RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR REVIEW AND APPROVAL OF CLINICAL TRIALS

MAY, 2021

Doc. No.: DIS/GDL/042	Revision Date: 18/05/2021	Review Due Date: 01/07/2024
Revision No.: 0	Effective Date: 01/07/2021	

GUIDELINES DEVELOPMENT HISTORY

DRAFT ZERO	16/04/2021
ADOPTION BY RWANDA FDA	18/05/2021
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 article 8, paragraph 7 and 12 with mandate to regulate and inspect clinical trials in Rwanda. Reference is made to the provisions of the technical regulation N° CBD/TRG/015 Rev_0 governing the conduct of clinical trials, the Authority issues *Guidelines N° DIS/GDL/033* for review and approval of clinical trials.

These guidelines have been developed to provide a model of review of clinical Trials to ensure the compliance with sound scientific aspects and regulatory requirements prior to approval and authorization by the Authority.

These guidelines were developed in reference to the existing guidelines of World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Good Clinical Practices (ICH E6) and other available literatures.

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

Dr. Charles KARANGWA
Acting Director General

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ACCRONYMES AND ABBREVIATIONS

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

1.0. GLOSSARY

In these guidelines:

''An applicant" means the Sponsor or Principal Investigator. The applicant shall therefore be responsible for signing the application form.

"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established by 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).

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

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

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

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

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

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

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

"Drug/Medicine" includes:

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

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

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

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

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

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

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

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

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

''Investigational medicinal Product" A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the

approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

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

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

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

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

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

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

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

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

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

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

dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

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

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

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

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

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

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

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

"Randomization" The process of assigning trial study participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
"Source Data" All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

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

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

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

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

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

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

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

2.0. INTRODUCTION

Clinical trials are planned scientific investigations conducted on humans and animals to gather information on safety and efficacy of medical products and health technologies. Such experiments involve the administration of investigational products in patients, healthy volunteers or animal species to generate data which can later be used for marketing authorization of a product.

These guidelines highlight the requirements that need to be followed by the authority during the review and authorization to conduct clinical trials. Good Clinical Practice (GCP) principles and other ethical considerations are considered with the aim of ensuring the safety and protection of trial participants in Rwanda.

3.0. SCOPE

These guidelines apply to the review of all scientific aspects and regulatory requirements for initial clinical trial application, additional data if applicable, amendments, clinical trial reports including progress, close out and safety reports.

These Guidelines cover the review of Clinical Trial Application (CTA) of both unregistered or registered medicines, vaccines and other biological products, herbal medicines, cosmetics, medical devices and in vitro diagnostics with new intended uses.

4.0. REVIEW OF CLINICAL TRIAL APPLICATIONS

The Clinical Trial Applications (CTAs) and Clinical Trial Application amendments (CTA-As submitted to the authority are not considered valid until they have been screened for completeness.

4.1 Screening of Clinical Trial applications

On receipt of Clinical Trial Application (CTA) or Clinical Trial Applications for amendment (CTA-A), the Authority shall assign the reference number to the application which will be communicated with applicant for future correspondences.

The application shall then be screened for completeness and compliance with the regulatory requirements within ten (10) working days from the submission date.

During the screening of CTA/CTA-A, the Authority shall record all administrative information related to the application using screening template **(Annex-1)** and a screening report is developed.

In case the applicant has provided incomplete information after screening, the Authority shall communicate in writing and request missing regulatory requirements.

The applicant shall submit missing requirements in writing to the Authority within fifteen (15) working days unless she/he requests for extension before deadline. Incomplete Clinical Trial applications will not be scheduled for full review.

4.2 **Full Review of Clinical Trial applications**

The accepted CTAs or CTA-As are subjected to the full review of protocol in order to understand the background, rationale, objectives, design, methodology, statistical considerations, organization of the clinical trial and the types of data being collected prior to the authorization. In addition, the Authority undertakes the detailed review of non-clinical data, chemistry, manufacturing and control (CMC) of investigational product(s) using the review template **(annex-2).**
The clinical trial application is subjected to the first and second reviews.

