RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON INSPECTION OF CLINICAL TRIALS IN RWANDA

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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 regulation N° CBD/TRG/015 governing the conduct of clinical trials especially in its article 32, the Authority issues *Guidelines N° DIS/GDL/033* on 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 of 1964, and that the quality, reliability, and integrity of data collected are credible.

These guidelines detail the steps and processes required during the 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. Charles KARANGWA
Acting Director General

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ACCRONYMES AND ABBREVIATIONS

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

1.0. 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

and of the methods and material to be used in obtaining and documenting informed consent of trial participants.

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

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

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

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

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

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

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

"Phase III trials" Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g., clinically-relevant investigation medicinal product interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind

design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

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

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

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

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

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

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

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

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

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

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

2.0. 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 an inspection of clinical trials in all phases including bio-equivalence 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 inspections as appropriate. It can support recognition of inspection findings and regulations actions for clinical trials between countries that apply the same standards and procedures of inspection.

The areas for the 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), IMP management, Clinical sample management, Trial Master File, Trial Management & Monitoring of related clinical trial data.

These guidelines will help the Authority to establish 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 inspectees are urged to adhere to the provisions of these guidelines while planning, preparing, conducting, and reporting clinical trial inspections.

2.1 SCOPE

The guidelines will apply to the inspection of all clinical trials approved by the Authority and conducted at investigator site (s), sponsors facility (ies), CROs, and other establishments 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.

2.2 OBJECTIVES OF INSPECTIONS

The objectives to conduct GCP/GLP inspections are:

- ✔ To ensure the safeguard the rights, safety and well-being of trial participants;
- ✔ To verify the quality and integrity of the clinical trial data;

- ✔ 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 take corrective actions to ensure compliance and enforcement actions when deemed necessary.

3.0. TYPES OF INSPECTIONS

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

a) Routine inspection
b) Follow-up inspection
c) Investigative or 'For cause' inspections

3.1 ROUTINE INSPECTIONS

Routine inspections are generally carried out before or after approval of a trial or when there are major amendments e.g., changes in principal investigators and additional site. The Authority may conduct inspection on limited aspects related to GCP compliance within a facility.

3.2 FOLLOW UP 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 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 GCP non-compliances that have been observed.

3.3 INVESTIGATIVE OR "FOR CAUSE" INSPECTIONS

An investigative inspection is one which is undertaken to deal with specific complaints received about lapses or non-compliance with standards. Examples of "for cause" inspections include:

a) Inconsistent data are found in the database (physical examinations, vital signs etc).
b) An unusual safety profile has been reported (safety or efficacy data inconsistent with other study sites).
c) An abnormal number of adverse events (AEs) are reported (too high or very low).
d) Suspicion of alleged violations of laws, regulations and/or guidelines.

4.0. CONDUCT OF INSPECTIONS

4.1 Notification of Inspection

In general, the Authority may contact the PI or sponsor notifying the date(s) of inspection one (1) months prior to the proposed announced inspection dates and asked to confirm availability. The notification will identify the study to be inspected and proposed sites. In relation to for cause or follow up inspections, the authority may provide a shorter notice period. The following information shall be requested by the Authority:

a) Participant status per trial site (number randomized, dropout rate, number of SAEs reported per site) at trial initiation or during the trial
b) Copies of Standards Operating Procedures (SOPs) along with amendments (e.g., monitoring procedures, informed consent procedures, SAEs reporting Procedures, Pharmacy Management Procedures, etc)
c) Trial Master file. In case of computerized system, the PI or sponsor may provide access to the system
d) Any other document deemed necessary by the Authority.

The inspection dates will be confirmed. The PI or sponsor shall submit the above documents within fourteen (14) days of the receipt of the notice of inspection

4.2 Preparation for inspection

The inspection plan is developed and finalized by the Authority before inspection which outline the units to be inspected, schedule of meetings to be held, and list of research team to be met.
Each member of 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.

4.3 Conduct of the inspection

4.3.1 Opening meeting

The purpose of the opening meeting between the inspector(s) and the inspectee(s) is to:

a) introduce the inspector(s) to the inspectee(s),
b) explain the regulatory framework for the conduct of the inspection;
c) introduce the inspectees and identify their roles and responsibilities,
d) provide clarification of the scope and the objectives of the inspection;
e) give a brief overview of the trial site

f) provide a short summary of the methods and procedures to be used for the conduct of the inspection;
g) confirm that the resources, documents and facilities needed by inspectors are available
h) confirm the time and date for the closing meeting and any interim meetings;

4.3.2 Data collection during inspection

The inspection shall be conducted in accordance with provisions of these guidelines. During the conduct of inspection, sufficient information to fulfil the inspection objective(s) should be collected through examination of relevant documents with direct access, interviews and observation of activities, equipment and conditions in the inspected areas using **Annex 1.**

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 regal access, these refusals should be documented and included in the inspection observations

4.3.2.1 **Interview with Research Team Member**

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.

