



Zambia Medicines Regulatory Authority

**GUIDELINES FOR GOOD CLINICAL PRACTICE IN CLINICAL TRIALS OF
MEDICINES AND ALLIED SUBSTANCES IN ZAMBIA**

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Table of Contents

i.	Abbreviations.....	3
ii.	Definitions	4
1.0	Introduction.....	18
2.0	Principles of ICH GCP - E6 (R3)	21
3.0	Responsibilities	21
3.1	Research Ethics Committee (REC) or Institutional Review Board (IRB) or Independent Ethics Committee (IEC)	21
3.2	Investigator	21
3.3	Sponsor.....	26
3.4	The Authority	30
4.0	Good Clinical Practice Inspections	32
5.0	Details of An Inspection By The Zambia Medicines Regulatory Authority	34
5.1	Selection of Clinical Trials For Inspection	34
5.2	What Does an Inspection Involve?.....	34
5.3	The Inspection	35
5.4	Trial Procedures	37
5.5	Trial Investigational Product (IP).....	39
5.6	Laboratory	40
5.7	Computer Electronic Data Systems.....	41
5.8	Exit Meeting / Inspection Report	42
6.0	Grading of Findings	44
7.0	References	46



i. Abbreviations

ADR	Adverse Drug Reaction (Adverse Device Reaction)
AE	Adverse Event
CoA	Certificate of Analysis
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Application
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
MA	Marketing Authorisation
NHRA	National Health Research Authority
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Manual
ZAMRA	Zambia Medicines Regulatory Authority

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 4 of 47
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ii. Definitions

The definitions below apply specifically to the terms used in this guide:

“Adult” A person who is eighteen (18) years of age or above.

“Adverse Drug Reaction (ADR) or Adverse Device Reaction (ADR)”

A response to a medical product which is noxious and unintended including lack of efficacy and which occurs at any dosage and can arise from:

- the use of product within the terms of the marketing authorisation
- the use of product outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

“Adverse Event (AE)” Adverse event is any untoward medical occurrence in a patient or clinical trial participant administered a medical product that may present during treatment with a medical product but which does not necessarily have a causal relationship with the use of the medical product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an Investigational Product, whether or not related to the Investigational Product (1).

“Adverse Events of Special Interest” An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or programme, for which ongoing monitoring and rapid communication by the Investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted (Based on CIOMS VII).

“Allied substances” include acaricides, cosmetics, disinfectants, food supplements, feed additives and supplements, medical and surgical sundries, medical devices and condoms (2).



“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 (1).

“Approval(s)” The affirmative decision in writing by the by The Authority or Institutional Review Board/Independent Ethics Committee that the clinical trial application has been reviewed and the clinical trial may be conducted within the constraints set forth by an Ethics Review Body, Good Clinical Practice (GCP), and the applicable regulatory requirements (1).

“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, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (1).

“Auditor” A person who carries out an audit.

“Audit Certificate” A declaration of confirmation by the auditor that an audit has taken place (1).

“Audit Report” A written evaluation by the sponsor's auditor of the results of the audit (1).



“Audit Trail” Documentation that allows reconstruction of the course of clinical trial processes (1).

“Authority” means the Zambia Medicines Regulatory Authority

“Auxiliary product(s)” include background therapy, rescue medication, challenge agents, and/or medical products to assess endpoints

“Blinding/Masking” A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware; and double-blinding usually refers to the participant(s), Investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s) (1).

“Case Report Form” A printed, digital or electronic document designed to record all of the required information stated in the protocol. There should be assurance of accurate input and presentation and it should allow verification.

“Certificate of Analysis (COA)” An authenticated document issued by an appropriate Authority that certifies the quality and purity of pharmaceuticals, animal and plant products.

“Challenge agent/organism/product” An agent administered to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.

“Child” A person who is below the age of eighteen (18) years, whether a marital or non-marital child (3).

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



“Clinical Trial” (CT) A research study in which one or more human participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIH) (4).

“Comparator (Product)” An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

“Compliance (in relation to trials)” Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

“Confidentiality” Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a participant's identity.

“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.

“Contract Research Organisation (CRO)” A scientific body (commercial or academic) contracted by a Sponsor to perform some of the Sponsor's trial-related duties and functions.

“Coordinating Committee” A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

“Coordinating Investigator” An Investigator assigned the responsibility for the coordination of Investigators at different centres participating in a multicentre trial.

“Data and Safety Monitoring Board (DSMB) or Independent Data-Monitoring Committee (IDMC) or Monitoring Committee or Data Monitoring Committee” An independent data-monitoring committee 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.

“Date of Commencement” For the purpose of the Clinical Trial Certificate and Quarterly Progress Report Form, this is defined as the date when the clinical trial starts to enroll participants.

“Direct Access” Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of participants' identities and sponsor's proprietary information (1).

“Drug/Medicine” means:

- Human medicine, veterinary medicine, medicinal product, herbal medicine or any substance or mixture of substances for human or veterinary use intended to be used or manufactured for use for its therapeutic efficacy or for its pharmacological purpose in the diagnosis, treatment, alleviation, modification or prevention of disease or abnormal physical or mental state or the symptoms of disease in a person or animal;
- A substance or mixture of substances prepared, sold or represented for use in:
 - Restoring, correcting or modifying organic functions in man, and
 - The diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it, in man, or
- Nutritional supplements

“Epidemic” The occurrence in a community or a region of cases of an illness, specific health related behavior or other health-related events clearly in excess of normal expectancy.