The review of clinical trial application is undertaken using the same set of criteria and performed following the first-in first-out rule (FIFO), except for clinical trials that are to be conducted in public health emergencies such as disease outbreaks, which may be exempted.

The authority reviews all documents submitted in CTAs and CTA-As in order to assess the quality, and safety of the investigational products including placebo and determine that the use of the drug for the purposes of the clinical trial does not endanger the health of clinical trial participants or other persons.

The CTA is reviewed by two different reviewers to ensure transparency and ensure review of safety, efficacy and quality of investigational products. The full review report will be developed using appropriate review template (**annex 2)**. Generally, the initial review of CTAs and CTA-As may result in queries or additional information that needs to be addressed by the applicant. In this situation a letter documenting all deficiencies in the application will be issued to the applicant.

4.3 **Timelines for review of Clinical Trial applications**

The review process of a clinical trial application by the Authority shall not exceed sixty (60) working days upon compliance with all requirements. However, the review process for non-routine review (reliance and/or public health emergencies) clinical trial applications shall not exceed thirty (30) working days upon compliance with all requirements.

These timelines shall not include the time taken by the applicant to respond to any request for additional information or clarification from the Authority. A stop-clock mechanism shall thus apply each time the Authority requests for additional information.

4.4 **Types of Clinical Trial reviews**

CTAs and CTA-As may be subjected to any of the four (4) types of reviews depending on the applicable criteria and after review, the authority shall communicate a list of queries or request for clarifications (if any) to the applicant. In this case, the applicant has fifteen (15) working days to submit the query responses/clarification unless she/he requests for extension before deadline.

4.4.1 **Internal or routine reviews**

The internal or routine reviews of CTA or CTA-As are conducted Rwanda FDA staff according to the current established procedures and timelines.

4.4.2 **Expert Reviews**

The expert reviews of Clinical trials apply when the authority hires/invites the external reviewers following to the internal procedures for the complex clinical trial applications that require special expertise. The experts will sign a confidentiality agreement with the Authority to ensure the protection of the clinical trial information.

4.4.3 **Joint Reviews**

The joint reviews of Clinical trial applications are carried out jointly by the Authority with other regulatory bodies at national, regional or international level. The applications are reviewed by experts from each participating regulatory body and the coordination is done by a designated regulatory authority. Therefore, a regulatory decision will be taken at national level once all the requirements are fulfilled.

4.4.4 **Expedited Reviews**

In case of public health emergencies, the Authority shall expedite the review of clinical trial for medical products aiming at preventing or treating life-threatening diseases especially when there

is no alternative treatment option, products listed by WHO Emergency Use Assessment and Listing (EUAL) Procedure and African Vaccine Regulatory Forum (AVAREF) readiness plan.

The expedited reviews of Clinical Trial Application apply where a regulatory decision is given to the applicant within 30 working days and this is applicable for only if one of the following criteria is met:

a) Clinical trial applications for investigational drugs to provide treatment where no therapy exists.
b) Clinical trials conducted in public health emergency for example during a disease outbreak.

The authority reserves the right to determine which application may undergo this kind of review where the criteria may be unclear.

4.5 **Review of additional information & updates**

The sponsor or principal investigator is responsible of preparing responses to queries raised by the Authority during the review process of CTAs or CTA-As. Any new information available for the investigational product such as adverse effects, updates to the Investigator Brochure, changes in formulation or manufacturer for the active ingredients or finished products shall be notified to the Authority.

The Authority shall review the query responses/clarifications provided and if the information is satisfactory, the CTAs or CTA-As approval process shall be initiated. If the applicant provides non -satisfactory query responses for two successive times for the same requested information, the application shall be rejected.

