RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR MONITORING AND REPORTING CLINICAL TRIAL SAFETY DATA IN RWANDA

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by Law N° 003/2018 of 09/02/2018, specifically in article 8, paragraph 7 and 12 with a mandate to regulate and inspect clinical trials in Rwanda. Reference is made to the provisions of the technical regulation N° DD/PVCT/TGR/001 Version 4 governing the conduct and inspection of clinical trials, the Authority issues Guidelines N° DD/PVCT/GDL/008 Version 3 for review and approval of clinical trials.

These guidelines outline the prescribed procedures for monitoring clinical trial safety data and specify the minimum criteria for submitting a comprehensive Adverse Event report. They delineate the categories of Adverse Events that must be reported and the corresponding timelines for submission.
Furthermore, the guidelines emphasize that Adverse Events should undergo thorough evaluation, explicitly stipulating that Clinical Trial Sponsors and delegated Principle Investigators bear the responsibility for the assessment and reporting of such events.

These guidelines were developed in reference to the existing guidelines of the World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Good Clinical Practices (ICH E6) and other available literature.
The authority has a legal responsibility for handling all Safety data occurring in Clinical Trials conducted in Rwanda. It is therefore intended that Safety data for Clinical Trials conducted in Rwanda will be managed and reported accordingly.

The reliability of safety data is contingent upon its thoroughness and proper management. Consequently, these guidelines aim at enhancing the knowledge of all scientists engaged in clinical trials at every stage, ensuring the consistent accuracy and trustworthiness of report content.
Rwanda FDA anticipates that these guidelines will facilitate the standardized and consistent documentation of clinical trial safety data, thereby streamlining the Authority's evaluation process and enabling well-informed conclusions, recommendations, or necessary regulatory decisions.

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Director General

DOCUMENT DEVELOPMENT HISTORY

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ACRONYMS AND ABBREVIATIONS

ADR	: Adverse Drug Reaction
AE	: Adverse Event
AEFI	: Adverse Event Following Immunisation
AESI	**:** Adverse Events of Special Interest
ATMPs	**:** Advanced Therapy Medicinal Products
AVAREF	: African Vaccines Regulatory Forum
CIOMS	**:** Council for International Organizations of Medical Sciences
CRO	: Contract Research Organization
CT	: Clinical Trial
DSMB	**:** Data and Safety Monitoring Board
DSMP	**:** Data and Safety Monitoring Plan
DSUR	**:** Development Safety Update Report
GCP	: Good Clinical Practice
HLT	**:** High Level Terms
IB	: Investigator's Brochure
ICH	: International Conference on Harmonization
ICSR	: Individual Case Safety Report
IEC	: Independent Ethics Committee
IMP	: Investigational Medicinal Product
IRB	: Institutional Review Board
IRMS	**:** Information Regulatory Management System.
MedDRA	**:** Medical Dictionary for Drug Regulatory Activities
NAA	**:** Assessment by Naranjo algorithm approach
PI	**:** Principal Investigator
QALYs	**:** Quality-Adjusted Life Years
RNEC	**:** Rwanda National Ethics Committee
Rwanda FDA	: Rwanda Food and Drugs Authority
SOP	: Standard Operating Procedure
SmPC	**:** Summary of Product Characteristics
SUSAR	: Suspected Unexpected Serious Adverse (Drug) Reaction
WHO	**:** World Health Organization

GLOSSARY / DEFINITIONS

In these guidelines, unless the context otherwise states:

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

''Adverse Drug Reaction (ADR)'': Adverse drug reactions, as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

''An Adverse Event Following Immunization (AEFI)'' is defined as any untoward medical occurrence which follows immunization. An AEFI does not necessarily have a causal relationship with the usage of the vaccine.

"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law No 003/2018 of 09/02/2018.

"Case Report Form" A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each study participant.
"**Child**" A person who is below eighteen (18) years of age or the definition of child as defined in the laws currently enforced in Rwanda.

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

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

"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.

''Expected ADR''; As opposed to "unexpected," an event that is noted in the investigator brochure or labelling (PL or SPC). Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events.

"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.

''Individual Case Safety Report (ICSR)/Safety report''is a document providing the most complete information related to an individual case at a certain point in time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point in time.

"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.

"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.
"Investigator" An individual who conducts a clinical investigation.

''Lack of Efficacy' 'Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

''Non-serious AE'': An event or reaction that is non-serious (does not meet any of the criteria for seriousness.

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

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

"Protocol" 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.

''Serious AE/ADR'': In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm, convulsions that do not result in hospitalization, development of drug dependency, etc).

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

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

"Sponsor" An individual, company, institution or organization 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.

''Suspected, Unexpected, Serious Adverse (Drug) Reaction (SUSAR)'': An adverse event that occurs in a clinical trial subject, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. Reports of these reactions are subject to expedited submission to health authorities.

"Human 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.