“Essential Documents” Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see **Appendix VI** of the Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia).



“Fast-track” is a process designed to facilitate the expedited review of clinical trial applications for the conduct of clinical trials during emergencies or on request of the applicant.

“Food/Dietary or Nutritional Supplement” Concentrated sources of nutrients or other substances produced in a pharmaceutical dosage form such as tablets, gelatine capsules (soft or hard), sachets, syrups and powders. Dietary components include herbs, vitamins and minerals (with concentration less than the recommended daily allowance), natural oils, royal jelly, pollen and bee propolis. All these ingredients can be included in dietary supplements on the condition that their sole function is supplementation and improvement of body function.

“Good Clinical Practice (GCP)” A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected (1).

“Good Clinical Practice (GCP) Inspection” The act by ZAMRA of conducting an official review of documents, facilities, records and any other resources that are deemed to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organisations (CRO’s) facilities, or at other establishments deemed appropriate by the ZAMRA.

“Good Manufacturing Practice (GMP)” a system for ensuring that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorisation.

“Herbal Medicinal Product” A preparation with therapeutic or any other human health benefits which contains raw or processed ingredients from one or more plants or materials of organic or animal origin.



“Impartial witness” A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant’s legally acceptable representative cannot read, and who reads the Informed Consent Form and any other written information supplied to the participant (1).

“Independent Ethics Committee (IEC)” An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants (1).

“Infectious human challenge trial” A trial that involve the deliberate exposure of human volunteers to infectious agents. Trial participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner (5).

“Informed Consent” (IC) A process by which a 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated Informed Consent Form (1).

“Institution (medical)” Any public or private entity or agency or medical or dental facility where clinical trials are conducted (1).

“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

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 11 of 47
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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 the trial participants (1).

“Interim Clinical Trial/Study Report” A report of intermediate results and their evaluation based on analyses performed during the course of a trial (1).

“Investigational Product” A product being tested or used as a reference in a Clinical Trial including a product with a Marketing Authorisation.

“Investigator’s Brochure” A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants (1).

“Investigator” A person, regardless of title or position, who is responsible for the design, conduct, or reporting of a clinical trial.

“Joint review” This process involves a joint assessment of the application by the Authority with the relevant IRBs and other receiving national drug regulatory agencies.

“Legally acceptable representative” An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant to the participant’s participation in the clinical trial (1).

“Lot Release Certificate (LRC)” An official document that authorises the manufacturer to release a specific lot of a product.

“Materials Transfer Agreement (MTA)” An MTA is a written contract a written contract between the provider and recipient of research material as prescribed under section fifty-three of the National Health Research Act (6).

“Medical Device” An instrument, apparatus, implement, a medical equipment, machine, contrivance, implant, in vitro reagent or any other similar or related article, including a component, part or an accessory which is:

- recognised in the official national formulary or pharmacopoeia or a supplement to them, or
- intended for use in the diagnosis of a disease or any other condition, or in the cure, mitigation, treatment or prevention of disease in humans and animals, or
- intended to affect the structure or a function of the body of the human being or other animal and which does not achieve any of its principal intended purposes through chemical action within the body of the human being or any other animal and which is not dependent on being metabolized for the achievement of any of its principal intended purposes (6).

“Monitor” A person appointed by the Sponsor or CRO to oversee the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the Protocol, SOPs, GCP and the applicable regulatory requirements.

“Monitoring” The act of overseeing the progress of a Clinical Trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (1).

“Monitoring Report” A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs (1).

“Multicentre Trial” A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one Investigator (1).

“Pandemic” An emergency occurring worldwide or over a wide area crossing international boundaries and affecting a large number of people.



“Participant Identification Number” A unique identifier assigned by the Investigator to each trial participant to protect the participant's identity and used in lieu of the participant's name when the Investigator reports adverse events and/or other trial related data.

“Participant/Trial Participant” An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

“Pharmacy” means a drugstore, druggist, chemist or any business or premises registered as such under section sixteen of the Medicines and Allied Substances Act No. 3 of 2013 (2).

“Placebo” An inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure (6).

“Principal Investigator” A person responsible for the conduct of the clinical trial at the clinical trial site(s), who is entitled to provide health care under the laws of the Country where that clinical trial site(s) is/are located.

An individual designated by the applicant organisation to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The applicant organisation may designate multiple individuals as Principal Investigators (PIs) who share responsibility for leading and directing the project, intellectually and logistically. When multiple PIs are named, each is responsible and accountable to the applicant organisation, or as appropriate, to a collaborating organisation for the proper conduct of the project or program including the submission of all required reports (6).

“Protocol” A document that describes the objective(s), design, methodology, statistical considerations and the organisation 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 (1).

“Protocol Amendment” A written description of a change(s) to or formal clarification of a protocol (1).



“Protocol Deviations” A change, divergence or departure from the study design or procedures defined in the approved protocol.

“Protocol Violations” means an accidental or unintentional change to, or non-compliance with the approved procedures (eg, the protocol, the informed consent document, recruitment process or study materials) outside the approved protocol. Protocol violations generally increase the risk and/or decrease the benefits; affects the participant’s right, safety or welfare and/or the integrity of the research data.