4.6 **Review of non-clinical and clinical data**

The Authority shall review the quality part of investigational Product (IP), non-clinical and clinical data submitted on i for clinical trial purpose.

4.5.1 Review of investigational product (s)

The authority shall review the quality part of the investigational products including placebo to ensure that the Chemistry, Manufacturing and Control (CMC) is consistently followed from active substance to finished products. The evidence of GMP or ISO compliance for all manufacturers shall be reviewed. The information will be assessed using template for the quality assessment of clinical trial application Number XXX

4.5.2 Non-Clinical overview

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials shall at least include duration and total exposure proposed in individual patients, characteristics of the drug (e.g. long half-life, biotechnology products), disease or condition targeted for treatment, use in special populations (e.g. women of childbearing potential) and route of administration

The reviewer shall comment on toxicology, pharmacology and pharmacokinetics to support the relevance of clinical trials. Studies conducted to establish the pharmacodynamics effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise. This shall take into account the pharmacology, pharmacokinetics, and toxicology results, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling). The review of non-clinical data shall be made using appropriate format **annexure-XX**.

4.5.3 Clinical overview

During the review of clinical trial application, the authority shall undertake the review of the following where applicable:

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

The template for assessment of clinical data using the annex-2:

4.7 **General review report for clinical trial applications**

The reviewers of CTAs will develop a first and Second assessment report that will be presented and discussed during the internal peer review committee which will make a recommendation for approval. The assessment report shall include details of administrative information and other relevant information on the different sections of the protocol.

5.0. **. REVIEW OF CLINICAL TRIAL PROTOCOL AMENDMENT**

The Authority will review any substantial amendment to an already approved trial protocol, trial arrangements and investigational product for approval before such amendments are carried out. The Authority will compare the new change to the previously submitted information in the protocol. The authority reviews the amended part of the protocol and its rationale using the template for review of amendments (annexure-XXX).

6.0. **CLINICAL TRIAL APPROVAL**

Upon successful review and approval of a clinical trial application, the authority issues a Clinical Trial Approval Certificate (CTAC) with specific number and conditions on the attachment. The CTAC will have the following information: protocol title, protocol number and version if applicable, name (s) of investigational product (s) including placebo, name (s) of investigator(s), name (s) of sponsor (s), name (s) of trial sites, name of Contract research Organization (CRO) if applicable, data of issuance and expiration date, name and signature of the director general of the Authority. The template of the CTAC is (attached as annexure XXXXXXX)

Upon completion and approval of Clinical trial Application for amendment, the authority issues approval certificate of amendment. The approval certificate for amendment shall keep the reference number of the initial CTAC with new reference number referring to the amendment as provided in the annex-XXXX.

6.1 Register and publication of Clinical trials

The Authority will establish, maintain and publish of a register or database of approved, rejected clinical trial applications. The information required for register of clinical trials will include the following:

a) Protocol title and number
b) Clinical trial certificate number
c) Investigational product (s)
d) Principal investigators and co-investigators
e) Sponsor
f) Clinical trial site
g) Clinical trial duration
h) Clinical Trial Phase
i) Status of the trial
j) Targeted number of trial participant

In addition, the Authority ensure that relevant information on approved, rejected and summary of evaluation report of clinical trial applications, suspended and/or terminated clinical trials is publicly available and updated on monthly basis.

7.0. ANALYSIS OF CLINICAL TRIAL REPORTS

The Authority will perform analysis of the safety, progress and final report reports of clinical trial and provide feedback for overall guidance. The Authority may take appropriate regulatory action(s) based on findings from deep analysis of above reports.

7.1. Analysis of safety reports

The Authority will record and analyze all received Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) reports. The analysis will be done in accordance with pre-established procedures described in standards operating procedures.

