed record indicated on the case report form (CRF) for each individual taking part in the trial. All clinical and experimental data (electronic or paper) shall be kept in a secured place for a period of 5 years and 20 years??// for New Drug Application (NDA) after completion of the trial and be made readily available for

review upon request by the Rwanda FDA. Publication policy, including a plan for the publication of the results (publishing plan) should be addresses here as well.

Ethical review provides an objective appraisal of the research proposal as it affects the participants and the general day to day functioning of the health system. The following bodies are involved in CT review processes in Rwanda and give authorization

- The Rwanda National Ethics committee (RNEC) is a central independent body which advises the Ministry of Health on the management of health research ethics in Rwanda. Among other things it is responsible for overseeing and accrediting Rwandan ethics committees/Local Institutional Review Boards (IRBs.)
- All clinical trials conducted in Rwanda must undergo ethical review by Rwanda National Ethics Committee.
- The Competent Regulatory Authority which is Rwanda Food and Drug Authority is regulating the conduct of clinical trials and is responsible for reviewing the study design, and in doing so, reviews all significant scientific aspects of the study and issue an approval letter.

Rwanda food and Drug Authority recommend that any amendment to the trial protocol, trial arrangements and investigational product shall be submitted to the institutional review board that originally approved the protocol and to the Rwanda FDA for approval before such amendments are carried out. If such amendments are necessary to protect the life of subjects, an urgent amendment may be carried out but the investigator shall inform the independent ethics committee and Rwanda FDA of such amendments with an immediate phone call followed by a written report depending on the type of amendment, within forty-eight (48) hours. Reports of all amendments shall include but not be limited to the following:

Reasons for the amendments, possible consequences for subjects already included in the trial. Possible consequences for the evaluation of the report, all amendment shall attract a fee which shall be determined as per Rwanda Food and Drugs Authority Fee Schedule???)

The Informed Consent (IC) is an essential component of ethical research. Obtaining informed consent implies the provision of information to potential participants regarding the nature of the research procedure, scientific purpose and alternatives to study participation. Informed consent may be difficult to achieve, especially when engaging people from disadvantaged and, vulnerable communities where literacy and education opportunities are inadequate and where there are language barriers. However, every effort must be carried out to achieve informed consent.

Participants' comprehension is addressed by laying out this information in a clear and simple style. In Rwanda, this must be achieved via the use of culturally acceptable practices including the use of the participant's language of choice. The conditions under which the consent is granted must be free of coercion, undue influence or incentives. Treatment for a given condition, which might be an attribute of the clinical trial design, should not be denied by the refusal to participate. Withdrawal from the clinical trial at any time will not result in undue clinical penalties to the participant. Rwanda FDA recommend a clear information session to be given individually or in a group according to the number of participants and this information should be documented on a sheet attached on the consent form. There should be a documentation in terms of assessment to ensure, that the aspect of understanding and comprehension in regard to participation of participants. The consent forms should be sent to Rwanda National Ethics committee before the site initiation for approval and stamp. The signed ICF, should be kept anonymous in a locked board with restricted access but available upon request by the competent authority.

The CTU should report to Rwanda FDA the report on progress on the trial. A good communication strategy, informing groups of staff as well as individuals about the general operations of the trial should be documented in TMF. Ultimately it is important to ensure the day-to-day business of the CTU can continue and remains largely unaffected by the poor communication among stakeholders especially the ethics comittee. Evidences of

communication via e mails or other forms of communication will be available on the site and made available upon request.

Investigators Brochure containing information on the following but not limited to: data on Chemical, physical and pharmaceutical properties and formulations, Preclinical, pharmacological and toxicological data, Human pharmacological and clinical data with the substance concerned and any other supporting documentation sufficient to establish quality, safety and efficacy where applicable.

Marketing experience in countries where the investigational product is being marketed or approved. Where appropriate there should be discussions of published reports. Sample of label to be used for the investigational products. Clear instructions on storage and handling of investigational products. An updated investigator's brochure should be submitted at least once a year, ???? or whenever it is updated within this period. Additional information and any changes that have been incorporated in the updated investigator's brochure should be highlighted for ease of review and evaluation and reference. Good Manufacturing Practice (GMP) certificate/statement from the country of manufacture for the product/ placebo issued by the competent recognized Authority.

