

**GUIDELINES ON GCP INSPECTION**

**OF CLINICAL TRIALS IN RWANDA**

**FEBRUARY, 2023**

# GUIDELINES DEVELOPMENT HISTORY

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# FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) established by the Law N° 003/2018 of 09/02/2018, is a regulatory Authority mandated to regulate and inspect clinical trials in Rwanda as stipulated in its article 8, paragraph 7 and 12. Reference made to the provisions of the technical regulations No CBD/TRG/015 governing the conduct and inspection of clinical trials especially in its article 34 and 38, the Authority Issues Guidelines No DIS/GDL/043on GCP Inspection of Clinical Trials in Rwanda.

The purpose of inspecting clinical trials is to ensure that the trials are being conducted in accordance with the standards of Good Clinical Practice. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, performing, monitoring, auditing, recording and reporting clinical trials that involve the participation of human subjects.

Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the quality, reliability, and integrity of data collected are credible.

These guidelines detail the steps and processes required during the GCP inspection of clinical trial conduct to ensure effective protection of trial participants and compliance with requirements as well as the clinical trial protocol.

Strict adherence to these guidelines will facilitate the acceptance of clinical data by international regulatory authorities, especially since these guidelines adopt the basic principles outlined by the International Committee on Harmonization of Good Clinical Practice (ICH-GCP) with some customization to fit the local requirements.

I am confident that the publication of these Guidelines will mark another milestone in our efforts to strengthen clinical research in Rwanda. The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

**Dr. Emile BIENVENU**

**Director General**

# TABLE OF CONTENTS

[GUIDELINES DEVELOPMENT HISTORY 2](#_Toc125092740)

[DOCUMENT REVISION HISTORY 2](#_Toc125092741)

[FOREWORD 3](#_Toc125092742)

[TABLE OF CONTENTS 4](#_Toc125092743)

[ACCRONYMS AND ABBREVIATIONS 6](#_Toc125092744)

[GLOSSARY 7](#_Toc125092745)

[1.0 INTRODUCTION 11](#_Toc125092746)

[1.1 Scope 11](#_Toc125092747)

[1.2. Objectives of GCP Inspections 11](#_Toc125092748)

[2.0 TYPES OF GCP INSPECTIONS 12](#_Toc125092749)

[2.1 Routine GCP Inspections 12](#_Toc125092750)

[2.2 Triggered GCP Inspections 13](#_Toc125092751)

[2.3 Follow up GCP inspections 13](#_Toc125092752)

[3.0 INSPECTION PROCESS 13](#_Toc125092753)

[3.1. GCP Inspection prioritization 13](#_Toc125092754)

[3.2. Inspection Team 14](#_Toc125092755)

[3.3. GCP Inspection of Multicenter trials 14](#_Toc125092756)

[3.4. Notification of GCP inspection 14](#_Toc125092757)

[3.5 Preparation for GCP inspection 15](#_Toc125092758)

[4.0 CONDUCT OF GCP INSPECTIONS 15](#_Toc125092759)

[4.1 Opening meeting 15](#_Toc125092760)

[4.2 Verification and collection of information during GCP inspection 16](#_Toc125092761)

[4.2.1 Legal and administrative aspects 16](#_Toc125092762)

[4.2.2 Organisational aspects 17](#_Toc125092763)

[4.2.3. Informed consent of trial participants 19](#_Toc125092764)

[4.2.4 Review of the trial participant data 19](#_Toc125092765)

[4.2.5 Data integrity in clinical trial 19](#_Toc125092766)

[4.2.6 Management of the investigational product(s) 20](#_Toc125092767)

[4.3 Interview with Research Team Members 21](#_Toc125092768)

[4.4 Inspection of trial site facilities, equipment and system 21](#_Toc125092769)

[4.5 Generating GCP inspection findings 21](#_Toc125092770)

[4.6 Clinical Trial Inspection Closing Meeting 21](#_Toc125092771)

[4.7. Remote GCP inspections 22](#_Toc125092772)

[4.8 Grading of clinical trial inspection findings 22](#_Toc125092773)

[4.8.1 Critical findings 22](#_Toc125092774)

[4.8.2 Major findings: 22](#_Toc125092775)

[4.8.3 Minor findings: 22](#_Toc125092776)

[4.8.4 Other findings: 22](#_Toc125092777)

[4.8.5. Considerations for grading of GCP inspection findings 23](#_Toc125092778)

[4.9 Outcome of GCP inspections 23](#_Toc125092779)

[4.9.1 Clinical trial Inspection Report 23](#_Toc125092780)

[4.9.2 Transparency & Confidentiality during GCP Inspections 23](#_Toc125092781)

[5.0 REGULATORY ACTIONS DURING GCP INSPECTIONS 24](#_Toc125092782)

[6.0 APPEAL ON GCP INSPECTION OUTCOMES 24](#_Toc125092783)

[APPENDIX I: GCP Inspection Process Flow chart 25](#_Toc125092784)

[ENDORSEMENT OF THE GUIDELINES 26](#_Toc125092785)

[ANNEXURE-I: CLINICAL TRIAL GCP INSPECTION CHECKLIST 27](#_Toc125092786)

[ANNEXURE-II: FORM OF MEMORANDUM OF GCP INSPECTION FINDINGS 33](#_Toc125092787)

[ANNEXURE-III: GRADING OF CLINICAL TRIAL INSPECTION FINDINGS 35](#_Toc125092788)

[ANNEXURE-IV: CLINICAL TRIAL GCP INSPECTION REPORT TEMPLATE 39](#_Toc125092789)

[ANNEXURE-V: GCP INSPECITION FINDINGS AND CAPA FORM 46](#_Toc125092790)

# ACCRONYMS AND ABBREVIATIONS

**ALCOA** Attributable, Legible, Contemporaneous, Original and Accurate

CAPA Corrective Action and Preventive Action

CRF Case Report Form

CRO Contract Research Organization

DSMB Data and Safety Monitoring Board

GCP Good Clinical Practice

**IB** Investigator's Brochure

ICH International Conference on Harmonization of Technical

IP Investigational Product

**IP** Investigational Product

**IRB** Institutional Review Board

RNEC Rwanda National Ethics Committee

SAE Serious Adverse Event

SOPs Standard Operating Procedures

TMF Trial Master File

# GLOSSARY

In these guidelines, unless the context otherwise states:

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

***“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.

***“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).

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

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

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

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

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

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

***“Ethical Clearance”*** An authorization to conduct a clinical trial issued by the Rwanda National Ethics Committee (RNEC) based on ethical issues related to trials involving human participants in Rwanda.

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

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

***“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.

***‘’Investigational 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”*** An individual who conducts a clinical investigation.

***“Sub-investigator”*** Any member of a clinical trial team, supervised by the investigator at a trial site and allowed to perform critical trial-related procedures

***“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.

***“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).

***“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 humans.

***“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 of 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.

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

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

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

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

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

***“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.

# 1.0 INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, performing, monitoring, auditing, recording and reporting clinical trials that involve the participation of human subjects.

These guidelines provide a set of harmonized procedures to conduct GCP inspection of clinical trials in all phases including bioequivalence studies. Further objectives include ensuring that there is a basis to assure ethical, scientific and data integrity of clinical trials. It may be used by inspectors from the Authority or in joint GCP inspections as appropriate. It can support recognition of GCP inspection findings and regulations actions for clinical trials between countries that apply the same standards and procedures of GCP inspection.

The areas for the GCP inspection of clinical trial conducted in Rwanda include but not limited to the clinical site organisation, administrative aspects, protocol compliance, informed consent, safety reporting, Source of data verification (SDV), IP management, Clinical sample management, Trial Master File, Trial Management & Monitoring of related clinical trial data.

These guidelines will help the Authority to establish a conducive environment for clinical trial conduct and oversight to ensure sustainable quality, scientifically sound clinical trials conducted in an acceptable and ethical way. Therefore, inspectors and inspected team are urged to adhere to the provisions of these guidelines while planning, preparing, conducting, and reporting clinical trial inspections.