''Unexpected ADR '': An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labelling (e.g. Package Leaflet (PL) or Summary of Product Characteristics SPC)) should be considered unexpected. When a Marketing

Authorisation Holder (MAH) is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

Suspected Adverse Drug Reaction (SADR) A noxious and unintended response to any dose of a drug or biologic product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out (ICH E2A).

CHAPTER I. INTRODUCTION

Rwanda FDA is a regulatory Authority established by the Law N° 003/2018 of 09/02/2018 and it is mandated to regulate the conduct and inspection of clinical trial. To achieve this mandate, The Authority ensures effective safety monitoring and requires any person conducting clinical trials to immediately report any serious or adverse effects or reactions observed during the trial.

Monitoring of safety is one of the crucial tasks for clinical trial implementation in Rwanda. International clinical trial guidelines and regulations require that clinical trials (CTs) be planned and performed to deliver outstanding evidence that investigational products are effective and that human trial participants can be reassured that the benefits far outweigh the risks, both during the development phases (I, II, III) and in post-marketing environment (Phase IV).

In spite of the progress made in the regulatory sphere with regard to the regulations of clinical trials and drug safety monitoring, there are still some shortcomings that hinder consistent and thorough monitoring and review of the safety and efficacy of investigational pharmaceutical products. Inconsistency in Monitoring and reporting of drug safety remains a concern worldwide. This is illustrated by extensive variation in reporting, issues in traceability of events, where many safety signals might be omitted.

These guidelines provide the requirements, procedures, roles, responsibilities and activities in pharmacovigilance for clinical trials, outline the reporting requirements among Investigators, CROs and Sponsors and safety data management, and communication, training requirements as well as monitoring and evaluation for regulatory decision making.

In this respect, the guidelines define proper management of safety reports from collection at the clinical trial site to communicate with Rwanda FDA, and describe how safety data should be handled. They also focus on reporting timelines for SUSARs and SAEs that require expedited reporting, to bring awareness to regulators, investigators, and sponsors studying the investigational pharmaceutical product, highlighting new important reactions, and facilitating proper actions.

Implementation of these guidelines will facilitate the effective conduct of clinical trials in Rwanda by ensuring the safeguard of the rights, safety and well-being of human trial participants and credible safety data.

I.1 SCOPE

Since Clinical Trials are experiments in humans, they must be carried out following established standards/guidelines in order to safeguard the rights, safety and well-being of the trial participants. These guidelines are scoped on the following:

a) All clinical trials conducted either in Phase I, II, III, or IV of a Clinical Trial. They also cover Bioavailability and Bioequivalence studies.
b) For Clinical Trials and studies on New Medicines, Vaccines and other biological products, herbal medicines, medicated cosmetics, medicated food supplements, Advanced Therapy Medicinal Products (ATMPs), medical devices and In Vitro Diagnostics(IVDs) for which safety/efficacy profile has not been determined;

c) For Clinical Trials and studies on registered medicines, vaccines and other biological products, herbal medicines, medicated cosmetics, medicated food supplements, medical devices, Advanced Therapy Medicinal Products (ATMPs), and diagnostics where the proposed clinical trials are outside the conditions of approval.

CHAPTER II. RESPONSIBILITIES OF STAKEHOLDERS AND PRINCIPLES FOR HANDLING SAFETY DATA IN CLINICAL TRIALS

II.1 Roles and Responsibilities of Stakeholders

II.1.1 Trial participants

Trial participants regarded as full partners in the research and thereby be kept well informed so that they understand their role and importance to make decisions regarding their participation and continuation in a study, and can enhance their willingness to adhere to all protocol requirements, and to inform investigator and study staff about any AEs that occurred during the Clinical Trials and the follow-up.

The following are the key responsibilities to be achieved by trial participants in the clinical trial:

a) If side effects occur after the trial ends, participants should still report them to the clinical trial team or sponsor, as they may provide valuable data for post-trial analysis.
b) Avoid engaging in activities or behaviours that are explicitly restricted by the trial protocol, as these could skew results or jeopardize safety.
c) Participants must report any physical, mental, or emotional changes they experience during the trial, even if they think the changes are minor or unrelated to the trial.
d) They should provide detailed descriptions of symptoms, including onset, duration, and severity, to help researchers assess potential adverse effects.
e) Follow the study protocol, including taking medications or undergoing procedures as instructed.
f) Inform the clinical trial team immediately if they experience adverse events or have concerns about their safety.
g) Notify the team of any new medical conditions, medications, or treatments they start during the trial.
h) Maintain accurate and complete records if required (e.g., diaries, questionnaires, or electronic logs) to track symptoms, medication adherence, and other trial-related data.
i) Attend all required follow-up visits to help researchers monitor long-term safety and effectiveness of the intervention and provide biological samples or undergo tests as required.
j) Contact the trial's designated safety contact (e.g., a hotline or on-call investigator) in case of adverse event.

II.1.2 Investigators

The investigator's responsibilities entail:

a) Assurance that their protocols are conducted in compliance with these guidelines,
b) Adherence to the Clinical Trial protocol and Data and Safety Monitoring Plan (DSMP) with respect to timely submission of SAEs, certain non-serious AEs and/or laboratory

abnormalities and unanticipated problems to the sponsor. Unanticipated problems include other incidents, experiences, and outcomes that are not AEs.

