RWANDA FDA
Rwanda Food and Drugs Authority

GUIDANCE FOR THERAPEUTIC OR VACCINE CLINICAL TRIAL APPLICATION EVALUATION DURING PUBLIC HEALTH EMERGENCY

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FOREWORD

This guidance for Therapeutic or Vaccine Clinical Trial Application Evaluation During Public Health Emergency have been prepared by Rwanda Food and Drugs Authority (Rwanda FDA). The guidance has been made under the provisions of Law N° 003/2018 of 09/02/2018 that establish Rwanda FDA, specifically outlined in Article 8, paragraphs 7 and 12, with the mandate to regulate and inspect clinical trials in Rwanda. Pursuant to the provisions of Technical Regulations No. FDISM/PVSM/TRG/001 Rev_2, which governs the conduct of clinical trials, the Authority has issued Guidance No. DD/PVCT/GDC/001 Rev - 01 for ***Therapeutic or Vaccine Clinical Trial Application Evaluation During Public Health Emergency.***

This guidance ensures compliance with scientific aspects and regulatory requirements, referencing 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 including relevant Regulation/Guidelines from sister National Regulatory Authorities/Agencies, European Medicines Agency and WHO Listed regulatory authorities in respect of the authorization procedures of the clinical trials.

Rwanda FDA anticipates that this guidance will facilitate the standardized and consistent documentation of Therapeutic or Vaccine Clinical Trial Application, thereby streamlining the Authority's evaluation process and enabling well-informed conclusions, recommendations, or necessary regulatory decisions.

Therefore, the Authority recognizes and commends the contributions of key stakeholders involved in the development, review, and validation of these guidance.

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	1. Review in new QMS control format 2. Text formatting in Chapters and updating table of content
01	First Issue

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ACRONYMS AND ABBREVIATIONS

ICH	International Conference on Harmonization
GCP	Good Clinical Practices
CTD	Common Technical Documents
WHO	World Health Organization
GMP	Good Manufacturing Practices
CRO	Contract Research Organization
NRA	National Regulatory Authorities
CTA	Clinical Trial Application
CT	Clinical Trial
PI	Principal Investigator
SmPC	Summary of Medical Product Characteristics
WOCBP	Women of Child-Bearing Potential
MTA	Material Transfer Agreement
IMP	Investigational Medicinal Product
IB	Investigator Brochure
IMPD	Investigational Medicinal Product Dossier
CMC	Chemistry, Manufacturing and Control processes
MoU	Memorandum of Understanding
QP	Qualified Personnel
USP	United States Pharmacopoeia
JP	Japanese Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
CEP	Certificates of Suitability
FIFO	First-In, First-Out

GLOSSARY / DEFINITIONS

In this guidance unless the context states otherwise:

"Therapeutic" refers to the use of treatment to cure or control a disorder (Therapy or Treatment)

"Authorities" refers the National Regulatory Authorities from partner states or agencies.

"Applicant" means a person including a Sponsor, Contract Research Organization, or in the case of investigator-initiated academic research studies, research institution or principal investigator, applying for a permit to conduct a clinical trial;

"Biological Product" means items derived from living organisms (ranging from normal or genetically modified microorganisms to fluids, tissues and cells derived from various animal and human sources) or containing living organisms;

"Investigational Product" in relation to a drug, medical device or herbal drug means a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with marketing authorization when used or assembled 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.

INTRODUCTION

This guidance outlines the process for evaluating clinical trial applications for therapeutics or vaccines during public health emergencies. It aims to ensure ethical and ICH GCP standards are met while expediting regulatory decisions to protect clinical trials participants' safety and well-being. The goal is to facilitate consistent and effective procedures during public health emergencies, allowing expedited approval of clinical trials through non-routine review procedures.

PURPOSE OF THE GUIDANCE

The purpose of the guidance is to define the criteria and steps that the reviewer will follow to review the clinical trial application following the essential information required during a public health emergency.

It is intended to permit clinical trials based on available data and unusual circumstances within a limited time. As part of the review procedures, it is expected that the applicant will provide further information on investigational product as the trial progresses. The review and authorization of the clinical trial shall allow the clinical development to proceed as planned after the initial submission and subsequent updates.

SCOPE OF THE GUIDANCE

This Guidance provides a special procedure for the evaluation of therapeutic or vaccine clinical trial applications in the event of a public health emergency.

CHAPTER I. CRITERIA FOR QUALIFICATION OF APPLICATIONS

Generally, expedited clinical trial authorization during public health emergency will be issued under the following conditions:

- The disease causative agent specified in the declaration of Public Health Emergency can cause a serious or life-threatening disease or condition;
- Based on the totality of scientific evidence available, including data from adequate sources, it is reasonable to believe that the investigational product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the agent specified in the declaration of emergency;
- The known and potential benefits outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life-threatening disease or condition that is the subject of the declaration;
- No adequate, approved, and available alternatives to the product for diagnosing,

preventing, or treating such serious or life-threatening disease or condition; and

- Feasibility of the implementation of the clinical trial design within the context of the emergency.

