GUIDELINES ON GOOD CLINICAL PRACTICE IN THE CONDUCT OF CLINICAL TRIALS INVOLVING HUMAN PARTICIPANTS

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Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional **Guidelines on the Good Clinical Practice in the conduct of Clinical Trials Involving Human Participants";** Doc. No. DPS/GDL/025, Revision No.:0, made this 11th **day of October 2019,** that take effect on **18th October 2019**.

Signature

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Disclaimer

Every effort has been made to ensure that the information in this guideline is accurate, complete, and conforms to the current Good Clinical Practice. However, the publisher, editor, and contributors cannot be held responsible for any errors of omission and/or commission. Readers who detect errors are invited to send corrections and suggestions to National Drug Authority, P.O. Box 23096, Kampala. E-mail: clinicaltrials@nda.or.ug.

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ACRONYMS

AE	Adverse Event
ADR	Adverse Drug Reaction
AVAREF	African Vaccines Regulators Forum
CAG/B	Community Advisory Group/Board
CIOMS	Council for International Organizations of Medical Sciences
CoA	Certificate of Analysis
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract/Clinical Research Organization
CTA	Clinical Trial Application
DSMB	Data Safety and Monitoring Board
DSUR	Development Safety Update Report
ECG	Electrocardiogram
FRECU	Forum for Research Ethics Committee Chairpersons in Uganda
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	Good Pharmacy Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
NDA	National Drug Authority

NDP/A	National Drug Policy and Authority
PI	Principal Investigator
PSUR	Periodic Safety Update Reports
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
STD	Sexually Transmitted Disease
UNCST	Uganda National Council for Science & Technology
UNHRO	Uganda National Health Research Organization
WHO	World Health Organization
WMA	World Medical Association

1.0 INTRODUCTION

The National Drug Authority was established in 1993 by the National Drug Policy and Authority statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap 206 of the laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority (NDA) to ensure the availability, at all times of essential, efficacious and cost-effective drugs to the entire Ugandan population as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.[1] In 2014, the National Drug Policy and Authority (Conduct of Clinical Trials) regulations were published to guide the application, registration and conduct of clinical trials in Uganda.[2]

Uganda provides a unique research environment particularly due to the high burden of disease and a diverse patient population that provides an opportunity to investigate various diseases and population-specific disease traits. The value of carefully constructed clinical trials as the optimum methodology for the testing and evaluation of new treatments and medicines is well recognized internationally as well as within the research community in Uganda.

Although achievement of scientific goals is the main reason for carrying out clinical research, the protection of research participants is paramount and as such, the outcomes of clinical trials are only acceptable when conducted in an ethical manner. It is widely accepted that all research participants are entitled to minimum guarantees that are transnational and non-negotiable.[3] These entitlements can be realized through in country systems and structures that support and promote Good Clinical Practice (GCP). An important component of these systems and structures are national guidelines for good clinical practice.

The conduct of clinical trials in Uganda is currently guided by the National Drug Authority Guidelines for the Conduct of Clinical Trials (2007). The National Drug Authority Good Clinical Practice Guidelines are not aimed at replacing, but to complement the current available guidelines (specifically Part 5 of Section I) in order to streamline and ensure the ethical conduct of clinical trials, the protection of human research participants and the credibility of the data generated in Uganda.

1.1 INTERPRETATION

The definitions given below apply specifically to the terms used in this guideline. They may have a different meaning in other contexts.

[1] The National Drug Policy and Authority Act, Cap 206 (1993).
[2] The National Drug Policy and Authority (Conduct of Clinical Trials) Regulations (2014).
[3] Studdert DM and Brennan T A (1998) Clinical trials in developing countries: scientific and ethical issues. Medical Journal of Australia, 169:545-548

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose shall be considered as adverse drug reactions. The phrase *responses to a medicinal product* means that a causal relationship between a medicinal product and an adverse reaction is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products, an ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (Refer to the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom an investigational medicinal product is administered, including occurrences which are not necessarily caused by or related to that product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (Refer to the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment

A written description of a change(s) to or formal clarification of a clinical trial protocol.

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products that is specified by the National Drug Authority and other national or international regulatory bodies.

Approval (in relation to Institutional Review Boards or IRBs)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution/site within the conditions set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

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 was

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).

Audit Report

A written evaluation of the results of an audit.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). In a single-blind study the participant(s) is unaware that they are the test or experimental or control group, and in a double-blind study the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) are unaware of the treatment assignment(s).

Care-giver

Any person other than a parent or guardian, who factually cares for a child (person below 18 years) and includes:

a) a foster parent;

b) a person who cares for a child with implied or express consent of a parent or guardian of the child;

c) a person who cares for a child while the child is in temporary safe care;

d) the person who is the head of a child and youth care center where a child has been placed;

e) the person who is the head of a shelter; and

f) a child and youth care worker who cares for a child who is without appropriate family care in the community.

Case Report Form (CRF)

A printed, optical, or electronic document designed to record data on each trial participant during the course of the trial as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic 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 objective of ascertaining its safety and/or efficacy.

Clinical trials are generally classified into four Phases i.e. I, II, III and IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, is given below:

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

Phase II: These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate the 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 determining the 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 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 drug 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 real-world conditions of use.

Phase IV: 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 premarketing 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.

Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic product conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (Refer to the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product)

A pharmaceutical or other product (which may be a 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/Agreement

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 Organization (CRO)

A company or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

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.

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 generated (see Appendix C: Essential Documents for the Conduct of a Clinical Trial).

Good Clinical Practice (GCP)

An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. GCP encompasses the design, conduct, performance, monitoring, termination, auditing, recording, analyses,

reporting and documentation of clinical trials/studies and which ensures that the trials/studies are scientifically and ethically sound; the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented; the data is credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Good Manufacturing Practice (GMP)

A system in pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Independent Data-Monitoring Committee (IDMC) (Data Safety and Monitoring Board, Safety Monitoring Committee, Data Monitoring Committee)

An independent 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.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved in the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who after reading the informed consent form and any other written information supplied to the subject witnesses the consent process.

Informed Consent

A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority. (see Appendix B).

Institutional Review Board (IRB)

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 subjects 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 the trial subjects.

Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

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.

Investigational labelling

Labelling developed specifically for products involved in a clinical trial (Refer to the National Drug Policy and Authority {Conduct of Clinical Trials) Regulations 2014 for the prescribed format}

Investigator's Brochure

A compilation of available clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in humans or animals. The data includes chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new safety data are generated, the Investigator's Brochure must be updated and the NDA should be notified in writing.

Investigator/Principal Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and is called the Principal Investigator.

Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

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).

Monitor

A person appointed by, and responsible to the sponsor or Contract Research Organization (CRO) for the monitoring and reporting of the trial and for verification of the data generated.

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.

Multicenter Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore maybe implemented by more than one investigator.

Nonclinical Study

Biomedical studies not performed on human subjects.

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 a change(s) to or formal clarification of a protocol.

Quality Assurance (QA)

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).

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.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities

Bodies with the power to regulate; in the context of clinical trials, these are the competent authorities that review submitted clinical data and conduct inspections of clinical trial sites.

National Drug Authority: The drug regulatory body mandated by the laws of Uganda to authorize the conduct of drug-related clinical trials in Uganda and is responsible for ensuring that all clinical trials of both registered and unregistered medicines comply with the necessary requirements for safety, quality and efficacy. Proof of safety, quality and efficacy must be submitted when applying to the NDA for authorization of a clinical trial to be conducted in Uganda.

Uganda National Council for Science and Technology (UNCST): The national body that has a statutory obligation to oversee and coordinate all research and development in Uganda. This body has overall responsibility to promote, ensure and monitor compliance by research ethics committees in Uganda with relevant legislation, regulations and guidelines. In so doing, the UNCST accredits and audits the performance of research ethics committees.

Uganda National Health Research Organization (UNHRO): Uganda's umbrella organization for health research coordination. Established in 2011 under the UNHRO Act, UNHRO works to coordinate, promote, provide guidance and regulation of health research and development in Uganda.

Research Ethics Committee (REC)

An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable 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 subjects. Research Ethics Committees must be registered and accredited by the Uganda National Council for Science and Technology.

Research Institution

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly/birth defect.

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).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' 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, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, a company, an institution, or an 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 subject. 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.

Standard Operating Procedures (SOPs)

Detailed written instructions to achieve uniformity in the performance of a specific function.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Site investigator

Any individual member of the clinical trial team designated and supervised by the principal 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.

Trial Participant

An individual who participates in a clinical trial, either as a recipient of the investigational/pharmaceutical product(s) or as a control. The individual may be:

a) a healthy person who volunteers to participate in a trial;
b) a person with a condition unrelated to the use of the investigational/pharmaceutical product; or
c) a person (usually a patient) whose condition is relevant to the use of the investigational/pharmaceutical product.

Trial Site

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

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).

Vulnerable participants

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial participants)

The physical and mental integrity of the participant(s) involved in a clinical trial.

1.2 PURPOSE OF THE GUIDELINES

The purpose of these guidelines is to provide clearly articulated standards of GCP in clinical trials conducted in Uganda that are relevant to the local context and to ensure that clinical trials conducted on human participants are designed and conducted according to sound scientific and ethical standards within the framework of GCP. The guidelines adopt the basic principles outlined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Use (ICH) Guidelines for Good Clinical Practice (E6), with some modifications to suit the local requirements. 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.

1.3 THE PRINCIPLES OF GOOD CLINICAL PRACTICE[4]

1.3.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

1.3.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

1.3.3 The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

1.3.4 The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

1.3.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

1.3.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

1.3.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

1.3.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

1.3.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

1.3.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

1.3.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

1.3.12 Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.

[4] International Conference on Harmonization Tripartite Guideline: Guideline for Good Clinical Practice, ICH E6(R2).

1.3.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

1.4 SCOPE OF GUIDELINES

These guidelines focus on the application of GCP principles in the conduct and regulation of drug-related trials on human participants in Uganda. These guidelines have not specifically addressed clinical trials on traditional medicines, non-pharmacological interventions including surgical procedures, medical devices and X-rays. However, these guidelines are such that, in the absence of alternatives, the basic principles outlined in this document may be used to guide any research involving human participants, particularly research involving experimental study designs.
These guidelines have been adapted from the following documents:

1.4.1 ICH Guideline for Good Clinical Practice, ICH E6 (R2) Guideline.
1.4.2 Harmonized Good Clinical Practice Guidelines for AVAREF countries.
1.4.3 World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (Appendix B)
1.4.4 International Ethical Guidelines for Health-related Research Involving Humans, Council for International Organizations of Medical Sciences (CIOMS), 2016
1.4.5 World Health Organization, WHO Technical Report Series, No. 850, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995.
1.4.6 World Health Organization (2000) Operational Guidelines for Ethics Committees That Review Biomedical Research.