## 1.1 Scope

These guidelines apply to the GCP inspection of all clinical trials approved by the Authority and conducted at investigator site (s), sponsor facility(ies), CROs, and other establishments involved in clinical trials deemed necessary.

The areas of the inspection include but are not limited to data and information relating to regulatory approvals, ethics review committee approval, protocols, consent forms, case report forms, IMP management, safety reports (SAEs and SUSARs), clinical trial reports (progress and final reports), participant and participant data, sponsors, investigators and personnel involved in the trial, and laboratory data.

## 1.2. Objectives of GCP Inspections

The objectives to conduct clinical trials inspections are:

* To safeguard the rights, safety and well-being of trial participants;
* To verify the quality and integrity of the clinical trial data submitted to the Authority;
* To assess the compliance with the protocol and applicable regulations, guidelines and standard operating procedures;
* To assess whether a clinical trial system is suitably designed, controlled, maintained and documented to fulfil the objectives for which it has been set up;
* To identify areas for quality improvement;
* To investigate a complaint about the conduct of the study at a particular site;
* To verify the implementation of corrective actions and preventive actions.

**1.3. GCP Inspection Criteria**

Compliance to the following will be determined during GCP Inspections:

1. Protocol and its supplementary documents
2. Applicable clinical trial regulatory requirements
3. Applicable requirements in the latest version of ICH Good Clinical Practice Guidelines
4. Applicable Site Standard Operating Procedures (SOPs) for clinical trials

Compliance with GCP standards will ensure that the rights, safety and well-being of trial participants, are protected, and that the results of the clinical trials are accurate and credible.

# 2.0 TYPES OF GCP INSPECTIONS

The Authority shall conduct following three main types of inspection for Clinical trial in Rwanda:

1. Routine GCP inspection
2. Triggered GCP inspections
3. Follow-up GCP inspection

The clinical trial sites may be inspected before the regulatory approval, while the trial is on-going, when trial participants are currently being enrolled in a trial or completed on a routine basis or sometimes when triggers by a complaint or there is a suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct. Generally, GCP inspections are announced. However, unannounced inspections may be possible.

## 2.1 Routine GCP Inspections

Routine inspections are inspections performed on a regular basis to monitor GCP compliance in the absence of specific trigger elements. These inspections are announced in advance and apply to ongoing clinical trials. The duration of the inspection and the number of inspectors will vary depending on the complexity of the clinical trial and the activities taking place at the site. They are typically scheduled for 3-5 days per site.

## 2.2 Triggered GCP Inspections

Triggered GCP inspections are conducted when there is a concern due to either the actual issues observed or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site or when a serious breach of GCP occurred. In addition, products with a major impact factor could be considered to require special attention. This type of inspection may be done announced or unannounced and apply to ongoing or completed clinical trials.

## 2.3 Follow up GCP inspections

A follow up is also referred to as re-inspection or re-assessment of the site. It is performed specifically to monitor the result of corrective and preventive actions of the site following previous inspection(s). Depending on the nature of the observation(s), and the work required the follow up inspection could be carried out within the agreed timelines after the previous inspection. The follow up inspection is limited to specified clinical trial non-compliances that have been observed.

# 3.0 INSPECTION PROCESS

## 3.1. GCP Inspection prioritization

The Authority will use a risk-based approach to select sites for GCP inspections. The Authorized trials with higher risk are more likely to be inspected. The majority of GCP inspections will be routine inspections of clinical trials that are ongoing or completed. However, other types of inspections including triggered inspections may also occur. The duration of the GCP inspection will vary depending on the complexity of the clinical trial, risk involved and activities conducted at the site and shall be scheduled for 3-5 days per site.

The selection of trial sites for the GCP inspection includes, but is not limited to the following criteria:

1. Nature of intervention or investigation product;
2. Clinical trial phase;
3. Inclusion of vulnerable populations in the trial;
4. Size of the trial (number of trial participants and sites
5. Route administration of the investigational product;
6. Significant or frequent reports of Serious adverse events;
7. Complaint on the conduct of the trial reported to the Authority.

## 3.2. Inspection Team

The GCP inspections of clinical trial must be performed by GCP inspectors appointed by the Authority according to the procedures in place. However, the Authority may involve experts in the GCP inspection of the clinical trial whose qualifications and experience correspond to the proposed clinical trial. In addition, the Authority may conduct joint inspections at the clinical trial site to ensure the safety and protection of participants in clinical trials and the integrity of collected data.

The inspection team will be constituted considering on the phase or type of trial, the investigational product, and other variables considered relevant on a case-by-case basis. The inspectors should be well qualified and have valid GCP certification obtained within 3 years as per ICH-GCP guidelines. The team will have a lead GCP inspector responsible for coordinating the inspection, collating the information from team members, and finalizing the inspection report.

## 3.3. GCP Inspection of Multicenter trials

Multicenter trials are usually conducted simultaneously by several investigators at different sites following the same protocol and its supplementary documents. The trial sites with more participants or frequent serious adverse event reports will be prioritized. However, the non-compliance of the GCP inspection from one clinical trial site can trigger further GCP inspections at other site (s) that were not planned for inspection.

In case of multi-centre clinical trials carried out in more than one country including Rwanda, the non-compliance of the GCP inspection performed by other regulatory authorities will trigger further inspection of the trial site (s) in Rwanda in order to ensure the protection and well-being of the trial participants in Rwanda.

## 3.4. Notification of GCP inspection

The Authority shall contact the inspectee notifying the date(s) of inspection one (1) months prior to the proposed announced inspection dates and ask to confirm the proposed dates. A subsequent reminder by the Authority may be sent within fourteen (14) days in case the inspectee fails to confirm the availability. If the inspectee fails to confirm the proposed inspection date, the Authority shall conduct the triggered GCP inspection.

The notification will identify the trial to be inspected and proposed sites. In relation to triggered or follow up inspections, the Authority may provide a shorter notice period. The following information shall be requested by the Authority:

1. Participant status per trial site (number of randomized, dropout rate, number of SAEs reported per site, etc.) at trial initiation or during the trial.
2. Copies of Standards Operating Procedures (SOPs) along with amendments (e.g., monitoring procedures, informed consent procedures, SAEs reporting Procedures, Pharmacy Management Procedures, etc.)
3. Trial-specific document such as Trial Master File (TMF) or Investigator Site File (ISF), a copy of the current protocol and protocol amendment and informed consent form, source data verification guidelines, investigational product management and accountability, product handling instructions, laboratory manual, randomisation code, breaking procedure, monitoring plans and reports.
4. Updated CV of principal investigator or co-investigators, and members of the DSMB if applicable
5. In case of computerized system, the PI or sponsor may provide access to the system
6. Any other document deemed necessary by the Authority.

When the GCP inspection dates are confirmed by both parties, the PI or sponsor shall submit the signed cover letter and aforementioned data to the Authority electronically or hard copy within 14 days of the receipt of the notice of GCP inspection to the following address:

**The Director General**

**Rwanda Food and Drugs Authority**

**P.O. Box 1948 Kigali, Rwanda**.

E-mail: [***info@rwandafda.gov.rw***](mailto:info@rwandafda.gov.rw).

## 3.5 Preparation for GCP inspection

The GCP inspection schedule and Clinical Trial GCP Inspection Checklist will be shared to the principal investigator within five (5) working days in order to prepare for the upcoming inspection. Each member of the inspection team should become familiar with all the relevant documents, including the study protocol(s), clinical trial report(s), case report forms, adverse event reports, trial site information, and other related documentation.