II.1.3 Sponsors and their representatives

The sponsor's responsibilities entail:

a) Reporting of SAEs/AEs, AESI, SUSARs to Rwanda FDA and the IRBs/IECs,
b) Informing the investigators about DSMB Decisions of any changes related to the benefits / risks ratio of Intervention,
c) Annual safety reporting to the Rwanda FDA and the IRBs/IECs.
d) To conduct causality assessment of the reported adverse events for regulatory decision making.

The sponsor should continuously weigh anticipated benefits and risks of the CT, which includes ongoing safety evaluation of investigational pharmaceutical product (IP), establish a system and written standard operating procedures (SOPs) to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and follow-up. Delegation of tasks does not remove the ultimate responsibility of the sponsor or investigator for the conduct of the clinical trial in accordance with the applicable legislation or regulations.

II.1.4 Rwanda National Ethics Committee (RNEC)

Rwanda National Ethics Committee (RNEC) and its IRBs (Institutional Review Boards) are expected to have the expertise to ethical oversight and monitor compliance with ethical guidelines and regulatory standards throughout the trial in collaboration with Rwanda FDA. It also reviews the reports of serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) and assessing whether appropriate actions are being taken.

II.1.5 Data and Safety Monitoring Boards (DSMB)

All Phase III clinical trials require monitoring by a DSMB. For earlier trials (such as Phase I and II), a DSMB may be appropriate if the studies have multiple clinical trial sites, involving particularly high-risk interventions, or vulnerable populations.

~~However, other monitoring schemes for earlier clinical trials may be appropriate depending on the risk to participants, the population being studied, and the research environment, etc.~~

DSMBs review:

a) Research protocols and plans for data and safety monitoring defining a listing of events that should be reported immediately to the DSMB and the format of reporting cumulative data at intervals.
b) Interim analyses of outcome data and cumulative toxicity data for safety and efficacy to determine whether the study should continue as originally designed, be changed, or be terminated.
c) Major proposed modifications (e.g., increasing target sample size, dropping an arm based on other study outcomes or toxicity results, modifying outcomes).

d) Published reports of related studies submitted to the DSMB to determine whether the monitored study needs to be changed or terminated.

II.1.6 Rwanda Food and Drugs Authority (Rwanda FDA)

Rwanda FDA will play a crucial role in the monitoring and reporting clinical trial safety data in order to ensure credible data and protection of safety, well-being and rights of human trial participants. The Authority will ensure the following but not limited to:

a) Development of the regulatory documents necessarily for enforcement of these guidelines.
b) To enhance capacity building to the stakeholders on safety monitoring and reporting in clinical trials.
c) To ensure proper management of safety data for regulatory decision making.
d) To conduct Trigged GCP inspections in case of reported SAEs leading to life threatening.
e) To re-evaluate the causality assessment reports of the reported adverse events for regulatory decision making.
f) To carry out signal detection and management for the reported signals emerging in the ongoing clinical trials.
g) To review the Development of Safety Update Reports (DSURs) submitted by the Sponsors, CROs, or Principal Investigators of the authorized ongoing clinical trials.
h) To review all progress, close-out and final reports submitted by the Sponsors, Principal Investigators or CROs for regulatory decision making.
i) Communication to the concerned stakeholders or public about regulatory decisions made relating to the safety data in clinical trials.

II.2 Main Principles in safety monitoring in Clinical Trials.

II.2.1 Principles

Participant's safety is an instrumental point in clinical research and development that should be considered at the earliest steps of investigation of a pharmaceutical product. Safety monitoring in Clinical Trials encompasses collection, reporting and evaluation of all events that might compromise participant's safety. AEs/ADRs, AESIs, and lack of efficacy comprise main safety objectives in CTs. However, some rare events that can jeopardize safety such as mistakes in IP administrations, e.g., overdose, serious deviation from the protocol or breach of the protocol, should be also considered within the holistic approach regarding safety evaluation in CTs and reported on standardized basis. Systematic approach with engagement of all stakeholders aimed at establishing clearly defined procedures, milestones and timelines will facilitate development of safety and efficacious medicines.

a) Procedures and Timeframes: Clear roles and regular, timely safety reviews are essential to identify risks and support decision-making. Frequent reviews are needed in early phases, while less frequent reviews may be suitable for drugs with established safety profiles.

b) Safety Data Management: Safety data collection through CRFs, SAE forms, and laboratory reports is critical for proper medical interpretation. Guidelines like ICH E6 and ICH E2B define data collection and reporting standards.

c) Evaluation of Safety Data: Regular assessment of all AEs, efficacy endpoints, and safety information should occur at the end of each study phase. Updates to product information may be necessary based on findings.

d) Decision-Making: Integrity of safety data ensures timely decisions. Any necessary changes to study protocols or safety procedures should be communicated to all relevant stakeholders such as investigators, sponsors, Rwanda FDA and RNEC/IRBs.

e) Advisory Bodies: A safety committee should provide expert advice on safety findings and guide actions. External experts may be consulted on an ad hoc basis for specific issues.