“Public Health Emergency” An outbreak of a disease with high mortality and which involves significant numbers of individuals and which may have a danger of international transmission.

“Quality Assurance (QA)” All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (1).

“Quality Control (QC)” The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (1).

“Randomization” The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias (1).

“Register” means as per the Medicines and Allied Substances Act No. 3 of 2013 (2).

“Registered Product or a Product with Marketing Authorisation” means the authorisation granted, under section thirty-nine of the Medicines and Allied Substances Act, for the placement of a medicine or allied substance on the market (2).



“Regulatory Authorities” Bodies having the power to regulate. The expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities (1).

“Reliance” implies that the work done (e.g inspection of a site or assessment of protocol) is shared by the trusted authority while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities

“Research Institution” Any public or private entity, agency, medical or dental facility which conducts Clinical Trials (6).

“Serious Adverse Event (SAE)” means any untoward medical occurrence during a clinical trial that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect (1).

“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) (1).

“Source Documents” Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial) (1).

“Sponsor” An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a trial. This excludes an individual company, institution



or organisation which has been requested to provide resources for a trial and does not benefit in any way from the results of the trial (6).

“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 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 (1).

“Standard Operating Procedures (SOPs)” Detailed, written instructions to achieve uniformity of the performance of a specific function (1).

“Sub-Investigator” Any individual member of the clinical trial team designated and supervised by the Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

“Study Pharmacist” A registered pharmacist appointed by the Sponsor/Principal Investigator to ensure the proper management of pharmaceutical investigational products to be used in the study.

“The Authority” means Zambia Medicines Regulatory Authority.

“Trial Site” The location(s) where trial-related activities are conducted (1).

“Unexpected Adverse Drug Reaction” An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (1).



“Vaccine” A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

“Validation of Computerized Systems” A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results (1).

“Vulnerable population” Defined by race/ethnicity, socio-economic status, geography, gender, age, disability status, risk status related to sexual orientation, and primary language, and among other populations identified as at-risk for health disparities (6).

“Well-being (of the trial participants)” The physical and mental integrity of the participants participating in a clinical trial (1).

“Well-Resourced Regulatory Authority” The national drug regulatory authorities which are members, or observers or associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1).

“WHO listed level Three or Four Authorities” implies the competence level of a national medicines regulatory agency based on the WHO global benchmarking tool.



1.0 INTRODUCTION

The Zambia Medicines Regulatory Authority (ZAMRA), hereinafter referred to as the Authority, regulates medicines and allied substances in accordance with the provisions of the Medicines and Allied Substances Act No. 3 of 2013, hereinafter referred to as “the Act”, and the relevant Regulations made thereunder.

This guideline for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia is issued by the Authority pursuant to Part VI, Sections 49-53 and Part IX, Section 68 of the Act and provides Investigators conducting Clinical Trials in Zambia with clear standards of Good Clinical Practice. The Guideline seeks to ensure that Clinical Trials conducted in Zambia are designed and conducted according to sound scientific and ethical standards within the framework of Good Clinical Practice. Compliance with these standards provides the public with assurance that the rights, safety and wellbeing of trial participants are protected and that clinical trial data are credible. The Authority may from time to time amend any part of this guideline.

This guideline is partly derived from the International Conference on Harmonization Good Clinical Practice (ICH GCP) and from the International Ethical Guidelines for Biomedical Research involving human participants prepared by the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO 2002).

Good Clinical Practice (GCP) is a system of shared responsibilities between clinical Investigators, industry/sponsors/monitors, institution/ethics committees, and government regulators. The Guideline is therefore addressed to Investigators, pharmaceutical companies, manufacturers and other sponsors of research, drug regulatory authorities, the general public, and all those who have an interest in clinical trial research in Zambia.

This Guideline will support the regulatory requirements of the Zambia Medicines Regulatory Authority as stipulated in part VI of the Medicines and Allied Substances Act No. 3 of 2013. It is therefore critical that research ethics committees, researchers, Principal Investigators of trials and

sponsors use this guideline to ensure a standardised and ethical approach to clinical trials conducted in Zambia.

This guideline is also applicable to academic and clinical contract research organisations and is intended to be applied during all stages of drug development including pre- and post-product registration and marketing, and is also applicable, in whole or in part to biomedical research in general. It also provides a resource for editors to determine the acceptability of reported research for publication and specifically, on any study that could influence the use or the terms of registration of a pharmaceutical product.

Objective

This guideline has the objective of providing researchers and other interested parties with clearly articulated standards of GCP in locally conducted research that address the local realities and contexts. This is to ensure that clinical trials involving human participants in Zambia are designed and conducted according to local requirements as well as according to the sound scientific and ethical standards within the accepted framework for good clinical practice.

Scope

This Guideline is addressed to Investigators, the pharmaceutical industry, Clinical Research Organisations and Sponsors of clinical trials, whether for academic purposes or for generation of data intended for inclusion in the regulatory submissions for medicinal products. This Guideline is intended to be applied during all clinical stages of product development prior to and after marketing authorisation. This guideline is also applicable to post-authorisation studies of medicines and allied substances in observational or safety monitoring studies. This guideline applies to clinical trials of medicines and allied substances for human use.