The inspectee should ensure that access is provided to all trial records, including trial participant medical records, Investigator Site File, Trial Master File, Case Report Forms and applicable standard operating procedures, where applicable

1. **CONDUCT OF GCP INSPECTIONS**

## 4.1 Opening meeting

The opening meeting between the inspector(s) and the inspectee(s) will:

1. Introduce the inspector(s) to the inspectee(s) and identify their roles and responsibilities
2. Confirm the GCP inspection schedule;
3. explain the scope of inspection and GCP Inspection regulatory framework;
4. give a brief overview of the trial site;
5. provide a short summary of the methods and procedures to be used for the conduct of the inspection;
6. confirm the availability of resources, access to records and facilities required for the GCP Inspection, and clarify matters relating to confidentiality;

### 4.2 Verification and collection of information during GCP inspection

After the opening meeting, the inspection begins. The inspectors assess the site compliance with both regulatory requirements and GCP standards. The essential documents to be reviewed during GCP inspection will depend on the stage of the trial as per regulatory requirements and provisions of the latest version of AVAREF and ICH GCP guidelines.

The GCP inspection checklist (**ANNEXURE-I**) adopted from AVAREF shall be used to record observations or comments, non-compliance and recommendation for improvement. The scope and activities examined during the inspections undertaken by the Authority may include different aspects:

### 4.2.1 Legal and administrative aspects

During the inspection, the inspection team shall verify whether the site is ready to conduct clinical trials. This includes verification of the authenticity and validity of the documents issued by the Authority and other relevant bodies.

1. **Ethical Clearance**

During the Inspection, the inspection team shall verify relevant records relating to ethics to ensure the protection of the rights and welfare of participants in clinical trials. This verification shall include but not limited to:

1. Validity and authenticity of RNEC ethical clearance and consent forms (reference number, dates, signatures, and stamp, etc.)
2. Reports submitted to the RNEC related to the serious adverse events occurring during the trial implementation and follow up as well as other relevant communications with RNEC if any;
3. Approval given for any advertisement, recruitment, screening, compensation and payments of trial participants.
4. **Regulatory Authority approval**

The inspection team shall ensure that:

1. Clinical Trial Approval Certificate was granted to conduct the trial prior to its initiation.
2. Revisions and changes/amendments to the protocol and related documents were granted approval prior to implementation.
3. Serious adverse events (SAEs) and other reports were submitted to the authority according to the timelines of relevant regulations and guidelines.

### 4.2.2 Organisational aspects

The inspection team will verify the compliance of the procedures and practices carried out by the investigator with those set out in the protocol and reports submitted to the Authority.

1. **Implementation of the trial at the site**

The site has to be ready to conduct clinical trials. Depending on the activities undertaken by the site, areas such as a clinic, pharmacy and laboratories should have enough space with appropriate infrastructure and equipment. The access to the storage of investigational products (IPs) and other services should be controlled as appropriate.

1. **Organisation and personnel**

The investigator is responsible for ensuring that an investigation is conducted according to the approved protocol, the investigational plan, and applicable regulations and guidelines. The contract between the sponsor and the investigator has to clearly define the responsibilities of each party. The inspectors shall verify if:

1. The clinical trial agreement (contract, MoU) is still valid, i.e., dated, period covering the trial, signatures by all parties;
2. The academic qualification and work experience as stated in the curriculum vitae and training records;
3. The research team complies with the multidisciplinary aspect as per trial requirements;
4. Training records are available and updated by checking certificates of training and training log or reports;
5. The training subjects were relevant to the trial objectives being implemented at the trial site.
6. **Facilities and equipment**

Each site should be equipped with adequate, calibrated and maintained equipment depending on the type of clinical trial to be conducted.

1. **Implementation of the protocol**

The Clinical trial should be conducted in accordance with the provisions of the approved study protocol and/or amendments. During the inspection, inspectors shall verify if:

1. The approved protocol is being implemented;
2. all trial participants enrolled met the inclusion and exclusion criteria;
3. dosing, meals (fed and fasting), sample collection were done as stipulated in protocol;
4. randomization, product information, reporting of serious adverse events, and preparation of reports are compliant with the requirements;
5. there are no deviations from the approved protocol;
6. violations to the protocol were reported;
7. reporting of results was/being done as required.
8. **Management of biological samples**

The aim of checking the management of biological samples is to examine conditions, and documentation regarding collection, analysing, storage and shipping conditions (if applicable) for proper management of biological samples. Laboratory of a Clinical research site should be able to analyse samples as specified in the protocol. In case the testing is outsourced, the contracts should define the responsibilities and scope of each party including sample transport, storage, preparation and methods used as well as reporting of results.

The inspectors shall review the contracts and appropriate SOP for sample handling at the time of inspection.

1. **Organisation of the documentation**

The site needs to have archiving facilities with sufficient space to ensure the protection of records from damage, i.e. fire, water, humidity, and deterioration. The site has to have procedures and records to place and retrieve documents and trial data. During the inspection, SOPs and records to archive electronic data and electronic records shall be verified.

1. **Monitoring and auditing**

The Sponsors generally perform site monitoring of a clinical trial to assure high quality trial conduct. The sponsor may perform such monitoring directly, or may utilize the services of an outside individual or organization (e.g., contract research organization). The “on site” monitors review individual case histories in order to verify adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and verify adherence to GCP principles.

1. **Use of computerised systems**

The use of validated computerized systems to generate data should be encouraged. Computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical trial should be validated. During the course of inspection, it will be necessary to ascertain their validation status. Computer system features, security, maintenance and controls, back up and data recovery should be inspected to ensure data integrity. The inspection team will ensure the availability of a central computerized system that is protected to ensure the backup or data recovery of clinical trials.

### 4.2.3. Informed consent of trial participants

The aim is to determine whether informed consent was obtained in accordance with ICH GCP principles. The trial participants have to be informed of the advantages and disadvantages of participating in a trial. This includes information on the IMP, possible adverse events, insurance, and other issues.

The inspection team will verify and confirm that:

1. The required information was presented to the participant, verbally and in writing;
2. If each participant signed the ICF prior to participating in the trial;
3. The contact details of the investigator or secretariat were given to trial participant

### 4.2.4 Review of the trial participant data

The aim of trial subject data review is to check whether the investigator team conducted the clinical trial according to the approved protocol and its amendments by source data verification. In the source data verification, it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to the latest version of the ICH Good Clinical Practice (signed and dated by the authorised person who did it and providing justification, if necessary). For a number of participants that will be determined within the inspection plan, (the sample might include the first and last patient enrolled etc) the following should be checked:

1. Characteristics of the participant the clinical trial
2. Participant’ visits calendar
3. Efficacy and safety assessment data
4. Concomitant therapy and intercurrent illness
5. Safety management and reporting

### 4.2.5 Data integrity in clinical trial

During the course of inspections, the authority shall verify the integrity of data generated in clinical trial and to assure the protection of trial participants, in addition to ensuring that clinical trial is conducted according to the applicable regulations and guidelines.

An open reporting culture in research sites should be encouraged as fundamental to data integrity promotion throughout the data lifecycle, including processes from generation or recording of data to destruction, if needed, and the intervening processes.

Decisions made, based on the outcome of clinical trials, rely on the integrity of the results and data obtained during the study. The data should be complete, attributable, legible, contemporaneous, original and accurate, commonly referred to as “ALCOA+.” This applies to all data and information as reflected in manual records and electronic data from computerized systems.

### 4.2.6 Management of the investigational product(s)

The aim is to verify whether all the activities related to the management of Investigational Product(s) has been done according to the protocol and appropriate SOPs at trial site.