CHAPTER III. MANAGEMENT OF SAFETY DATA IN CLINICAL TRIALS

III.1 Safety Monitoring of Adverse Events

The Safety Monitoring of Adverse Events involves the processes for detecting, reporting, and evaluating adverse events during clinical trials to ensure participant safety. It focuses on timely reporting, risk assessment, and regulatory oversight to support informed decisions and protect public health throughout the clinical trial lifecycle.

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

III.2 Reporting of Safety data from Clinical Trials

Reporting of safety data can be done either in periodic or expedited manner.
Periodic safety reporting requirement applies to clinical trials both pre- and post-marketing. In addition to an annual and bi-annual progress reports, a quarterly line listings with a brief safety summary shall be submitted Rwanda FDA and RNEC.

Furthermore, safety reports (SUSARs, SAEs) are required to be expeditiously reported in order to bring awareness to regulators, investigators studying the pharmaceutical product and sponsors on new important reaction and possibly to facilitate other actions.

For products with a well-established safety profile and when most clinical trials are Phase IV in the approved indication(s) and product used in case of emergency use authorisation or compassionate use**,** it is strongly recommended that the PSUR replaces the annual DSUR in format prescribed by E2C Guidelines.

III.2.1 Reporting of Serious Adverse Events/severe adverse events

In line with regulations governing the conduct and inspection of clinical trials in Rwanda, the Sponsor/ Principal investigator (PI) will:

a) Report to the sponsor all serious adverse events (SAEs), both expected or unexpected, immediately but no later than twenty-four(24) hours upon receiving notice of such an event;
b) Report to the Authority all serious adverse events (SAEs), both expected or unexpected, immediately but no later than forty-eight (48) hours upon receiving notice of such an event. A detailed written report on the event within a further seven (7) calendar days;
c) Also SAEs and SUSARs occurring from sites outside the country for multicenter trials shall be reported to Rwanda FDA.
d) Report adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations;
e) Submit follow up medical reports on the SAEs evolution or outcome and action taken;
f) Submit autopsy reports and terminal medical reports in case the SAEs resulted in death of trial participants;
g) Submit causal relationship report between SAEs and the Investigational pharmaceutical product that is established, evaluated, and clarified for further assessment.
h) All reports submitted will be kept CONFIDENTIAL.

III.2.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

a) Report to the sponsor all Suspected Unexpected Serious Adverse Reactions (SUSARs) immediately but no later than twenty-four(24) hours upon receiving notice of such an event;

b) Report to the Authority all Suspected Unexpected Serious Adverse Reactions (SUSARs), both expected or unexpected, immediately but no later than forty-eight (48) hours upon receiving notice of such an event. A detailed written report on the event within a further seven (7) calendar days;

c) Submit follow up medical reports on the SUSARs evolution or outcome and action taken;

d) Submit autopsy reports and terminal medical reports in case the SUSARs resulted in death of trial participants.
e) Submit causal relationship between SUSARs and the Investigational product that is established, evaluated, and clarified for further assessment;
f) In case of multi-countries trial including Rwanda, the sponsor shall submit a line list of all SUSARs occurring in other sites with action taken by the respective regulatory bodies.

III.2.3 Reporting the other Unanticipated problems

Other situations that shall be communicated to Rwanda FDA within 14 calendar days are those that

a) Might materially influence the benefit-risk assessment of Investigational Product or would be sufficient to consider changes in product administration or in the overall conduct of a clinical trial.
b) Marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.
c) Appropriate medical and scientific judgment should be applied for each situation e.g.
   i. For an "expected" severe adverse drug reaction (ADR), any clinically significant increase in the frequency of its occurrence.
   ii. A substantial risk to the trial participants, such as a lack of efficacy of an investigational product used to treat a life-threatening disease.
   iii. A major safety finding from a newly completed animal study (such as carcinogenicity).
   iv. If reactions associated with active comparator drug or placebo occur, the sponsor shall report such reactions to Rwanda FDA on routine basis.

NB:

a) Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), and unanticipated problems arising from sites outside Rwanda in multicenter trials, must be promptly reported upon notice.
b) The regulatory timeline begins when the sponsor receives a safety or problem report.
c) Regulatory action shall be initiated for each non-compliance with prescribed reporting timelines

III.2.4 Individual Case Safety Reports (ICSRs) in clinical trials

ICSRs must be assessed by trained experts in clinical medicine and codification, following standardized procedures for data entry using MedDRA® terminology. Adverse Events data should be presented as Preferred Terms (PT) within the relevant System Organ Classes (SOCs), with flexibility for higher-level terms when needed.

Initial reports must include: identifiable patient, suspect investigational product, reporting source, and a serious, unexpected event with a suspected causal link.

Follow-up information should be submitted as it becomes available.

