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TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES FOR CONDUCTING GOOD CLINICAL PRACTICE (GCP) AND GOOD CLINICAL LABORATORY PRACTICES (GCLP) INSPECTION

SECOND EDITION

November, 2020

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Acknowledgements

This is the second edition of the Guidelines for Conducting Good Clinical and Laboratory Practices Inspection developed by the Tanzania Medicines and Medical Devices Authority (TMDA). The edition has been made to embrace new knowledge and experience gained during implementation of the previous edition.

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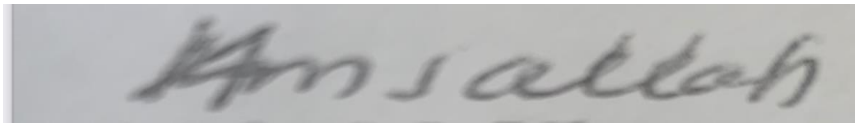

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Abbreviations

ADRs	-	Adverse Drug Reactions
AEs	-	Adverse Events
BE	-	Bioequivalence
CAPA		Correction Action and Preventive Action
CRF	-	Case Report Form
CRO	-	Contract Research Organization
CTPV	-	Clinical Trials and Pharmacovigilance
CUHAS	-	Catholic University of Health and Allied Sciences
DMC	-	Director of Medicines and Cosmetics
DSMB	-	Data and Safety Monitoring Board
EC	-	Ethics Committee
ECG	-	Electrocardiography
GCP	-	Good Clinical Practice
GCLP	-	Good Clinical Laboratory Practice
GMP	-	Good Manufacturing Practice
IB	-	Investigator's Brochure
ICH	-	International Conference on Harmonization
IHI	-	Ifakara Health Institute
IP	-	Investigational Product
IRB	-	Institutional Review Board
IVRS	-	Interactive Voice Response System
KCMC	-	Kilimanjaro Christian Medical Centre
NatHREC	-	National Health Research Ethics Committee
NIMR	-	National Institute for Medical Research
NPRA	-	National Pharmaceutical Control Bureau - Malaysia
NRA	-	National Regulatory Authority
MUHAS	-	Muhimbili University of Health and Allied Sciences
PI	-	Principal Investigator
QA	-	Quality Assurance
QC	-	Quality Control
SAE	-	Serious Adverse Event
SAHPRA	-	South African Health Products Regulatory Authority
SANAS	-	South African National Accreditation System
SOPs	-	Standard Operating Procedures
TMDA	-	Tanzania Medicines and Medical Devices Authority
TMF	-	Trial Master File

Foreword

Clinical trials are planned experiments designed to evaluate the benefits of one or more treatments, in human participants and animal species with a specific medical condition. Considering the complexities involved in the design, conduct and analysis, trials need to be inspected to ensure that they comply with TMDA requirements, trial protocol, ICH-GCP/GCLP and applicable standard operating procedures (SOPs). It is with standpoint that these guidelines have been developed.

The TMDA has been conducting inspections since 2009 by following the principles as outlined in the ICH-GCP, WHO and TMDA guidelines and procedures. During the course of discharging this function, a number of challenges have been encountered to include investigators and sponsors not knowing which standards or requirements they are being inspected against.

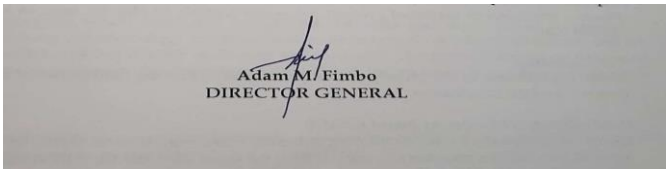
The first edition of the *Guidelines for conducting Good Clinical and Laboratory Practices Inspection* which was approved in June, 2017 allowed for the effective implementation of clinical trial inspection activities in the country. The guidelines outlined technical requirements and practices that should be adopted when planning for, carrying out and reporting trial inspection activities.

The current edition has no changes with regards to general and technical requirements for conducting clinical trial inspections. The edition is a result of Financial Act of 2019 which transformed the then TFDA to TMDA and to be in consistence with the requirements of the quality management system being implemented by the Authority.

TMDA inspectors and Inspectees of clinical trials are the target group for these guidelines and the same are expected to follow what has been delineated in the document. Adherence to requirements outlined will enable consistent conduct of trial inspections including uniform reporting.

It should also be noted that the TMDA is also responsible for regulating trials involving animal species as per the Tanzania Medicines and Medical Devices Act, Cap 219. Principles and practices, which have been highlighted in the guidelines, are also applicable to trials of this nature. Likewise, trials related to medical devices and health technologies will also be inspected based on these guidelines and applicable ISO standards.

Inspectors and inspectees of clinical trials are therefore urged to read these guidelines and apply what have been documented. Inspectees are further advised to extend maximum cooperation to TMDA Inspectors during Inspection of their trials and strive to comply with regulatory requirements. It is only through inspection that the TMDA will be able to prove that the trial is or was conducted according to study protocol, SOPs, GCP/GCLP principles and laid-down regulatory requirements



Glossary
In the context of these guidelines the following words/phrases are defined as follows:

Act
Means the Tanzania Medicines and Medical Devices Act, cap 219.

Adverse Drug Reactions
Means all noxious and unintended responses to a medicinal product related to any dose. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

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

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

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

Clinical Trial/Study
Means any investigation in human study participants 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 object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

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

Code of Conduct

Means a set of rules outlining the responsibilities of or proper practices for an individual or organization.

Code of Ethics
Means a set of standards, rules, guidelines, and values that govern and guide ethical business behavior in a company, profession, or organization of it's employees, interactions among the employees, and interactions between the employees and the general public.

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

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

Direct Access
Means permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical trial. Inspectors should take all reasonable precautions to maintain the confidentiality of study participants' identities and sponsor's or applicant's proprietary information.

Documentation
Means 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
Means documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Ethical Clearance
Means an authorization to conduct a clinical trial issued by the National Institute for Medical Research (NIMR) based on ethical issues related to trials involving human participants in Tanzania.

Good Laboratory Practice (GLP)
Means intension to promote the quality and validity of test data. It is a managerial concept covering the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported (OECD GLP Guideline).

Good Clinical Laboratory Practice (GCLP)
Applies to those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity

of data generated by analytical laboratories

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

National Health Research Ethics Committee
Means the Ethics Committee of National Institute for Medical Research of Tanzania with the responsibility of ensuring that the rights, safety and well-being of human study participants involved in a trial in Tanzania are protected and to provide public assurance of that protection, by, among other things, reviewing and approving/ providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities and the methods and materials to be used in obtaining and documenting informed consent of the trial study participants.