All role players involved with clinical trials should also be familiar with other national and international guidelines, including but not limited to the following current versions or their successors:

- Declaration of Helsinki (2013)

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 20 of 47
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- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (ICH E6)
- ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11)
- Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research involving Human Subjects (2016)
- CIOMS with WHO International Ethical Guidelines for Epidemiological Studies (2009)
- Clinical Trial Compensation Guidelines, Association of British of Pharmaceutical Industry (ABPI) Guidelines (2014)
- European Union requirements at http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
- World Health Organisation WHO Technical Report Series, No. 850 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995)
- World Health Organisation Handbook for Good Clinical Research Practice (GCP) (2005)
- World Health Organisation Good Clinical Laboratory Practice (GCLP) (2009)

In the event of an interpretation conflict between this guideline (Zambia GCP, version 1.0) and an international guideline, Zambia Guidelines take precedence.

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 21 of 47
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2.0 PRINCIPLES OF ICH GCP - E6 (R3)

Refer to ICH E6 (R3) and its subsequent updates

3.0 RESPONSIBILITIES

3.1 Research Ethics Committee (REC) or Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

The Research Ethics Committee should conform to the requirements of the National Health Research Authority and National Health Research and ICH E6 (R3) and its subsequent updates.

3.2 Investigator

The Investigator shall meet the following requirements:

- 3.2.1 The Investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through an up-to-date Curriculum Vitae. The Investigator's qualifications should be in accordance with Section 2.12 of Authority's Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia.
- 3.2.2 The Principal Investigator (PI) must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in the country and who is responsible for the conduct of the clinical trial at a trial site. A Principal Investigator must have had previous experience as a Principal Investigator or a co-Investigator in at least two Clinical Trials in the relevant professional area.
- 3.2.3 The Investigator should be thoroughly familiar with the characteristics and appropriate use of the Investigational Product as described in the protocol, in the



current Investigator's Brochure, in the product information sheet and in other information sources.

- 3.2.4 Have a clear understanding and willingness to obey the ethical and legal requirements of the trial.
- 3.2.5 To permit monitoring and auditing of the trial and inspection by the Authority or appointed representatives.
- 3.2.6 The Principal Investigator should maintain a list (delegation log) of appropriately qualified persons to whom he/she has delegated clinical trial-related duties.
- 3.2.7 The Principal Investigator shall ensure that all members of the study team have evidence of GCP training within the past 3 years. GCP certificates shall be required for all key members of the study team.
- 3.2.8 The Investigator should have a valid practicing license from a relevant professional body and be registered with the National Health Research Authority, as applicable.
- 3.2.9 All Investigators in a clinical trial as well as the clinical trial monitor must have had formal training in Good Clinical Practice (GCP) within the last three years.
- 3.2.10 Upon signing the application, the Principal Investigator accepts the responsibility that all applicable regulations and requirements will be adhered to. Furthermore, the Principal Investigator is responsible for ensuring that the trial is based on and implemented according to well-founded ethical and scientific principles, as expressed in the Declaration of Helsinki and its current revisions, as well as in local and international GCP guidelines.
- 3.2.11 Adequate Resources



- 3.2.11.1 The Principal Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 3.2.11.2 The Principal Investigator should have an adequate number of qualified staff and adequate facilities for the duration of the trial to properly and safely conduct the clinical trial.
- 3.2.11.3 The Principal Investigator should ensure that all persons assisting with the clinical trial are adequately informed about the Protocol, Investigational Product and their clinical trial-related duties and functions.

3.2.12 Medical Care of Trial Participants

- 3.2.12.1 A qualified medical practitioner should be responsible for all clinical trial-related medical decisions. The qualified medical practitioner should also be licensed with the relevant professional body in Zambia. The medical care given to, and medical decisions made on behalf of the participants must always be the responsibility of a qualified medical practitioner, or when appropriate, a qualified dentist registered with the relevant professional body in Zambia.
- 3.2.12.2 During and following a participant's participation in a trial, the Investigator should ensure adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values related to the clinical trial. The participant should be informed when medical care is needed for intercurrent illness for which the Investigator becomes aware.



3.2.13 Other Investigator Responsibilities

- 3.2.13.1 Before initiating a clinical trial, the Principal Investigator should have written approval from the Authority and other relevant bodies.
- 3.2.13.2 The Principal Investigator should conduct the clinical trial according to the approved protocol.
- 3.2.13.3 The Principal Investigator shall not implement any deviation from or changes to the Protocol and Informed Consent Form without prior review and approval of the Authority except when the changes involve only logistical or administrative aspects of the trial, e.g. monitor or telephone number changes, or are based on issues relating to the immediate safety of participants already recruited into the trial.
- 3.2.13.4 The Principal Investigator shall have in place Standard Operating Procedures (SOPs) for Investigational Products (IP), including, the following:
- i. The IP(s) should be kept by a pharmacist who maintains records of the delivery process and ensures that the product is processed and stored correctly.
 - ii. The pharmacist should maintain an inventory of the IP at the site, those used by each participant, and those returned to the sponsor or alternative disposition of unused product(s).
 - iii. The Investigational Product(s) should only be used on the consented participants participating in the trial.



- iv. The Principal Investigator should ensure that the IP are used only in accordance with the approved protocol.
- v. The Principal Investigator should ensure that if there is blinding, it is maintained, but there should be criteria or procedure for breaking the code.
- vi. The Principal Investigator or a person designated by the PI should explain the correct use of the IP to each participant and should check at appropriate intervals during the clinical trial that each participant is following the instructions. In the case where the IP is administered to the participant, the proper administration should be ensured.