Sponsor and Principal Investigator shall report ICSRs by using CIOMS-I form standards attached in the **Appendix Nº....**and be submitted to Rwanda FDA within the timeline available at 2.1 of this guidelines.

III.2.5 Development Safety Update Reports (DSURS)

The Development Safety Update Report (DSUR) is a common standard for periodic reporting on medical products under development (including marketed medical products that are under further study).

The main focus of the DSUR shall be the data and findings from interventional clinical trials. The relevant information from post-marketing studies shall also be included in the PSUR, because clinical development of a drug frequently continues following marketing approval, . DSUR shall concentrate primarily on the investigational product, providing information on comparators only where relevant to the safety of trial subjects.

The format, presentation and content of DSUR and an outline of points to be considered in its preparation and submission timelines shall follow current ICH guidelines E2F on Development Safety Update Report.

The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

a) Clinical trials using an investigational product (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
b) Clinical trials conducted using marketed medical products in approved indications (i.e., therapeutic use trials (Phase IV);
c) Therapeutic use of an investigational products;
d) Clinical trials conducted to support changes in the manufacturing process of investigational products;
e) Any other significant findings pertinent to the safety of the investigational products.

Sponsors/Marketing Authorization Holders shall be required to submit annual DSURs/PSURs of their products to the Authority.

III.2.6 Investigator's Brochure (IB)

The IB should be compiled using all available information and evidence that justifies the clinical trial and supports the safe use of the Investigational Product (IP).

If the IP is authorized and used according to its marketing authorization, the approved Summary of Product Characteristics (SmPC) can be used in place of the IB. However, if the clinical trial conditions differ from the authorized use, the SmPC should be supplemented with relevant non-clinical and clinical data to support its use in the trial.

For further details on the IB's contents, refer to Section 7.0 of the ICH E6 Guidelines and should be submitted to the Authority on annual basis. Nevertheless, when a new safety information is available triggering a new safety profile of IP and protocol changes, the Sponsor and Principal Investigator shall inform the Authority with the necessary actions to be taken.

III.2.7 Progress reports

These reports elucidate data on reported adverse events emerging from ongoing clinical trials during a specific period approved by Rwanda FDA.

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

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

The progress report shall be submitted using the format published on www.rwandafda.gov.rw, and the Authority records it in the approved database and reviews it for regulatory decision-making.

III.2.8 DSMB Report

Authenticated and signed DSMB Report or minutes of the DSMB Meeting shall be submitted to Rwanda FDA within 15 calendar days from the date of the report as per the DSMB Charter.

III.2.9 Interim Analysis Report

In a case the approved protocol prescribes for interim analyses, a comprehensive report on findings and subsequent recommendations shall be submitted at Rwanda FDA within 30 calendar days of the results.

III.2.10 Site Close out report

The PI shall submit to the Authority the close-out report to document that all activities required for trial are completed, and copies of essential documents are held in the appropriate files, within thirty (30) calendar days from the day of last enrolment of trial participant. The content and format of the close-out report will comply with the close-out reporting format-I which is published on Rwanda FDA website. In this report, the management of remaining investigational products (IP) will be highlighted and copy (ies) of disposal certificate should be provided as annexes to the report.

III.2.11 Trial Final Report

The final report of the clinical trial shall be submitted to the Authority within ninety (90) calendar days of the completion or termination of the clinical trial using the standard format as per ICH E3 (Guideline's structure and content of clinical trial report). The content and format of Final Trial Report will comply with final trial report format which is published on Rwanda FDA website.

Any unexpected safety issue that changes the risks-benefit analysis and is likely to have an impact on trial participants should be reported together with proposed actions to be taken. The Authority will record and analyse all received progress, close-out and final reports from approved clinical trials and provide feedback.

After completion of analysis of the final report, the Authority updates the registry for clinical trials in Rwanda. The analysis will be done in accordance with pre-established procedures described in standards operating procedures.

III.3 Other considerations

III.3.1 Reports from blinded trials

In blinded trials eg double blind studies, when a serious adverse event is judged reportable on an expedited basis, the blind may only be broken for that specific patient by the sponsor even if the investigator has not broken the blind. It is recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

There are several disadvantages to maintaining the blind under the circumstances described which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised. If the event is serious, new, and possibly related to the medicinal product, then if the IB is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading.

Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data. However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with Rwanda FDA in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

III.3.2 Unblinding clinical trials

Blinded CTs bring specific requirements for unblinding expedited single case reports. This process has been defined in the ICH guidelines and CIOMS recommendations.
Breaking the blind for a single subject should be considered only when knowledge of the treatment assignment is deemed essential by the subject’s physician for the subject’s care.
Suspected adverse drug reactions that are both serious and unexpected, and thus subject to expedited reporting, should generally be unblinded.

However, there are likely to be special circumstances where an exception to this rule would be appropriate, for example, where the efficacy endpoint is also Serious Adverse Events (SAEs). In this case, the circumstance and the process to be followed should be clearly defined in the protocol and the sponsor should seek agreement from Rwanda FDA. Such exceptions should be clearly described in the protocol and IB. Exceptions to unblinding are not always clear cut.