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

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

Inspectee
Means any party inspected by inspectors from TMDA to include investigator site, Contract Research Organization and Sponsor.

Institutional Research Ethics Committees (IRECs)
Means independent bodies established within research institutions such as MUHAS, IHI, KCMC, CUHAS, UDSM etc constituted of medical, scientific and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human study participants involved in a trial in Tanzania by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and materials to be used in obtaining and documenting informed consent of the trial study participants.

Interim Clinical Trial/Study Report
Means a report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational medicinal Product
Means a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with 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 Veterinary Product
Means any biological or pharmaceutical form of, or any animal feed containing one or more active substances being evaluated in a clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

Investigational product
Means an investigational product refers to a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used in a clinical trial

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

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

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

Monitoring Report
Means 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.

Multi-centre Trial
Means a clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

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

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

Phase III trials
Means trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant investigation medicinal product interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

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

Pre-clinical Studies
Means biomedical studies not performed on human study participants.

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

Protocol
Means 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
Means a written description of change(s) to or formal clarification of a protocol.

Quality Assurance
Means all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with TMDA and ICH – GCP requirement(s).

Quality Control
Means 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
Means the process of assigning trial study participants to treatment or control groups using an

element of chance to determine the assignments in order to reduce bias.

Serious Adverse Event (SAE) or Serious Adverse Drug Reactions (Serious ADR)
Means any untoward medical occurrence at any dose that:
- Results in death,
- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Congenital anomaly/birth defect

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

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

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

Standard Operating Procedures
Means detailed written instructions to achieve uniformity of the performance of a specific function.

Study Animal
Means any animal that participates in a clinical study, either as a recipient of the investigational veterinary product or as a control

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

Traditional Medicines
Means the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness

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

Study participant Identification Code
Means a unique identifier assigned by the investigator to each trial study participant to protect the study participant's identity and used in lieu of the study participant's name when the investigator reports adverse events and/or other trial related data.

Trial Site
Means the location(s) where trial-related activities are actually conducted

INTRODUCTION

Quality improvement in clinical research involves quality control and quality assurance processes. These two dynamic processes have a critical introspective role in continually monitoring and evaluating clinical trial activities. They involve systematic evaluation of all information gathered during trials and application of this information to make changes to the trial systems in order to increase the trial's ability to fulfill quality requirements.

Inspection of clinical trial activities is a quality assurance process, which ensures that the trial is conducted in accordance with the study protocol, procedures, ICH- GCP/GCLP and regulatory requirements and that the data is accurate and valid. Audit of trial activities is also part of quality assurance process carried out by Sponsors of clinical trials. Monitoring of trial activities is part of quality control process and it is usually conducted by study Monitors.

All clinical studies, carried out in Tanzania, pertaining to medical products and health technologies for humans and animals are required to comply with Good Clinical and Laboratory Practices. Section 69 of the Tanzania Medicines and Medical Devices Act, Cap 219 and its Regulations provides for the Authority to monitor clinical trials from the beginning to the end in order to ensure adequate protection of the general public and animals against any risks or adverse effects. The Act further requires the Authority to satisfy itself that all specific and general conditions subject to which the trial was authorized are being strictly observed by the person(s) conducting the trial and that to all intents and purposes the trial achieve its aims and objectives.

Clinical trials may be inspected prior to commencing the trial, while the trial is underway or after its completion. An inspection may also be conducted when triggered by a complaint or suspicion of serious non-compliance, integrity issues, scientific or ethical misconduct.

An inspection may be conducted at the qualified investigator (clinical trial) site, facility of the sponsor, Contract Research Organizations (CRO) facilities and other establishment deemed appropriate by TMDA.

These guidelines highlight general conditions and other pertinent requirements that are necessary for carrying out clinical trial inspections. They are divided into five (5) main sections, which include introduction, objectives, and conduct of inspection, observations and regulatory actions. Moreover, these Guidelines define procedures to be followed when preparing and planning for inspection, reporting requirements including format and classification system adopted for non-conformances observed during clinical trial inspection.

It is expected that what has been delineated in this document will be followed when executing clinical trial inspection activities. Responsible personnel are therefore required to read these guidelines together with the Guidelines for Application to Conduct Clinical Trials in Tanzania when planning, preparing for, conducting and reporting clinical trials.

1. SCOPE

These guidelines will be applicable to inspection of all clinical trials which have been approved by Tanzania Medicines and Medical Devices (TMDA) and conducted at investigator site, sponsor's facility (ies), Contract Research Organisation(s) and other establishment(s) deemed appropriate by TMDA.

The inspection activities will also apply to trials involving human participants as well as animal species and therefore those related to human medicines, veterinary medicines, biological products (including vaccines), medical devices and health technologies.

2. OBJECTIVES OF GCP/GCLP INSPECTION

The following are the objectives of GCP/GCLP inspection;

a) To ensure the rights, safety and well-being of human study participants and animals have been protected
b) To determine whether the trial was conducted in accordance with applicable ICH-GCP, WHO-GCLP requirements, ISO standards, ethical standards and Tanzania Medicines and Medical Devices (Clinical Trials Control) Regulations and Guidelines for Applications to Conduct Clinical Trials
c) To determine whether the data submitted in the dossier are credible and accurate
d) To assure the integrity of scientific testing and study conduct
e) To take corrective action to ensure compliance and enforcement actions when deemed necessary

3. TYPES OF INSPECTION

There are four (4) types of inspection as outlined below;

4.1 Routine inspections

Routine inspections are generally carried out before or after approval of a trial or when there are major amendments e.g. changes in principal investigators and additional site(s).

4.2 Concise inspections

Concise inspection is the evaluation of limited aspects relating to GCP compliances within a facility. A limited number of GCP requirements are selected by the inspector to serve as indicators of the overall GCP compliances by the inspectee site.

4.3 Follow up inspections

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

4.4 Investigative or For cause inspections

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

a. A recruitment centre has high or very low patient recruitment rates that are unexpected given the research site's location and demographics.
b. Inconsistent data are found in the database (physical examinations, vital signs etc).
c. An unusual safety profile has been reported (safety or efficacy data inconsistent with other study sites).
d. An abnormal number of adverse events (AEs) are reported (too high overflow).
e. There is a suspicion of alleged violations of the Act, Regulations and/or Guidelines.