In the event that these guidelines differ from any of the above texts, these guidelines will apply.

1.5 GUIDELINES AND LEGISLATION

These guidelines were developed within the framework of:

1.5.1 Section 40 and section 64 of the National Drug Policy and Authority Act, Cap 206.
1.5.2 Regulation 7 (Authorization of clinical trials), regulation 14 (Protection of subjects), regulation 15 (Responsibilities of a sponsor) and regulation 16 (Responsibilities of the principal investigator) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014.

1.6 ROLES AND RESPONSIBILITIES OF VARIOUS PARTIES/BODIES INVOLVED

This section outlines the roles and responsibilities of the various parties involved in clinical trials in Uganda. Specifically, these include:

1.6.1 **The National Drug Authority**

All clinical trials of both registered and non-registered drugs must be authorized by the NDA. The NDA has a statutory obligation to ensure that the drugs available in the country fulfill the necessary requirements for safety, quality and efficacy. For NDA to approve any

clinical trial application, approval from a REC and registration with UNCST are a pre-requisite. NDA reserves the right to offer final approval for drug-related clinical trials. It is acceptable to NDA that parallel submissions are made to the NDA and the UNCST by the applicant however; the final decision by the NDA will be made after ethical clearance of the clinical trial. It is important that queries and amendments required by either body are conveyed, for information, to the other. In the case of an ongoing trial where there are serious breaches of Good Clinical Practice (GCP), the NDA can terminate the trial.

1.6.2 **The Uganda National Council for Science and Technology (UNCST)**

The UNCST was instituted to implement the provisions of the UNCST Act 1990, CAP 209 and its primary goal is to develop and implement ways of incorporating science and technology in the national development process. This body has an overall responsibility to promote, ensure and monitor compliance of research ethics committees in Uganda with relevant legislation, regulations and guidelines. In so doing, the UNCST will accredit and audit the performance of research ethics committees. This body reports directly to the Minister of Science, Technology and Innovation.

1.6.3 **Research Ethics Committees**

The main responsibility of Research Ethics Committees (RECs) in Uganda is to ensure the protection and respect of the rights, safety and wellbeing of participants involved in research and to provide public assurance of that protection by reviewing, approving and providing comments on clinical trial protocols, the suitability of investigator(s), facilities, methods and procedures used to obtain informed consent.

1.6.4 **The Principal Investigator (PI):** The principal investigator is a Ugandan based scientist who has the sole or joint responsibility for the design, conduct, delegation of trial responsibilities, analysis and reporting of the trial. The PI is accountable to the Sponsor and regulatory authorities as required by these Guidelines. The PI should be knowledgeable and have an understanding of the drug, its toxicology and safety. In the case of a multi-center trial there must be a sub investigator appointed by the PI and responsible for the implementation of the approved protocol at each site.

1.6.5 **The Sponsor:**

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

1.6.6 **The Monitor:**

The monitor is appointed by and reports to the sponsor. The monitor is responsible for overseeing the progress of a clinical trial and ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP), Good Pharmacy Practice (GPP), all guidelines and other applicable legislation and regulations.

1.6.7 **The Auditor:**
The auditors are independent individuals appointed by sponsors, local and other regulatory authorities to conduct a systematic and in-depth examination of trial conduct and compliance with the protocol, standard operating procedures (SOPs), GCP, GCLP, GPP and the applicable regulatory requirements. An audit is separate from routine monitoring or quality control functions.

1.6.8 **GCP Inspector:**
The GCP inspector is a qualified employee of a local and/or international regulatory authority whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites/sponsors/CROs/bioequivalence facilities as required/instructed by the regulatory authority. Most inspection visits will be pre-arranged but some will not especially where there is suspected serious breaches of the GCP or malpractice.

1.7 PROCEDURES FOR REVIEW AND APPROVAL OF APPLICATIONS[5]

1.7.1 **Receipt of applications**
An application for regulatory approval must be made to the NDA in the form stipulated in the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014. On receipt of an initial application, NDA will screen the application for completeness. Application for conduct of a clinical trial shall be complete in the first instance if it includes all required documents, appendices, proof of payment of the prescribed fees and one copy of the complete checklist. Applicants will be issued a letter acknowledging receipt and if proof of payment is received, the application will be issued a Clinical Trials Application (CTA) number.

1.7.2 **Supplementary Information and Updates**

Any new information available for the product such as adverse events, changes in formulation or manufacturer for the active ingredients or finished products must be reported to NDA. If changes such as protocol amendments, consent form updates and additional trial sites are made, NDA should be informed in writing.

1.7.3 **Review of Clinical Trial Applications**

Clinical Trial Applications (CTAs) are reviewed once complete on a first-in first-out basis. After the evaluation process, the NDA may issue in writing;

a) Request for additional information or documentation when appropriate
b) A notice of rejection with the reasons for the decision
c) A clinical trial certificate with conditions

[5] National Drug Authority Guidelines for the Conduct of Clinical Trials (2007).

1.7.4 **Approval**

The NDA will consider the clinical trial application and supporting documents, evidence of approval of the REC(s) and any other relevant information. NDA may approve the trial application or may reject the application and specify the reasons for rejection. Approval will be dependent on receipt of approval of the protocol by the local Independent REC in consultations with UNCST.

The Approval for importation of trial related medicines will be dependent on the approval of the conduct of the clinical trial. This decision will be communicated to the applicant in writing. In case of rejection, the applicant may appeal and provide additional information where applicable.

1.7.5 **Termination of a trial:**

If an authorized clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, and should inform the NDA.

In addition, if the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the REC. The investigator should provide the sponsor and the REC a detailed written explanation of the termination or suspension.

If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the REC and provide the REC a detailed written explanation of the termination or suspension.

If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

The National Drug Authority may, by notice, suspend or terminate a clinical trial based on the reasons stated in the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014.

1.7.6 **Final Report by the Investigator**

Upon completion of the trial in Uganda, the Sponsor should inform the NDA in writing within ninety (90) days after completion of the study using the format prescribed in the NDP/A Conduct of Clinical Trials regulations 2014.

2.0 PROTECTION OF STUDY PARTICIPANTS

2.1 GUIDING DOCUMENTS

The welfare and rights of the participants is the responsibility of the principal investigator and the primary goal of the Research Ethics Committee. The principal investigator must comply with the guidance set out in these Guidelines, Uganda National Guidelines for Conducting Research Involving Human Participants (2014), the Declaration of Helsinki (2013), ICH Guidelines for Good Clinical Practice (2016) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

2.2 ETHICAL REVIEW

All medical research involving human participants must undergo an independent ethical review. The REC which undertakes the review must be accredited by the UNCST.[6] In the evaluation of clinical trial protocols or study applications, the REC must ensure that participants are protected in accordance with national and international standards and guidelines.

The REC shall determine that basic ethical considerations are considered as per the Uganda National Guidelines for Conducting Research Involving Human Participants (2014).

2.3 RESEARCH INVOLVING VULNERABLE PERSONS AND GROUPS

2.3.1 Description

According to the Declaration of Helsinki, vulnerable groups and individuals “may have an increased likelihood of being wronged or of incurring additional harm.” This implies that vulnerability involves judgments about the probability and degree of physical, psychological, or social harm, as well as a greater susceptibility to deception or having confidentiality breached.

In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests. This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests.

In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests. This may happen when people are marginalized, stigmatized, or face social exclusion or prejudice that increases the likelihood that others place their interests at risk, whether intentionally or unintentionally.

[6] For more information on accreditation and ethical review refer to UNCST Guidelines for Research Involving Humans as Research Participants

Although research ethics committees can require special protections only for potential participants collectively for a particular project, researchers and others involved in research must take into account factors that render individual participants vulnerable and take appropriate steps to mitigate those factors. This can aid in identifying the special protections needed for persons who may have an increased likelihood of being wronged or of incurring additional harm as participants in research. Different characteristics may also co-exist, making some individuals more vulnerable than others.

2.3.2 Characteristics

Some characteristics can make it reasonable to assume that certain individuals are vulnerable, for example:

Capacity to consent: One widely accepted criterion of vulnerability is limited capacity to consent or decline to consent to research participation. Examples of individuals with this characteristic are;

I. Individuals with psychiatric conditions
II. Individuals in emergency situations
III. Minors: Children and adolescents.

Individuals in hierarchical relationships: The characteristic of vulnerability in this case is the possibility of diminished voluntariness of the consent of potential participants who are in a subordinate relationship. Their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree to participate in the study or by fear of disapproval or retaliation if they refuse. Examples are;

a) Medical and nursing students,
b) Subordinate hospital and laboratory personnel,
c) Workers in settings where research studies are conducted, and
d) Members of the armed forces or police.

Institutionalized persons: Residents of nursing homes, mental institutions, and prisons are often considered vulnerable because in a confined setting they have few options and are denied certain freedoms that non-institutionalized persons enjoy. Some individuals with this characteristic may also have diminished capacity to consent, and therefore require the additional protections for participants who lack decisional capacity. Examples include residents of;

a) Nursing homes
b) Mental institutions
c) Prisons

Women: Although women in general may not be considered vulnerable, specific circumstances in which women could be vulnerable in research include:

a) Studies with female or transsexual sex workers
b) Research on sexual and intimate partner violence

c) Studies with women involved in trafficking
d) Refugees and asylum seekers
e) Studies of abortion in jurisdictions where abortion is illegal
f) Research with women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative.

Pregnant women: Pregnant women may not be considered vulnerable simply because they are pregnant. Specific circumstances, such as risks to the fetus, may require special protection.

Group vulnerability: Despite the importance of avoiding classification of entire groups as inherently vulnerable, circumstances exist that require research ethics committees to pay special attention to research involving certain groups. In some resource-limited countries or communities, examples include;

a) Lack of access to medical care
b) Membership in ethnic and racial minorities
c) Other disadvantaged or marginalized groups

Other potentially vulnerable individuals: Among members of groups that have traditionally been considered vulnerable, the following are frequently mentioned:

a) People receiving welfare benefits or social assistance, the poor people and the unemployed
b) People who perceive participation as the only means of accessing medical care
c) Some ethnic and racial minorities
d) Homeless persons, nomads, refugees or displaced persons
e) People living with disabilities
f) People with incurable or stigmatized conditions or diseases
g) People faced with physical frailty, for example because of age and co-morbidities.
h) Individuals who are politically powerless
i) Members of communities unfamiliar with modern medical concepts.
j) Furthermore, in some contexts vulnerability might be related to gender, sexuality and age.