The number of multi-centered clinical trials being undertaken in Rwanda has increased dramatically in recent years. There is a need to ensure that designs of such studies are appropriate for the local setting and that particular modifications are made to the local study when required e.g. inclusion/exclusion criteria. Special attention should also be paid to the sampling strategy when reviewing multi- centered clinical trials. Furthermore, it is unacceptable for developed country participants to have better standards of care offered in the study when compared to local participants. When Rwanda is chosen for a clinical trial while the trial is not undertaken in the country of origin an explanation should be sought about why this is the case. Other issues in multi-center studies include the appropriateness of incentives and compensation and packages to trial participants, remuneration packages for investigators and insurance [15]

Rules of blinding would be applied to avoid all kinds of bias and this would be addressed in the section of study design , consideration should be given to the provision and storage of documents so as to not inadvertently un-blind staff to the treatment allocation, participants identifier, and site code would be predefined and addressed during randomization and participant code allocation, this blinding status should remain consistent during the whole process unless unblended upon request in the event that significant issues is identified. An emergency unblinding call centre should be established in case ……..

The sponsor should ensure all subjects must be satisfactorily insured against possible injuries that might arise during the conduct of the clinical trial. For all Sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provided prior to study initiation. Rwanda FDA reserve the right to judge in case the trial does not expose the safety of the

The samples to be shipped outside of the Country should comply with the signed Clinical Trial Sample Transfer Agreement or Material Transfer Agreement(MTA) signed between parties (Sponsor and Rwanda FDA) (Annex)????

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

An independent data-monitoring committee or data core 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.

The Sponsor shall include charter of work, membership and curriculum vitae of the DSMB when applicable. To include a Rwandan???? Or not

All the concerns about material transfer agreement will has been addressed in the agreement approved by Rwanda FDA (**Annex ….**)

Sponsors and Principal Investigators shall have as their primary concern the protection of the life, health, privacy and dignity of the patients or healthy volunteers who participate in such trials.

1. The Sponsor

The first responsibility of the sponsor is submission to the FDA for approval:

Before initiating any site for a clinical trial(s) in Rwanda, the Sponsor and the Principal Investigator must obtain approval from the Rwanda FDA to begin the trial(s). The protocol should be submitted in duplicate. It is the responsibility of both the Sponsor and the PI to ensure that the protocol satisfies the requirements of the protocol checklist seen in the back ground section of this guideline

2.Investigator

A qualified person or physician, who is an investigator or a sub- investigator for the trial, should be responsible for all trial-related medical decisions.

The Principal Investigator shall ensure that a qualified pharmacist supervises the management of the investigational product.

3. Qualification of Principal Investigators

Principal Investigator(s) directly in charge of a trial and at each site in a multi-centre trial shall be in good standing with the Good Clinical Practice in Rwanda and should be responsible for the proper conduct of the trial and must fulfil the following criteria:

- Be medically qualified and clinically competent
- Be sufficiently experienced in clinical evaluation of medicinal products

- Be experts in the pathology and the clinical handling of the particular disease or condition under study.
- Have evidence of Good Clinical Practice training of not more than 2 years.
- First time Principal Investigators shall be required to participate in the next GCP training of the Authority as a prerequisite for a Clinical Trial approval.

- A Sponsor's GCP???? certificate shall not be considered for his respective trial.
- Performance of Principal Investigators in regulatory compliance assessment with regards to previous clinical trials conducted would have an impact on the suitability/adequacy of the Principal Investigator for new clinical trial applications. The Trial Master File (TMF) shall contain CVs as evidence of such qualifications specified by the applicable regulatory requirement(s).

- Non-medically qualified scientists may participate as co-investigators or in other roles, but not as Principal Investigators.
- Veterinary personnel or surgeon may be the Principal Investigator or clinician for zoonotic studies.???

The Authority shall approve a clinical trial requests as may be prescribed by RFDA for the initiation and conduct of clinical trials in Rwanda. The approval process shall involve establishing adequate procedures and/or requirement for review of the clinical trial application. The Authority may require protocol revisions whenever it deems necessary.