- 3.2.13.5 The Principal Investigator shall ensure that the participants have signed and dated the consent form or given their consent in an acceptable form before participating in the trial.
- 3.2.13.6 The Principal Investigator shall guarantee the confidentiality of the research data, the clinical trial participants' details, and information provided by the Sponsor.
- 3.2.13.7 The Principal Investigator shall ensure that all data is accurately collected and recorded.
- 3.2.13.8 The Principal Investigator shall ensure that all serious adverse events are reported promptly to the Authority within timelines specified in the Authority's Clinical Trial guidelines. The PI shall also ensure proper protection procedures or treatments are administered to clinical trial participants with serious adverse events.



- 3.2.13.9 The Principal Investigator shall submit all relevant clinical trial documentation to the Authority in a timely manner for validation, auditing and inspection.

3.3 Sponsor

- 3.3.1 The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and regulatory requirements.
- 3.3.2 The Sponsor is responsible for selecting Investigators according to the availability of adequate clinical trial environment facilities and resources. In addition, the Sponsor shall ensure that the Investigator has sufficient training, qualifications and capability.
- 3.3.3 The Sponsor shall agree with Investigator(s) on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical trial report.
- 3.3.4 Before the initiation of the clinical trial, the agreement between the Sponsor and Investigators should be in writing as part of the protocol submitted for Authority's approval or in a separate agreement. The Sponsor, in a written document, may agree to transfer all related activities of the clinical trial to designated research institutions. However, the ultimate responsibility for the trial lies with the Sponsor.
- 3.3.5 The Sponsor shall provide an up-to-date Investigator's Brochure, which includes information about the products with respect to their physical, chemical, pharmacokinetic and pharmacodynamic properties obtained from animals as well as human participants and currently available results of relevant clinical trials.



An updated Investigator's Brochure shall be submitted whenever it is updated.

3.3.6 The Sponsor shall obtain the Investigator's/institutions' agreement on the following items:

3.3.6.1 The conduct of the trial in compliance with Good Clinical Practices and with the approved protocol; and to follow procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol.

3.3.6.2 The Sponsor and all Investigators shall sign and date the protocol of the trial to confirm the agreement.

3.3.7 The Sponsor shall ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration and in the clinical trial population to be studied.

3.3.8 The Sponsor shall ensure that the IP (including active comparator(s) and placebo) are manufactured in accordance with Good Manufacturing Practices and are adequately packed and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with the regulatory requirements. For IPs without Marketing Authorisation, the product dossiers shall be submitted.

3.3.9 The Sponsor shall determine for the IP, acceptable storage temperature and conditions, storage times, reconstitution fluids and procedures, and devices for product infusion if any.

3.3.10 In blinded trials, the coding system for the IP shall include a mechanism that permits rapid identification of the products in case of a medical emergency but does not permit undetectable breaks of the blinding.



- 3.3.11 If formulation changes are made to the IP or comparator products during the clinical development, the results of the pharmaceutical and pharmacokinetic profile of the product shall be made available to the Authority before the use of the reformulated IP in clinical trials.
- 3.3.12 The Sponsor shall appoint qualified and suitably trained individuals to monitor the trial.
- 3.3.13 The Sponsor should provide insurance cover for all clinical trial participants. The Sponsor's policies and procedures should address the costs of treatment of trial participants in the event of clinical trial-related injuries.
- 3.3.14 The financial aspects of the trial should be documented in an agreement between the Sponsor and the Investigator/institution.
- 3.3.15 The Sponsor should report to the Authority and all relevant institutions all adverse events occurring during the clinical trial. The Sponsor should expedite reporting of all serious adverse events to the Ethics Committee and the Authority. The Sponsor and the Investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial participants. *(Refer to **Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia**).*
- 3.3.16 When a trial is prematurely terminated or suspended by the Sponsor/Investigators, the Authority and the Ethics Committee should be informed of the decision to terminate/suspend the trial and the reasons thereof by the Sponsor/Investigators. *(Refer to **Guidelines for Authorisation of Clinical Trials for further details**).*
- 3.3.17 When the trial is prematurely terminated, the Sponsor should ensure the PI submits a report to the Authority.



3.3.18 When the trial is completed, the Sponsor should ensure the PI submits a preliminary report to the Authority. *(Refer to Guidelines for Authorisation of Clinical Trials for further details on timelines)*

3.3.19 The Sponsor should strengthen local capacity for ethical, scientific review, biomedical research and provide healthcare services as described in sections 20, 21 of the International Ethical Guidelines for Biomedical Research involving Human Participants (CIOMS 2002).

3.3.20 Sponsors and Investigators have an ethical obligation to ensure that biomedical research projects contribute effectively to national or local capacity building. Capacity building may include, but is not limited to, the following activities:

3.3.20.1 Foster development of technologies appropriate to health-care and biomedical research

3.3.20.2 Training of research and health-care staff

3.3.20.3 Educating and engaging the community from which research participants will be drawn in clinical trial-related topics

3.3.21 The Sponsors are ethically obliged to ensure the availability of:

3.3.21.1 health-care services that are essential to the safe conduct of the research;

3.3.21.2 treatment of participants who suffer injury as a consequence of research intervention; and

3.3.21.3 services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.