4.3.2.2 **Visit to Trial Site Facilities**

The team of Inspectors shall visit facilities used to conduct the clinical trial being inspected and take appropriate photos to support the inspection report where necessary. The inspection team shall inspect the following units: laboratory, pharmacy, data management and trial equipment, other applicable infrastructure and overall trial operations.

4.3.2.3 **Trial Document Review**

During the course of inspection, the team of inspectors shall review essential documents pertaining to study being inspected. If available, the documents and data to be verified against source raw data shall include but are not limited to:

a) Protocol specific inspections may include:
   - ✔ Trial Master File
   - ✔ Legal and administrative aspects: communication with the ethics Committee, communication with the Regulatory Authority, and Other Communications:
   - ✔ Organisational aspects:

- implementation of the trial at the investigator site
- Facilities and equipment
- Management of biological samples
- Organisation of the documentation
- Monitoring and auditing
- Use of computerised systems
- Informed consent of trial participants
- Details of impartial witness if any
- Review of the trial participant data
- Adverse event reporting
- Management of the investigational medicinal product(s)
- Protocol deviations
- Other, as required

b) System Inspection may include:
- ✔ Organisation and personnel
- ✔ Facilities and equipment
- ✔ Sponsor/CRO operating Procedures
- ✔ Implementation and termination of the clinical trial
- ✔ Monitoring
- ✔ Investigational Medicinal Product
- ✔ Sample management
- ✔ Safety and adverse events reporting
- ✔ Data handling and clinical trial report
- ✔ Documentation archiving
- ✔ Sponsor audit and quality assurance system
- ✔ Management process for protocol deviations
- ✔ Delegation of duties

c) Specific clinical trial inspection:
- ✔ Implementation and termination of the clinical trial
- ✔ Investigational Medicinal Product
- ✔ Case Report Form data verification
- ✔ Data handling and clinical trial report (CTR)
- ✔ Clinical trial documentation and archiving
- ✔ Audit trials

4.3.3 Areas of Inspection

The scope and activities examined during the inspections undertaken by the authority may include different aspects:

4.3.3.1 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.

a) **Ethical approval**

During the Inspection, the inspection team shall verify the relevant records relating to the work of the EC or IRB responsible for reviewing the trials to ensure that the protection of the rights and welfare of participant in clinical trials. This verification shall include but not limited to:

- Reference number, dates, signatures of clearance of the Ethics Committee and other relevant communications
- Reports submitted to the EC or IRB as well as reporting of any serious adverse events occurring during the trial
- Approval given for any advertisement and recruitment of trial participant, compensation, payments, and screening.

b) **Authority approval**

The inspection team shall ensure that:

- The Clinical Trial approval was granted in writing to conduct the trial prior to its initiation. The approval date versus trial start date, signature on the approval certificate, conditions imposed.
- revisions and changes to the protocol and related documents were granted approval prior to implementation.
- Serious adverse events (SAEs) and other reports were submitted to the authority according the timelines of relevant regulations and guidelines.

4.3.3.2 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:

a) **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 medicinal products (IMPs) and other services should be controlled as appropriate.

b) **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. The contract between the sponsor and the investigator has to clearly define the responsibilities of each party. The inspectors shall verify if:

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

c) **Facilities and equipment**

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

d) **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:

- The approved protocol is being implemented
- all trial participants enrolled met the inclusion and exclusion criteria
- dosing, meals (fed and fasting), sample collection were done as stipulated in protocol
- randomization, product information, reporting of serious adverse events, and preparation of reports are compliant with the requirements
- there are no deviations from the protocol
- violations to the protocol were reported
- reporting of results was/being done as required

e) **Management of biological samples**

The aim of checking the management of biological samples is to examine, conditions and documentation regarding collection, storage, 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, methods to be used, and reporting of results.

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

f) **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.

g) **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.

h) **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 central computerized system that is protected to ensure the back up or data recovery of clinical trial.