Rwanda FDA shall order the person conducting the clinical trial to stop or suspend the trial immediately if at any stage during the conduct of a clinical trial if RFDA is satisfied that it is in the public interest to do so.

RFDA shall monitor a clinical trial from the beginning to the end in order to ensure adequate protection of the general public against the risk or adverse events from authorized clinical trials. This is to satisfy itself that the specific and general conditions to which the trial was authorized are being strictly adhered to by the person(s) conducting the trial and that the trial will achieve its objectives.

Rwanda FDA shall conduct on-site inspections to ensure: the safety of clinical trial participants, the quality and reliability of data obtained in a trial, and the facilities used continue to be acceptable throughout the clinical investigation. Rwanda FDA shall assess Investigators' compliance to regulatory requirements to ascertain the competence of the Investigator to conduct clinical trials in Rwanda.

Principal Investigators and the sponsor participating in a clinical trial are responsible for proper reporting of Serious Adverse Events (SAEs).

The Sponsor should expedite the reporting of all adverse drug events (AEs) that are both serious and unexpected to the Rwanda FDA. Reporting should occur within the timeframe and format specified by RFD. (Refer to Appendix

Every Serious Adverse event to the investigational product shall receive immediate medical attention and reported to RFD within forty-eight (48) hours.??? The SAE report form shall be completed and detailed information such as laboratory results submitted to enable causality assessment report. All fatal cases shall be accompanied by a formal autopsy report. In exceptional circumstances where a formal autopsy is not practicable, provision of a verbal autopsy report shall be prior approved by RFDA and shall be given with ample reasons.

The verbal autopsy conducted and the report submitted shall be in accordance with W.H.O Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children [16]

3.4.6. Any frequent adverse event to the product shall receive immediate medical attention and reported to the Rwanda FDA within seven (7) days???. In order to monitor the outcomes of all SAEs, The Principal Investigator is required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes. All additional information should be clearly marked as update information and should include the Protocol Number and Participant Number as well.

Rwanda FDA should be informed in writing on the exact date of commencement of the study. Quarterly reports of the progress of a clinical trial starting from the date of issuance of the clinical trial approval letter shall be submitted to Rwanda FDA in the recommended format. (Refer to APPENDI number….). Quarterly progress reports must be submitted to Rwanda FDA within 21 days??? after the end of the previous quarter???? A quarter shall be considered as three months beginning from the date of initiation of a specific clinical trial. If the trial does not begin or delayed as per the date of commencement on the Clinical Trial approval letter issued, Rwanda FDA shall be informed of the new date of commencement within ninety (90) days??? of issuance of the Clinical Trial approval.

Failure to inform RFDA of the commencement or otherwise of the study within this period shall have regulatory implications including but not limited to the payment of administrative charges for the re-issuance of the Clinical Trial approval letter on its expiration. If the trial is interrupted before its purpose is achieved, the reason shall be conveyed in writing to The RFDA within ten (10) working days? This shall include: Justification for the premature ending or of the temporary halt of the trial; Number of patients receiving treatment at the time of the study termination; Proposed management of patients receiving treatment at the time of halt or study termination; Implications of the discontinuation on the evaluation of the final results. The Principal Investigator/Sponsor shall notify in writing no later than 30 days??? after the completion of a clinical trial and submit preliminary report on the ethical evaluation of the trial. Identify one or two members of staff to be on call as 'runners' to respond to requests made

Duly signed and authenticated DSMB reports and/or minutes shall be forwarded to The Rwanda FDA upon request.

In addition to the report referred to above, the person who conducted the trial shall, not later than 90 days??// after the completion of the trial, compile and submit to the Rwanda food and Drug Authority a comprehensive formal report in regards to the ICH E3 Guideline for the Structure and Content of Clinical Study Reports. The report shall include a short but comprehensive summary of the essential findings of the trial and of its methodology and course. The Final report shall be submitted in hard and soft copies. Publication of the report in a scientific journal or other medium for the purpose of disseminating the information obtained to stakeholders may be encouraged only after 30 days??? of acknowledgement of receipt by RFDA