2.3.3 Special considerations

To the extent that these and other people have one or more of the characteristics discussed above, research ethics committees must review the need for special protection of their rights and welfare, the multiple levels of vulnerability and include such protections when necessary. However, researchers and research ethics committees must avoid making judgments regarding the exclusion of such groups based on stereotypes. One proposed

mechanism that can be used to avoid stereotyping is consultation with relevant stakeholders, where feasible, before, during and after the conduct of the research.

Special protections for these groups can include;[7]

a) Allowing no more than minimal risks for procedures that offer no potential individual/direct benefits for participants
b) Supplementing the participant's agreement by the permission of family members, legal guardians, or other appropriate representatives
c) Requiring that the research be carried out only when it is targeted at conditions that affect these groups.
d) Safeguards can be designed to promote voluntary decision-making, limit the potential for confidentiality breaches, and otherwise work to protect the interests of those at increased risk of harm.
e) Appointment of advocates to the research ethics committee when such proposals for clinical trials on institutionalized individuals are under review.

The research protocol must include a description of provisions to protect such individuals from being conscripted into research.

2.4 COMMUNICATION AND COMMUNITY INVOLVEMENT

Research intended to be carried out at community level (e.g. vaccine trials) should ideally ensure adequate consultation with civil society organizations that may exist within affected communities at all phases of the trial. Sponsors are encouraged to establish Community Advisory Groups/Boards (CAGs/CABs). CAGs/CABs act as liaisons between the investigator and the community and help promote mutually beneficial and meaningful partnership between health researchers and community stakeholders by offsetting power differentials that may exist.

A CAG/CAB can be viewed as a community representing body that:

a) Provides a mechanism for community consultation that contributes to protecting the rights, welfare and safety of individual research participants and communities.
b) Promotes ethical conduct in clinical research.
c) Contributes to addressing and resolving grievances about the research process.
d) Gives advice on accrual and retention of trial participants.
e) Voices concern around the development, implementation and outcomes of specific clinical and other health-related studies.

[7] For further, more detailed, discussion on special considerations for vulnerable participants, refer to CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2016) Guidelines 15-19.

Researchers are encouraged to ensure that information flow mechanisms are developed between investigators and participating communities and that those communities are educated on the aspects of research before recruitment begins.

3.0 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR AND PARTICIPATING INVESTIGATORS

The Principal Investigator (PI) has to enter an agreement with a sponsor to conduct a clinical trial. He/she is responsible for the conduct of the clinical trial at the trial site(s). In the event that the clinical trial will have multiple sites in Uganda, it shall be the responsibility of the principal investigator to appoint co-investigators that will be responsible for the various trial sites in Uganda.

Clinical trials, including multi-center studies, must be undertaken by a local PI, resident in Uganda.

If a sponsor is involved in the clinical trial, the trial must be designed, conducted and reported in collaboration with both the sponsor and the principal investigator. If there is no sponsor, the principal investigator must clearly state in the protocol who takes on the role of the sponsor in the initiation, management and/or funding of the clinical trial.

The following section outlines the responsibilities of the principal investigator and other investigators designated by the Sponsor to undertake certain trial-related activities in the conduct of clinical trials.

3.1 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

Prior to commencement of the trial, the PI must:

3.1.1 Ensure that approval(s) from the relevant accredited local REC and the NDA are obtained and that the trial is issued a Clinical Trial Certificate.

3.1.2 Have read and understood the relevant investigational product information (Investigator's Brochure or Package Insert) developed by the sponsor for the clinical study.

3.1.3 Have thorough knowledge and understanding of the protocol, related documents and the regulatory requirements of the NDA, other relevant regulatory bodies and other relevant laws of Uganda.

3.1.4 Have read, understood and agreed to adhere to the protocol, the Declaration of Helsinki, ICH Guideline for Good Clinical Practice, these Guidelines and other relevant legislation.

3.1.5 Undertake to use the investigational and comparator product(s) only for the purposes of the study as described in the protocol.

3.1.6 Take responsibility for accountability of the investigational product(s).

3.1.7 Document clearly the sequence of events to be followed in the conduct of the clinical trial, including timeframes, roles and responsibilities of other individuals involved in the conduct of the trial.

3.1.8 Ensure the availability of all necessary facilities, equipment, and finance to conduct the trial.

3.1.9 Develop and document proper mechanisms to ethically obtain informed consent of participants.

3.1.10 Accept the involvement of monitors to review and verify the quality control procedures and conduct data verification.

3.1.11 Accept the possibility of an audit by an independent auditor appointed by the sponsor, and/or an inspection by the NDA, ethics committee, or applicable regulatory authority to access the participants' records.

3.1.12 Ensure that they have the responsibility to make trial results (both positive and negative) publicly available within a reasonable timeframe.

3.1.13 Have the responsibility to share possible benefits of research results with participants.

3.1.14 Generate the information package for the participant, and where applicable with the sponsor.

3.1.15 Ensure proper safety reporting procedures as stipulated in NDP/A Conduct of Clinical Trials regulations.

3.2 QUALIFICATIONS AND AGREEMENTS

3.2.1 The Principal Investigator (PI)/Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s) and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the accredited research ethics committee, and/or the NDA.

3.2.2 The PI/investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure,[8] in the product information and in other information sources provided by the sponsor.

3.2.3 The PI/investigator should be aware of, and should comply with, Good Clinical Practice (GCP) and the applicable regulatory requirements.

[8] See section 7: Investigator's Brochure for a more detailed discussion of the contents of the Investigator's Brochure.

3.2.4 The principal investigator should maintain a list of appropriately qualified persons to whom the PI/investigator has delegated significant trial-related duties.

3.3 ADEQUATE RESOURCES

3.3.1 The principal investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period.

3.3.2 The principal investigator should have sufficient time in terms of workload to properly conduct and complete the trial within the agreed trial period.

3.3.3 The principal investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

3.3.4 The principal investigator should ensure that all persons involved in the conduct of the trial are adequately informed and trained on the protocol, the investigational product(s), and their trial-related duties and functions.

3.3.5 The principal investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

3.3.6 If the principal investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the principal investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

3.4 MEDICAL CARE OF TRIAL PARTICIPANTS

3.4.1 A qualified physician (or dentist, when appropriate), who may be the principal investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

3.4.2 During and after a participant's involvement in a trial, the principal investigator should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The PI/investigator should inform a participant when medical care is needed for inter-current illness of which the PI/investigator becomes aware.

3.4.3 It is recommended that the investigator inform the subject's primary clinician about the subject's participation in the trial if the subject has a primary clinician and if the subject agrees to the primary clinician being informed.

3.4.4 Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the PI/investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

3.5 COMMUNICATION WITH IRB/IEC

3.5.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

3.5.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

3.5.3 During the trial, the investigator/institution should provide to the IRB/IEC all documents subject to review.

3.6 COMPLIANCE WITH THE PROTOCOL

3.6.1 The principal investigator should conduct the trial in compliance with the protocol as agreed with the sponsor and which was approved by the REC and the NDA. The principal investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

3.6.2 The principal investigator should not implement any changes to the protocol without agreement by the sponsor and prior review and documented approval from the REC and the NDA of such amendment. An exception to this would be where it is necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involve only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s) or other administrative information). As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be documented and submitted to: (a) the REC for review and approval, (b) the sponsor for agreement and, (c) the NDA.

3.6.3 The principal investigator, or person designated by the principal investigator, should document and explain any changes to the approved protocol.[9]

3.6.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or

[9] See Section 6: Protocol, for details on clinical trial protocol and protocol amendments

change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the IRB/IEC, sponsor and regulatory authorities.

3.7 INFORMED CONSENT OF TRIAL PARTICIPANTS

3.7.1 In obtaining and documenting informed consent, the principal investigator or delegate should comply with the ethical principles that have their origin in the Declaration of Helsinki, the National Guidelines for Research Involving Humans as Participants (2014) and these Guidelines. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other information to be provided to subjects.

3.7.2 The principal investigator is responsible for ensuring that an adequate information package, in an acceptable format, is available for use in the process of seeking informed consent from participants to participate in the study. The informed consent form must include contact details of at least one member of the investigating team. Where the participant is illiterate, verbal consent should be obtained in the presence of and countersigned by a literate, impartial witness. However, verbal consent may only be obtained in studies that present no more than minimal risk or in studies where for justifiable reasons written consent may not be feasible. This judgment shall be made by the IRB/REC.

3.7.3 If the trial is a multi-site, and/or multi-country study, the site principal investigator must ensure that informed consent procedures take cognizance of the characteristics of the site participants and tailor the informed consent content and procedures accordingly.

3.7.4 The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written informed consent form, and written information should receive the REC's approval/favorable opinion in advance of use. The participants or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information should be documented.

3.7.5 Neither the principal investigator, nor the trial staff, should coerce or unduly influence a participant to participate or to continue to participate in a trial.

3.7.6 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the

institution, the sponsor, or their agents from liability for negligence and/or malpractice.

3.7.7 The principal investigator and/or a person designated by the principal investigator, should fully inform the participant or, if the participant is unable to provide informed consent, the participants' legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval by the REC.

3.7.8 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.

3.7.9 Before informed consent may be obtained, the principal investigator, or a person designated by the principal investigator, should provide the participant or the participant's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.

3.7.10 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the participant or the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.

3.7.11 If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the impartial witness should sign and personally date the consent form. By signing the consent form, the impartial witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

3.7.12 Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:

a) That the trial involves research.

b) The purpose of the trial.

c) The trial treatment(s) and the probability for random assignment to each treatment (where appropriate).

d) The trial procedures to be followed, including all invasive procedures.

e) The participant's responsibilities.

f) The fact that participation in the trial is voluntary and refusal to participate or withdrawal from the trial will not prejudice the ongoing care of the person in any way.

g) Those aspects of the trial that are experimental.

h) The foreseeable risks of harm or inconvenience to the participant and, when applicable, to an embryo, fetus, or nursing infant.

i) The expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this. (e.g. Phase I Clinical Trial).

j) The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks

k) The compensation and/or treatment available to the participant in the event of trial related injury within the framework of clinical trials insurance.

l) The anticipated expenses, if any, to the participant for taking part in the trial including loss of time at work, school or home as the case may be.

m) Allowed access by the sponsor, NDA, UNCST, relevant research ethics committee and / or other regulatory authority including international regulatory authorities (pending that they have received permission to do so from UNCST) to participant records.

n) Provide a contact name and number of the PI and/or site investigator.

o) The identity of a sponsor and any potential conflict of interests.

p) The requirement to preserve the confidentiality of the participant.

q) The expected duration of the trial.

r) The foreseeable circumstances and/or reasons under which participation in the trial may be terminated.

s) The approximate number of participants involved in the trial.