4. CONDUCT OF INSPECTION

5.1 Preparation for GCP/GCLP Inspection

During the preparation of the inspection, the plan will be established depending on the type of inspection to be conducted. The TMDA shall notify the applicant not less than 2 weeks except for triggered/cause inspection using a standard letter, that an inspection shall be conducted. In the notification letter, the applicant is requested to confirm in writing, phone or email that the sites have received the notification for the inspection and will make all required documents available for direct access by the Inspectors.

5.2 Opening Meeting

This is the initial phase when carrying out clinical trial inspection. In this phase, inspectors will conduct meeting with responsible persons at the trial site. The purpose of an opening meeting is to:

a. Explain the regulatory framework for the conduct of the inspection
b. Introduce the inspector(s) to the inspectee(s) and vice versa
c. Be informed of any departmental or other practices which affect the implementation of quality systems or GCP/GCLP by the inspectee(s)
d. Identifythedistributionofdutiesandfunctionsfortheconductofthetrialamongthe inspectee(s)
e. Review the scope and the objectives of the inspection
f. Provide a short summary of the methods and procedures to be used to conduct the inspection
g. Confirm that the resources, documents and facilities needed by the inspector(s)

are available

h. Confirm the time and date for the closing meeting and any interim meetings
i. Clarify the inspection plan, if necessary

5.3 Conduct of the Inspection/Collecting Information

The inspection activities will be detailed on the inspection plan. Nevertheless during the inspection, the Inspector(s) may adjust the plan to ensure the inspection objectives are achieved. Sufficient information to accomplish the inspection objective(s) will be collected through examination of relevant documents with direct access, interviews and observation of activities, equipment and conditions in the inspected areas.

If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has legal access, these refusals should be documented and included in the inspection observations. The aspect of inspection and different areas that will be inspected will depend on the site inspected as highlighted in the appendices I – V attached with these guidelines.

5.4 Inspection Observations

All inspection observations will be documented. If appropriate, copies will be made of records containing inconsistencies or illustrating non-compliance.

At the end of the inspection, the inspector(s) will review all observations to determine which observations are to be reported as non-compliance and/or quality system deficiencies. The inspector(s) will then ensure that these are documented in a clear, concise manner and are supported by objective evidence. All reported observations will be identified with reference to specific requirements of the standard(s) or other related documents against which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organization will also be documented.

5.5 Closing/Exit meeting

At the end of the inspection, the inspector(s) will hold a closing meeting with the inspectee(s). The main purpose of this meeting is to present inspection observations to the team of inspectee(s) to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s). The inspector and inspectee(s) will also sign the memorandum form, appendix VI listing all the noncompliance findings noted during the clinical trial inspection, a copy of which will be left at the investigator's site.

5.6 Reporting after the inspection

The inspector shall prepare a narrative inspection report detailing inspection observations 14 days after the inspection. The final report will be sent to the inspectee within 30 days after completion of the inspection. The inspection report should fully describe the nature and scope of the inspection. The report details will be as per the format in **Appendix VII.**

The inspectee(s) is required to respond to all non-conformances made with corrective actions for every observation. The inspectee(s) should submit written corrective actions in both soft & hard copy format within the agreed timeline in the memorandum form. Should corrective actions be found, *not satisfactory'*, additional actions will be requested from the inspectee(s) and if necessary follow up inspection may be conducted for verification.

5. CLASSIFICATION OF CLINICAL TRIAL INSPECTION OBSERVATIONS

The classification of observation is intended to classify severity of non-conformances observed during clinical trial inspection. Overall, the evaluation should commensurate with the nature and extent of the deviations (i.e. severity). Situations involving fraud, misrepresentation or falsification of source data or records linked with clinical trials will be a critical observation.

Deficiencies or deviations will be noted by Inspectors during inspection and confirmed in writing in the inspection memorandum form during post inspection briefing. Non-conformances will be classified as critical, major and minor as outlined below:

6.1 Critical on-conformances

Include observations describing a situation that results in fatal, life threatening or unsafe conditions for study participants and animals enrolled in a clinical trial. They present an immediate or latent undue risk to the rights, health and safety of participants and animals. The conduct of unauthorized trials, adulteration, misrepresentation and falsification of records are also classified as critical observations. **Appendix VIII** of these guidelines outlines the observations that are considered to be critical.

6.2 Major non-conformances

Include observations describing a marked deviation or deficiency, other than a critical one, that may result in undue health risks to the clinical trial participants, animals, in other persons or animals or could invalidate the data. **Appendix IX** is a list of observations that are considered as major.

Major observations may be reclassified as critical, depending on the nature and extent of the deviation. For example, widespread or systematic deficiencies, such as lack of evidence that informed consent was obtained from most of participants enrolled in a trial or marked deviations from the inclusion/exclusion criteria that endanger the Health and safety of study participants and animals could result in a "critical" classification. Isolated departure, such as lack of a signed informed consent form from a single participant, would also be classified as "major" classification.

Note: In all situations, when a major observation is reclassified as critical observation, a justification will be provided.

6.3 Minor non-conformances

Include observations that are classified as not critical or major, but which indicates a deficiency and/or deviation. **Appendix X** contains a list of minor observations.

6. REGULATORY ACTION (S) TO BE TAKEN BY TMDA

After inspection, TMDA may take the following regulatory action(s) depending on the non-conformances observed;

a. Issuing warning letter
b. Temporary withdraw or suspension of the trial authorization
c. Permanent withdrawal of trial authorization
d. File case to the police department for court proceedings

7. APPEAL

Any person aggrieved by a decision of the Authority in relation to any finding raised from GCP/GCLP inspection of any medical product and health technologies may within sixty (60) days from the date of notice of the decision, make representations in writings to the Authority by submitting additional data to support the representations.

If after reconsideration of the representations, TMDA still withdraw or suspend the clinical trial, the Inspectee may, if not satisfied with the decision; within sixty (60) days appeal in writings to the Minister responsible for heath giving grounds for the appeal.