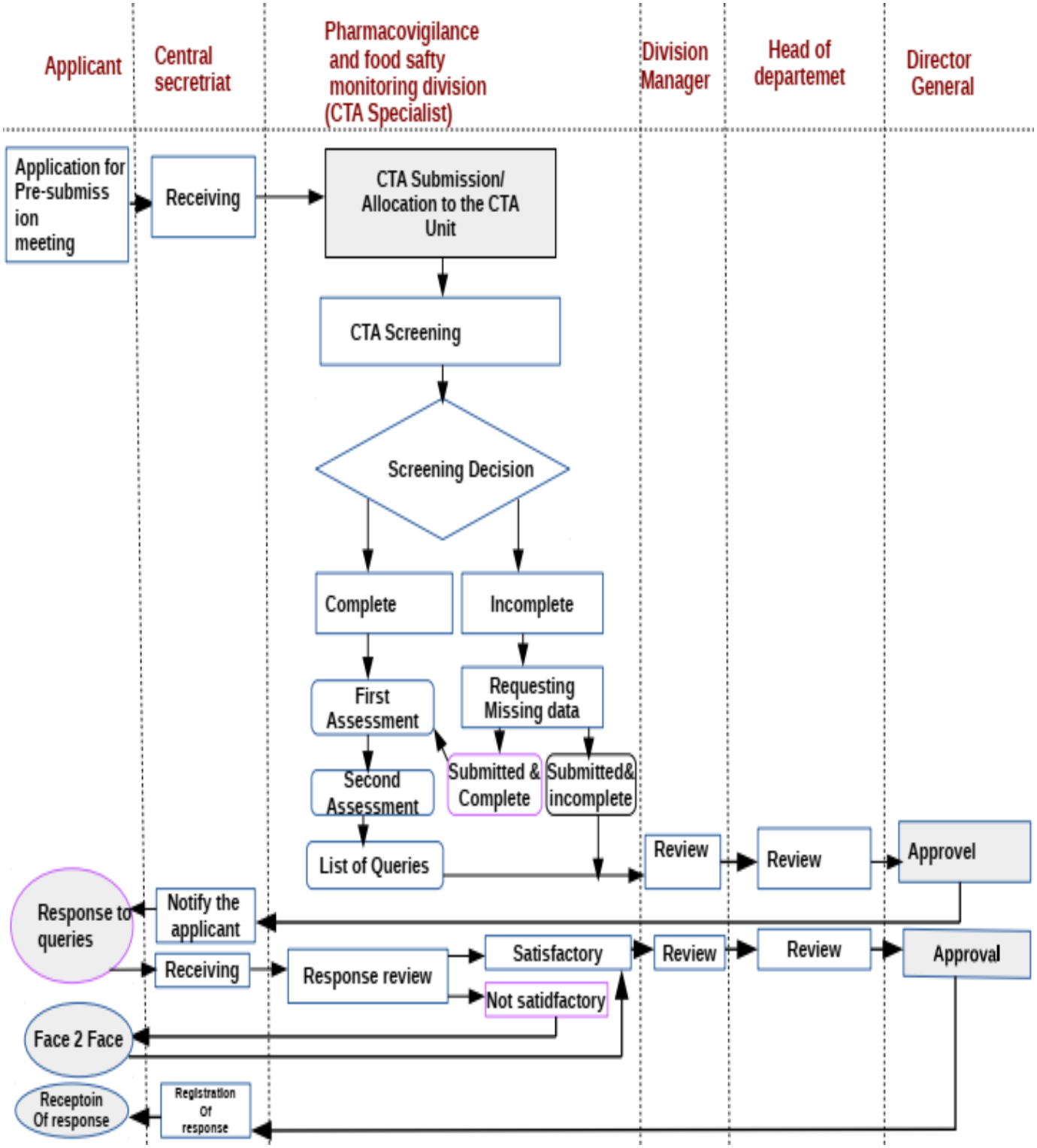
7.2. Review of progress and final reports

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

8.0. POST TRIAL PROTOCOL REVIEW

The authority shall review the post-trial access protocol of completed clinical trials to ensure equitable access of the treatment for the safety and welfare of trial participants until the product is commercially available. Upon satisfactory information, the Authority shall issue a notification letter for Post-Trial Access.