4.3.3.3 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:

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

4.3.3.4 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 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:

a) Characteristics of the participant the clinical trial
b) Participant' visits calendar
c) Efficacy and safety assessment data
d) Concomitant therapy and intercurrent illness
e) Safety management and reporting

4.3.3.5 Data integrity in clinical trial

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

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.

4.3.3.6 Management of the investigational medicinal product(s)

The aim is to verify whether all the activities related to the management of Investigational Medicinal Product(s) have been done according to the protocol and appropriate SOPs at trial site. Clinical research sites usually have a pharmacy where IMPs are stored and dispensed under appropriate conditions. The inspection team during the inspection shall very and confirm that:

- access is controlled and that access records reflect entry and exit against the clinical trial activities such as dates for receiving and storage of IMPs, dispensing, issuing, returns, and disposal;
- SOP content for the various activities including receiving, checking, storage, dispensing, labelling, and reconciliation of IMPs. Verify the related records to ensure compliance with the protocol and SOPs
- SOP and records to monitor the conditions under which the IMPs 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 IMPs was assessed
- Records relating to the IMP, 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
- Check the suitability of storage conditions and their records (fridge, freezer and controlled substances…)
- Cross check the records such as label sheets, randomization, CRFs, and reconciliation record for the IMPs
- Whether IMP 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
- SOP for safe disposal of damaged or expired IMPs

The inspectors should check that where required 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 Medicinal Products.

4.3.4 Grading of clinical trial inspection findings

The grading of observations/ deficiencies made in the conduct of inspections of Clinical Trials are classified into three categories; critical, major and minor. A summary for the criteria for judging deficiencies as critical, major or other are detailed in **Annexure-2.**

4.3.4.1 **Critical deficiencies**

Critical deficiencies 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. They present the situation that results in fatal, life-threatening or unsafe conditions for study participants. Critical deficiencies are totally unacceptable and may result in rejection of data and/or regulatory actions. The observations may include fraud, adulteration, misrepresentation, falsification of records, absence of source documents and poor-quality data are classified as critical deficiencies.

4.3.4.2 **Major deficiencies:**

The major deficiencies are conditions, practices or processes that might adversely affect the rights, safety or well-being of the participants and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles. Major deficiencies may result in rejection of data and/or regulatory actions.

4.3.4.3 **Minor deficiencies:**

Minor deficiencies 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. Observation classified as minor implies the necessity for improvement of conditions, practices and processes.

4.3.4.4 **Other observation or comments:**

Other observations or comments are conditions, observations, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data. In this regard, the inspection team may highlight in the report the observations or suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

4.3.5 Recording of inspections findings

During the inspection, the inspectors shall record all observations and findings using appropriate GCP inspection check list (Annex-1) to determine which are to be reported as findings according to the grading as highlighted in the **Annexure-2**. The findings should be well documented in a clear, concise manner and are supported by objective evidence.

The overall inspection report concludes that the clinical trial site is:

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

4.3.6 Clinical Trial Inspection Closing Meeting

At the end of the inspection, a closing meeting with the purpose of presenting inspection findings and comments to the inspectee(s) will be held at clinical trial site. During the closing meeting, on the last day of inspection, the preliminary deficiencies 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.

The inspector(s) or the inspectee(s) will also sign the memorandum form **Annexure-3**. listing all the non-compliance findings noted during the clinical trial inspection of which a copy will be left at investigator's site.

4.3.7 Clinical trial Inspection Report

Once the inspection has been completed, a written inspection report outlining nature and scope of the inspection, deficiencies observed during inspection is issued to the sponsor/investigator within fifteen (15) working days from the last day of inspection. The inspection report details will be written in the format shown in the **Annexure-4**. The inspectee is required to respond to all highlighted deficiencies with corrective and preventive actions (CAPAs) in soft copy 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.

5.0 TRANSPARENCY AND CONFIDEFINTIALITY DURING INSPECTIONS

The Authority will conduct inspections of clinical trials in a transparent manner in accordance with provisions of regulations, guidelines and standards operations procedures. All trials will be inspected using the same inspection tools.

The Authority will establish a Clinical Trial Registry (CTR) that include authorized, ongoing, suspended, terminated and/or completed which will be publicly accessible. The rights of research participants in terms of privacy and confidentiality must be protected and maintained.