APPENDIX I: INSPECTION AT INVESTIGATOR SITE

The TMDA will inspect the following at the investigator site;

1. ORGANISATIONALASPECTS

1.1 Organization and Personnel

a. Organization charts (facility management and scientific organization charts)
b. Documentation of delegation of responsibilities by the principal investigator including CV and Certificates.
c. Systems for QA and SOP system where available
d. Risk Management Plan, e.g. handling of defective equipment and consequences
e. Staff–qualification, responsibilities, experience, availability, training programmes, training records, CV
f. Numbers of clinical trials being performed and their nature
g. Proportion of time allocated to clinical trial work

1.2 Implementation of the study at the site

a. Contracts between the sponsor or sponsor's representative and the investigator
b. Qualifications and experience of the investigator's team in the considered clinical area
c. Documentation describing the distribution of duties and functions for the conduct of the trial
d. Compatibility of the workload of the investigator and the staff with the requirements of the study
e. Organization of the site for the study(organization chart, specific training, specific equipment, specific procedures)
f. Compliance with the planned time schedule for the study
g. Correct implementation of the correct versions of the protocol and its amendments

1.3 Facilities and equipment

The inspection may include a review of the following:

a. Equipment used
b. Presence of equipment necessary for sample collection, transportation and storage onsite as applicable
c. Facilities whether are accessible, adequacy of power supply. Presence of laboratory, pharmacy and archive areas, communication facilities, etc.
d. Their suitability for the protocol requirements and the characteristics of the study being inspected

1.4 Management of biological samples

The following aspects regarding the management of biological samples will be inspected;

a. Collection: person in charge of this task, dates and handling procedures
b. Storage of the samples before analysis or shipping
c. Shipping conditions

1.5 Organization of the documentation

Inspection will cover;

a. Source documents (e.g. patient's charts, X-ray,etc.)
b. Informed consent documents
c. Case Report Form (CRF)
d. A sample of data should be verified from the study report and or CRF to the source documents

1.6 Monitoring and auditing (where applicable)

The following will be examined,

a. Monitoring and follow-up by the sponsor, number of visits at the site, scope and dates of the visits, content of the monitoring visit reports, visits log and monitoring plan.
b. Actions recommended by the monitor.
c. Audit certificates (from sponsor file)

1.7 Use of computerized systems

If computerized systems have been used for the trial, validation status will be ascertained. Computers may be study specific and supplied by the sponsor (eCRFs, e- patient diaries, IVRS, etc.) They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording, etc.)

2. INFORMED CONSENT OF TRIAL PARTICIPANTS

The TMDA will assess whether informed consent was obtained in accordance with GCP Guidelines by checking the following;

a. The signed and self-dated (by the participants and by the person who conducted the informed consent process) consent form actually used and approved by the NatREC/IRB and TMDA.
b. The information sheet actually used and approved by the IREC/IRB and TMDA.
c. The practice of giving a copy of the informed consent to the participants
d. Consent for access to medical records by the authorities

3. TRIAL PARTICIPANT'S DATA

Trial participants' data will be evaluated to determine whether approved protocol was followed by checking;

a. Organization, completeness and legibility
b. Corrections to the data recorded in the CRF were done according to TMDA Guidelines

3.1 Inclusion and exclusion criteria of study participants

The following will be checked during inspection;

a. Participants included in the clinical trial existed and participated in the trial
b. Medical records of study participants
c. Participants included fulfilled the inclusion and exclusion criteria

3.2 Participant's visits calendar

The TMDA will determine whether the participants' visits calendar established in the protocol was followed.

3.3 Efficacy and safety data

Inspectors will verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the trial. They will also verify whether adequate data management procedures are in place.

3.4 Concomitant medication and diseases

Inspectors will check whether concomitant therapy and inter-current illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

4. MANAGEMENT OF INVESTIGATIONAL PRODUCT(S)

The following documents will be reviewed;

a. Instructions for handling of Investigational Product(s) and trial related materials
b. Shipping records for products and trial related material (for example receipt date(s) of product delivery and quantity
c. TMDA importation permit of IP (s)
d. Documentation regarding allocation of treatment, randomization and code breaking
e. IP accountability at site (pharmacy or investigator)
f. Date and quantity dispensed or returned, identification of recipients (patients code or authorized persons)
g. Date and quantity returned to the sponsor.
h. Documentation of destruction of IP(s) (if destroyed at the site), dates and quantity.
i. Treatment compliance

In addition, the following will also be checked;

a. The suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.)
b. Specific SOPs for this activity from the pharmacy or institution
c. Control of access to the IP (s) from reception to dispensing
d. Verification of the labelling for compliance with applicable regulations

APPENDIX II: INSPECTION AT CLINICAL LABORATORIES

1. GENERAL ASPECTS

1.1 Scope of work and responsibilities.

Inspectors will check for;

a. The accreditation status of the laboratory (the methods) focusing on fulfillment of requirements and relevance of accreditation in the context of clinical trial(s)
b. Proportion of work in connection to clinical trials.

1.2 Organization and Personnel

Areas to be inspected will include;

a. Organization charts (facility management and scientific organization charts)
b. Systems for QA and QC, including programme for internal audits
c. SOP system (distribution, availability including holidays etc., audit-trail, clinical trials, archiving etc)
d. Risk Management, e.g. handling of defective equipment and consequences
e. Staff – qualifications, responsibilities, experience, availability, training programme, training records, CV

1.2 Contractual arrangements

a. Procedures for contracts and sub-contracts, protocol, amendments, definition of source data, agreements for reporting
b. Methods and procedures (including sample handling)
c. Agreed access and availability for monitoring, audit and inspection
d. Data recording, handling and archiving
e. Security and protection of subject confidentiality

1.4 Facilities/Premises

Suitability and adequacy of premises- e.g. adequate degree of separation of works areas to avoid mix-ups, contamination and interference. Environmental conditions, e.g. temperature, airflow and air pressure, microbiological contamination. Security and safety, e.g. fire, water and pest control.

1.5 Apparatus/ Equipment, Materials, Reagents

a. Apparatus available (working or not and their suitability for testing methods; sample type)
b. Records of operation, maintenance, justification and calibration.
c. Quality of general supplies including tap water, analytical water, gases etc.

d. Recordsofthevalidationforthemethodsusedforthemeasuringequipmentand apparatus (including computerized systems) and logbooks
e. Record for materials and reagents preparation
f. Definition of source data and source documents, retrieval and archiving
g. Data generated in automatic systems e.g. listings, graphs, record traces or computer printouts.