3.7.13 Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During the

course of the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participant.

3.7.14 When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g., minors, or subjects with impaired mental status), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant should sign and personally date the written informed consent.

3.7.15 Except as described in the next section, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in participants who personally give consent and who sign and date the written informed consent.

3.7.16 Non-therapeutic trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally.
b) The foreseeable risks to the subjects are no more than minimal.
c) The negative impact on the participant's well-being is minimized and low.
d) The trial is not prohibited by the laws of Uganda.
e) The approval of the REC is expressly sought on the inclusion of such participants, and the written approval covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

3.7.17 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 3.7.12) should be requested.

3.8 INVESTIGATIONAL PRODUCT(S)

3.8.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the Principal Investigator.

3.8.2 Investigational products which are unregistered medicines may only be imported into the country after the clinical trial has been authorized by the NDA. Samples of the investigational product to be imported before trial approval require a special importation permit from the NDA.

3.8.3 The principal investigator may assign some of the principal investigator's duties for investigational product(s) accountability at the trial site(s) to a pharmacist.

3.8.4 The principal investigator and/or a pharmacist, who is designated by the principal investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s).[10] These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Principal investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

3.8.5 The investigational product(s) should be stored as specified by the manufacturer and in line with Good Pharmacy Practice (GPP) and Good Manufacturing Practice (GMP) and the NDA regulations and conditions.

3.8.6 Investigational products unused at the conclusion of a trial should be disposed of in line with the NDA regulations or returned to the sponsor as the case maybe. Evidence of this disposition shall be submitted to the NDA.

3.8.7 The principal investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

3.8.8 The principal investigator, or a person designated by the principal investigator should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

3.9 MONITORING AND AUDITING

3.9.1 The functional relationship between the principal investigator, the monitor and the sponsor must be clearly defined and stated in writing in the study protocol and related documents.

[10] If it is a new investigational product, NDA will specify the conditions under which the product is made available in Uganda.

3.9.2 These documents should also define a list of essential documents and detail how they are to be handled and stored. The principal investigator/investigator(s) should attend the initial briefing (site activation meeting) between the monitor and all staff involved in the study.

3.9.3 The principal investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits.

3.9.4 In addition, the principal investigator /investigator(s) should accept the possibility of an audit or monitoring visit by an independent auditor appointed by the sponsor, and/or an inspection by the NDA, REC, or relevant local and international regulatory authorities.

3.10 CHANGE OF PRINCIPAL AND/OR SITE-INVESTIGATOR

3.10.1 If the principal and/or site-investigator withdraw(s) for any reason(s) before completion of the study, a suitably qualified successor should be appointed by the sponsor to take over responsibility for the conduct of the study and the Principal Investigator shall fill form 37 in the National Drug Policy & Authority (Conduct of Clinical Trials) Regulations 2014.

3.10.2 Before the study continues, information about the new principal and/or site-investigator should be submitted by the sponsor for approval to the REC, the UNCST, the NDA and any other relevant regulatory authority. The change in principal and/or site-investigator should also be notified to the participants in the study.

3.11 DATA MANAGEMENT

3.11.1 The Principal Investigator is responsible for the collection, quality, recording, maintenance and retrieval of source data arising from the clinical study. A fully comprehensive collection of information on the participant, the administration of the investigational product(s) and the outcome of the protocol procedures should be developed using Case Report Forms (CRF). The design of the CRF should facilitate observation of the participant and should be consistent with the study protocol. The protocol should specify which data will be entered directly into the CRF and will not be supported by other source data. The source document must be signed and dated by the clinician identified in the protocol, or designated person, on a visit by visit basis and then stored securely.

3.11.2 The Principal Investigator should make the data available to the sponsor/person designated by the Sponsor to enable the conduct of data editing and audit according to the protocol/contract.

3.11.3 Corrections to CRFs can only be made by the principal investigator, co-investigator or designated person. Where existing data are incorrect, a single line should be drawn through the data in such a way that the original entry is not obscured, and the correct data inserted nearby. All corrections should be initialed and dated by the individual making the correction.

3.11.4 Data collected by direct entry onto a computer or other electronic device should only be entered by the principal investigator or a designated person. The computer system or electronic device should have sufficient protection from malware, have restricted access and should ideally record a data trail of all changes made to CRFs. The system should be designed in such a way that the data changes are documented and that there is no deletion of entered data in order to maintain, edit and audit the data trail. Once a hard copy of the computer stored data has been made, procedures for editing are as for paper CRFs.

3.11.5 The Sponsor may maintain a separate record of requests for clarification and correction (monitor's notes).

3.11.6 The Principal Investigator should be available (or delegate a suitable representative in exceptional circumstances) for agreed visits by the monitor during the study and also co-operate in the data editing, quality control and audit.

3.12 SAFETY CONSIDERATIONS

a) Drug trials have the potential to cause short and long term negative effects. Decisions and actions relevant to the clinical management and safety of the participant in acute or emergency situations are the responsibility of the principal investigator.
b) The principal investigator is responsible for ensuring that adequate provisions are made and documented for dealing with any expected and unexpected adverse events that may occur in the study participants.
c) The informed consent document should specify what action is to be taken in the event that the investigational products are withdrawn due to adverse drug reactions. In such a situation appropriate therapy required to manage the adverse drug reaction should be made available within the study framework at no cost to the patient, in consultation with the local health care service where applicable, or through the patient's medical insurance where applicable unless exceptions have been agreed upon by all parties. In all instances, any trial-related injury and/or resultant disability must be covered under the clinical trials insurance policy obtained from a licensed local insurance company.

d) It shall be the responsibility of the principal investigator to ensure that participants obtain their claim from the local insurance company in the event of any trial-related injury and/or resultant disability.
e) In some situations, it may be appropriate for the sponsor to develop standard operating procedures for the clinical management of some adverse events. These operating procedures should be included in the protocol and its related documents and updated appropriately.
f) During the progress of the study the principal investigator is obliged to be acquainted with, and consider, new data on the investigational product, either supplied by the sponsor or published in the literature or availed through any other relevant authority or publicly accessible and appropriate platforms.

3.13 REPORTING OF SERIOUS ADVERSE EVENTS

a) The Principal Investigator must inform the sponsor, within the time specified in the protocol, of any serious or unexpected adverse events occurring during the study.

b) The Principal Investigator shall within seven (7) calendar days of becoming aware report to the Authority, any serious adverse event which occurs in a subject during a clinical trial.

c) Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol and the National Drug Policy & Authority (Conduct of Clinical Trials) Regulations 2014. All serious adverse events (SAEs) and unexpected events should be reported to the sponsor within 48 hours of becoming aware except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not requiring immediate reporting.

d) The sponsor should, within fifteen calendar days of becoming aware, report to the NDA any suspected unexpected serious adverse reactions (SUSARs).

e) The sponsor should inform the principal investigator of any SUSAR which occurs during the course of another clinical trial for which the sponsor is responsible, where the reaction is in relation to an investigational medicinal product being used in the clinical trial.

f) The initial reports should be followed promptly by detailed, written follow-up reports after investigations have been completed no later than fifteen (15) calendar days of becoming aware of the event.

g) The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participant's names, personal identification numbers, and/or addresses. The principal investigator should also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse drug reactions to the REC and the NDA.

h) The sponsor should keep detailed records of the adverse events relating to a clinical trial which are reported by the principal investigator.

i) The NDA should keep a record of all suspected unexpected serious adverse reactions relating to an investigational medicinal product which are reported to the NDA.

j) The NDA may, by written notice, request for the adverse events from the sponsor or principal investigator.

k) For reported deaths, the investigator should furnish the sponsor, NDA and the REC with any additional requested information (e.g, autopsy reports and terminal medical reports).

3.14 RANDOMIZATION PROCEDURES AND UNBLINDING

3.14.1 The principal investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. In blinded studies the circumstances under which the code would be broken and the procedure for unmasking the identity of the treatment received by each participant should be stated in the protocol and known by the staff involved in the clinical management of the participants.

3.14.2 If the trial is blinded, the principal investigator should promptly document and explain to the sponsor and the NDA any premature unblinding of the investigational product(s) (e.g. accidental unblinding, unblinding due to a serious adverse event).

3.15 PROGRESS REPORTS AND FINAL STUDY REPORTS

The Principal Investigator is obliged to submit progress reports as required by the sponsor, the REC(s), the UNCST and the NDA. These reports should contain information on how the study is progressing, the number of participants included in relation to the number screened and the target sample size, the number of dropouts and withdrawals, adverse events and if the planned time schedule is still appropriate. The format and frequency of reporting shall be as prescribed by the relevant authorities. On completion of the trial, the PI, where applicable, should provide the REC, NDA, UNCST and any other relevant regulatory authorities with a summary of the trial's outcomes and a statement on how the trial has been conducted in accordance with these guidelines and other applicable regulatory requirements.

3.16 TRIAL RESULTS

3.16.1 Sponsors and investigators have an ethical obligation to disseminate research results, whether positive or negative, in a timely manner and using appropriate mechanisms. It is however important that the dissemination of research findings be

done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.

3.16.2 In collaborative research with pharmaceutical or other companies, the conditions of publication should be spelt out clearly in the protocol. Research ethics committees and the relevant regulatory authorities should be satisfied that there is no interference with the right to publish and that the local policies on data sharing and dissemination are complied with.

3.16.3 The sponsor, and where there is no sponsor, the principal investigator should, within 90 days after conclusion of the clinical trial, inform the NDA of the conclusion of the trial using the format for the clinical trial report in Schedule 2 of the National Drug Policy & Authority (Conduct of Clinical Trials) Regulations 2014.

4.0 RESPONSIBILITIES OF THE SPONSOR

4.1 SUBMISSION TO THE NDA FOR APPROVAL

Before initiating a clinical trial(s) in Uganda, the sponsor and the principal investigator must obtain approval from the NDA to conduct the trial(s). It is the responsibility of both the sponsor and the PI to ensure that the protocol satisfies the regulatory requirements as stipulated in the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014 as well as other applicable regulatory requirements.

4.2 CONFIRMATION OF REVIEW BY RESEARCH ETHICS COMMITTEE

4.2.1 The sponsor should obtain from the principal investigator documented research ethics committee (REC) approval/favorable opinion.

4.2.2 If the REC states conditions to its approval/favorable opinion based upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to participants, and/or other procedures, the sponsor should obtain from the principal investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the research ethics committee.

4.2.3 The sponsor should obtain from the principal investigator documentation and dates of any ethics committee re-approvals/re-evaluations, and of any withdrawals or suspensions of approval.