APPENDIX I: Clinical Trial Application Review Process Flow chart



ENDORSEMENT OF THE GUIDELINES

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

ANNEX 1: Clinical Trial Application Screening Format

Date of the submission (covering letter)		
Date of receipt (Rwanda FDA stamp)		
Application Reference Number	**XX**/CTA/RwandaFDA/2021	
Date of Application Screening		
Date of 1st assessment		
Date of 2nd assessment		
Type CT Application	☐ New Application ☐ Amendment Application ☐ Additional Information	
Title of Clinical Trial Application		
Protocol Reference Number		
Protocol Version Number (where applicable)		
Name and complete address of CA Applicant		
Names of Principal Investigator		
Names of Co-Investigator		
Names of Sponsor (If applicable)		
Name and address of the Contract research Organisation (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted.		
Phase of Trial (if applicable)		
Number of Clinical Trial Site.		
List of Clinical Trial Sites		
Duration of Clinical Trial		
First assessor	Name	Signature

Second assessor	Name	Signature
Name of Investigational Product (IP) Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.		
IP Therapeutic Classification		
IP Route of Administration		
IP storage Information		
Conclusion of the CT Assessment	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**	
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*		
Clinical Trial Commitments (if any)		
General remarks to next assessors: *List issues identified during the assessment for the follow up assessment, such as*		

information to be confirmed, to be verified, etc.	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	
SUMMARY OF REVIEW	

The Clinical trial assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

- The assessment report should be typed with "Times New Roman 12" fonts. The format of tables must not be changed.
- The 1st assessor's (R1) comments should be introduced in **red**.
- The 2nd assessor's (R2) comments should be written in **blue**.
- Deficiencies should be highlighted in yellow (in either red or blue text depending) in the body of the report. The assessor should write the deficiencies in the form of a question to the applicant. The question should be written such that it can be understood without reading the assessment report.
- The R2s should not delete the comments and questions raised by the R1s. They may instead strikethrough the text. In case of a disagreement, this should be clearly indicated and a justification for the disagreement should be provided by the R2.
- At end the end of R2 reports, take all agreed points to be communicated with the Clinical Trial Applicant to the appropriate section" point to be communicated with the applicant".

	Clinical Trial Application Number (CTA number):	
	Clinical Trial Application (CTA) Title	

#	CTA CHECKLIST OF REQUIRED DOCUMENTS	
a.	**Cover letter addressed to Director General of the Authority**	☐ **Provided** ☐ **Not Provided**
	Comments:	
b.	**A duly filled and signed clinical trial application form obtained from Rwanda FDA**	☐ **Provided** ☐ **Not Provided**
	Comments:	
c.	**General investigational plan**	☐ **Provided** ☐ **Not Provided**
	Comments:	
d.	**Clinical trial Protocol (detailed content Annex 2)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
e.	**Investigators' brochures**	☐ **Provided** ☐ **Not Provided**
	Comments:	
f.	**Capacity building plans including training and updating of staff involved in the trial**	☐ **Provided** ☐ **Not Provided**
	Comments:	
g.	**Clinical study reports (accomplished Clinical trial phases):**	☐ **Provided** ☐ **Not Provided**
	Comments:	

h.	**National Ethics Committee Clearance**	☐ **Provided** ☐ **Not Provided**
	Comments:	
i.	**Participant Information Leaflet (PIL).**	☐ **Provided** ☐ **Not Provided**
	Comments:	
j.	**Informed Consent Forms (English, French and Kinyarwanda)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
k.	**Curriculum vitae (CVs) of Principal investigator and Co- investigators**	☐ **Provided** ☐ **Not Provided**
	Comments:	
l.	**Joint declaration by Sponsor (or representative) and National Principal Investigator in prescribed format (Annex 3)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
m.	**Evidence of accreditation of the designated Laboratories or other evidence of Good Laboratory Practice (GLP) and assay validation**	☐ **Provided** ☐ **Not Provided**
	Comments:	
n.	**Letters of Access (if applicable) authorizing the Authority to access related files (Drug master, Site Reference Files) must be submitted.**	☐ **Provided** ☐ **Not Provided**
	Comments:	
o.	**Filled in Quality Overall Summary – Chemical Entities Template. (Annex 4)**	☐ **Provided** ☐ **Not Provided**