2. TRIAL RELATEDASPECTS

2.1 Handling of samples

a. Samples obtained from participants in the clinical laboratory (date and time), identification, labeling, conditions, preparation, storage
b. Documentation of receipt (date and time), identification, condition, relabeling and storage of samples by identifiable person
c. Procedures for acceptance or rejection of samples for analysis

2.2 Examination or testing

a. Compliance with protocol and specified test methods
b. Traceability and identification of samples and controls
c. Recording of data, acceptance and release of results
d. Handling of non-conformance, repeat analysis / re-analysis, and results within critical / alert ranges
e. Competence, training and experience of personnel

2.3 Procedures for Risk Management

a. Post-analysis of samples
b. Storage (anonymization, decoding), retrieval and destruction of samples

2.4 Material and methods

a. Material and methods according to the specification stated in the protocol / contract and/or required according to European Pharmacopoeia, British Pharmacopoeia, or other established Pharmacopoeia
b. Validation status of the methods, appropriately setting of limits of detection / quantification, precision/accuracy, known inferences and specific control measures
c. Participation in proficiency scheme, if applicable

2. REPORTING

Various areas of reporting laboratory results will be assessed depending on the type of study and complexity including;

a. Procedures for reporting and evaluation of results and for data transfer.
b. Systems for alerting results that are unexpected and/or significant deviations from pre- specified limits.

c. Transcription of raw data into the report;
d. Identification of laboratory
e. Unique identification and localization of the participant
f. Identification of investigator
g. Date and time of sample collection, and time of receipt
h. Date and time of examination and release of report
i. Source of primary sample type and any comments of its quality
j. Description of the examination and of its results
k. If applicable, detection limit, uncertainty of each measurements, and reference intervals
l. Where appropriate, interpretation of results and other comments
m. Identification of the person releasing the report
n. Attribution of review and release of the report(s) to responsible personnel.
o. Procedures for alterations and amendments of reports.
p. Procedures for complaints and corrective actions.

APPENDIX III: CONDUCT OF THE COMPUTER SYSTEMS INSPECTION

TMDA will inspect computer systems that contain clinical trial data. The aspects of the systems to be inspected will include but not limited to;

1. SECURITY OF COMPUTERIZED SYSTEMS

The inspector will assess whether;

a. The system is being applied for intended purpose stated in the protocol
b. The Data entered into and generated from the system is restricted and is being monitored appropriately
c. There are designated personnel responsible for maintenance of the computerized system.
d. There are measures to detect and/or shield the system from malware/virus
e. There are backups

2. ACCESSIBILITY

The inspector will assess whether;

a. Data in the Computerized System is readily accessible upon request by inspector
b. The Computerized System is able to assimilate all information from various sources (including laboratory devices, word processing systems etc.,) in a central, secure repository that can be readily accessed by authorized personnel.

3. AUDIT TRAILS

The inspector shall

a. Check the Computerized System organization for availability of time-stamped records that allow reconstruction of the course of events relating to creation, modification and detection of an electronic record.
b. Assess availability of means within the computerized system to ascertain authenticity, integrity and confidentiality of electronic records.

4. ELECTRONIC SIGNATURES

The inspector shall check for the ability within the system to attribute clinical data to all employees involved in the generation of said data. Electronic signature if used has to be maintained even for former employees.

5. VALIDATION

The inspector shall inspect the following aspects of the computerized system;

a) Availability of means of validation of the Computerized System
b) Whether the Validation of the computerized System cost effective and can be done in a timely manner.

APPENDIX IV: INSPECTION AT SPONSOR SITE AND/CLINICAL RESEARCH ORGANIZATIONS

The following items will be reviewed during inspection at sponsor site/CRO;

1. SPONSOR/CRO QUALITY SYSTEMINSPECTION

1.1 Organization and personnel

Inspectors will assess whether the sponsor site/CRO has a well-established organization for clinical research activities and has a sufficient number of qualified and trained personnel for each area by reviewing;

a. Organizational charts that identify the key personnel in each area.
b. The independence of the quality assurance unit.
c. The job description, qualifications and training of the individuals involved at any stage of the clinical trial process
d. Functions of the organization/CRO

1.2 Facilities and equipment

Inspectors will evaluate the facilities used for archiving or IP storage as well as the equipment used. Special attention will be paid to computer systems (hardware, software, communications, etc.), in order to evaluate their validation status, and their adequacy for the requirements of the trial(s) being inspected.

1.3 Operating Procedures

Various procedures will be reviewed in order to verify their compliance to TMDA requirements to include but not limited to;

a) Implementation and termination of the clinical trial

The procedures will be reviewed for:

i. Document preparation (format and content and distribution of protocol, amendments, informed consent documents, investigator brochure, CRF and any other trial documents)
ii. Investigators selection and training.
iii. Compliance to TMDA and other regulatory requirements

b) Monitoring

The procedures will be reviewed to determine the inclusion of;

i. Description of monitoring activities (visits, frequency and extent of data review)
ii. Content and handling of monitoring reports

iii. Agreements for direct access to source documents by the sponsor personnel (or their appointed representatives) and by regulatory authorities and confidentiality of information about participants.

c) Investigational Product(s)

Inspectors will check whether there are procedures for:

i. Quality control requirements
ii. Manufacturing, packaging and labeling
iii. Supplying, accountability, returns and destruction
iv. Randomization and code breaking

d) Sample management

The procedures established for handling **biological samples** obtained in clinical trials will be reviewed.

e) Safety and adverse events reporting

Review will be done for:

i. Expedited Adverse Drug Reaction reporting to the TMDA and IREC/IRB, where applicable
ii. Serious adverse events notification by investigators
iii. Management of the serious adverse events reported by investigators
iv. Safety updates and periodic safety reports
v. Validation of computer systems used

f) Data handling and clinical trial report

Inspectors will check whether there are procedures for;

i. Data handling, data analysis and their control procedures
ii. Clinical trial report preparation according to ICH standards
iii. Validation of the computerized systems used
iv. Audit trails (for paper and computer systems)

g) Documentation archiving

Inspectors will determine whether the system established by the sponsor/CRO guarantees that the general documentation, which has to be archived at the sponsor/CRO site (according to ICH-GCP/GCLP), is available, complete and maintained in good conditions during the period of time established.

h) Sponsor audit and quality assurance system

Inspectors will determine if the procedures include:

i. Audits of key clinical trial processes including monitoring, data management, safety reporting, report production, archiving and computer system validation activities.
ii. Audits of contractors/sub-contractors
iii. In addition, inspectors will also review:
    - The processes for communicating and addressing audit observations, including the format and distribution of audit reports.
    - The procedures for dealing with serious and/or persistent GCP/GCLP non- compliances.

1.4 Audit trails

Inspectors will evaluate audit trails mechanisms and whether there are procedures in places for generation and implementation of audit programme(s)/plan(s).