4.3 QUALITY MANAGEMENT

The sponsor should implement a quality management system throughout all stages of the trial process. The Sponsor should focus on the critical trial activities essential to ensuring human subject protection and the reliability of trial results.

Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity of procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

4.3.1 **Critical Process and Data Identification:** During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

4.3.2 **Risk Identification:** The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, and informed consent process).

4.3.3 **Risk Evaluation:** The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring.
b) The extent to which such errors would be detectable.
c) The impact of such errors on human subject protection and reliability of trial results.

4.3.4 **Risk Control:** The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or

reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

4.3.5 **Risk Communication:** The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

4.3.6 **Risk Review:** The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

4.3.7 **Risk Reporting:** The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, section 9.6 Data Quality Assurance).

4.4 QUALITY ASSURANCE AND QUALITY CONTROL

4.4.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

4.4.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

4.4.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

4.4.4 Agreements made by the sponsor with the principal investigator and any other parties involved with the clinical trial, should be in writing as part of the duly signed protocol or in a separate agreement.

4.5 CONTRACT RESEARCH ORGANIZATION (CRO)

4.5.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a Contract Research Organization (CRO), but the ultimate responsibility for the quality and integrity of the trial data always rests with the Sponsor. The CRO should implement quality assurance and quality control.

4.5.2 The CRO, to which trial related duties have been delegated, must have the required skills, experience and competencies to safely conduct clinical trials.

4.5.3 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing and evidence of a mutual agreement provided. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

4.5.4 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

4.5.5 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

4.6 MEDICAL EXPERTISE

The Sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

4.7 TRIAL DESIGN

4.7.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

4.7.2 If the study is a multicenter and/or multi-country study, any differences in trial designs between the Uganda site(s) and other sites, must be clearly documented and explained in the study protocol and related documents.

4.8 TRIAL MANAGEMENT, DATA HANDLING, AND RECORD KEEPING

4.8.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

4.8.2 The sponsor is responsible for establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings. A duly signed IDMC Charter shall be submitted to the NDA prior to recruitment of participants. The decision not to constitute an IDMC should be clearly documented and justified in the protocol.

4.8.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) Ensure and document that the electronic data processing system(s) conform(s) to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation). The sponsor should base their approach to validation of such systems 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.

b) Maintain SOPs for using these systems. They should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail).

d) Maintain a security system that prevents unauthorized access to the data.

e) Maintain a list of the individuals who are authorized to make data changes.

f) Maintain adequate backup of the data.

g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

h) Ensure the integrity of the data, including any data that describes the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

4.8.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

4.8.5 The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant.

4.8.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial.

4.8.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of Uganda.

4.8.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2

years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

4.8.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the relevant local and international regulatory authorities.

4.8.10 Any transfer of ownership of the data should be reported to the appropriate authority as required by the applicable regulatory requirement(s).

4.8.11 The sponsor specific essential documents should be retained for not less than 2 years or until, at least, two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

4.8.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed.

4.9 INVESTIGATOR SELECTION

4.9.1 The sponsor is responsible for selecting the investigator(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. If the organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multi-center trials, their organization and/or selection is the sponsor's responsibility.

4.9.2 Before entering an agreement with an investigator to conduct a trial, the sponsor should provide the investigator(s) with the protocol and an up-to-date Investigator's Brochure and should provide sufficient time for the investigator to review the protocol and the information provided.

4.9.3 The sponsor should obtain the investigator's agreement:

a) to conduct the trial in compliance with these Guidelines, the principles of GCP, the requirements of the NDA and with the protocol agreed upon by the sponsor and given approval by the relevant research ethics committee.

b) to comply with procedures for data recording/reporting.

c) to permit monitoring, auditing and inspection.

d) to retain the trial-related essential documents until the sponsor informs the investigator/institution that these documents are no longer needed.

The sponsor and the principal investigator should sign the protocol and/or an agreement as per the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014.

4.10 ALLOCATION OF RESPONSIBILITIES

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions. These must be clearly documented in the protocol related documents.

4.11 COMPENSATION TO PARTICIPANTS AND INVESTIGATORS[11]

4.11.1 The sponsor shall ensure that all participants in clinical trials are covered by valid clinical trials insurance for research-related injury and/or damage. The clinical trials insurance policy shall be obtained from or through a licensed local insurer.

4.11.2 For the avoidance of doubt, compensation should be paid regardless of whether the participant is able to prove that the sponsor has been negligent in relation to research or development of the medicinal product under trial or that the product is defective and therefore, the sponsor is under strict liability in respect of injuries caused by it.

4.11.3 There is no obligation for the sponsor to pay compensation:

a) For the failure of a medicinal product to have its intended effect or to provide any other benefit to the participant.

b) For injury caused by other licensed medicinal products administered to the participant for the purpose of comparisons with the product under trial.

c) To participants receiving placebo in consideration of its failure to provide a therapeutic benefit.

d) to the extent that the injury has arisen through:

i. the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse event; or

ii. through contributory negligence or significant departure from the trial protocol by the participant.

4.11.4 The undertaking given by a sponsor extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial but not to treatment extended beyond the end of the trial at the instigation of the sponsor. The use of unlicensed products beyond the trial is wholly the responsibility of the treating doctor/dentist or the physician of record. The NDA must be informed in writing of any such post-trial activities.

4.11.5 The fact that a sponsor has agreed to abide by these Guidelines in respect of a trial does not affect the right of a participant to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Nevertheless, participants will normally be asked to accept that any payment made under the Guidelines will

[11] Association of the British Pharmaceutical Industry Compensation Guidelines

be in full settlement of their claims. Clinical trials insurance in no way replaces a clinician's malpractice insurance.

4.11.6 The sponsor should indemnify the principal investigator against claims that may arise during or from the clinical trial, except claims that are as a result of malpractice or negligence of the sponsor.

4.12 TRIAL INCENTIVES

a) Incentives for potential trial participants to volunteer for research purposes need careful consideration. Incentives should not be so excessive so as to unfairly influence a participant's inclusion in a trial. Incentives such as financial, transport, and food should be fair and reasonable without 'making the patient an offer they cannot refuse' and thereby influence the potential participant to overlook other important considerations. The sponsor must ensure that participants are reimbursed for all reasonable costs incurred by their participation in the trial.
b) The sponsor must also ensure that information on incentives offered to participants involved in the trial is included in the protocol and informed consent documents. If the study is multi-center, information on the incentives given to participants at all the different trial sites, irrespective of if these are multinational, must also be provided. Differences in the incentives across sites must be explained.

4.13 FINANCING

a) The financial aspects of the trial should be documented in an agreement between the sponsor and the principal investigator/Contracted Research Organization/institution.
b) A declaration must be signed by both the sponsor and the principal investigator which states that there are sufficient funds available to complete the study.

4.14 INFORMATION ON INVESTIGATIONAL PRODUCT(S)

a) When planning the trial, the sponsor should ensure that sufficient safety and efficacy data from pre-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.
b) The sponsor should update the Investigator's Brochure as significant new information becomes available.

4.15 MANUFACTURING, PACKAGING, LABELLING AND CODING INVESTIGATIONAL PRODUCT(S)

a) The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable is characterized as appropriate to the stage

of development of the product(s), is manufactured in accordance with any applicable Good Manufacturing Practices (GMP) and is coded and labeled in a manner that protects the blinding, if applicable. The labeling should comply with the NDA requirements specifically the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014. The product labels used in clinical trials should clearly state that it is *for clinical trial use only*, provide information on the expiry date and provide the sponsor and/or manufacturer contact details.

b) The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. Compliance with the Good Pharmacy Practice (GPP), where applicable, will be required. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

c) The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage. In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency but does not permit undetectable breaks of the blinding.

d) If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials and submitted to the NDA for review and authorization.

4.16 SUPPLYING AND HANDLING INVESTIGATIONAL PRODUCT(S)

4.16.1 The sponsor is responsible for supplying the principal investigator with the investigational product(s).

4.16.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation that is, approval from the appropriate REC and the NDA and other applicable regulatory authority.[12]

4.16.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance

12 The clinical trial certificate from the National Drug Authority is a pre-requisite for issuance of an import license

with the NDA approved protocol and/or where available, applicable regulatory requirement(s)).

4.16.4 The sponsor should:

a) Ensure timely delivery of investigational product(s) to the principal investigator /investigator(s).

b) Maintain records that document shipment, receipt, accountability, stock, return, and destruction of the investigational product(s).

c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaims).

d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition. Disposal must be done according to NDA regulations.

4.16.5 The sponsor should:

a) Take steps to ensure that the investigational product(s) are stable over the period of use.

b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

4.17 RECORD ACCESS

4.17.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, REC review, and regulatory inspection.

4.17.2 The sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, REC review, and regulatory inspection.

4.18 SAFETY INFORMATION

4.18.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

4.18.2 The sponsor should promptly notify, in writing all concerned investigator(s) and the NDA and REC of findings that could affect adversely the safety of participants, impact the conduct of the trial, or alter the REC's approval/favourable opinion to continue the trial. Study participants should also be informed of any new information that could adversely affect their safety.

4.19 ADVERSE DRUG REACTION REPORTING

4.19.1 The sponsor should expedite the reporting of all adverse drug reactions (ADRs) that are both serious and unexpected to all concerned investigator(s)/institutions(s), REC(s), and to the NDA.[13]

4.19.2 The expedited reporting should occur within the timeframe and format specified by the NDA. Serious unexpected adverse events suspected to be related to the investigational product(s) or investigation procedures should be reported to the relevant REC as soon as possible, and in line with the requirements of these Guidelines.

4.19.3 If the study is multi-center, the sponsor should ensure that all serious and unexpected adverse drug reactions that occur in other study sites are also reported within fifteen (15) calendar days of becoming aware of them.

4.19.4 The sponsor should submit to the NDA and REC all updates to the IB, Development Safety Update Reports (DSURs) and Periodic Safety Update Reports (PSURs) as required by applicable regulatory requirement(s). Review of reported serious and unexpected adverse drugs events need to include analysis, evaluation and complete account of the entire body of safety information of the drug, as such data may have emerged during the course of clinical trials by the principal investigator and in the international data set.

4.20 MONITORING

The monitor should be appointed by the sponsor in line with the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014 and is an important communication link between the sponsor and the investigator(s).

4.20.1 The main purpose of trial monitoring is to verify that;

a) The rights and the well-being of human subjects are protected.
b) The reported trial data are accurate, complete and verifiable from source documents.

[13] For more information on reporting of adverse drug reactions, refer to; Directorate of Product Safety, ©2009 National Pharmacovigilance Center: A Guide to Detecting and Reporting Adverse Drug Reactions, May 2009, First Edition. Version NDA2009/1

c) The conduct of the trial is in compliance with the currently approved protocol and amendments, with GCP and with applicable regulatory requirements.