3.3.22 The Sponsor shall appoint a Monitor to oversee the progress of a clinical trial and to ensure that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirements.

3.3.23 The monitor must be qualified by education, training and experience. The monitor must have excellent knowledge in local regulatory requirements. The monitor must have evidence of Good Clinical Practice training within the last 3 years.

3.4 The Authority

3.4.1 The Authority shall approve a clinical trial by issuing a Clinical Trial Certificate in a prescribed format for the initiation and conduct of clinical trials in Zambia. The approval process shall involve establishing adequate procedures and/or requirement for review of the clinical trial application. The Authority may require protocol revisions whenever it deems necessary.

3.4.2 The Authority may amend a Clinical Trial Certificate issued if adequate justification for the amendment is given by an applicant.

3.4.3 A Clinical Trial Certificate issued shall be revoked if conditions for which the certificate was issued are violated.

3.4.4 The Authority shall order the Principal Investigator to stop or suspend the trial immediately if at any stage during the conduct of a clinical trial, the Authority is satisfied that it is in the public interest to do so.

3.4.5 The Authority shall constitute a Technical Committee comprising of Experts in relevant professional fields to provide expert opinion on matters related to Clinical Trials, including Clinical Trial authorisation. The Authority shall serve as Secretariat to the Technical Committee.

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 31 of 47
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3.4.6 The Authority shall monitor a clinical trial from the beginning to the end to ensure adequate protection of the general public against the risk or adverse events from authorised clinical trials. This is to satisfy itself that the specific and general conditions to which the clinical trial was authorised are being strictly adhered to by the Investigator(s) and that the clinical trial will achieve its objectives.

3.4.7 The Authority shall conduct on-site inspections to ensure:

3.4.7.1 the safety of clinical trial participants,

3.4.7.2 the quality and reliability of data obtained in a trial, and

3.4.7.3 the facilities used continue to be acceptable throughout the clinical investigation.

3.4.8 The Authority shall assess Investigators' compliance to regulatory requirements to ascertain the competence of the Investigator to conduct clinical trials in Zambia.

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 32 of 47
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4.0 GOOD CLINICAL PRACTICE INSPECTIONS

- 4.1 The Authority shall inspect any clinical trial for which authorisation has been given, as and when necessary.
- 4.2 Periodic Inspections of the clinical trial sites shall be conducted to ensure compliance with protocol, SOPs, guidelines, Good Practices (GXP), ethics and applicable regulatory requirements.
- 4.3 The inspections may be carried out routinely and/or for specific reasons and shall be either announced or unannounced.
- 4.4 An inspection would consist of a comparison of the procedures and practices of the Principal Investigator with the commitments set out in the protocol and reports submitted to the Authority by the Investigator or the sponsor.
- 4.5 During the inspection, the Authority shall assure itself that:
 - 4.5.1 The facilities used by the Investigator continue to be acceptable for the purposes of the study.
 - 4.5.2 The approved study protocol for the clinical trial is being followed.
 - 4.5.3 Any changes to the protocol have been approved by the respective Ethics Committees and the Authority.
 - 4.5.4 Accurate, complete and current records are being maintained.
 - 4.5.5 Serious Adverse Events (SAEs) are reported to the sponsor and to the Authority and the Ethics committee within the stipulated time as specified in the Guidelines



for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia and other respective guidelines.

- 4.5.6 The Investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.
- 4.6 To facilitate the above, the Authority may require the submission of specific data listings before or during the conduct of an inspection.
- 4.7 During an inspection, inspectors:
- 4.7.1 Should be given easy access to the clinical trial sites, pharmacies and laboratories at all times
 - 4.7.2 Should have easy access to all patient files and raw data utilised for and generated during the clinical trial. All site data and documents, including participant files, must be available for verification.
- 4.8 All observations and findings shall be verified to ensure the credibility of data and to assure that the conclusions that would be presented are derived correctly from the raw data.
- 4.9 Before an inspection, the Principal Investigator (or the co-Investigator) shall be informed of the impending inspection either in writing, by phone, or electronically.
- 4.10 An unannounced inspection may, however, be conducted if the Authority has reasonable cause to believe that the approved protocol is being violated.



5.0 DETAILS OF AN INSPECTION BY THE ZAMBIA MEDICINES REGULATORY AUTHORITY

5.1 Selection of Clinical Trials for Inspection

Selection of approved clinical trials for inspection shall be based on the benefit-to-risk ratio, considering, but not limited to the underlisted:

5.1.1 The phase of the clinical trial

5.1.2 The nature of the investigational product.

5.1.3 The marketing authorisation status of the investigational product

5.1.4 The population under study

5.1.5 Capacity of clinical trial site

5.1.6 Previous experience of the Authority with sponsor/Principal Investigator with respect to compliance to good practices, protocol and regulatory requirements.

5.2 What does an Inspection Involve?

The inspection may involve:

5.2.1 A comparison of the practices and procedures of the clinical Investigator with the commitments made in the application to conduct a clinical trial;

5.2.2 A comparison of the data submitted to the Authority with the source data; and/or



- 5.2.3 A system inspection of the sponsor, clinical laboratory or CRO generating data for submission to regulatory authorities. This may include inspection of both the clinical facility and analytical facility.