In addition, inspectors will examine the procedures related with:

a. Pre-selection and ongoing assessment of contractor/subcontractors
b. Documentation of duty delegation and its time recording
c. Handling contract amendments/revisions

2. SPECIFIC TRIAL RELATED ISSUES

2.1 Implementation and termination of the clinical trial

Inspection will review:

a. Distribution of sponsor's duties or functions
b. Information given to investigators and/or specific training
c. Investigator selection and agreements
d. Fulfillment of TMDA requirements
e. Submission and approval of amendments
f. Critical dates: TMDA approval, initiation of the study, patient enrolment period, closing of the trial sites, termination of the study

2.2 Monitoring

Inspectors will check;

a. Monitoring plan/SOPs (availability, content and compliance to it)
b. Frequency and extent of the monitoring activities made
c. Monitors "qualifications
d. Monitoring visit reports and the review of the reports by sponsor/CRO
e. Corrective actions and preventive actions induced by monitoring visits

2.3 Investigational Product(s)

Inspectors will review documentation about:

a. Manufacturing, packaging, labeling and quality control
b. Supplying, accountability, returns and destruction (IP tracking system)
c. Randomization and code breaking
d. Blinding
e. Shipment
f. Condition of shipped product on receipt and during storage

2.4 Safety and adverse events reporting

Inspectors will assess;

a. Notification, follow up and reporting of serious adverse events and other non-serious adverse events requiring expedited reporting according to protocol
b. Safety updates and their communication

2.5 Case Report Form data verification

A selected number of CRFs will be checked to verify:

a. Adherence with the protocol as well as data accuracy, completeness, legibility and timeliness
b. CRF corrections
c. Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well as with IP (s) delivery

2.6 Data handling and clinical trial report (CTR)

Inspectors will assess;

a. Data tracking system from CRF to the database
b. Validation of computer systems used
c. Data Management
d. Statistical analysis as established in the protocol
e. Clinical trial report content
f. Quality control applied
g. System for review of CTR, including signatures

2.7 Clinical trial documentation and archiving

Inspectors will determine if all essential documents listed in the ICH Guidelines for GCP, are available during the inspection.

2.8 Audit (where applicable)

Inspectors will determine if the clinical trial was audited and reports exist.

APPENDIX V: INSPECTION OF BIOANALYTICAL ASPECT, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE TRIALS

1.0 BIOANALYTICAL PART OF BIOEQUIVALENCE TRIALS

1.1 General organization of the site

1.1.1 Activity

The following will be inspected:

a. Nature of the activities carried out at the laboratory
b. Proportion of bioequivalence trials conducted
c. The analytical methods used, particularly for complex methods

1.1.2 Personnel

The following will be inspected:

a. Organization charts, validate the time of the inspection and at the time when the inspected trial was conducted
b. Number and categories of people employed
c. Qualification, training and experience of the personnel
d. Individual work load of people involved

1.1.3 Quality assurance system;

The following will be checked:

a. Quality assurance system in place at the laboratory
b. Existence, availability, accessibility and validity of SOPs
c. List of SOPs used for the trial
d. SOP awareness by people in charge

1.1.4 Installations and equipment

The suitability of the facilities and equipment available, their appropriateness for the activity of the laboratory and for the bioequivalence trial will be inspected.

1.1.5 Archiving of documentation

The following will be inspected:

a. Nature of the documents kept
b. Place of archiving
c. Access control to that place
d. Conditions of storage and of protection of the documents
e. Person responsible for the archives
f. Documentation of file movements
g. Duration of retention of the files

1.2 Sample tracking

1.2.1 Receipt

The following will be checked:

a. Responsibilities for receipt and handling of biological samples
b. Organization of the receipt system, including outside workdays/hours
c. Sample registration
d. Controls performed on receipt
e. Dates and times of receipt of the samples, and acknowledgement of receipt
f. List of samples received for each dispatch
g. Shipment conditions(temperature)
h. Condition of the samples on receipt
i. Any anomalies noted
j. Known sample stability

1.2.2 Storage

The following will be inspected:

a. Storage conditions of the trial samples
b. Compliance of these conditions with the protocol and the conditions used during method validation
c. Assessment of the risk of confusion between samples
d. Identification of the freezer(s)used
e. Temperature records of the freezer
f. Calibration of the thermometer and its traceability to national/international standards
g. Alarms and other surveillance measures
h. Labelling of the samples, if they are still available
i. Documentation of freeze/thaw cycles undergone by the samples

1.2.3 Destruction

Inspectors will check for the date of destruction or return of the samples.

1.3 Sample analysis

1.3.1 Bioanalytical method used

Inspectors will check for consistency of the trial report with the SOP describing the bioanalytical method and other documents available.

1.3.2 Equipment

The following will be inspected:

a. Equipment (make, model)

b. Availability of the equipment. If the equipment is no longer visible at the site at the time of the inspection, review the documentation that could show that the equipment needed was indeed available when the trial was conducted
c. Availability of instructions for use
d. Compliance with specific conditions necessary for the trial, if any
e. Documentation relating to the qualification, checks, and maintenance of the equipment.

1.3.3 Reagents

The main points that will be checked are:

a. Labeling of reagents, including the expiry date
b. Traceability of the reagents used
c. Compliance with specific storage conditions, if any

1.3.4 Reference substances

The main points that will be checked are:

a. Availability and contents of the certificates of analysis; - expiry dates
b. Storage conditions
c. Conditions for access to reference substances

1.3.5 Calibration and control samples

The main points that will be checked are:

a. Dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample
b. Accuracy of the calculation of nominal concentrations
c. Conditions and duration of storage of the stock solutions and working solutions
d. Calibration and control samples, compared to their stability, as described in the validation report
e. Matrix used, including the anticoagulant, if any

1.3.6 Development of the method

A quick overview of the origin and of the development of the bioanalytical method will be assessed to identify critical steps in the procedure.

1.3.7 Method validation

The following will be checked:

a. Validation protocol
b. Dates of the validation
c. Adequate documentation of all operations
d. Completeness of the validation report, when compared to the various experiments performed
e. Consistency of the validation report with the source documents
f. Chromatogram integrations
g. The exclusion of calibration samples, if any

The main validation parameters are the following:

a) Stability:
    i. Of the stock solutions
    ii. Of the samples (bench-top, freeze/thaw cycles, long-term)
    iii. If applicable, of extracted samples before their injection

b) Specificity /selectivity
c) Accuracy
d) Precision
e) Limit of quantification
f) Response function
g) Carry-over
h) In case of mass spectrometric methods: matrix effect
i) Effect of a dilution, if applicable
j) Effect of the anticoagulant

1.3.8 Assays

The following will be checked;

a. Nature and completeness of the documentation available
b. Adequacy of the documentation of all operations
c. Completeness of the analytical report
d. Number, date and composition of the analytical runs
e. Identification of samples and tubes
f. Assessment of the risk of sample mix-ups
g. Assessment of the risk of sample cross-contamination
h. Chromatogram integrations
i. Calculation of the concentrations
j. Compliance with pre-defined criteria for the exclusion of calibration samples
k. Criteria of acceptance of the runs, and compliance with pre-established criteria
l. Audit trail settings and information recorded in the audit trails
m. Practicalities of repeat analysis and the criteria for choosing the result to be reported
n. Maintenance of blinding, if required by the protocol
o. Practicalities of data transfer
p. Consistency of the analytical report with the source documents

2.0 PHARMACOKINETIC AND STATISTICAL ANALYSES

2.1 Pharmacokinetics

The following will be checked:

a. Quality system in place
b. Identity, qualification and responsibilities of the personnel involved
c. Software used
d. Practicalities and control of data entry
e. Sampling times used
f. Method used for calculation of pharmacokinetic parameters

g. Selection of data for the calculation of the terminal half-life, if applicable
h. Consistency of the raw data with the trial report.
i. Pharmacokinetic parameters can be recalculated before or during the inspection if needed.