1.1. CONSIDERATIONS

1.1.1. General Considerations

i) Considerations of clinical trial applications under these circumstances shall depend on the complexity of the clinical trial and abide by the existing regulatory provisions.

ii) The Authorities shall facilitate the review and approval of clinical trials during public health emergencies to ensure the availability of safe and effective interventions to mitigate the risk associated with public health emergencies.

iii) The Authorities shall allocate appropriate infrastructure and human resources for Good Review Practice. For the review of CTA, the reviewer shall possess regulatory expertise, scientific expertise, time management, documentation management and systematic approaches.

iv) It is the responsibility of the investigator and sponsor to ensure the protection of the CT subjects using a high-quality investigation product or intervention that is suitable for its intended purpose and to appropriately address those quality attributes that may impair patient safety.

Moreover, the key considerations for the evaluation of clinical trials during emergencies include:

- Relevance to Emergency: Assessing the relevance of the trial to the emergency and the potential impact on patient care
- Resource Allocation: Ensuring that the evaluation process does not detract from critical emergency response efforts
- Ethical Oversight: Maintaining ethical standards in the evaluation process despite the urgency of the emergency
- Regulatory Support: Collaborating with regulatory authorities to expedite review processes without compromising thoroughness and compliance
- Data Quality: Assessing the reliability of data collected during the trial, considering potential challenges posed by the emergency
- Transparency and Communication: Providing clear and transparent communication about the evaluation process and its implications for decision-making
- Adaptability: Being prepared to adapt evaluation procedures to accommodate the unique circumstances of the emergency

1.1.2. Specific Considerations

The reviewer shall consider the use of benefit-risk assessment of the intervention and shall ensure that the submitted clinical trial application dossier and related documents comply with regulatory requirements and shall be in the format as prescribed in the Authority's guidelines. The contents of each module of clinical trial application dossier shall include statements pertaining to compliance with regulatory requirements.

The clinical trial application shall accommodate exhaustive information related to the quality of the investigational product and trial design supporting the intended purpose including:

A) PROTOCOL

The Sponsor and Investigator are responsible for ensuring that the protocol is followed and that the Authority regulatory requirements and ICH GCP Guidelines are adhered to.

The reviewer shall take into account to review the study protocol as follows:

i) Background information:

- Name and description of the investigational product(s);
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trials must be provided;
- A summary of the known and potential risks and benefits, if any, to human subjects should be provided;
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s) often accompanied by the signatures of the sponsor and PI.

ii) Primary Objectives and endpoints

- Ensure that the primary objectives are clearly defined, relevant, measurable and achievable;
- Verify that the chosen endpoints are appropriate for evaluating the intervention's effectiveness and safety;

iii) Study population

- Assess the eligibility criteria for participants to ensure they are clearly defined and justified;
- Consider the gender and age allocation of participants, and determine whether a specific group is excluded or underrepresented and provided justification;
- For registered products: consider the contraindications included in the SmPC for the investigational product, comparator, and auxiliary medical products;

- The inclusion of a vulnerable population is justifiable only if this information cannot be obtained from non-vulnerable populations;
- For incapacitated or minor participants, the trial should offer some direct benefit to them or public health and should justify the foreseeable risks and inconveniences.

iv) Study Design and Methodology

- A phase of the trial should be clearly defined and study objectives should correspond to the study phase;
- Evaluate the appropriateness of the study design (e.g. randomized controlled trial, cohort study) for addressing the research question;
- When applicable, check for proper randomization procedures and blinding methods to minimize bias and ensure the reliability of study outcomes, the randomization ratio should be clearly defined, and procedure for blinding and procedures for emergency unblinding should be clearly defined and found acceptable;
- Check if the methodology aligns with the research objectives and is likely to produce reliable and valid results;
- There should be a schedule of assessment that provides an overview of the entire study procedures and visits;
- Study procedures, study visits, monitoring of participants, risk minimization measures, and follow-up should be adequately described and acceptable;
- Criteria for discontinuing participants from treatment/trial should be clearly defined and must be found acceptable;
- Procedures to collect data from those who withdraw have to be specified;
- Clinical trial termination criteria should also be defined;
- When applicable for contraception measures, trials including WOCBP should clearly list effective contraceptive methods to be used for pregnancy prevention, since pregnancy is mostly an exclusion and treatment discontinuation criteria.