Clinical research sites usually have a pharmacy where IPs are stored and dispensed under appropriate conditions. The inspection team during the inspection shall very and confirm that:

1. access is controlled and that access records reflect entry and exit against the clinical trial activities such as dates for receiving and storage of IPs, dispensing, issuing, returns, and disposal;
2. SOP content for the various activities including receiving, checking, storage, dispensing, labelling, and reconciliation of IPs. Verify the related records to ensure compliance with the protocol and SOPs
3. SOP and records to monitor the conditions under which the IPs are stored. Verify the labelling requirements against the room storage conditions such as temperature and relative humidity observed from the calibrated devices. If there values outside the specifications, verify if they were investigated and if any prospective impact on the IPs was assessed.
4. Records relating to the IP, such as import license, proof of purchase, shipping letter, storage conditions during transport, certificate of analysis, stock card, and dispensing record including dates, quantity and signatures;
5. Check the suitability of storage conditions and their records (fridge, freezer and controlled substances…);
6. Cross check the records such as label sheets, randomization, CRFs, and reconciliation record for the IPs;
7. Whether IP labels contain the correct information such as the study number, “for clinical trial use only”, participant number, period, randomization, dosage form, and route of administration, as appropriate;
8. SOP for safe disposal of damaged or expired IPs.

The inspectors should check where required that these documents have been signed and dated by the responsible persons according to the site SOP and/or applicable requirements related to the management of Investigational Products.

If access to any record or copying is refused, or there any withholding of documents or denial of access to areas to which inspector has legal access, these refusals should be documented and included in the inspection observations

### 4.3 Interview with Research Team Members

During the Inspection, the team of inspectors will interview the research team member to determine how the clinical trial is or being conducted. The interview responses may trigger the deep review of essential documents pertaining to the clinical trial being inspected.

### 4.4 Inspection of trial site facilities, equipment and system

The team of Inspectors shall inspect facilities, equipment and system used to conduct the clinical trial being inspected and take appropriate documented evidence to support the inspection report where necessary. The inspection team shall inspect the following units: consultation room, laboratory, pharmacy, data management room, trial equipment and instrument, clinical trial documentation, and other applicable infrastructure covering the trial operations.

### 4.5 Generating GCP inspection findings

The GCP inspection evidences should be evaluated against the inspection criteria in order to determine inspection findings. These findings can indicate compliance or non-compliance with inspection criteria. The inspection findings should include compliance and good practices along with their supporting evidence, opportunities for improvement, and any recommendations to the inspectee. The findings should be well documented in a clear, concise manner using the inspection checklist (**ANNEXURE-I**) adopted from AVAREF and supported by objective evidence.

### 4.6 Clinical Trial Inspection Closing Meeting

At the end of the inspection, a closing meeting with the purpose of presenting inspection findings to the inspectee(s) will be held at the clinical trial site. During the closing meeting, on the last day of inspection, the preliminary findings noted during inspection will be highlighted. This meeting will help to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by both parties. This is also an opportunity to discuss the findings, request/provide clarifications and supporting documentation, as needed, and also ask questions.

The inspector(s) or the inspectee(s) will also sign the Memorandum Form of GCP findings (**ANNEXURE-II**) listing all the non-compliant findings noted during the clinical trial inspection of which a copy will be left at the investigator’s site.

### 4.7. Remote GCP inspections

During public health emergencies, the authority may perform GCP inspections remotely using video or teleconferencing, where access to the clinical sites is difficult. If a remote inspection reveals issues that require on-site inspection, or the inspection objectives could not be met remotely, then the site will be inspected physically**.**

### 4.8 Grading of clinical trial inspection findings

The grading of findings from GCP inspections of Clinical Trial sites are classified into three risk categories: critical (Risk-1), Major (risk-2), Minor (risk 3) and other findings.

### 4.8.1 Critical findings

Critical findings are conditions, practices or processes that adversely affect the rights, safety or well-being of the participants and/or the quality and integrity of data or that represent a serious violation of regulations and guidelines. They present the situation that result in fatal, life-threatening or unsafe conditions for study participants. The critical findings may include fraud, adulteration, misrepresentation, falsification of records, absence of source documents and falsified data are classified as critical findings.

### 4.8.2 Major findings:

The major findings are conditions, practices or processes that describes a situation where a marked findings, other than a critical one, may result in undue health risks for the clinical trial participants or in other persons and/or could invalidate the data.

### 4.8.3 Minor findings:

Minor findings are conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the participants and/or the quality and integrity of data. The minor findings imply the necessitate actions for improvement of conditions, practices and processes.

### 4.8.4 Other findings:

Other findings are conditions, practices or processes that inspection team may highlight in the report on how to improve quality or reduce the potential for a deviation to occur in the future.

### 4.8.5. Considerations for grading of GCP inspection findings

The GCP inspection findings classification may vary depending on circumstance, severity of the findings, corrective actions and preventive actions that may be taken and nature of the investigational product. In some circumstances an otherwise major findings may be categorised as critical. However, a finding reported after a previous inspection and not corrected may be given higher classification.

### 4.9 Outcome of GCP inspections

The results of a GCP inspection is inspection report and a close out letter describing the outcome with the applicable regulations and guideline(s) issued by the Authority. The overall inspection report concludes that the clinical trial site is:

1. **Compliant**- only minor and major observations were reported;
2. **Non-Compliant**-one or many critical observations; or a repetition of major observations reported during a previous inspection and may result in suspension or termination of the trial.

### 4.9.1 Clinical trial Inspection Report

Once the inspection has been completed, an inspection report will be written in the format shown in the **ANNEXURE-IV** and is issued to the sponsor/investigator within twenty (20) working days from the last day of inspection. The inspectee is required to acknowledge the receipt of GCP report and propose corrective and preventive actions (CAPAs) to all highlighted findings within fifteen (15) working days.

In case CAPAs are satisfactory, the Authority will issue the Inspection closing letter. However, if CAPAs are not satisfactory, additional actions will be requested by the Authority and when necessary, a follow up inspection may be conducted for verification. Once the CAPA is deemed acceptable, the Authority will send a GCP inspection close out letter.

### 4.9.2 Transparency & Confidentiality during GCP Inspections

The Authority will conduct GCP inspections of authorized clinical trials in a transparent manner from preparation, planning and conduct of inspections in accordance with provisions of regulations, guidelines and standards operations procedures in place. All trial site will be inspected using the same inspection standards and tools. The rights of trial participants in terms of privacy and confidentiality must be protected and maintained.

# 5.0 REGULATORY ACTIONS DURING GCP INSPECTIONS

Based on the findings of the GCP inspection, the Authority may proceed with administrative regulatory actions if the inspectee fails to address critical and major findings according to the provisions of regulations and laws enforced in Rwanda. However, the Authority may not wait for CAPA to administrative regulatory actions in cases of deliberated misconduct such as fraudulent documentation or continuation of the clinical trial can have an adverse effect on trial participants. The following regulatory actions depending on the GCP inspection findings may be taken:

1. Issuance of a warning letter;
2. Temporary suspend of the trial;
3. Permanently terminate the trial and revocation of clinical trial Approval certificate
4. Blacklist the principal investigator or sponsor;
5. File case for court proceedings;
6. **APPEAL ON GCP INSPECTION OUTCOMES**

Any person aggrieved by a decision of the Authority in relation to any finding raised from GCP inspection of clinical trials may appeal to the Authority according to the timelines set out in regulations for conduct of clinical Trials in Rwanda.

# APPENDIX I: GCP Inspection Process Flow chart

**P**

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The inspectees should submit the Inspection dossier to the Authority within 15 working days of receipt of the notice

Notification of CT Inspection

One (1) month prior to the proposed date of Inspection.

The GCP Inspection dates are confirmed with the inspectees; the Inspection plan is developed and finalized

GCP Inspection Conduct:

* Opening meeting
* Interview
* Visit to the facilities,
* Document review
* Closing meeting

The GCP inspection takes place as scheduled at the trial site to be inspected.