2.2 Statistics

The following will be checked:

a. Quality system in place
b. Identity, qualification and responsibilities of the personnel involved
c. Software used
d. Practicalities and control of data entry
e. Data line listings and tables of results
f. Consistency of the raw data with the calculated pharmacokinetic parameters and with the trial report

APPENDIX VI: CLINICAL TRIAL INSPECTION MEMORANDUM FORM

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

CLINICAL TRIAL INSPECTION OBSERVATION FORM

Date of Inspection:

Name and address of the site: ……... …… …… ..... Title of study: ……..……..…… …… …… …… …… …… ……	
Item(s) requiring attention: …… …… …… …… …… …… …… …… …… …… …… …… …… ……	Action(s) agreed to be taken: …… …… …… …… …… …… …… …… …… …… …… …… …… ……
Name of inspectors: Signature: 1……. ……. 2……. ……. 3……. …….	Name of inspectees: Signature: 1……. …… 2……. …… 3……. ……

APPENDIX VII: CLINICAL TRIAL INSPECTION REPORT FORMAT

COVER PAGE

1. Title of inspection (activity and title of trial):

2. Name of inspectors

3. Date

1.0 GENERAL INFORMATION

Application Number
Name and Address of inspected site
Date of Inspection
Protocol Number
Version Number
Name of Inspectors
Name and Address of Principal Investigator(s)
Other Investigators
Persons contacted during inspection
Name and Address of Sponsor
Name and Address of Study Monitor
Name of the Investigational Product(s)
Purpose of inspection
Date of previous inspection (if applicable)
Study status (ongoing, closed etc)

2.0 BRIEF INFORMATION OF THE SITE

3.0 BRIEF DESCRIPTION OF THE TRIAL

4.0 DESCRIPTION OF THE INSPECTION

5.0 STANDARD AGAINST WHICH INSPECTION WAS CONDUCTED

6.0 SCOPE OF INSPECTION

7.0 FINDINGS

7.1 Organization and Management
7.2 Facility and Equipment
7.3 Management of Investigational Product(s)
7.4 Review of Data and Informed Consent
7.5 Assessment of Efficacy and Safety Data
7.6 Documentation

7.7 Computerized system
7.8 Monitoring and Auditing
7.9 Clinical Laboratory

8.0 SUMMARY OF THE FINDINGS/OBSERVATIONS

Critical, major and minor observations should be summarized. Other actions taken during inspection should as well be noted down.

9.0 CONCLUSIONS

Depending on the findings of the inspection, the conclusion will be either of the following;

a) Conclusion for critical non-conformances

Based on the findings of the inspection, the conduct of the trial entitled "…....." did not comply with TMDA GCP guidelines, ICH - GCP/GCLP, the Tanzania Medicines and Medical Devices Act Cap 219 and its clinical trials control Regulations, 2013.

The Principal Investigator is hereby directed with immediate effect to stop recruitment/enrolment of new study participants (*in case of safety issues of IP for all participants will also be stopped*). In addition PI should take medical care of all participants who have been enrolled.

b) Conclusion for Major non-conformances

Based on the findings of the inspection, a decision on the compliance of the conduct of the trial entitled "……..." with TMDA GCP guidelines, ICH - GCP/GCLP, the Tanzania Medicines and Medical Devices Act Cap 219 and its clinical trials control Regulations, 2013 will be made after the Principal Investigator response to the observations has been assessed.

The Principal Investigator is expected to respond to all non – conformances observations and for each include a description of the corrective action implemented or planned to be implemented, and the date of completion or target date for completion. In addition, for observations classified as "major", supporting documentation should be submitted with the response as objective evidence of completion of corrective actions. The acceptability of corrective actions will be assessed through evaluation of the response to each observation and will be followed up by early re – inspection of the site to verify effective implementation of corrective actions.

c) Conclusion for Minor non-conformances

Generally, it was observed that the conduct of the trial entitled "……..." is in accordance with the Tanzania Medicines and Medical Devices Act Cap 219 and its clinical trials control Regulations, 2013 and applicable guidelines.

The Principal Investigator should rectify all non - conformances which were noted and submit report on CAPA.

RECOMMENDATIONS

Title	Name of Inspector	Signature	Date

APPENDIX VIII: LIST OF CRITICAL OBSERVATIONS

1. Clinical trial not authorized by TMDA.
2. Sponsor imported drugs for the purpose of conducting clinical trials without having received authorization from TMDA prior to importation.
3. Use of prohibited substance(s) without having received prior authorization.
4. Misrepresentation or falsification of information of data submitted to obtain authorization to conduct clinical trials.
5. Clinical trial on-going after authorization suspended or cancelled.
6. Importation of a clinical trial drug when authorization is suspended or cancelled.
7. Information contained in the application for amendment falsified, misleading or deceptive.
8. Failure to notify TMDA after amendments was implemented in cases where the clinical trial endangered the health of trial participants or other persons.
9. Failure to stop a clinical trial during a suspension or cancellation.
10. Evidence of fraud such as "fabricating" subjects, falsification of study data.
11. Statement/s on label is/are false or misleading.
12. Sponsor withholding data (e.g.: for purpose of deception).
13. No records of serious adverse drug reactions which occurred inside and/or outside Tanzania.
14. No records in respect of use of a drug in a clinical trial.
15. No records with respect to enrollment of clinical trial subjects.
16. Providing false, misleading or deceptive samples of the drug or additional information relevant to the drug or the clinical trial.
17. Principal Investigator does not have the qualifications to conduct the clinical trial.
18. Decisions related to the trial are not under the supervision of the Principal Investigator.
19. Trial related medical care decisions not under the supervision of the physician.
20. Drug not manufactured, handled or stored in accordance with the applicable good manufacturing practices (GMP) requirements.
21. Sponsor failed to report serious and unexpected adverse drug reactions to TMDA.