4.20.2 Selection and Qualifications of Monitors

a) Monitors should be appointed by the sponsor. The Monitor is tasked with trial oversight and reporting on the progress of a study. (Refer to Form 32 in Schedule 1 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014)

b) The monitor should ideally have adequate medical, pharmaceutical and/or scientific qualifications. Acceptable qualifications for a monitor depend on the type of study and the investigational product. The monitor should be fully cognizant of the product under investigation, clinical research procedures and the requirements of the protocol and related documents.

c) A written record should be kept of the monitor's visits, telephone calls and letters to the principal investigator.

d) The monitor or other contact person, appointed by the sponsor and known to the principal and co-investigator, should be available at any time for consultation or reporting of serious adverse events

4.20.3 **Extent of Monitoring**

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.

4.20.4 **Monitor's Responsibilities**

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a) Acting as the main line of communication between the sponsor and the investigator.

b) Verifying that the investigator has adequate qualifications and resources and these remain adequate throughout the trial period, that facilities including laboratories and equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

c) Verifying, for the investigational product(s):

   i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

   ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

   iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

   iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

   v) That the disposition of unused investigational product(s) at the trial sites complies with both the NDA regulatory requirement(s) and the sponsor's requirements.

d) Verifying that the investigator follows the approved protocol and all approved amendment(s) where applicable.

e) Verifying that written informed consent was obtained before each subject's participation in the trial.

f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

i) Verifying that the investigator is enrolling only eligible subjects.

j) Reporting the subject recruitment rate.

k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date, and maintained.

l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor should specifically verify that:

   i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
   ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
   iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
   iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
   v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

o) Determining whether all adverse events (AEs) are appropriately reported within the timelines required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

p) Determining whether the investigator is maintaining the essential documents.

q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

4.20.5 **Monitoring Report**

a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
b) Reports should include the date, site, name of the monitor, and name of the investigator or other individuals contacted.
c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.
e) These reports should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

4.20.6 **Monitoring Plan**

The Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

4.21 AUDIT

The following considerations should be made when sponsors perform audits as part of implementing quality assurance:

4.21.1 **Purpose:** The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, GPP and other applicable regulatory requirements.

4.21.2 **Selection and Qualifications:** The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits. The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

4.21.3 **Auditing Procedures:** The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports. The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants, and any identified problem(s). The observations and findings of the auditor(s) should be documented and accessible to the REC and the NDA. The audit report should be submitted to the NDA when evidence of GCP and/or protocol non-compliance is established, or in the course of legal proceedings. When required by applicable law or regulation, the sponsor should provide an audit certificate.

4.21.4 **Non-compliance:** Non-compliance with the protocol, SOPs, GCP, GCLP, GPP and/or applicable regulatory requirement(s) by an investigator, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. If the monitoring and/or auditing identify serious and/or persistent non-compliance on the part of an investigator, the sponsor should terminate the investigator's participation in the trial. The sponsor must promptly notify the NDA,

REC and/or other relevant regulatory authority(s) of serious and/or persistent non-compliance on the part of an investigator, and also promptly inform the relevant authorities when an investigator's participation is terminated because of non-compliance.

4.21.5 **Premature Termination or Suspension of a Trial:** If a trial is prematurely terminated or suspended, the sponsor should promptly inform the principal investigators, and the NDA of the termination or suspension and the reason(s) for the termination or suspension. The REC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by the applicable regulatory requirement(s).

4.21.6 **Clinical Trial/Study Reports:** Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the relevant regulatory authorities as required by the applicable regulatory requirement(s).

4.22 INSPECTIONS[14]

4.22.1 As prescribed by the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014, the NDA may inspect the conduct of a clinical trial by on-site visits. The NDA may conduct both announced and unannounced inspections.

4.22.2 Such an inspection should consist of a comparison of the procedures and practices of the investigator with the commitments set out in the protocol and reports submitted to the NDA by the investigator or the sponsor. Inspections may include a data audit. The NDA, REC, UNCST and other international regulatory authorities should have easy access to all patient files and raw data utilized and generated during the trial for purposes of verification.

4.22.3 All site data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. Verification processes must therefore be specified and justified.

4.22.4 Inspections may be carried out randomly, and/or for specific reasons. NDA officers should be given easy access to the trial sites and laboratories at all times, announced or unannounced.

4.22.5 The inspection should determine whether the principal investigator has custody of the required records or, if not, who has assumed this responsibility. The archives should be tested for retrieval.

[14] See Appendix B for details of an inspection by NDA

4.22.6 Sponsor and investigator sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including participant files must be available for inspection by the NDA.

4.23 PUBLICATION OF TRIAL RESULTS

The Principal Investigator has a duty and right to publish trial results, irrespective of the sponsor's consent. Trial results should always be reported to the relevant accredited RECs, the NDA and especially the UNHRO which is mandated to oversee dissemination of research results. For collaborative and multi-center trials, publication conditions need to be clearly outlined in the protocol and approved by the relevant regulatory authorities especially the REC and the UNCST.

4.24 NON-COMPLIANCE PROCEDURES

The Sponsor has an ethical duty to inform the appropriate REC and NDA of possible instances of serious contravention of GCP during the course of a clinical trial that affect participant's safety, the credibility of data and/or the ethical conduct of the trial.

4.25 MULTI-CENTER STUDIES

4.25.1 Multi-center trials must adhere to all national regulatory requirements with the design ensuring consideration and adaptation of the local context into the general study design. It is important to put the following into consideration regarding multi-center trials.

a) Inclusion and exclusion criteria must be appropriate to consider local realities as well as trial site-specific differences.

b) The informed consent procedure must be tailored to local conditions and ICFs translated into local language submitted to the REC for approval.

c) Study design differences between the Uganda site(s) and other sites must be fully explained as well as differences between sites within Uganda. Study extrapolations and conclusions should be relevant to the Uganda context.

d) Where necessary, that the site-investigators develop site-specific standard operating procedures and/or a site implementation plan to guide the respective sites on implementation of the protocol at that site.

4.25.2 For multi-center trials the Sponsor should ensure that:

a) All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and which has received prior approval/favorable opinion by the REC and the NDA.

b) The case report forms are designed to capture the required data at all multi-center trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data. Collection of additional data that is specific to sites should be clearly stated in the site-specific implementation plan.

c) The responsibilities of coordinating investigator(s) and other participating investigators are documented prior to the start of the trial.

d) All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

e) Communication between investigators at the various sites is facilitated. There should be an overall/country principal investigator to oversee the running of operations, provided they are conducted within the same country.

5.0 DATA MANAGEMENT

5.1 QUALITY CONTROL

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.1 The sponsor should base their approach to validation of electronic data processing systems 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.

5.1.2 The sponsor should maintain a documented record of standard operating procedures that guide step-by-step retrospective assessment of data quality and study performance. These SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

5.1.3 Data integrity processes should ensure that blinding with regard to treatment assignment is safeguarded, that confidentiality of the database is secured and that access is controlled following standard operating procedures.

5.1.4 Satisfactory maintenance and back-up procedures for computer databases must be provided.

5.1.5 Case Report Forms should be designed to meet the specific data requirements set out in the study protocol.

5.1.6 The effects of missing and inaccurate data should be minimized to maintain data quality. The system for routinely checking the data collection and entry throughout the course of the trial should be documented.

5.1.7 Checks for validity and consistency of the database should be on separate items as well as on predetermined combinations of items in the CRFs. The Standard Operating Procedure for data editing should ensure that any queries about data validation are brought to the attention of the investigators.

5.1.8 Database lock should be done after completion of the validation and editing processes are documented.

5.1.9 The treatment code may be broken after completion of the above processes.

5.2 THE FINAL STUDY REPORT

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authorities with any reports required. All aspects (statistical and clinical) of the protocol should be integrated in order to obtain a final study report that is entirely consistent with the study data generated. Essential elements in the presentation of the results of a study of an investigational product include:

a) baseline comparisons between the treatment groups;
b) the number of participants actually randomized into the study by treatment group and the number of participants excluded from any of the analyses, by reason and by treatment group;
c) major efficacy and safety results by treatment group in the form of tables, graphs, test variables and statistical parameters (e.g. p-values) as appropriate;
d) an assessment of between-group differences with confidence intervals;

An account must be made of missing, unused or spurious data during statistical analyses. All omissions of this type must be documented to enable review to be performed.

5.3 PRESERVATION OF RECORDS

Both the principal investigator and the sponsor are obliged to retain records and data from the study for safety reasons and for audit and inspection subsequent to study completion.

Samples, documents and any computer records should be retained in a secure place to prevent undue access, loss or tampering.

5.4 ARCHIVING BY THE PRINCIPAL INVESTIGATOR

5.4.1 The principal investigator is responsible for maintaining copies of all documentation which contains identifying source data and other essential documentation including, the study protocol and amendments, applications to the ethics committee, serious adverse event reports, Investigational medicinal product accountability records on storage and use and all other correspondence relating to the study.

5.4.2 The sponsor shall keep the records, documents and information of a clinical trial specified in Regulation 4 (4) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014 at the clinical trial site for a period of twenty years, after completion of the clinical trial.

5.4.3 In the event that the PI is unable to maintain custody of the study documents and samples, written communication should be provided to the sponsor of the location of the records and the name of the person responsible for their retention.

5.4.4 Adequate steps must be taken to ensure that the hospital case records of all participants in clinical research are retained for at least two years after the final granting of a marketing authorization and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

5.4.5 Agreements made between the PI and sponsor must be preserved and available on request by the NDA, REC, independent auditors or the study sponsor.

5.5 ARCHIVING BY THE SPONSOR

5.5.1 The sponsor should retain copies of all essential documentation relating to the study which do not contain participant identifying information. These include reports to the NDA, records of monitor-investigator contacts and investigational product supplies.

5.5.2 The files should also include information on the person(s) at the study site maintaining custody of the participant lists and responsibility for the archiving of the investigator's documents.

5.5.3 The period and conditions under which the documents should be kept are the same as those required of the principal investigator.

6.0 CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a clinical trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 GENERAL INFORMATION

a) Protocol title, Version number, and Date. Any amendment(s) should bear the amendment number(s) and date(s).
b) Name and address of the sponsor and monitor (if other than the sponsor).
c) Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
d) Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
e) Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
f) Name(s) and address(es) of the clinical laboratory and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 BACKGROUND INFORMATION

a) Name and description of the investigational product(s).
b) A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
c) Summary of the known and potential risks and benefits, if any, to human subjects.
d) Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
e) A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
f) Description of the population to be studied.
g) References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 TRIAL OBJECTIVES AND PURPOSE

A detailed description of the objectives and the purpose of the trial.