**AREAS & ASPECTS of GCP** **Inspection:** Legal & Administrative aspects; Organizational aspects; Informed consent, Review

of trial data & data integrity; IP management

**C**

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**T**

**Overall GCP Inspection report** & conclusion that the trial site: COMPLIANT or NON-COMPLIANT.

Closing meeting and sign of memorandum form

**Grading of GCP Inspection findings**: Deficiencies classified according to the impact on trial subjects & Data integrity as CRITICAL, MAJOR, MINOR

**F**

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**P**

GCP Inspection Report is issued to the Inspectees (Sponsor/PI) outlines the nature & scope of the inspection, observed findings within 20 working days. Required response to all highlighted deficiencies with CAPAs within 15 working days

CAPAs submitted and

Not satisfactory, additional regulatory actions such follow up inspection will be taken.

CAPAs submitted and satisfactory, the Authority issues a CLOSING LETTER

Not satisfactory, additional regulatory actions such follow up inspection will be taken.

# 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** | **Dr. ERIC NYIRIMIGABO** | **Dr Emile BIENVENU** |
| **Signature** |  |  |  |
| **Date** |  |  |  |

# ANNEXURE-I: CLINICAL TRIAL GCP INSPECTION CHECKLIST

|  |  |
| --- | --- |
| **ADMINISTRATIVE INFORMATION** | |
| Date of Inspection | DD/MM/YYYY |
| Name of the site |  |
| Physical Address of the site |  |
| Protocol Number |  |
| Stage of study |  |
| Before trial commencement |  |
| During clinical conduct |  |
| After completion |  |
| Principal Investigator |  |
| Sub/Co-Investigator | 1…………………………………………………………  2…………………………………………………………  3…………………………………………………………  4………………………………………………………… |
| Study Title | ……………………………………………………………………………………………………………….. |
| Regulatory Authority approval date  Version &Date | ………………………………………………………..  …………………………………………………………  …………………………………………………………  ………………………………………………………………….. |
| Ethical Approval date for informed consent form  1)……………………………………………………………………….  2)……………………………………………………………………… |  |
| Names of Inspectors | 1…………………………………………………………  2…………………………………………………………  3…………………………………………………………  4………………………………………………………… |
| Screening date 1st Participant |  |
| How many Participants enrolled |  |
| Randomization date of 1st Participant |  |
| How Many participants withdrew from the study? |  |
| How many participants completed the study |  |
| How many SAEs were reported |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **DATA INTEGIRITY** | **YES** | **NO** | **NA** |
| There is a written data integrity policy |  |  |  |
| There is an SOP describing principles of data integrity ensuring ALCOA |  |  |  |
| Data and results were reviewed and considered complying to data integrity requirements. (If “no”, complete comments section below) |  |  |  |
| Comments |  |  |  |

**A. FACILITY INSPECTION**

|  |  |  |  |
| --- | --- | --- | --- |
| **CONSULTING AREA** | **YES** | **NO** | **NA** |
| 1. Is the consulting area where the Clinical trial team evaluates the participants during visits adequate in size? |  |  |  |
| 2. Are there lock-up cupboards for confidential documents? |  |  |  |
| 3. Is the trial specific equipment available in the consulting room? |  |  |  |
| 4. If not, is the area where procedures are performed adequate and easily accessible? |  |  |  |
| **COMPLIANCE TO THE TRIAL PROTOCOL** |  |  |  |
| 1. Is the trial being carried out in accordance with the trial protocol provisions? |  |  |  |
| 2.Are the SOP mentioned in the protocol being implemented? (Note: You can provide a detail of SOP mentioned)  1. ……………………………………………………  2…………………………………………………….  3………………………………………………………. |  |  |  |
| 3. Was the dose in the protocol the same as the dose dispensed? |  |  |  |
| **PROCEDURE ROOM** |  |  |  |
| 1. Are all protocol specified equipment calibrated and validated? |  |  |  |
| 2. Are SOPs on how to use equipment available? |  |  |  |
| 3. Is the blood sampling area kept according to infection control procedures? |  |  |  |
| 4. Is an SOP on handling of biological waste available? |  |  |  |
| 5. Is an emergency trolley available in the procedure area?   * Is the trolley locked and are keys available and controlled? * Is the emergency trolley frequently checked? * Are medicines stored within their expiry dates? * Are oxygen and accessories available checked and signed? * Are investigators ALS trained? * Is clinical staff CPR trained? |  |  |  |
| **PHARMACY MANAGEMENT (INVESTIGATIONAL PRODUCTS STORAGE AREA)** | **YES** | **NO** | **NA** |
| 1. Are the Pharmacy access controlled, temperature and humidity? |  |  |  |
| 2. Are Investigational products stored as per temperature or humidity? |  |  |  |
| 3. In case of vaccines are a spillage SOP available and the study team trained to handle such an incidence? |  |  |  |
| 4. Are electronic or hand-written logs available? |  |  |  |
| 5. Is an SOP on how to handle electricity or temperature failure in the pharmacy available? |  |  |  |
| 6. Are the investigational products for different studies clearly identified and stored in separate lock-up cupboards? |  |  |  |
| **ARCHIVE** |  |  |  |
| 1.Is there an agreement between the Sponsor and the Clinical trial site/CRO on archiving of documentation |  |  |  |
| 2. Was access to the archive facility restricted? |  |  |  |
| 3. Are records of retrieval of documents from the archive available? |  |  |  |
| 4. Was the archive storage area fireproof and pest controlled |  |  |  |
| **CLINICAL LABORATORY** |  |  |  |
| 1. Is the clinical laboratory at the same site? |  |  |  |
| 2. If not, are procedures in handling biological samples clearly documented? |  |  |  |
| 3. Is the laboratory accredited for the tests to be performed? |  |  |  |
| 4. Are all testing procedures used in the laboratory validated? |  |  |  |
| 5. Are all instruments adequate? |  |  |  |
| 6. Are all instruments and equipment calibrated and maintained/ |  |  |  |
| 7. Are updated signed CVs of analysts available? |  |  |  |
| 8. Are the frequencies of QC checks for each instrument before analysis documented? |  |  |  |
| 9. Are there SOPs for receipt, storage of chemicals and preparation of solution available? |  |  |  |
| 10. Is an SOP for waste disposal (e.g.: organic and biological waste) available? |  |  |  |
| 11. Are normal values ranges for medical/laboratory/technical procedures and/or tests and wherever applicable their updates during the trail available? |  |  |  |