Therefore, it would be important to establish, in advance, clear criteria for the diagnosis and agreement from all concerned authorities for the exception. Defining the criteria and establishing a procedure for making decisions should go a long way toward maintaining consistency and conformity to the exception.

Once a case is unblinded the question of whether or not to report comparator or placebo cases arises, especially given that the expectedness decision upon which the unblinding was based generally relates to the experimental drug. Individual cases which, when unblinded, are found to involve trial participant on placebo will usually not be reported as expedited reports.

On the other hand, it is recommended that unblinded comparator cases be reported to Rwanda FDA and/or LTR of Comparator on an expedited basis, regardless of expectedness. Likewise, serious suspected adverse reactions for open-label comparators should be sent on an expedited basis to the Authority and/or LTR regardless of expectedness by using CIOMS VI.
WHO "Operational Guidelines for the Establishment and Functioning of DSMB" recommends DSMBs to determine unblinding criteria during the course of the study.A third party data analyst (e.g. an independent biostatistician) might provide a breakdown of AEs to the DSMB members.

When significant trends in the data require further interpretation, it may only be necessary to unblind the statistician or epidemiologist, and not all the DSMB members. The unblinded person then reports to the other members if there is cause for concern. The unblinding procedures should be defined in advance and supported by documentation which indicates who has access to the unblinded data. In blinded studies, the charter should outline whether and when the DSMB will receive completely or partially unblinded data ".

Scientific and ethical issues should be additionally considered in vaccines CTs. Unblinding in vaccine CTs is different from the need for unblinding in drug studies. Early unblinding may affect the objectives of CTs, might lead to unfavourable social resonance, especially for some pandemic vaccines. Usually, unblinding in vaccine CT is a rare event. Seldom there is a need to provide a subsequent treatment for the trial participant. It is recommended to establish clear unblinding criteria and procedures can minimize problems associated with unnecessary unblinding vaccine CTs.

III.3.3 Post-study Events

Any Post study serious adverse events collected by sponsor after the patient has completed a clinical trial (including any protocol required post-treatment follow up) should be reported to Rwanda FDA. Such cases shall be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required. When additional medically relevant information is received for a previously reported case, the reporting time is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non-serious to serious).

III.4 Timelines and pathways for submission of clinical trial reports.

a) All clinical trial reports shall be submitted to Rwanda FDA by the sponsor or sponsor"s designee through Integrated Regulatory Information Management System (IRIMS) or any other platforms as directed by Rwanda FDA.
b) All clinical trial reports shall be sent to the Authority within fourteen (14) calendar days after the end of reporting period. This requirement is not applicable to the expedited safety report (SAEs,SUSARs,etc.)

III.5 Management of Safety Reports

a) All safety reports on registered and new investigational products shall be reported using the CIOMS form as published on Rwanda FDA website and completed forms are sent to info@rwandafda.gov.rw or via Information Regulatory Management System (IRMS).
b) The Authority records them in its clinical trial safety database and analyses them for regulatory decision making and provides feedback to the reporters including sponsors and principal investigators.
c) The Authority may require additional information in case the event reported resulted in the death of a trial participant or conduct a safety inspection at the trial site.
d) The evaluation of causality assessment reports submitted by Sponsor shall be conducted as per regulatory procedures in place.
e) The PI shall continue the follow-up on the outcome of the reported SAEs and SUSARs and submit the final report at the Rwanda FDA.

III.6 Safety-Signal Detection and Evaluation in Clinical Trials

The concept, definition and methods for signal detection have been primarily associated with pharmacovigilance in a post-marketing phase based mainly on spontaneous reports. However, CTs create an initial source of information and should be taken into account for early signal detection.
Modern statistical methods for the evaluation of safety signals in clinical trials make this possible (Bayesian methods). Nevertheless, the signal detection process during early development will generally be based on clinical judgment.
To ensure standardized signal detection and evaluation processes, data quality and completeness are paramount. The CIOMS VI Working Group recommends the following principles for the effective signal detection and evaluation:

a) ICSRs from studies should be as fully documented as possible,
b) There should be diligent follow-up of each case, as needed,
c) The reporter's verbatim AE terms must be retained within all relevant databases,
d) Personnel with knowledge and understanding of both clinical medicine and the dictionary used should review all codified terms to ensure consistent and accurate codification of reported ("verbatim") terms,
e) Primary analyses of AE data should be based on the investigator's assigned terms or diagnoses, carefully and properly coded by the sponsor.

III.7 Assessment of Adverse Events

Analysis of safety data can be considered at three levels. First, the extent of exposure (dose, duration, number of patients) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common adverse events, laboratory test changes etc. should be identified, classified in some reasonable way, compared for treatment groups, and analysed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration etc.
Finally, serious adverse events and other significant adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event, whether identified or not identified as drug-related, or who died. Sponsors should ensure that all adverse

events reports are assessed before being submitted to Rwanda FDA. The assessment should consider the following:

III.7.1 Seriousness

A serious adverse event (experience) or reaction is any undesired medical occurrence that may result at any dose:

a) Results in death,
b) Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization,
d) Results in persistent or significant disability/incapacity, or
e) Is a congenital anomaly/birth defect.
f) Any other event which may jeopardize the patient or may require intervention to prevent one of the above outcomes.