6.4 TRIAL DESIGN

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

a) A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

b) A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages. It should align with the purpose of the study.

c) A description of the measures taken to minimize/avoid bias, including:

   i. Randomization.

   ii. Blinding.

d) A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

e) The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

f) A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

g) Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

h) Maintenance of trial treatment randomization codes and procedures for breaking codes.

i) The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

a) Participant inclusion criteria.

b) Participant exclusion criteria.

c) Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

   i. When and how to withdraw subjects from the trial/investigational product treatment.

   ii. The type and timing of the data to be collected for withdrawn subjects.

   iii. Whether and how subjects are to be replaced.

   iv. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 TREATMENT OF PARTICIPANTS

a) The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

b) Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

c) Procedures for monitoring subject compliance.

6.7 ASSESSMENT OF EFFICACY

a) Specification of the efficacy parameters.
b) Methods and timing for assessing, recording, and analyzing of efficacy parameters.

6.8 ASSESSMENT OF SAFETY

a) Specification of safety parameters.

b) The methods and timing for assessing, recording, and analyzing safety parameters.

c) Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

d) The type and duration of the follow-up of subjects after adverse events. Procedures for unmasking the identity of treatment.

6.9 STATISTICS

a) A description of the statistical methods to be employed, including timing and procedures for any planned interim analysis(es).

b) The number of subjects planned to be enrolled. In multi-center trials, the numbers of enrolled subjects projected for each trial site should be specified.

c) Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

d) The level of significance to be used.

e) Criteria for the termination of the trial.

f) Procedure for accounting for missing, unused, and spurious data. Methods for analyzing incomplete data such as premature withdrawals, missing observations, should be clearly specified.

g) Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

h) The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, valuable subjects).

6.10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, ethics committee review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 QUALITY CONTROL AND QUALITY ASSURANCE

A detailed study monitoring plan should be submitted.

6.12 ETHICS

Description of ethical considerations relating to the trial.

6.13 DATA HANDLING AND RECORD KEEPING

Quality control should be applied to each stage of data handling to ensure that all data is reliable and has been processed correctly.

6.14 FINANCING AND INSURANCE

Financing and insurance if not addressed in a separate agreement.

6.15 PUBLICATION POLICY

Publication policy, if not addressed in a separate agreement.

7.0 INVESTIGATOR'S BROCHURE

7.1 INTRODUCTION

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with information to facilitate their understanding of the rationale for, and their compliance with many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. In this case, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. Revisions that are more frequent may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs and the NDA. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 GENERAL CONSIDERATIONS

The IB should include:

7.2.1 Title Page: This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and brand name), and the release date. An edition number and a reference to the number and date of the edition it supersedes should be provided.

7.2.2 Confidentiality Statement: The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team, the IRB/REC and regulatory authorities.

7.3 CONTENTS OF THE INVESTIGATOR'S BROCHURE

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents.

7.3.2 Summary: A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

a) Species tested
b) Number and sex of animals in each group
c) Unit dose (e.g., milligram/kilogram (mg/kg))
d) Dose interval
e) Route of administration
f) Duration of dosing
g) Information on systemic distribution
h) Duration of post-exposure follow-up
i) Results, including the following aspects:
    i. Nature and frequency of pharmacological or toxic effects
    ii. Severity or intensity of pharmacological or toxic effects
    iii. Time to onset of effects
    iv. Reversibility of effects
    v. Duration of effects
    vi. Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on mg/kg basis.

a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

i. Single dose
ii. Repeated dose
iii. Carcinogenicity
iv. Special studies (e.g. irritancy and sensitisation)
v. Reproductive toxicity
vi. Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

i. Pharmacokinetics (including metabolism and absorption, plasma protein binding, distribution, and elimination).

ii. Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

iii. Population subgroups (e.g, gender, age, and impaired organ function).

iv. Interactions (e.g, product-product interactions and effects of food).

v. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g, formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.

8.0 REFERENCES

A Guide to Detecting and Reporting Adverse Drug Reactions, May 2009, First Edition. Version NDA2009/1, National Pharmacovigilance Centre.

Clinical Trial Compensation Guidelines, Association of the British Pharmaceutical Industry,

Harmonized Good Clinical Practice (GCP) Guidelines for AVAREF countries (2009).

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (2016)

International Conference on Harmonization Tripartite Guideline: Guideline for Good Clinical Practice, ICH E6(R2).

International Ethical Guidelines for Biomedical Research Involving Human Participants, Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization, Geneva.

Medical Research Council. (1998) MRC Guidelines for Good Clinical Practice in Clinical Trials. Medical Research Council, London United Kingdom.

National Drug Authority Guidelines for the Conduct of Clinical Trials (2007).

Penslar RB & Porter JP (1993) Institutional Review Board (IRB) Guidebook. Office for the Protection from Research Risks – National Institute of Health.

South African Good Clinical Practice Guidelines, Second Edition

Studdert DM and Brennan T A (1998) Clinical trials in developing countries: Scientific and Ethical issues. Medical Journal of Australia, 169:545-548

The National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014.

The National Drug Policy and Authority Act, Cap 206 (1993).

World Health Organization (2000) Operational Guidelines for Ethics Committees That Review Biomedical Research. Geneva.

World Medical Association (2000) Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

9.0 APPENDIX A: WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must

seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    a) Where no proven intervention exists, the use of placebo, or no intervention, is acceptable
    b) Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
    c) The patients who receive any intervention less effective than the best proven one, placebo or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an

intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

10.0 APPENDIX B: DETAILS OF AN INSPECTION BY THE NATIONAL DRUG AUTHORITY

10.1 SCOPE OF AN INSPECTION

The Inspection may involve:

a) a comparison of the practices and procedures of a clinical trial with the commitments made in the application to conduct the trial.
b) a comparison of the data submitted to the sponsor and NDA with the source data.
c) 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.

10.2 THE INSPECTION

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

10.2.1 **Pre-Inspection Contact:** Where appropriate, appointments for inspection of a trial site should be made by telephone call or email. A written confirmation of the inspection date, time and program (if applicable) may be forwarded to the site, the sponsor company or the CRO.
The time span between initial contact and actual inspection should be as short as possible. Undue delay of the inspection on the part of the investigator may be investigated.

10.2.2 **Opening Meeting:** The purpose of this meeting is for the Inspector(s) to explain the purpose of the inspection, i.e. routine or for -cause, to outline the scope of the inspection and to obtain a brief review of the organization of the site being inspected.

10.2.3 **The Inspection Purpose:** 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:

a) To ascertain whether the investigator is thoroughly familiar with the properties of the investigational medical product(s) as described in the investigator's brochure.

b) To ensure that investigator has sufficient time to conduct and complete the clinical study.

c) To ensure that the investigator has adequate staff and appropriate facilities (including laboratories) available for the duration of the study and to ensure that other studies do not divert essential participants or facilities away from the study in hand.

d) To establish whether the investigator has studied the protocol and whether the designated personnel have been adequately informed of their responsibilities.

e) To determine if Research Ethics Committee and National Regulatory Authority approval has been obtained.

f) To determine the manner in which the investigational products are handled and stored, and that the investigational products are dispensed to study participants in accordance with the protocol and that any unused products are returned to the Sponsor. Reconciliation of trial medication must be provided.

g) To ensure that the confidentiality of all information about participants is respected (by all persons involved).

h) In addition, the investigator needs to provide retrospective data on numbers of participants who would have satisfied the proposed eligibility criteria during preceding time periods in order to assure an adequate recruitment rate for the study.

i) The investigator also needs to provide an up-to-date curriculum vitae.

j) The Investigator is medically responsible for those participants who are under his/her care for the duration of the study and must ensure that appropriate medical care is maintained after the study. Where appropriate, fully functional resuscitation equipment should be immediately available in case of emergency.

k) Clinical significant abnormal laboratory values or clinical observations must be followed up after completion of the study.

10.3 ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the NDA as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The list of essential documents which has been developed follows. The documents include but are not limited to the list contained in the tables that follow.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the NDA.

10.3.1 **Before the Clinical Phase of the Trial begins**

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	✓	✓
SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	✓	✓

INFORMATION GIVEN TO TRIAL PARTICIPANT: • INFORMED CONSENT FORM (including all applicable translations) • ANY OTHER WRITTEN INFORMATION • ADVERTISEMENT FOR PARTICIPANT RECRUITMENT (if used)	• To document the informed consent • To document that participants will be given appropriate written information (content and wording) to support their ability to give fully informed consent • To document that recruitment measures are appropriate and not coercive	✓ ✓ ✓	✓ ✓
FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	✓	✓
INSURANCE STATEMENT (where required)	To document that compensation to participant(s) for trial-related injury will be available	✓	✓
SIGNED AGREEMENT BETWEEN INVOLVED PARTIES e.g.	To document agreements		
Investigator/institution and sponsor		✓	✓
Investigator/institution and CRO		✓	✓

Sponsor and CRO			✓
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF A REC OF THE FOLLOWING: - Protocol and any amendments - CRF - Informed consent form(s) - Any other written information to be provided to the participant(s) - Advertisement for participant recruitment (if used) - Participant compensation (if any) - Any other documents given approval/favorable opinion	To document that the trial has been reviewed and given approval/ favorable opinion by a REC. To identify the version number and date of the document(s).	✓	✓
INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the REC is constituted in agreement with GCP	✓	✓

NATIONAL DRUG AUTHORITY APPROVAL OF PROTOCOL	To document that appropriate authorization by the NDA has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	✓	✓
CURRICULUM VITAE AND/ OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants	✓	✓
NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	✓	✓
MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/ TESTS – Certification or – Accreditation or – Established quality control and/or external quality assessment or – Other validation (where required)	To document the competence of the facility to perform required test(s), and support reliability of results	✓	✓
SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the participants		✓

INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial related materials	✓	✓
SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	✓	✓
CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		✓
DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participants' treatment	✓	✓
MASTER RANDOMIZATION LIST	To document method for randomization of trial population		✓
PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with the trial initiation monitoring report)		✓
TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with the pre-trial monitoring report)	✓	✓

10.3.2 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
INVESTIGATOR'S BROCHURE UPDATES	To document that the investigator is informed in a timely manner of relevant information as it becomes available	✓	✓
ANY REVISION TO: - Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to participants - advertisement for participant recruitment (if used)	To document revisions of these trial related documents that take effect during trial	✓	✓
DATED, DOCUMENTED APPROVAL/FAVORABLE OPINION OF REC OF THE FOLLOWING: Protocol amendment(s)	To document that the amendment(s) and/or revision(s) have been participant to REC review and were given approval/favorable opinion. To identify the version number and date of the document(s).	✓	✓