5.3 The Inspection

Details of the various phases of an inspection, including pre-inspection contact; the opening meeting and the actual inspection are outlined below:

5.3.1 Pre-Inspection Contact:

- 5.3.1.1 Where appropriate, appointments for inspection of an investigational site should be made by a telephone call and/or an e-mail. A written confirmation of the inspection date, time and program (if applicable) may be forwarded to the Principal Investigator, the sponsor company or the Contract Research Organisation (CRO).

- 5.3.1.2 The PI should ensure that all the key staff of the trial are present during the inspection. The time span between initial contact and actual inspection shall be as short as possible. Any unjustified delay of the inspection on the part of the clinical Investigator will be investigated.

5.3.2 Opening Meeting:

The purpose of this meeting is for the Inspector(s) to:

- 5.3.2.1 Explain the purpose of the inspection, i.e. Routine or for -cause,
- 5.3.2.2 Outline the scope of the inspection
- 5.3.2.3 Obtain a brief review of the organisation of the site being inspected.

5.3.3 The Purpose of the Inspection:

The overall purpose of the conduct of the inspection should be to establish whether the Investigator has fulfilled his/her GCP responsibilities. This includes the following:

- 5.3.3.1 To ascertain whether the Investigator is thoroughly familiar with the characteristics of the investigational product(s) as described in the Investigator's Brochure.
- 5.3.3.2 To ensure that Investigator has sufficient time to conduct and complete the clinical study,
- 5.3.3.3 To ensure that the Investigator has adequate staff and appropriate facilities (including laboratories) available for the duration of the study, and
- 5.3.3.4 To establish whether the Investigator has studied the protocol and whether the assisting personnel have been adequately informed of their responsibilities.
- 5.3.3.5 To determine if the Authority's and Ethics Committee and other relevant approvals have been obtained with stipulated conditions adhered to.
- 5.3.3.6 To determine in what manner the Investigational Products are handled and stored, and that Investigational Products are dispensed to study participants in accordance with the protocol and that any unused products are disposed of accordingly. Reconciliations of IP(s) must be provided.
- 5.3.3.7 To ensure that the confidentiality of all information about participants is respected (by all persons involved).



- 5.3.3.8 To review essential documents of the clinical trial. Refer to the Guidelines for Authorisation of Clinical Trials of Medicines and Allied Substances in Zambia for more details.
- 5.3.3.9 In addition, the investigator needs to provide retrospective data on the number of participants who would have satisfied the proposed entrance criteria during preceding time periods in order to assure an adequate recruitment rate for the study.
- 5.3.3.10 The Investigator is responsible for clinical care of participants during the study and must ensure that they are linked to appropriate clinical care after the study. Where appropriate, fully functional resuscitation equipment should be immediately available in case of emergency. Clinically significant abnormal laboratory values or clinical observations must be followed up after completion of the study until resolution or linked to appropriate care.

5.4 Trial Procedures

This part identifies the nature of the information that shall be obtained during each inspection to determine if the clinical Investigator is meeting his/her obligation as trialist. This outline provides only the minimal scope of the inspection and the inspector shall extend the inspection as the facts evolve. The inspection conducted shall be sufficient in scope to determine compliance with Good Practices.

Scientific data shall not be evaluated during the inspection, but only to verify documentation and validate data. An inspection may include the following checks:

- 5.4.1 The protocol, including amendments, must be signed by the Investigator.
- 5.4.2 Ethics Committee and regulatory approval documentation.



5.4.3 Validation of signed informed consent documents. Signatures shall be checked against evidence on patient files. It would be determined whether written informed consent was obtained for all participants prior to entry into the study and whether the informed consent process was recorded in the participants' medical records. A copy of the patient information sheet presented may also be obtained.

5.4.4 Participant records shall be verified.

5.4.5 The condition, organisation, completeness and legibility of the Investigator's raw data files may need to be described.

5.4.6 Necessary processes would be put in place to determine whether there is adequate documentation to assure that all enrolled participants did exist and were available for the duration of their stated participation in the study.

5.4.7 The raw data in the clinical Investigator's records would be compared with the completed case report forms.

5.4.8 The following shall also be determined:

5.4.8.1 Whether the number and type of participants entered into the study were confined to the protocol limitations

5.4.8.2 Whether the inclusion and exclusion criteria as specified in the protocol were followed

5.4.8.3

5.4.8.4 Observations, information, and data on the condition of the participants at the time of entering into the trial.

5.4.8.5

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 39 of 47
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5.4.8.6 Observations and data on the condition of the participant throughout participation in the investigation, including results of lab tests, development of unrelated illness and other factors which might alter the effects of the test.

5.4.8.7

5.4.8.8 Records confirming that relevant tests were carried out.

5.4.8.9

5.4.8.10 Whether clinical laboratory testing (including ECGs, X-rays and other special investigations), as noted in the case reports, cannot be evaluated by the presence of completed laboratory reports in the source documents.

5.4.8.11

5.4.8.12 The occurrence of adverse reactions would be determined. The reporting of these events to the Authority and the Ethics Committee shall be documented.

5.4.8.13

5.4.8.14 All persons obtaining raw data or involved in the collection or analysis of such data would be identified.

5.5 Trial Investigational Product (IP)

With regard to trial IP the following are considered as important in an inspection:

5.5.1 Determination of accounting procedures for the test and comparator IPs.

5.5.2 Dates and quantity of IPs dispensed as well as the recipients must be available as well as corroboration by raw data notations.