Import licence to import products for clinical trials shall only be granted to recognized clinical research entity whose protocol has been approved by the Rwanda food and Drug Authority or registered pharmaceutical companies upon presentation of the ISO certificates and other required documents to conduct clinical trial in accordance with these guidelines. An application for importation of investigational products, placebo and trial products, shall receive prior approval from RFDA. Application to import investigational product and placebo shall be made

by submitting certificate of analysis of investigational product and placebo for all batches to be imported. an application for import permits must be processed through Rwanda FDA website the approval shall be granted after responding to all queries raised by the Authority. The Principal Investigator shall notify the Authority within 48 hours through ……. of each respective consignment of investigational product and placebo batches received on site. The notification shall include the following details: Name of product(s), Quantities received and Batches received. All import permit applications shall bear the full name and address of the innovator, the Sponsor and the recognized clinical research entity, the name/description of the investigational product, placebo and quantity to be imported. Both the investigational medicinal product and the placebo shall be appropriately labelled with the approved labels to indicate they are samples for the conduct of clinical trials only. Products imported may be inspected by officials of the Rwanda Food and Drug Authority at the port of entry before they are released to the recognized clinical research entity. Rwanda FDA may order for destruction or re-exportation of the products intended for clinical trials if The RFDA has any reason to believe that there is a protocol violation resulting in the termination of the study.?? / The above notwithstanding, all other statutes governing importation procedures and tax liabilities in Rwanda shall apply to imported products regulated by RFDA. The Principal Investigator shall document the source, proof of purchase, quantities purchased and Certificate of Analysis for each batch of Investigational Products and Placebo purchased locally.

The application shall indicate the phase of clinical trial that is intended; Appendix …. of these Guideline

For timelines relating to the submission of serious adverse events (SAE), refer to Appendix ……. of these Guideline

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

A person who contravenes these Guidelines commits an offence and is liable on summary conviction
to penalties in line with the provisions of ……?????..

Appendix I_ Serious Adverse Events (SAE) Reporting Timelines

Type of ADR Report	Time Frame For Reporting	Format
Report from site in Rwanda		
Serious Adverse Events	Immediately where possible and in any event, within 48 hours after becoming aware of the information	A Serious Adverse Events form previously approved by the Rwanda Food and Drugs Authority must be completed and submitted after the site becomes aware of an event. Electronic submissions must be E2B compliant.
Follow-up reports	Immediately when any of the underlisted occurs: i. Change in the severity of SAE initially reported.	Follow-up reports should include an assessment of the any findings.

	ii. Whenever there is any new development on an initially reported SAE. iii. When the SAE resolves.	All fatal cases must be followed up with formal autopsy report1.
Frequent adverse events (greater than or equal to 1% but less than or equal to 10%)	Immediately where possible and in any event, within 7 days after becoming aware of the information	Line listing
Non-Serious Adverse Events	On request and where applicable, submitted as part of an application for registration	Individual reporting in accordance with the data elements specified in the ICH guidance Document E2A

	REPORTS FROM FOREIGN SITES (For multicentre studies with Rwanda as a participating country)	
Serious Events	Immediately where possible and in any event, within 7 days after becoming aware of the information.	Line listing Reports should include an assessment of the importance and implication of any findings.
Foreign regulatory decisions that affect the safety or use of the product	7 days	Detailed report Records with respect to all adverse events in respect of the drug that have occurred inside or outside the country, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event may be added.
OTHER REQUIREMENTS		
Literature reports that affect	7 days	Detailed report and / or copy

the safety of the product		of the publication Records with respect to the enrolment of clinical trial subjects including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons may be added.
Notification of change in nature, severity or frequency of risk factors	28 days	Complete and accurate records with respect to each change made to the Investigator's Brochure, including the rationale for each change and documentation that supports each change