	Comments:	
p.	**Declarations by Principal investigator and Co-investigators (Annex 5)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
q.	**Evidence of agreement between the Sponsor and the Investigator.**	☐ **Provided** ☐ **Not Provided**
	Comments:	
r.	**Case Report Forms (CRFs)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
s.	**Serious Adverse Events reporting form (Annex 6)**	☐ **Provided** ☐ **Not Provided**
	Comments:	
t.	**Valid insurance policy cover of study participants**	☐ **Provided** ☐ **Not Provided**
	Comments:	
u.	**Certificate of Good Manufacturing Practice (GMP) for manufacture of the trial product and/or placebo**	☐ **Provided** ☐ **Not Provided**
	Comments:	
v.	**Trial product labels and package Insert/s for other trial medicines.**	☐ **Provided** ☐ **Not Provided**
	Comments:	
w.	**Mock up labels for the Investigational products.**	☐ **Provided** ☐ **Not Provided**

	Comments:	
x.	**List and Charter of the Data Safety Monitoring Board/Committee (DSMB).**	☐ **Provided** ☐ **Not Provided**
	Comments:	
y	**Declaration of Conflict of Interest, Financial Disclosure by the investigator**	☐ **Provided** ☐ **Not Provided**
	Comments:	
z	**Evidence of payment of prescribed fees for CTA or CTAA**	☐ **Provided** ☐ **Not Provided**
	Comments:	

Please copy and paste the QOS to assess the dossier against the Trial Protocol

Attachments:

1) Protocol:
2) Proof of Payment:
3) Commitment if any:

Annex 2: Assessment Template for Clinical Trial Application (CTA)

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

Date of the submission (covering letter)		
Date of receipt (Rwanda FDA stamp)		
Application Reference Number	**XX**/CTA/RwandaFDA/2021	
Date of Application Screening		
Date of 1st assessment		
Date of 2nd assessment		
Type CT Application	☐ New Application ☐ Amendment Application ☐ Additional Information	
Title of Clinical Trial Application		
Protocol Reference Number		
Protocol Version Number (where applicable)		
Name and complete address of CA Applicant		
Names of Principal Investigator		
Names of Co-Investigator		
Names of Sponsor (If applicable)		
Name and address of the Contract research Organisation (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted.		
Phase of Trial (if applicable)		
Number of Clinical Trial Site.		
List of Clinical Trial Sites		
Duration of Clinical Trial		
First assessor	Name	Signature
Second assessor	Name	Signature
Name of Investigational Product (IP)		

Proprietary Product Name (if relevant)	
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
IP Therapeutic Classification	
IP Route of Administration	
IP storage Information	
Conclusion of the CT Assessment	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	
General remarks to next assessors: *List issues identified during the assessment for the follow up assessment, such as information to be confirmed, to be verified, etc.*	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	