v) Study treatment

- Consider the dose(s)/dose steps, dose rationale, route of administration, schedule, treatment duration, and dose modifications;
- A justification should be provided for the selected dose(s);
- Check the IB or SmPC (for registered products) for safety risks associated with trial treatments;
- The choice of comparator, active comparator, or Placebo is crucial. When there is no proven intervention available, a placebo can be used as a comparator and patients receiving the

placebo should not be subject to any risk of serious or irreversible harm. The composition of the placebo must be clearly defined. A lower degree of detail (justification) is required for trials where the placebo group will also receive active treatment.

vi) Sample Size, Power Calculations and Analytical Methods

- Review the sample size calculation to ensure it is based on appropriate statistical methods and assumptions;
- Verify that the sample size is adequate to detect meaningful differences and ensure the study's statistical power;
- Analytical methods to be employed;
- Review how missing values will be handled.

vii) Biological samples used in the study (if applicable)

- Procedures to collect, store, and future use of biological samples should be described appropriately;
- If samples will be shipped to an external/central laboratory, an MTA should be provided;
- Evidence of competency/accreditation of the laboratory to carry out the analysis should be provided.

viii) Data Management and Quality Control

- Review the procedures for data management;
- Check the data capture tool to be used if it is robust enough and fit for purpose;
- Validation protocols and reports should be available for the data capture tool;
- Evaluate mechanisms in place for quality control and assurance throughout the trial;
- Review the data management plan for more comprehensive information.

ix) Benefit/risk assessment

- The protocol should contain an acceptable evaluation of the anticipated benefits and risks of
- participating in the trial;
- Acceptable measures should be put in place to address the known and potential risks of
- participating in the trial and to protect participants;
- Based on medical and ethical principles, the anticipated benefits to the participants or public
- health should justify the foreseeable risks and inconveniences.

B) INVESTIGATOR'S BROCHURE

The reviewer shall consider that the IB is a compilation of the clinical and nonclinical data on the IMPs that are relevant to the study of the product(s) in human subjects. The investigator shall submit an IB with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial, and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. The data shall include the dose, dose frequency and dosing frequency, method of administration and safety monitoring procedures and shall provide exhaustively reference safety information.

C) INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

Information to be provided for the investigational product should focus on the risk aspects and should consider the nature of the investigational product, the state of development/clinical phase, patient population nature and severity of the illness as well as the type and duration of the clinical trial itself. As a consequence, it will not be possible to define very detailed requirements applicable to all sorts of different products.

The investigational product shall contain, but not limited to, the following content:

- IMPs should be produced in accordance with the principles and the detailed guidelines of GMP for Medicinal Products;
- The IMPD should be provided in a clearly structured format;
- The IMPD should include the most up-to-date information relevant to the chemistry, manufacturing and control processes (CMC);
- For drug substances or IMPs to be used in clinical trials reference to either the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Partner State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) is acceptable after review. The Suitability of Ph. Eur. can be demonstrated with certificates of suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM);
- Reference to an Active Substance Master File or a CEP of the EDQM is neither acceptable nor applicable for biological/biotechnological active substances as they are less easily characterization and structure may or may not be completely defined or known;
- The IMPD dossier shall contain all prerequisite modules (Module 1: Administrative Information; Module 2: Quality Overall Summary, Non-clinical Overview and Summary, Clinical Overview and Summary; Module 3: Quality, Module 4: Non-clinical Study Reports;

Module 5: Clinical Study Reports) as per ICH M4 according to the stage of development;

- Simplified IMPD can be acceptable depending on the stage of IP development and for marketed products, SmPC may be sufficient.

D) GOOD MANUFACTURING PRACTICE COMPLIANCE

GMP compliance should be demonstrated for all sites responsible for manufacture, testing, packaging, labelling, import and Qualified Personnel (QP) release of all non-authorized or modified authorized IMPs in clinical trials. Proof of GMP compliance should be issued by a competent authority and considered country-specific requirements.

E) SAFETY ISSUES, EFFICACY CLAIMS, RELEVANT LITERATURE, AND MONITORING

- Review the measures for identifying, monitoring, and reporting adverse events;
- Ensure the trial has adequate safety monitoring plans to protect the well-being of participants;
- The sponsor shall adequately monitor the conduct of a clinical trial as per the monitoring plan, put in place measures to minimize risk (s) and if applicable identify the need for oversight by an independent data safety monitoring board.

1.2. ETHICAL CONSIDERATIONS

The ethical considerations of clinical trial evaluation protocols are of paramount importance in ensuring the safety and well-being of participants, as well as the integrity and validity of the research.

1.2.1. General Ethical considerations

These considerations encompass a wide range of issues, including:

- Informed consent: Participants must be provided with clear and accurate information about the study, including its purpose, procedures, risks, and benefits, and must give their voluntary consent to participate.
- Protection of privacy and confidentiality: Participants' personal information and medical data must be kept confidential and protected from unauthorized access or disclosure.
- Minimization of harm: All reasonable steps must be taken to minimize the risks of harm to participants, including careful screening and monitoring, and the use of appropriate safety

measures.