**B. STUDY SPECIFIC INSPECTION**

|  |  |  |  |
| --- | --- | --- | --- |
| **CONTRACT AND AGREEMENTS** | **YES** | **NO** | **NA** |
| 1. Did the contract or the protocol describe any transfer of responsibility between the sponsor and the investigator? |  |  |  |
| 2. Was a confidentiality agreement signed between the sponsor and the investigator(s)? |  |  |  |
| 3. Was there a signed and dated financial agreement between the sponsor and the investigator available? |  |  |  |
| 4. Was an insurance certificate that covers the duration of the study available? |  |  |  |
| 5. Was there is a signed conflict of interest declaration? |  |  |  |
| 6. Has the final version of the protocol been signed by all appropriate persons? |  |  |  |
| **REGULATORY APPROVALS** |  |  |  |
| 1. Was regulatory approval for the protocol obtained before the start of the study?…………………………………………………………...... |  |  |  |
| 2. Was the version number of protocols used in the study versus the version number of the approved protocol identified? |  |  |  |
| 3. Was regulatory approvals of any new investigators obtained? |  |  |  |
| **INVESTIGATOR BROCHURE** |  |  |  |
| 1. Was an investigator brochure and updates available on file with the date and version corresponding to that submitted Rwanda FDA |  |  |  |
| **INFORMED CONSENT** |  |  |  |
| 1. Was the informed consent form version that was used approved by Ethics committee |  |  |  |
| 2. Was a written SOP used to solicit informed consent? |  |  |  |
| 3. Did all the subjects sign the consent form before any study related procedure? |  |  |  |
| 4.Did all the subjects receive a copy of the signed informed consent form? |  |  |  |
| 5. Did participants receive information regarding insurance? |  |  |  |
| 6. Was an assessment of understanding of the contents of the informed consent done? |  |  |  |
| 7. Did the principal investigator or person designed by the principal investigator conduct the informed consent appropriately |  |  |  |
| 8. Was participants given sufficient time to decide whether or not to participate in the study? |  |  |  |
| **RESPONSIBILITIES OF THE INVESTIGATOR** |  |  |  |
| 1. Were updated CV and adequate training certificate available? (check for GCP training) |  |  |  |
| 2. Did the investigator have sufficient personnel for the conduct of the study? |  |  |  |
| 3. Was a record of the pre-trial training for all staff available? |  |  |  |
| 4.Were the signatures of the staff involved in the study recorded? |  |  |  |
| 5. Was a participant identification log available? |  |  |  |
| 6. Was a participant enrolment log available? |  |  |  |
| 7. Were the facilities at the site adequate for safe and proper conduct of the trial? |  |  |  |
| 8. Did the investigator have a contingency plan for medical care in case of emergency? |  |  |  |
| 9. Were significant trial related duties and functions delegated to qualified persons documented? |  |  |  |
| 10. Were all the inclusion criteria and none of the exclusion criteria met by participants? |  |  |  |
| 11. Was the sixth monthly progress report sent to the IEC/IRB? |  |  |  |
| 12. Was the sixth monthly progress report sent to the regulatory Authority? |  |  |  |
| 13. Were treatment compliance documented for all participants? |  |  |  |
| 14. Were all SAEs/AEs reported within the specified timelines to Rwanda FDA |  |  |  |
| 15. Were all SAEs/AEs reported within the specified timelines to the Sponsor? |  |  |  |
| **INVESTIGATIONAL PRODUCT** |  |  |  |
| 1. Were the records of shipping letters of the investigational product(s) (e.g.: dates, batch numbers, quantities, letters) from the Sponsor to the investigator available? |  |  |  |
| 2. Were all study medications kept in a securely locked, temperature-controlled area accessible only to authorized persons? |  |  |  |
| 3. Were the records of storage conditions e.g.: temperature control log available? |  |  |  |
| 3. Were records of the products used available as dosage form. Strength, batch number, expiry date, certificate of Analysis, other coding that identifies the specific characteristic of the product tested? |  |  |  |
| 4. Were Valid certificates of analyses (CoA) for the study products available? (Check stability, expiry dates) |  |  |  |
| 5. Were instructions for handling investigational product and trial related materials available? |  |  |  |
| 6. Was the dispensing of the investigational product done according to the protocol/SOPs? |  |  |  |
| 7. Was dispensing done by a registered Pharmacist or b y a person with a dispensing license? |  |  |  |
| 8. Did the labelling of the investigational products reflect clinical research purposes only? |  |  |  |
| 9. was there a record of reconciliation at the end of the dispensing? |  |  |  |
| 10. Were retention samples available? |  |  |  |
| 11. Were there proof that conditions as stated in the protocol have been maintained during shipment and storage of products? |  |  |  |
| 12. Was drug accountability done? |  |  |  |
| 13. Were decoding procedures (for blinded trials) available? |  |  |  |
| 14. Was documentation on disposal of investigational products available? |  |  |  |
|  |  |  |  |
| **RECORD KEEPING AND DATA HANDLING** | **YES** | **NO** | **NA** |
| 1. Were records of key trial related procedures e.g.: CRF, source documents |  |  |  |
| 2. Was a signature sheet reflecting signatures and initials of all persons We’re authorized to make entries and or corrections on CRFs available? |  |  |  |
| 3. Were corrections to the CRF/eCRF verified during the inspection done in such a way that it leaves an audit trial? |  |  |  |
| 4. Were the CRFs verified during the inspection signed, initiated and dated by the investigator? |  |  |  |
| 5. Did each page of the case report form identify the participant and the study? |  |  |  |
| 6. Was there an SOP for data entry/corrections in the CRF? |  |  |  |
| 7. Was the security of data protected in the eCRF? |  |  |  |
| 8. Were there any discrepancies between Adverse Events recorded in the source documents and those reported in the CRF? |  |  |  |
| 9. Was follow up to all the adverse events reported satisfactory? |  |  |  |
| 10. Were concomitant therapies included in the CRF verified during the inspection? |  |  |  |
| **QUALITY ASSURANCE** |  |  |  |
| 1. Did a quality system exist to ensure compliance with GCP/GLP training? |  |  |  |
| 2. Was records available for training of staff, including proof of GCP training? |  |  |  |
| 3. Was there a procedure available for internal monitoring of the quality system? |  |  |  |
| 4. Was an audit certificate available? |  |  |  |
| 5. Was there documentation on SOP training? |  |  |  |

Done at ………………………….on ……………../………………/…………

Inspector’s Signature

| **#** | **Print name** | **Functions** | **Signature** |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

# ANNEXURE-II: FORM OF MEMORANDUM OF GCP INSPECTION FINDINGS

| 1. **ADMINISTRATIVE INFORMATION** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Clinical trial(s) names | | | |  | | | |
| Trial protocol title | | | |  | | | |
| Rwanda FDA CTAC number | | | |  | | | |
| Trial site address | | | |  | | | |
| Total number of sites | | | |  | | | |
| Investigational product(s) | | | |  | | | |
| Names and contact of Principal Investigator | | | |  | | | |
| Date of inspection | | | |  | | | |
| 1. **LIST OF GCP INSPECTION FINDINGS AT THE INSPECTED SITE** | | | | | | | |
| **#** | **Reference** | **Findings details** | | | | **Documented evidences** | |
| 1 | ICH GCP E6 (R2) section 4.6 | Document the first sentence as a brief summary of the observation. Add details as necessary.  E.g.: Management of IP at the site was inadequate. | | | |  | |
|  |  | 1. Add an example to substantiate the observation e.g. The pharmacist did not complete the IMP inventory log every day | | | |  | |
|  |  | 1. Add an example to substantiate the finding e.g. The shelf on which the IP was stored, was not labelled with the Protocol number and IP name, | | | |  | |
|  |  | 1. Add an example to substantiate the observation. You may add more rows if applicable, by clicking outside the end of this row on the right. | | | |  | |
| 1. **SIGNATURE OF MEMORANDUM OF FINDINGS** | | | | | | | |
| **Inspection team** | | | **Institution** | | **Date** | | **Signature** |
|  | | |  | |  | |  |
|  | | |  | |  | |  |
|  | | |  | |  | |  |
| **Inspection team** | | | **Institution** | | **Date** | | **Signature** |
|  | | |  | |  | |  |
|  | | |  | |  | |  |
|  | | |  | |  | |  |