Revision(s) of: – informed consent form – any other written information to be provided to the participant – advertisement for participant recruitment (if used) Any other documents given approval / favorable opinion. Continuing review of trial (where required)			
NATIONAL DRUG AUTHORITY APPROVAL FOR: – protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	✓	✓
CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants	✓	✓
UPDATES TO NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/LABORATORY/ TECHNICAL	To document normal values and ranges that are revised during the trial	✓	✓

PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL			
UPDATES OF MEDICAL / LABORATORY / TECHNICAL PROCEDURES/TESTS certification; or accreditation; or established quality control and/or external quality assessment; or other validation (where required)	To document that tests remain adequate	✓	✓
DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	✓	✓
CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	To document identity, purity, and strength of investigational product(s) to be used in the trial		✓
MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		✓

RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS letters meeting notes notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	✓	✓
SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each participant in trial. Also, to document direct access permission	✓	
SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	✓	
SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	✓	
DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	✓	
NOTIFICATION BY PRINCIPAL INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by principal investigator to sponsor of serious adverse events and related reports in accordance with regulatory requirements	✓	✓

NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR TO NDA AND REC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by sponsor and/or investigator to NDA and REC of unexpected serious adverse drug reactions in accordance with regulatory requirements	✓	✓
NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with regulatory requirements	✓	✓
INTERIM OR ANNUAL REPORTS TO REC AND NDA	Interim or annual reports provided to the REC and to NDA in accordance with accordance with regulatory requirements	✓	✓
PARTICIPANT SCREENING LOG	To document identification of participants who entered pre-trial screening	✓	✓
PARTICIPANT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all participants allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any participant	✓	
PARTICIPANT ENROLMENT LOG	To document chronological enrolment of participants by trial number	✓	

INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	✓	✓
SIGNATURE SHEET	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	✓	✓
RECORD OF RETAINED BODY FLUIDS/TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	✓	✓

10.3.3 **After Completion/Termination of the Trial**

After completion or termination of the trial, all of the documents identified in sections 10.3.1 and 10.3.2 should be in the file together with the following:

Title of Document	**Purpose**	**Located in Files of**	
		Investigator/ Institution	**Sponsor**
INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to participants, returned by the participants, and returned to sponsor	✓	✓

DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	✓ (if destroyed at Site)	✓
COMPLETED PARTICIPANT IDENTIFICATION CODE LIST	To permit identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	✓	
AUDIT CERTIFICATE (if available)	To document that audit was performed		✓
FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		✓
TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		✓
FINAL REPORT BY INVESTIGATOR TO THE REC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY	To document completion of the trial	✓	
CLINICAL STUDY REPORT	To document results and interpretation of trial	✓ (if applicable)	✓

10.4 TYPES OF INSPECTIONS

Routine Inspections: Routine inspections are inspections carried out as part of NDA's pre-authorization and ongoing monitoring of GCP compliance by NDA inspectors. The duration of the inspection and the number of inspectors present in an inspection will vary depending on the complexity of the clinical trial and activities conducted at the site.

Follow-up Inspections/Re-inspections: These inspections are carried out to verify corrective and preventive action reported by the site. These are usually focused on those areas that were found non-compliant with critical or several major observations.

For-cause/Triggered Inspections: These are inspections requested because there is a concern due to either the actual issues observed, whistle-blower reports or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site. The scope and activities examined during such inspections are decided upon a case by case basis, relative to the nature of the concern.

10.5 INSPECTION PROCEDURES

This section identifies the nature of the information that must be obtained during each inspection to determine if the principal investigator is meeting his/her obligations. This outline provides only the minimal scope of the inspection and the inspector should extend the inspection as the facts evolve. The inspection conducted should be sufficient in scope to determine compliance with Good Clinical Practice.

An inspection shall include the following checks:

a) The protocol, including amendments must be signed by the principal investigator.

b) Research Ethics Committee and Regulatory approval documentation must be verified.

c) Signed informed consent documents must be validated. The signatures need to be checked against evidence on patient files. It must be determined whether written informed consent was obtained for all participants prior to the entry into the study and whether this was recorded in the participants' medical records. A copy of any information presented orally must be available.

d) Participant records must be verified.

e) The condition, organization, completeness and legibility of the investigator's raw data files need to be described.

f) It needs to be determined whether there is adequate documentation to assure that all inspected participants did exist and were available for the duration of

their stated participation in the study. The raw data in the clinical investigator's records needs to be compared with the completed case record forms.

The following also shall be determined:

a) Whether the number and type of participants entered into the study were confined to the protocol limitations.

b) Whether the inclusion and exclusion criteria as specified in the protocol were followed.

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

d) Observations and data on the condition of the participants throughout participation in the trial, including results of laboratory tests, development of unrelated illness and other factors which might alter the effects of the investigational product.

e) Records of exposure of the participant to the investigational product.

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

g) The occurrence of adverse reactions must be determined. The reporting of these events to NDA and the Ethics Committee must be documented.

h) All persons obtaining raw data or involved in the collection or analysis of such data need to be identified.

10.6 TRIAL MEDICATION

The following are important in an inspection with regard to trial medication:

a) Access to the storage area must be controlled.

b) Accounting procedures for the test and comparator drugs must be determined.

c) Dates, quantity and recipients of trial medication dispensed must be available as well as corroboration by raw data notations.

d) The blinding of medication, if appropriate, must be validated to ensure protection of the study from bias.

e) It needs to be determined whether distribution of the investigational medicinal product was limited to those persons under the investigator's direct supervision.

f) The storage area may be inspected and storage conditions of the IMP must be verified with the manufacturer instructions.

g) Temperature and humidity in the area must be monitored and controlled. Appropriate logs must be available for this.

h) Products must be stored as per required temperature and humidity.

i) There should be an SOP on how to handle electricity or temperature failure in the area

j) Preparation of investigational product must be done according to the approved protocol by suitably qualified staff.

k) In case of vaccines, there must be an SOP for spillage and the study team must be trained to handle these kinds incidences.

l) There should be clear segregation of different study investigational products and these must be clearly identified.

m) Transportation and handling of investigational product(s) must be as per cold chain requirements.

n) Documents regarding shipment, receipt, administration, destruction and/or return of investigational product(s) must be available.

o) It needs to be determined whether the test article is a controlled substance and whether it is securely locked.

p) Access to the controlled substance must be restricted to the investigator and the responsible pharmacist.

10.7 COMPUTER ELECTRONIC DATA SYSTEMS

If electronic data systems are involved in gathering data, storing data, or transmitting data to the sponsor, these need to be identified and their capabilities established. The following are important:

a) What is the source of data entered into the computer?

b) Who enters data?

c) When is data entered?

d) Who has access to computer? Security codes?

e) How is data previously entered changed? Audit trail? By whom?

f) How is data submitted to sponsor? (hard disk, floppy disk, fax, modern network, mail, messenger)

g) How are errors, omissions, etc., in the data received, corrected and how are they documented?

10.8 CLOSING MEETING

At the closing meeting the inspectors convey the findings of the inspection to the investigator and the study team. The matters discussed at this meeting should be in line with the report written by the inspectors. The grading of observations is not communicated in this meeting but in the inspection report.

10.9 INSPECTION REPORT

A written report outlining deficiencies observed during inspection is then issued to the PI. In general, written reports are issued in paper format, and an electronic copy may be sent to the PI. The NDA may also share findings of their inspection with the other regulatory bodies; UNHRO, UNCST, FRECU and the REC of record.

10.10 CLASSIFICATION/GRADING OF INSPECTION FINDINGS

Observations should be classified into the categories Critical, Major or Minor.

10.10.1 **Critical observation:**

Conditions, practices, processes or regulatory offences that adversely affect the rights, safety or well-being of the participant(s) and/or the quality and integrity of data.

10.10.2 **Major observation:**

Conditions, practices, processes or regulatory offences that might adversely affect the right, safety or well-being of the participant(s) and/or the quality and integrity of data. Several major observations can lead to the conclusion that a study is not of a satisfactory level of compliance with GCP.

10.10.3 **Minor observation:**

Conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the participant(s) and/or the quality and integrity of data. Numerous minor non-compliances may add up to a major non-compliance.

10.10.4 **Comments:**

Observations that might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

10.11 CONSEQUENCIES OF NON-COMPLIANCE WITH GCP AND THE APPROVED PROTOCOL

Non-compliances as noted during the inspection shall lead to any of the following actions by the NDA;

10.11.1 Request for a CAPA report
10.11.2 Issue of a warning letter
10.11.3 Suspension of the clinical trial
10.11.4 Termination of the clinical trial
10.11.5 Issue of a penalty specified in the NDP/A Act.

10.12 RESPONSE TO THE INSPECTION REPORT AND CLOSURE OF INSPECTION

The principal investigator must provide a response to the deficiencies outlined in the inspection report within 4 weeks of receipt of the report and should include a proposal for corrective and preventive action and a timeline for completion of those actions. The responses are reviewed by the inspection team to determine whether or not they are acceptable. Once an acceptable response has been received from the company, the inspection will be closed.

10.13 JOINT INSPECTIONS

Where the need arises, the NDA may conduct inspections of clinical trial sites in conjuction with other relevant regulatory bodies.

11.0 APPENDIX C: LIST OF FORMS AND FORMATS IN THE NDP/A (CONDUCT OF CLINICAL TRIALS REGULATIONS) 2014.

11.1 FORMS

a) Form 29: The Clinical Trial Application Form
b) Form 30: Letter of Authorization from Holder of Patent of Drug, Licensed Person or Manufacturer of Drug
c) Form 31: Declaration by Principal Investigator
d) Form 32: Declaration by Monitor
e) Form 33: Declaration by Sponsor and Principal Investigator of Funds of the Clinical Trial
f) Form 34: Pharmaceutical Data on Dosage Form

g) Form 35: Clinical Trial Certificate

h) Form 36: Application for Deviation from Clinical Trial Certificate

i) Form 37: Application for Additional Investigators, Change of Investigators or Additional Clinical Trial Sites

j) Form 38: Labelling Investigational Drug Products for Clinical Trial.

11.2 FORMATS

a) Format of Clinical Trial Protocol

b) Format of Investigator's Brochure

c) Format of Clinical Trial Report

d) Format of Report for Terminated Clinical Trial

12.0 DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and/or reasons for revision
11 Oct. 2019	0	DPS/GDL/025	Helen Byomire Ndagije Dr. Rachel Kyeyune Bakyayita Florence Wanyenze Dr. Evans Tusubira Huldah Nassali Victoria Nambasa Bukenya Sheila Ampaire Kasibante Sharon Norah Kiggundu Pius Ariho Mugumya Ismail Ntale	This is the first issue of this document