III.7.2 Relationship with the Investigational Product

The Sponsor or site investigator shall assess the relationship between the AE and the Investigational Product(s) to determine whether there is a reasonable possibility that the Investigational Product(s) caused or contributed to the SAE. The assessment shall be based on clinical judgment which often relies on the following:

a) A temporal relationship between the event and administration of the Investigational Product(s)
b) A plausible biological mechanism for the agent to cause the AE
c) Another possible etiology for the AE
d) Previous reports of similar AEs associated with the Investigational Product or other agents in the same class
e) Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable

The outcome of assessment will be categorized into:

a) Related when there is a reasonable possibility that the AE may be related to the Investigational Product(s) and
b) Not related when there is no reasonable possibility that the AE is related to the Investigational Product (s).

When a SAE is assessed as “not related” to Investigational Product(s), an alternative etiology, diagnosis, or explanation for the SAE should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated, as required.

When the Investigational Product is a fixed-dose combination agent, an assessment of attribution will be made for each component and the combination agent.

III.7.3 Expectedness

When there is reasonable possibility that the adverse event may be related to Investigational Product, the investigator should further classify them into either expected or unexpected.
Assessment of the expectedness of an AE with the IP is performed only for the SUSAR reporting category.

a) **Expected AEs:** These are AEs that have been previously observed with use of the Investigational Product (s) and are listed in the package insert or Investigator's brochure. Expectedness is not based on what might be anticipated from the pharmacological properties of the Investigational Product.
b) **Unexpected AEs:** These are AEs for which the nature or severity (intensity) is not consistent with the applicable agent information (Investigator's Brochure, package insert, or summary of agent characteristics).

III.7.4 Severity

All events reported to Rwanda FDA in an expedited fashion must be graded for severity.
The severity of the parameters ranges from grade 1 (mild) to grade 4 (potentially life threatening). Death is defined as grade 5 severity.
Unless stated otherwise in the protocol, Investigators shall use the following Adverse Event grading scale to determine the severity of the AE;

- Mild (1),
- Moderate (2),
- Severe (3),
- Potentially Life-Threatening (4),
- Death (5)

The severity of an AE does not determine whether an event meets the definition of seriousness, which is based on participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning.

III.7.5 Individual Clinically Significant Laboratory Abnormalities

Clinically significant changes should be discussed. A narrative of each trial participant whose laboratory results abnormality was considered a serious adverse event shall be submitted to the Rwanda FDA.

When toxicity grading scales are used, changes graded as severe should be discussed regardless of seriousness. An analysis of the clinically significant changes, together with a recapitulation of discontinuations due to laboratory measurements, should be provided for each parameter.

The significance of the changes and likely relation to the treatment should be assessed, e.g., by analysis of such features as relationship to dose, relationship to drug concentration, disappearance on continued therapy, positive Dechallenge, positive Rechallenge, and the nature of concomitant therapy.

III.7.6 Methodology for Causality Assessment of Adverse Events.

The reported adverse events should be systematically reviewed to determine whether they are possibly related to the investigational products or intervention in line with ICH-E2D. As approved

by Rwanda FDA, the sponsor must use the Naranjo algorithm for novel investigational product and WHO Causality Assessment Criteria Methods for the registered investigational product to determine the relatedness of AE/ADR/AEFI. For vaccines and other biologicals, causality assessment shall follow WHO User manual for causality assessment of AEFI. Causality assessment of AEFIs is presented to showcase the differences in the AE/ADR and AEFI assessment.

The approved templates **(Appendix No: ……..)** for all aforementioned causality assessment methods in clinical trials are published on www.rwandafda.gov.rw.

III.7.6.1 Assessment by Naranjo algorithm approach (NAA)

NAA is a standardized tool used to assess the likelihood that an adverse drug reaction (ADR) is caused by a specific drug. It is a questionnaire-based method consisting of 10 questions that address different factors including:

a) Temporal relationship between drug administration and the adverse event.
b) Dechallenge and Rechallenge responses (e.g., does the reaction improve when the drug is stopped, or reappear when reintroduced?).
c) Alternative causes (e.g., underlying conditions or other medications).
d) Known adverse effects of the drug in question.
e) Dose dependence of the reaction.

Each question is scored with points (e.g., +1, 0, or -1), and the total score categorizes the causality into one of four levels:

i. **Definite (≥ 9 points):** Strong evidence that the drug caused the ADR.
ii. **Probable (5–8 points):** Likely that the drug caused the ADR, but some uncertainty remains.
iii. **Possible (1–4 points):** The ADR might be related to the drug, but other factors could explain it.
iv. **Doubtful (≤ 0 points):** Unlikely that the drug caused the ADR.