**ANNEXURE-III: GRADING OF CLINICAL TRIAL INSPECTION FINDINGS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **ADMINISTRATIVE INFORMATION** | | | |
|  | Clinical trial(s) names |  | | |
|  | Rwanda FDA CTAC number |  | | |
|  | Trial protocol title |  | | |
|  | Trial site address |  | | |
|  | Total number of sites |  | | |
|  | Investigational product(s) |  | | |
|  | Names and contact of Principal Investigator |  | | |
|  | **CRITICAL FINDINGS (Not exhaustive)** | | **YES** | **NO** |
|  | Conduct of clinical trial that is not authorized by Rwanda FDA | |  |  |
|  | Sponsor imported Investigational product (IP) without import license from Rwanda FDA | |  |  |
|  | Use of prohibited substance(s) without having received prior authorization from the Authority | |  |  |
|  | Misrepresentation or falsification of information of data submitted to obtain authorization to conduct clinical trials | |  |  |
|  | Clinical trial on-going after the authorization has suspended or cancelled | |  |  |
|  | The application for amendment that contains falsified, misleading or deceptive information | |  |  |
|  | Failure to notify the Authority after amendments were implemented in cases where the clinical trial endangered the health of trial participants or other persons | |  |  |
|  | Evidence of fraud such as "fabricating" trial participants, falsification of study data | |  |  |
|  | Lack of records of SAEs which occurred from trials inside and/or outside Rwanda | |  |  |
|  | Lack of records in respect of use of investigational product in a clinical trial. | |  |  |
|  | Lack of records with respect to the enrolment of clinical trial participants | |  |  |
|  | Lack of records of qualifications of the PI to conduct the clinical trial | |  |  |
|  | Failure to report serious and unexpected adverse drug reactions to the Authority | |  |  |
|  | Change of IP in Clinical trial without Authorization from the Authority | |  |  |
|  | The sponsor failed to ensure sufficient and robust monitoring of the trials, leading to data integrity issues | |  |  |
|  | The investigator lost control of data between database lock and pdfs being sent to the site | |  |  |
|  | Updated documents containing new expected adverse reactions that had not previously been approved as substantial amendments were used for expectedness assessments. | |  |  |
|  | **MAJOR OBSERVATIONS** | | **YES** | **NO** |
|  | Information contained in the trial application was incomplete or incorrect. | |  |  |
|  | Failure to disclose all clinical trial sites to the Authority. | |  |  |
|  | Failure to provide all necessary information, not previously provided in the application, prior to the sale or importation of a drug at a clinical trial site. | |  |  |
|  | Failure to notify the Authority when changes made to the chemistry and manufacturing information or to the approved protocol. | |  |  |
|  | Failure to implement an amendment at a clinical trial site. | |  |  |
|  | Failure to provide to the Authority with information regarding an immediate amendment to the protocol | |  |  |
|  | Clinical trial was not conducted in accordance with the protocol | |  |  |
|  | Protocols not amended, informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the clinical trial drug which endanger the health of the clinical trial subject or other person. | |  |  |
|  | Failure to obtain EC approval prior to implementation of amendments to protocol or informed consents forms | |  |  |
|  | Informed consents not administered properly or not signed and dated | |  |  |
|  | Informed consent not obtained from trial participants before enrollment in the trial or after major amendments to the informed consent form | |  |  |
|  | No source data to substantiate clinical trial results | |  |  |
|  | Sponsor did not notify the Principal Investigator of serious unexpected adverse drug reactions that occurred at other sites | |  |  |
|  | No procedures in place for reporting new safety information to the Principal Investigator | |  |  |
|  | Significant clinical endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms. | |  |  |
|  | No systems in place for drug accountability | |  |  |
|  | Source data was not verified for quality, completeness and integrity | |  |  |
|  | Systems and procedures that assure the quality of every aspect of the clinical trial were not implemented | |  |  |
|  | The informed consent did not contain all of the required information | |  |  |
|  | Individuals involved in the conduct of the clinical trial are not qualified by education, training or experience to perform their respective tasks | |  |  |
|  | Incomplete documentation of protocol deviation | |  |  |
|  | Lack of documentation that Sponsor was informed of protocol deviations | |  |  |
|  | No security procedures in place for electronic records or electronic signatures | |  |  |
|  | The electronic data system was not validated | |  |  |
|  | Sponsor has no or incomplete records of all adverse events which occurred inside or outside Rwanda | |  |  |
|  | Incomplete records respecting the enrolment of clinical trial participants | |  |  |
|  | No records concerning shipment, receipt, use, disposition, return or destruction of the investigational products | |  |  |
|  | Quantities of drug not accounted for through the various stages of shipment, receipt, disposition, return or destruction of the lot of the investigation | |  |  |
|  | Copies of the protocol/amendments and informed consents approved by the EC not retained for each clinical trial site | |  |  |
|  | Absence of EC attestation for each clinical trial site stating that it has reviewed and approved the protocol, the informed consent and that it functions in compliance with GCP | |  |  |
|  | Incomplete records in respect of the use of a drug in a clinical trial | |  |  |
|  | Sponsor did not comply with the prescribed timeline for reports of fatal or life-threatening adverse drug reactions | |  |  |
|  | Sponsor did not inform the Authority that the clinical trial was discontinued in its entirety or at a clinical trial site within 15 days after the date of the discontinuance | |  |  |
|  | Sponsor did not provide to the Authority with the reasons for the discontinuance and its impact on the proposed or on-going clinical trials | |  |  |
|  | Sponsor did not inform all Investigators of the discontinuance of a trial, the reason for the discontinuation or did not advise them in writing | |  |  |
|  | Sponsor, after having discontinued a clinical trial, resumed selling or importing the drug without having submitted the required information to the Authority | |  |  |
|  | Clinical trial ongoing at one or more sites after Sponsor stated that the trial was discontinued at those sites | |  |  |
|  | **MINOR OBSERVATIONS (Not Exhaustive)** | | **YES** | **NO** |
|  | Sponsor did not maintain copies of previous investigator's brochures pertaining to the clinical trial drug. | |  |  |
|  | Date for the commencement of a clinical trial at one or more trial sites was earlier than that stated in the application. | |  |  |
|  | Sponsor did not notify the Authority in writing within 15 days after the date of the change that requires notification. | |  |  |
|  | Delegation of tasks incomplete, signature log incomplete. | |  |  |
|  | Correction of data not initiated and/or dated. | |  |  |
|  | Minor errors in transcribing data from source documents to case report forms. | |  |  |
|  | Source data stored in unsecured location. | |  |  |
|  | Labelling of the products not complying with requirements. | |  |  |
| **SUMMARY OF EVENTS** | | | **Date** | **Ref.** |
|  | Regulatory Authority approval for Protocol and amendments | |  |  |
|  | Ethics approval for Protocol and amendments | |  |  |
|  | Ethics approval for Informed consent form | |  |  |
|  | Annual ethics approval Renewal | |  |  |
|  | General screening Trial specific screening | |  |  |
|  | Randomization | |  |  |
|  | Dosing/administration after approvals | | YES | NO |
|  | Number of subjects enrolled | |  |  |
|  | Number of subject withdrawals | |  |  |
|  | Number of subjects lost to follow up | |  |  |
|  | Number of subjects who completed the study | |  |  |
|  | Number of SAEs reported | |  |  |
|  | Number of protocol deviations and violations | |  |  |
|  | Was CAPA taken? | | YES | NO |
|  | Is there a Risk Management Plan and it is being adhered to? | | YES | NO |

**Inspector’s Signature**

| **#** | **Inspectors’ name** | **Functions** | **Signature** |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

**ANNEXURE-IV: CLINICAL TRIAL GCP INSPECTION REPORT TEMPLATE**

|  |  |
| --- | --- |
| **GCP INSPECTION Report N°** | |
| Inspected Sites and address |  |
| Type of inspection : | Complete as applicable e.g Routine Investigator Site Inspection (ISA) |
| Protocol number: | If applicable |
| Protocol title: | If applicable |
| Principal Investigator and site address (Country): |  |
| CTAC reference number |  |
| Names of Inspector(s): |  |
| Other Inspector (s): |  |
| Inspection dates: |  |
|  |  |
| Inspection Report date: | Report date: Draft VXX, dd-Mmm-yyyy OR Version X, dd-Mmm-yyyy for final report |
| Due date for reply from Inspectee: | dd-Mmm-yyyy |

**BACKGROUND**

Brief description of the Trial

*<Insert comments as appropriate>*

Reason and scope of the inspection

*[Insert reason(s) for the inspection(s), i.e. by Rwanda FDA as part of a centralised procedure. Please give the date of the request. Please give a short description of the scope of the inspections. This information should be from the inspection request and pre-inspection discussions with assessors.]*

2.1.1. Opening meeting

*<Insert comments as appropriate>*

2.1.2 Closing Meeting

*<Insert comments as appropriate>*

**Documents reviewed**

Study specific documents reviewed in preparation for the GCP inspection:

*List the documents, version number and date, amending as applicable, for example:*

* Protocol and amendments version xxx
* Investigator Brochure version xxx
* Ethics Committee (EC)/Competent Authority