2.Background and Rationale
(Insert a brief, concise introduction into the clinical problem and previous treatments and developments, i.e., pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature (citations by consecutive numbering, with list at end of this

section; important or not readily available references may be included with the paper submission, if appropriate). This section should also contain information on the new drug). Provide rationale for conducting the study in Rwanda
Assessor's comments:
1. **Objective of the trial**
(Insert the objectives that are the same as the objectives contained in the protocol. Include the primary objective and secondary objectives) ***Primary Objective(s):*** ***Secondary Objective(s):***
Assessor's comments:
2. **Endpoints**
(Insert the endpoints that are the same as the endpoints contained in the body of the protocol. Include the primary endpoint and important secondary endpoints) ***Primary Endpoint(s):*** ***Secondary Endpoint(s):***
Assessor's comments:
3. **Design**
3.1 *Insert summary description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design). Provide a simple summarized snapshot of your study design not to exceed a single page. This section should include a diagram that provides a quick to 1 page. Please present an overview of your study design in a schematic diagram and tables. The data presentation can be adapted depending on the nature of your study and can be customized according to your protocol.* *Example: complete the tables with study-specific information and adapt the table(s) to illustrate your study design.*

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

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

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

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

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

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

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

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

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

Assessor's comments:

4. **Study participants**

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

4.2 *State the Inclusion criteria:*

4.3 *State the Exclusion criteria*

Assessor's comments:

5. **Premature Withdrawal / Discontinuation Criteria**

5.1 ***Withdrawal criteria:***

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

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

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

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

6. **Drug Formulation**

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

6.2 *Instructions for safe handling;*

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

Assessor's comments:

7. **Dosage Regimen**

7.1 *Rationale for dose selection*

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

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

7.2.2 *Dose(s):*

7.2.3 *The dosing schedule(s):*

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

7.2.5 *The treatment period(s):*

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

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

7.2.8 *Procedures for monitoring participant's compliance:*

7.2.9 *Wash-out period*

(Description for pre-, during- and post-trial, as applicable)

Assessor's comments:

8. **Pre-study Screening and Baseline Evaluation**

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

9. **Treatment / Assessment Visits**

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

Assessor's comments:

10. **Efficacy Variables and Analysis**

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

10.2 *Provide specification of the efficacy parameters.*

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

Assessor's comments:

11. **Assessment of Safety**

11.1 *Specification of safety parameters:*

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

11.3 *Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.*

11.4 *The type and duration of the follow-up of subjects after adverse events*

11.5 *RISKS: (Identify potential risks and mitigation strategies (e.g. need for and risks associated with long)*
11.6 *term immunosuppression)*

11.7 *DATA and SAFETY MONITORING PLAN (DSMP):*

(Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)

11.8 *Immune Monitoring and immunosuppression: (Describe and justify the plan for immunosuppression and immune monitoring (if applicable)*

Assessor's comments:

12. **Assays/methodologies**

12.1 *Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies (Provide a more detailed summary of assay methods and summarize assay qualification/validation. Indicate where specialized testing will be conducted)*

12.2 *The names and contact addresses of the laboratories to be used for the study;*
12.3 *State the location of the attached draft Material Transfer Agreements (MTAs) in the submission;*
12.4 *State the duration for long term storage of samples and the area to be stored*

Assessor's comments:

13. **Statistical analysis plan**

13.1 *Specify the planned sample size to be used in the study and its justification*

13.2 *Summary of description of the statistical methodologies to be used to evaluate the effectiveness of the investigational product, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance and the statistical model to be used.*
13.3 *Analysis of trial parameters (primary/ secondary endpoints), population, demographics, as applicable.*
13.4 *Efficacy analysis methods and results of efficacy end-point analysis.*
13.5 *Safety analysis methods and results of safety end-point analysis.*
13.6 *Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/ pharmacological etc parameters, as applicable.*
13.7 *Pharmacokinetic endpoint analysis, as applicable.*
13.8 *Interim analysis and role of Data Safety Monitoring Board, as applicable*

Assessor's comments:

14. **Outcome criteria**

(Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives)

Assessor's comments:

15. **Data management**
(Describe procedures for recording, processing, handling, and retaining raw data and other study documentation)
Assessor's comments:
16. **Monitoring plan**
(Summary of the monitoring plan) *State the location of the detailed monitoring plan in the submission*
Assessor's comments:
17. **Ethical considerations**
17.1 *State the ethical clearance reference number and institutions that have approved the trial* *Institution review Board ethical clearance: Number and date* *NIMR ethical clearance number and Date:*
17.2 ***Insurance Details :*** 17.2.1 *Insert local Insurance Company name and address:* 17.2.2 *policy cover number:* 17.2.3 *Validity:* 17.2.4 *Expiry Date:* 17.2.5 *State the location of the Insurance cover in the submission:*
17.3 ***Participant Information sheets and Informed Consent forms:*** *(The contents should be as per ICH guidelines, these guidelines and declaration of Helsinki)* 17.3.1 *.State the version number and dates for both English and Swahili versions* 17.3.2 *State the location of the Participant Information sheets and Informed Consent forms in the submission*
17.4 *State the amount to be reimbursed to the participants*
17.5 *Treatment and/or management of participants and their disease condition(s) after completion of trial*
17.6 *Follow-up of trial study participants after the conclusion of the trial*
17.7 *In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:*
17.8 *Identification of the provider and recipient*
17.9 *Identification of the material and the volume of material*
17.10 *Definition of the trial and how the material will and will not be used.*
17.11 *Maintenance of confidentiality of background or supporting data or information, if any*
17.12 *Indemnification and warranties (where applicable)*
17.13 *Details on post-trial access to the products*
Assessor's comments:

ANNEX 3: Template of Clinical Trial Certificate

ANNEX 4: Template of additional data response

Date of the submission (covering letter)	
Date of receipt (Rwanda FDA stamp)	
Application Reference Number	
Date of Application Screening	
Date of 1st assessment	
Date of 2nd assessment	
Type CT Application	☐ New Application ☐ Amendment Application ☐ Additional Information

Title of Clinical Trial Application		
Protocol Reference Number		
Protocol Version Number (where applicable)		
Name and complete address of CT Applicant		
Names of Principal Investigator		
Names of Co-Investigator		
Names of Sponsor (If applicable)		
Name and address of the Contract research Organization (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted.		
Phase of Trial (if applicable)		
Number of Participants (Trial subjects)		
Number of Clinical Trial Site.		
List of Clinical Trial Sites		
Duration of Clinical Trial		
First assessor	Name:	Signature:
Second assessor	Name	Signature
Name of Investigational Product (IP) Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.		
IP Therapeutic Classification		
IP Route of Administration		

IP storage Information	
Conclusion of the CT Assessment	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	
General remarks to next assessors: *List issues identified during the assessment for the follow up assessment, such as information to be confirmed, to be verified, etc.*	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	

The Clinical trial assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

- The assessment report should be typed with "Times New Roman 12" fonts. The format of tables must not be changed.
- The 1st assessor's (R1) comments should be introduced in **red**.
- The 2nd assessor's (R2) comments should be written in **blue**.

- Deficiencies should be highlighted in yellow (in either red or blue text depending) in the body of the report. The assessor should write the deficiencies in the form of a question to the applicant. The question should be written such that it can be understood without reading the assessment report.
- The R2s should not delete the comments and questions raised by the R1s. They may instead strikethrough the text. In case of a disagreement, this should be clearly indicated and a justification for the disagreement should be provided by the R2.
- At end the end of R2 reports, take all agreed points to be communicated with the Clinical Trial Applicant to the appropriate section'' point to be communicated with the applicant''.

ASSESSMENT OF ADDITIONAL DATA FOR CLINICAL TRIAL

Question from Previous CT Assessor (1)
Response from CT Applicant (1)
Comment from CT Assessor (1)
Question from Previous CT Assessor (2)
Response from CT Applicant (2)
Comment from CT Assessor (2)
Question from Previous CT Assessor (3)
Response from CT Applicant (3)
Comment from CT Assessor (3)
Question from Previous CT Assessor (4)

Response from CT Applicant (4)
Comment from CT Assessor (4)
Question from Previous CT Assessor (5)
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Response from CT Applicant (5)
Comment from CT Assessor (5)
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