Generally, the Naranjo algorithm is widely used because it provides a systematic and reproducible way to assess causality, but it may not account for all clinical scenarios, particularly those involving complex drug interactions or rare side effects.

III.7.6.2 Assessment by WHO User manual for causality assessment of AEFI

The WHO Causality Assessment for Adverse Events Following Immunization (AEFI) provides a structured approach to assess whether an observed adverse event is linked to vaccine administration. It is commonly used in vaccine clinical trials and post-marketing surveillance to ensure vaccine safety. The methodology involves a step-by-step process as outlined in the WHO User Manual**:**

Causality assessment using this method can be performed through the following steps:

Step 1: Verify the diagnosis of AEFI by confirming that the reported event is well-documented and fits a recognized medical condition.
Step 2: Determine consistency with Established Vaccine Reactions by checking if the adverse event is consistent with known vaccine reactions, including timing and type of reaction.
Step 3: Assess temporal relationship (TR) in order to check if the timing of the event aligns with the expected time window for known vaccine-associated adverse events.

Step 4: Consider other explanatory factors by ruling out alternative causes such as underlying medical conditions, infections, or exposure to other medications or toxins.

Step 5: Categorization of the AEFI: The event is categorized into one of the following outcomes:

a) Consistent with a causal relationship to vaccination that lead to the strong evidence supports causation.
b) Indeterminate outcome: Insufficient evidence to conclude causation.
c) Inconsistent with a causal relationship to vaccination: Evidence supports other causes unrelated to vaccination.
d) Unclassifiable: Inadequate information prevents classification.

III.7.6.3 WHO Causality Assessment Criteria Methods

This methodology can be applied only for the registered investigational products except the innovative and registered vaccines and other biological products. This method is referred to be a systematic approach used in clinical trials and pharmacovigilance to evaluate the likelihood of a causal relationship between a suspected drug and an adverse event. It is widely used to ensure consistent and standardized assessments. Its template **(Appendix No:……)** is published on www.rwandafda.gov.rw

III.8 General Benefit-Risk Considerations

a) The benefits of IPs are crucial in regulatory decisions involving safety issues. Balancing benefits and risks requires quantitative benefit assessments, measuring disease burden reduction, cure rates, symptom improvement, response rates, and quality-adjusted life years (QALYs).
b) Risk assessment is a complex, stepwise process involving risk identification, confirmation, characterization, and quantification, using diverse data sources like ADR reports, Clinical data, non-clinical data, epidemiology, literature, quality investigations, and exposure data.
c) Evaluating an "acceptable level of risk" lacks standardization and must begin early in clinical development. Risk acceptance varies among patients, sponsors, and regulators, influenced by disease indication, safety, efficacy, alternative therapies, and cultural or ethnic factors.
d) Despite lacking validated metrics, "acceptable risk" should be discussed with Rwanda FDA, disease specialists, and, where possible, patients or advocacy groups.

III.9 Regulatory Decision Making

a) After analysis the safety reports including the SAEs/SUSARs reports, they will be presented and appraised by the Rwanda FDA Technical Advisory Committee on Clinical Trials. If they are critical, the Authority being advised by the committee shall temporally suspend the clinical trial in order to protect the right, safety and well-being of trial participants.

b) If there is any reported SAEs/SUSARs on high risk for ongoing clinical trial and leading to death or life threatening, the Authority may conduct triggered GCP inspection on that trial site. Based on GCP inspection report which was presented and appraised by the Rwanda FDA Technical Advisory Committee on Clinical Trials; and Causality Assessment Report, the other regulatory decision will be taken into consideration.

III.10 Reliance and Mutual Recognition

Reliance and Mutual Recognition facilitate collaboration between the Authority and other regulatory authorities in the oversight of clinical trials. By recognizing decisions from trusted counterparts, the Authority streamlines safety monitoring, reduces duplication, and ensures timely responses to adverse events. Reliance and mutual recognition can be done as follows:

a) Regulatory Collaboration through the use of shared frameworks like the International Council for Harmonisation (ICH) guidelines is ensured to harmonize adverse event reporting in clinical trials.
b) For multinational clinical trials, the decision on the reported SAEs/SUSARs from a trial site of one territory can trigger the regulatory decision for other countries in which the trial is being carried out.
c) Leveraging global safety databases (e.g., WHO's VigiBase) for cross-country adverse event monitoring.

III.11 Safety Conclusion

The safety assessment of the investigational drug should focus on events leading to dose adjustments, additional medications, serious adverse events, withdrawals, and deaths. High-risk or vulnerable groups, such as children, pregnant women, the frail elderly, or those with abnormal drug metabolism, should be carefully evaluated.

The safety evaluation should outline implications for the drug's potential uses, highlight new or unexpected findings, and address their significance, including inconsistencies. Results should be discussed in the context of existing data, noting clinical relevance, specific benefits, precautions for at-risk groups, and considerations for future studies.

The rights, safety and well-being of trial participants shall prevail and when violated, regulatory actions shall be considered.

ENDORSEMENT OF THE GUIDELINES

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