Site initiation report version xxx

IND safety reports/SUSARs

Monitoring Plan version xxx

Site personnel interviewed:

e.g. Dr XXX, Principal Investigator (PI)

e.g. Ms XXX, Clinical Research Associate (CRA)

***Organization and Management***

< Insert summary comments as appropriate>

***Facility and Equipment***

< Insert summary comments as appropriate>

***Management of Investigational Product (s)***

< Insert comments as appropriate>

***Documentation and Trial Master File***

< Insert comments as appropriate>

*(Contract and agreements, regulatory approvals, compliance to the trial protocol, investigator brochure, informed consent, ethical clearance, Patient information leaflet, safety reporting forms, progress and close out reports etc.)*

***Record Keeping and data Handling***

< Insert comments as appropriate>

*(Use of computerized systems, Data integrity in clinical trial, Efficacy and safety assessment data Safety management and reporting*

***Monitoring and Auditing***

< Insert comments as appropriate>

***Clinical Laboratory*** (Management of biological samples, etc)

< Insert comments as appropriate>

***Quality assurance***

< Insert comments as appropriate>

**GCP Inspection Report Summary**

*The summary should be stand-alone i.e. the reader should be able to understand it without needing to refer to the main body of the report. There should be nothing in the summary that is not in the main body of the report.*

This was a < insert type of GCP inspection to match the GCP inspection plan, for e.g. Routine, internal/contracted Investigator Site GCP inspection > conducted on the < insert as applicable, for e.g. Protocol number and name>study by the QA department or Contract inspector on behalf of the QA department. The inspection was conducted at <insert title, name and designation of inspectee and address where inspection was conducted, e.g. Dr/Prof Name & Surname, Principal Investigator (PI) at Name of Site in Location, Suburb, City, Country>.

The inspection was conducted per the inspection plan dated dd-Mmm-yyyy

The purpose of the inspection was to confirm<amend as applicable for e.g. whether the safety and rights of the research participants were protected, and the study was conducted per the approved protocol, all applicable Good Clinical Practices (GCPs), national and international regulatory requirements and the Declaration of Helsinki>.

The focus of the inspection was on <insert as applicable, matching to inspection plan e.g. participant data and site procedures>.

The PI, Dr*/Prof* Name & Surname, joined the site in Month and Year. Comment on the PI’s oversight and evidence of involvement in the trial.

Critical observations: number

Major observations: number

Minor observations: number

Critical observations were noted relating to elaborate on the critical observations observed.

Major observations were noted relating to elaborate on the major observations observed.

The inspector/s concluded that <provide a summary of the adequacy of the site, PI oversight, quality of the data, etc.>.

Details of the observations made during the inspection are documented in the section “inspection observations and action plan” of this report. An appropriate Corrective and Preventive Action (CAPA) (as applicable) for each observation documented must be provided by the inspectee (s), together with the name of the person responsible to implement the CAPA and the planned date for completion (or date completed).

**Grading of GCP Inspection findings**

The inspection observations are graded per the criteria as detailed below. Several minor (or major) observations may collectively be considered as equal to a major (or critical) observation.

**Critical findings:**

A deficiency with a significant risk of or having a major impact on participant safety, data integrity or study outcome, and / or seriously affects regulatory compliance or could lead to regulatory action.

**Major findings:**

A deficiency that is a significant deviation from GCP / regulatory requirements, procedural documents, or regulatory / industry expectations, with actual or potential effect on participant safety, data integrity or study outcome.

**Minor findings:**

A deficiency which does not affect the safety of participants or significantly affect the integrity of study results or study outcome, but is not compliant with GCP / regulatory requirements, or regulatory / industry expectations.

**Other findings:**

A suggestion for improvement to quality, safety or efficiency. There is no GCP non-compliance. Action can be taken.

*This* inspection *report is not intended to be an all-inclusive list of deficiencies and represents only those detected during the inspection. Corrective and/or preventive actions should be implemented across participants, or sites as applicable.*

**Quality of the data, ethical conduct and GCP compliance**

*<Insert comment as appropriate>*

*[Discuss the implication of any major or critical findings on data quality {cross reference to section 3.3 or the IRs} and compliance with the GCP principles and ethical standards. This section may need to be specific on which data were affected and to what extent. The section may need to discuss the results of any responses by the inspectee/sponsor that are re analyses (extrapolations/ sensitivity).]*

*[Statement on GCP compliance and whether the trial was conducted in accordance with internationally accepted ethical standards, describe the areas where deviations from full GCP-compliance were detected if applicable, and to what extent GCP compliance is impaired.]*

**Recommendations for the acceptability of the clinical trial data**

*<Insert comment as appropriate>*

**Signatures**:

|  |
| --- |
| **Name and surname**  **Designation** |
| **Name and surname**  **Designation** |

|  |
| --- |
| **Report Distribution and GCP inspection Team** |
| **Issued to:** This will be completed by the Lead *inspector* |
| **Distribution:** This will be completed by the Quality Assurance Manager |
| **Inspection team:** *<insert the inspector name/s here>* |

**GCP FINDINGS AND RECOMMENDATIONS**

| **#** | **Grading** | **Reference** | **Findings details** | **Recommendations and timelines** |
| --- | --- | --- | --- | --- |
| 1 | Critical, Major, Minor or Others | ICH GCP E6 (R2) section 4.6 | Document the first sentence as a brief summary of the observation. Add details as necessary.  E.g.: Management of IP at the site was inadequate. |  |
|  |  |  | 1. Add an example to substantiate the observation e.g. The pharmacist did not complete the IMP inventory log every day |  |
|  |  |  | 1. Add an example to substantiate the finding e.g. The shelf on which the IP was stored, was not labelled with the Protocol number and IP name, |  |
|  |  |  | 1. Add an example to substantiate the observation. You may add more rows if applicable, by clicking outside the end of this row on the right. |  |

| **#** | **Grading** | **Reference / Classification** | **Findings details** | **Recommendations and timelines** |
| --- | --- | --- | --- | --- |
| 2 | Major |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

| **#** | **Grading** | **Reference / Classification** | **Findings details** | **Recommendations and timelines** |
| --- | --- | --- | --- | --- |
| 3 | Minor Findings |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

| **#** | **Grading** | **Reference / Classification** | **Findings details** | **Recommendations and timelines** |
| --- | --- | --- | --- | --- |
| 4 | Other findings |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

**Confirmation that CAPA has been agreed:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name and Surname, Designation, Signature, Date Name and Surname, Designation, Signature, Date

**Confirmation that all CAPAs have been closed:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name and Surname, Designation, Signature, Date Name and Surname, Designation, Signature, Date

Following review and approval of the responses to each inspection observation with proposed CAPA

**ANNEXURE-V: GCP INSPECITION FINDINGS AND CAPA FORM**

|  |  |  |
| --- | --- | --- |
| **#** | **ADMINISTRATIVE INFORMATION** | |
|  | Clinical trial(s) names |  |
|  | Rwanda FDA CTAC number |  |
|  | Trial protocol title |  |
|  | Trial site address |  |
|  | Total number of sites |  |
|  | Investigational product(s) |  |
|  | Names and contact of Principal Investigator |  |
|  | Date of inspection |  |
|  | Number of Findings |  |

| **#** | | **Grading** | **Reference** | **Findings details** | | **Proposed CAPA** | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | | Critical, Major, Minor or Others | ICH GCP E6 (R2) section 4.6 | Document the first sentence as a brief summary of the observation. Add details as necessary.  E.g.: Management of IP at the site was inadequate. | |  | |
|  | |  |  | Add an example to substantiate the observation e.g. The pharmacist did not complete the IMP inventory log every day | |  | |
|  | |  |  | Add an example to substantiate the observation. You may add more rows if applicable, by clicking outside the end of this row on the right. | |  | |
| **#** | **Inspectee’ name** | | | | **Functions** | | **Signature** |
|  |  | | | |  | |  |
|  |  | | | |  | |  |
|  |  | | | |  | |  |