New information impacting on risk benefit profile of product or conduct of trial	7 days	Communicate with appropriate scientific and medical judgments being applied to each situation. Additional information may include copies of diagnostic test results, laboratory reports or medical record progress notes
Periodic Update Safety Reports (PSUR)	▪ Upon request by RFDA ▪ Within 30 days when it is a condition of	As a Follow Up Report including copies of diagnostic test results, laboratory reports or medical record progress notes

	registration for a new medicinal product	

APPENDIX II: OTHER TIMELINES

ACTION	REFERENCE	TIMELINE
Notification for the implementation of an urgent amendment necessary to protect the life of subjects		Immediate phone call, followed by a written report within forty-eight (48) hours
Quarterly progress reports		Within 21 days after the end of the previous quarter. A quarter in this instance is considered as three

		months beginning from the date of initiation of a specific clinical trial.
Notification of Trial initiation		Immediately trial commences or within ninety (90) days of issuance of the Clinical Trial approval if the trial does not begin or is delayed as per the date of approval letter.. Failure of notification within the stipulated time would invalidate the Clinical Trial approval letter issued. A new approval may attract administrative fees.
Notification of interruption of an approved trial before achievement of its purpose.		Within ten (10) working days???
Submission of preliminary report on the ethical evaluation of the trial after completion.	3.5.1.6	Not later than 30 days after??? the completion of a clinical trial

Final Report of Clinical Trial as per ICH E3 Guideline (unless otherwise specified on clinical trial approval letter)	3.5.3	Not later than 90 days after the completion of the trial

PROCESSING OF SUBMITTED DOCUMENTS BY THE FDA

ACTIVITY	TIMELINE****
Processing of Clinical Trial applications	60 days
Processing of import permits for Investigational Products	10 days
Processing of quarterly progress and safety reports	15 days
Notification of receipt of electronic submissions including SAE reports	5 days
Communicating GCP Inspection findings	21 days
Processing of applications for protocol amendment	30 days
Processing of final Clinical Trial reports	30 days

****Timelines specified are working days and excludes clock stop time

7.2. APPENDIX II: Food and Drugs Authority Clinical Trials Quarterly Progress Report Form

SECTION A: ADMINISTRATIVE INFORMATION			
Rwanda FDA Clinical Trial approval Number: ……	Expected Date of Commencement (as indicated on the approval letter): ……...../……./…….	Actual Date(s) of Commencement (at the Study Centre(s): ....……/……./…….	Protocol Number: …… ……
Study Title:			
Reporting Period	From….....to……..		
Principal Investigator:	Name:		
	Address:	Phone: Mobile: E-mai	

		l :
Co-Investigators:	Name(s):	Phone: M o b i l e : E - m a i l :
Other Study Contact (if applicable):	Name: Address:	Phone: M o b i l e : E - m

	a i l :

SECTION B: STUDY STATUS (Check one category only)

Enrolment has not begun

☐

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Enrolment closed on: _____ (insert date): Subjects are receiving treatment/intervention

Enrolment closed on: _____ (insert date): Subjects are in follow-up only.

Analyzing data

Data analysis completed

SECTION C: INFORMATION ON SUBJECTS & STUDY ACTIVITIES	
a. Number of participants consented and screened..... b. Total number of subjects consented and screened who are eligible for the study..... c. Number of subjects to which the investigational product(s) has been administered..... d. Number of subjects left to be enrolled in the coming months (years).....	
e. Number of participants who have discontinued the study: - by Investigator: - voluntarily: - due to SAE: f. Have there been any Serious Adverse Events (SAEs)? g. Total number of SAEs:___. (attach line list of SAEs documented for the quarter)	Yes No

h. Have these SAEs been reported to the Rwanda Food and Drugs Authority i. If No, explain ……..... .....……..... j. Have there been any changes to the protocol since the Rwanda Food and Drugs Authority issue the approval ?	Yes No Yes No
k. Is this amendment submitted to the Rwanda Food and Drugs Authority? l. If No, explain ……..... .....……..... m. Date for the end of the study	Yes No
n. Date for the final study report	

SECTION D: COMMENTS (if any)

SECTION E: SIGNATURE

_____. Signature of Principal Investigator

Date

Return this form and all supporting
documentation to Rwanda FDA
P. O. BOX
Kigali, Rwanda

or submit via e-mail to ……..

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7.3 APPENDIX III: Phases of Clinical Trials

PHASE I

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

- Be aged between 18 and 65 years and in good mental health and not pregnant or lactating.

- Not have any illness which could potentially affect the results of the trial, or which could create special conditions for unfavourable effects of the drug.

The number of volunteers participating in this phase of clinical trials shall not be less than twenty-four (24).

PHASE II

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

PHASE III

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

PHASE IV

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

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