5.5.3 The blinding procedures , if applicable, must be validated to ensure protection of the study from bias.

5.5.4 It shall be determined whether distribution of the IP was limited to those persons under the Investigator's direct supervision.

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 40 of 47
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5.5.5 The storage area may be inspected.

5.5.6 It would be determined whether the IP is a controlled substance and whether it is securely locked

5.5.7 Access to the controlled substance must be restricted to the Investigator and the responsible pharmacist.

5.6 Laboratory

5.6.1 The Authority, during an inspection, would determine the systems and procedures that are followed within an organisation that is analysing samples from clinical trials in compliance with the requirements of Good Practices.

5.6.2 Inspections of a laboratory being used to analyse samples from a clinical trial shall be in accordance with provisions outlined in the Good Clinical Laboratory Practice Guidelines published by WHO/TDR.

5.6.3 Transfer of Biological Samples

The Inspector shall review records confirming that approval was obtained from NHRA before any biological samples were transferred from/to a clinical trial site.

5.6.4 Equipment/apparatus

5.6.4.1 The Inspector shall ascertain that all equipment/apparatus, whether used to generate data (e.g. analytical equipment, or balances), or to maintain standard conditions (e.g. refrigerators or air conditioning equipment), is adequate for the task and operating within its specifications.



5.6.4.2 The Inspector shall check that records have been kept of operation, maintenance, verification, calibration and validation of measuring equipment and apparatus (including computerised systems)

5.6.4.3 Calibrations should be traceable to national or international standards of measurement as appropriate.

5.7 Computer Electronic Data Systems

5.7.1 If electronic data systems are involved in gathering data, storing data, or transmitting data to the sponsor, these would be identified and their capabilities established. Data should be collected, processed, and stored in compliance with the Electronic Communications and Transactions Act No 21 of 2009.

5.7.2 The Inspector will verify that electronic data systems are Attributable, Legible, Contemporaneous, Original, and Accurate (ALCOA+¹) for the proper verification of source documents to ensure data integrity, validity, and participant safety among other aspects. Thus, the following aspects will be considered:

5.7.2.1 The source of data entered into the computer

5.7.2.2 The qualification of the personnel to enter data

5.7.2.3 Time/stage when the entry is done

5.7.2.4 Provision for access to data and computer

¹ ALCOA principles have been updated to ALCOA+. The original principles remain with four additions: Complete, Consistent, Enduring and Available



5.7.2.5 Security codes

5.7.2.6 Procedure and persons responsible for changes and audit trail.

5.7.2.7 Procedure for submission of data to sponsor? (hard disk, fax, modern network, mail, messenger)

5.7.2.8 Procedures for corrections (errors, omissions, etc.) in the data received and documentation

Note: Electronic system must be validated in accordance with Code of Federal Regulations (21 CFR Part 11)

5.8 Exit Meeting / Inspection Report

5.8.1 At the post inspection meeting the inspectors would convey the findings of the inspection to the Investigator and other key members of the study team. The inspection reports shall eventually reflect discussions had at the exit meeting.

5.8.2 The matters discussed at this meeting shall be in line with the report written by the inspectors.

5.8.3 When significant violations of GCP are observed, reports shall contain sufficient narrative and accompanying documentation to support the findings. When it is apparent that the study has been conducted in substantial compliance with the guidelines, an abbreviated report may contain the following:

5.8.3.1 The comparison of raw data recorded in the case report forms to that of the source data, including the number of records compared and what was compared (patient charts, hospital records, lab slips and etc.)

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 43 of 47
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- 5.8.3.2 A statement about the trial IP accountability records
- 5.8.3.3 A statement about protocol adherence, which should be characterised and quantified.
- 5.8.3.4 A statement about the obtaining of informed consent from each participant.
- 5.8.3.5 A statement identifying the specific individual responsible for each significant aspect of the study.
- 5.8.3.6 A statement on follow-up of adverse events (including death) if any occurred.
- 5.8.4 If deficiencies were found during the inspection in any of these or in any of the areas it needs to be explained and, where applicable, documentation attached as exhibits.
- 5.8.5 Inspections conducted 'for-cause' would have full reporting. (A for-cause inspection may be the result of prior knowledge or suspicion of alleged violations of the regulatory requirements. A for-cause inspection may concentrate on the data verification on specific areas of the study or may expand the data verification to cover multiple studies. This inspection may also result when a study is of singular importance to the approval of registration of an IP.)



6.0 GRADING OF FINDINGS

Critical	
Definition	Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the participants and/or the quality and integrity of data. Critical observations are considered totally unacceptable.
Possible consequences	Rejection of data and/or legal action required.
Remark	Observation classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.
Major	
Definition	Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the participants and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.
Possible consequences	Data may be rejected and/or legal action required.
Remark	Observations classified as major, may include a pattern of deviations and/or numerous minor observations.
Minor	
Definition	Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the participants and/or the quality and integrity of data.
Possible consequences	Observations classified as minor, indicate the need for improvement of conditions, practices and processes.



Remark	Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.
Comments: Definition	The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 46 of 47
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	Document No.: CT/GUD/002 Guidelines for Good Clinical Practice in Clinical Trials of Medicines and Allied Substances in Zambia	Page 47 of 47
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