- Fair selection of participants: Clinical trials should be designed to ensure fair and equitable selection of participants, without discrimination based on factors such as race, gender, or socioeconomic status.
- Independent review: Clinical trial protocols should be reviewed by an independent ethics committee or institutional review board to ensure that they meet ethical standards and protect the rights of participants.
- Transparency and accountability: Researchers and sponsors of clinical trials should be transparent about their research methods and findings, and should be accountable for any ethical violations or misconduct.

The reviewer from each regulatory authority shall ensure that the above considerations are well described under specific sections of the protocols during emergency circumstances. Under these conditions, there are special considerations for public health authorities to respond to the emergency, mitigating the impact on the population and promoting recovery. All the necessary ethical approvals shall be obtained for the study from a competent Ethics Committee.

1.2.2. Other ethical considerations on Informed Consent and Assent

- Assess the informed consent process to ensure it complies with ethical standards and regulatory requirements;
- Verify that informed consent contains full information and participants shall understand about the trial, potential risks, and benefits before providing consent.
- In times of emergencies when a patient faces a sudden life-threatening medical condition requiring immediate medical intervention and it's not feasible to get informed consent before taking necessary medical actions, and no other alternative effective treatment modality; the legal representative consent and the subject consent to continue their participation in the trial once capable as per the protocol;
- If the subject (or their legal representative) does not give consent to continue in the trial, they shall be informed of their right to object to the use of data obtained from the clinical trial. This ensures that even if they do not wish to continue participating, their data protection rights are respected.

1.3. OTHER CONSIDERATIONS

1.3.1. Reliance or recognition

In case of emergency, the Authority applies reliance /recognition pathways as non-routine procedure for clinical trial authorization.

1.3.2. Joint review

A joint review of a clinical trial within a National Regulatory Authority (NRA) involves the collaborative assessment of the trial by multiple experts within the regulatory authority. This approach shall streamline the evaluation process, promote consistency in decision-making, and leverage the expertise of different reviewers. The Authorities shall use this approach to expedite the review process and enhance the quality of the evaluation through collective input and knowledge sharing from available MoUs with relevant stakeholder (s).

CHAPTER II. TIMELINES FOR PROCESSING AN APPLICATION

The review of clinical trial applications is undertaken using the same set of criteria regardless of the applicant. The review prioritization follows the first-in first-out rule (FIFO), except for clinical trials that are conducted in public health emergencies such as disease outbreaks, which may be exempted from screening and considered for expedited review.

The clinical trial review process shall be conducted and provide approval of clinical trial application in 10 working days for products already registered for other indications and 15 working days for novel products.

Requirements for filing a clinical trial application during an emergency shall be the same as required under country-specific guidelines for clinical trial applications.

2.1.AUTHORIZATION VALIDITY AND REGULATORY DECISIONS

2.1.1. Validity

The Authorities have established relevant processes for the review and approval of clinical trials under public health emergencies, including considerations for expedited review during emergent situations or public health emergencies. For the most current and specific information regarding trial clearance procedures, it is recommended to refer to the provisions within the Authorities relevant guidelines.

2.1.2. Suspension or Termination

The suspension or termination of a clinical trial can occur if there are concerns about participant safety, lack of efficacy, data integrity issues, protocol violations, ethical issues, or failure to adhere to regulatory requirements. The Authorities shall take such actions to protect the well-being of trial participants and ensure compliance with regulations

ENDORSEMENT OF THE GUIDELINES

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APPENDIX 1. REFERENCES

1. Regulations Governing the Conduct and Inspection of Clinical Trials in Rwanda; https://rwandafda.gov.rw/wp-content/uploads/2023/04/Regulations%20Governing%20the%20Conduct%20and%20Inspection%20of%20Clinical%20Trials%20in%20Rwanda.pdf
2. Guidelines for Clinical Trial Applications in Rwanda; https://rwandafda.gov.rw/wp-content/uploads/2023/04/Guidelines%20for%20Clinical%20Trial%20Applications%20in%20Rwanda.pdf
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5. Guidelines for conduct of clinical trials during emergencies, FDA Ghana; https://www.fdaghana.gov.gh/img/organisation/GUIDELINES%20FOR%20TRIALS%20IN%20EMERGENCIES-.pdf
6. ICH M4 Common technical document (CTD) for the registration of pharmaceuticals for human use - organisation of CTD - Scientific guideline; https://www.ema.europa.eu/en/ich-m4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd-scientific-guideline

APPENDIX 2. EMERGENCY CLINICAL TRIAL APPLICATION PROCESSING TIMELINE