6.0 REGULATORY ACTIONS DURING INSPECTIONS

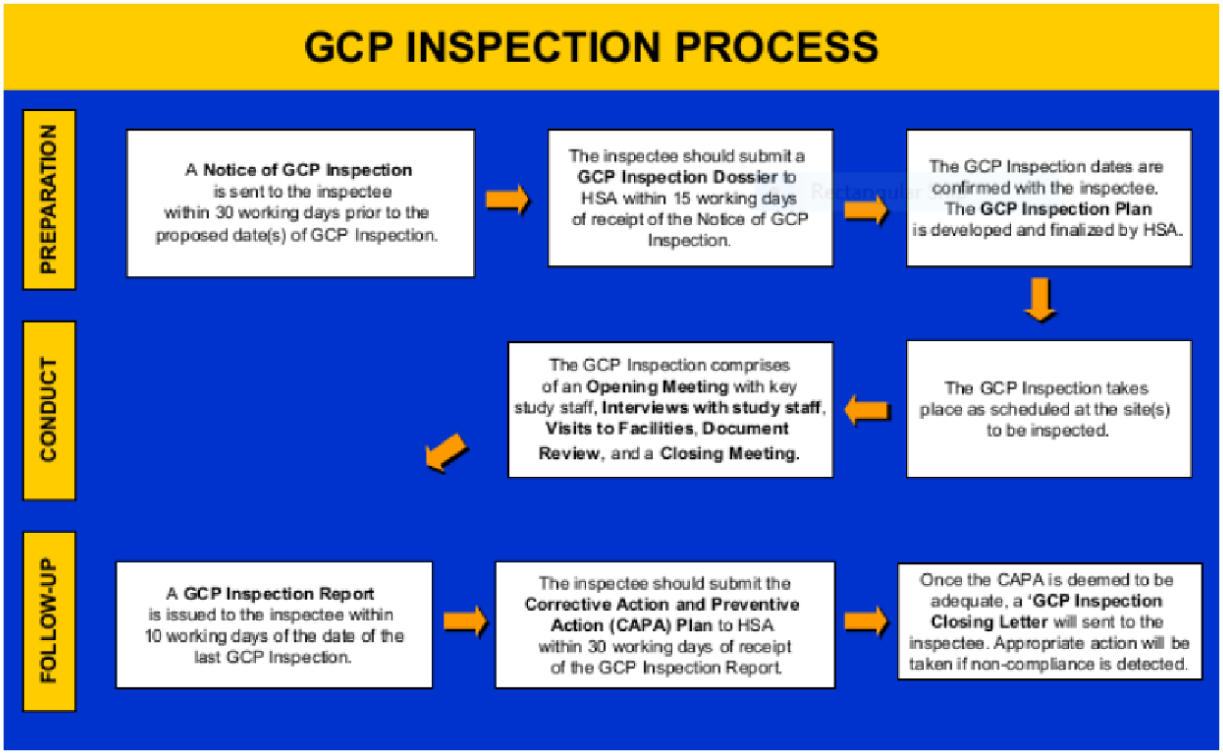
After inspection of clinical trials, the Authority may take the following regulatory action depending on the deficiencies observed:

a) Issuing warning letter
b) Temporary suspend of the trial authorization
c) Permanently terminate the trial
d) File case to the police for court proceedings

7.0 APPEAL ON INSPECTION OUTCOMES

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

APPENDIX I: GCP Inspection Process Flow chart



ENDORSEMENT OF THE GUIDELINES

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

Annex 1: Check List for clinical trials inspection

Date of Inspection	……../……/…….
Name and 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 Participant withdrew from the study?	
How many Participants completed the study	

How many SAEs were reported	

A. FACILITY INSPECTION

CONSULTING AREA	**YES**	**NO**	**NA**
1. Is the consulting area where the PI 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 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 to 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 MANAMAGEMENT (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 qualified?			
6. Are all instruments and equipment's 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 (eg: 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 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?			
INESTIGATOR 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 used the same as the one 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 from 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?			
RESPONSABILITIES OF THE INVESTIGATOR			
1. Were updated CVs 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 to 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 sixth monthly progress reports sent to the IEC/IRB?			
12. Was sixth monthly progress reports 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 medication kept in securely locked, temperature-controlled area accessible only to authorized persons?			
3. Were the records of storage conditions eg: 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 of 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 for clinical research purpose 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 product available?			
RECORD KEEPING AND DATA HANDLING	**YES**	**NO**	**NA**
1. Were records of key trial related procedures eg: CRF, source documents			
2. Was a signature sheet reflecting signatures and initials of all person's persons authorized to make entries and or corrections on CRFs available?			
3. Were corrections to the CRF/e CRF 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, 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**

Annex 2: List of Clinical Trial inspection findings

Annex 3: Clinical Trial Inspection Memorandum Form

Annex 4: Clinical Trial inspection Report template