Note: The List is not exhaustive for all critical observations.

APPENDIX IX: LIST OF MAJOR OBSERVATIONS

1. Information contained in the application was incomplete or incorrect.
2. Failure to report EC that previously refused to approve a trial.
3. Failure to disclose all clinical trial sites to TMDA.
4. Failure to provide all necessary information, not previously provided in the application, prior to the sale or importation of a drug at a clinical trial site.
5. Failure to notify TMDA when changes made to the chemistry and manufacturing information or to the approved protocol.
6. Failure to disclose a previous EC refusal.
7. Failure to implement an amendment at a clinical trial site.
8. Failure to provide to TMDA with information regarding an immediate amendment to the protocol.
9. Failure to obtain EC approval of the protocol or the informed consent forms prior to initiation of a clinical trial.
10. Clinical trial was not conducted in accordance with the protocol.
11. Protocols not amended, informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the clinical trial drug which endanger the health of the clinical trial subject or other person.
12. Failure to obtain EC approval prior to implementation of amendments to protocol or informed consents forms.
13. Informed consents not administered properly or not signed and dated.
14. Informed consent not obtained from subjects before enrollment in the trial or after major amendments to the informed consent form.
15. No source data to substantiate clinical trial results.
16. Sponsor did not notify the Principal Investigator of serious unexpected adverse drug reactions that occurred at other sites.
17. No procedures in place for reporting new safety information to the Principal Investigator.
18. Significant clinical endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms.
19. No systems in place for drug accountability.
20. Storage or handling controls in place for drugs were in adequate.
21. Source data was not verified for quality, completeness and integrity.
22. Systems and procedures that assure the quality of every aspect of the clinical trial were not implemented.
23. The informed consent did not contain all of the required information.
24. Inadequate monitoring of the clinical trial site by the sponsor.
25. Individuals involved in the conduct of the clinical trial are not qualified by education, training or experience to perform their respective tasks.
26. Incomplete documentation of protocol deviation.
27. Lack of documentation that Sponsor was informed of protocol deviations.
28. No security procedures in place for electronic records or electronic signatures.
29. The electronic data system was not validated.
30. Sponsor has no or incomplete records of all adverse events which occurred inside or outside Tanzania.
31. Incomplete records respecting the enrolment of clinical trial subjects.

32. No records concerning shipment, receipt, use, disposition, return or destruction of the drug.
33. Quantities of drug not accounted for through the various stages of shipment, receipt, disposition, return or destruction of the lot of the drug.
34. No signed/dated Principal Investigator undertaking for each clinical trial site prior the commencement of his/her responsibilities.
35. Copies of the protocol/amendments and informed consents approved by the EC not retained for each clinical trial site.
36. Absence of EC attestation for each clinical trial site stating that it has reviewed and approved the protocol, the informed consent and that it functions in compliance with GCP.
37. No edit trails for changes to electronic records, to identify who made the changes or when.
38. No provisions for retention of records.
39. Incomplete records in respect of the use of a drug in a clinical trial.
40. Sponsor did not comply with the prescribed timeline for reports of fatal or life-threatening adverse drug reactions.
41. Sponsor did not submit, within the prescribed timeline, an assessment of the importance and implication of any findings made.
42. Sponsor did not inform TMDA that the clinical trial was discontinued in its entirety or at a clinical trial site within 15 days after the date of the discontinuance.
43. Sponsor did not provide to TMDA with the reasons for the discontinuance and its impact on the proposed or on-going clinical trials.
44. Sponsor did not inform all Investigators of the discontinuance of a trial, the reason for the discontinuation or did not advise them in writing.
45. Sponsor did not stop the sale/importation of the drug as of the date of the discontinuance.
46. Sponsor, after having discontinued a clinical trial, resumed selling or importing the drug without having submitted the required information to TMDA.
47. Clinical trial ongoing at one or more sites after Sponsor stated that the trial was discontinued at those sites.

Note: The List is not exhaustive for all major observations.

APPENDIX X: LIST OF MINOR OBSERVATIONS

1. Sponsor did not maintain copies of previous investigator's brochures pertaining to the clinical trial drug.
2. Date for the commencement of a clinical trial at one or more trial sites was earlier than that stated in the application.
3. Sponsor did not notify TMDA in writing within 15 days after the date of the change that requires notification.
4. Delegation of tasks incomplete, signature login complete.
5. Correction of data not initialed and/or dated.
6. Minor errors in transcribing data from source documents to case report forms.
7. Source data stored in unsecured location.
8. Labeling of the products not complying with requirements.

Note: The List is not exhaustive for all minor observations.

Bibliography

Department of Health. (2000). *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*, Johannesburg, South Africa.

Health Canada, http://www.hc-sc-gc.ca(Accessed: 17th June, 2008)

ICH. (1996). *Guideline for Good Clinical Practice*, E6 (R1), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Recommended for Adoption at Step 4 of the ICH Process by the ICH Steering Committee.

MHRA. (2006). GCP Inspection Findings Classification, Medicines and Healthcare products Regulatory Authority, London, United Kingdom.

MHRA. (2007). Guidance for Formulating Responses to GCP Inspection Findings, Version 1, Medicines and Healthcare products Regulatory Authority, London, United Kingdom.

MHRA. (2007). Routine Inspection Process, Medicines and Healthcare products Regulatory Authority, London, United Kingdom.

Pharmacy Board. (2002). Inspectors Handbook, Pharmacy Board, Ministry of Health, Dar-es-Salaam, Tanzania.

SANAS. (2008). Checklist for GCLP, pp. 1 – 35, South African National Accreditation System, South Africa.

SANAS. (2005). Checklist for Good Clinical Practice, pp. 1 – 41, South African National Accreditation System, South Africa.

TMDA. (2008). Draft Guidelines for Application to Conduct Clinical Trials in Tanzania, Tanzania Medicines and Medical Devices Act, Dar-es-salaam, Tanzania.

TMDA. (2007). Draft Good Manufacturing Practices Inspection Manual, Tanzania Medicines and Medical Devices Act, Dar-es-salaam, Tanzania.

TMDA. (2003). The Tanzania Medicines and Medical Devices Act, No.1, 2003, Government Printer, Dar-es-salaam, Tanzania.

WHO. (2002). Handbook for Good Clinical Research Practice: Guidance for Implementation, World Health Organization, and Geneva, Switzerland.

WHO. (1995). Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products, Technical Report Series No. 850, Annex 3, World Health Organization, Geneva, Switzerland.

NPRA. (2018).Malaysian Guideline For good Clinical Practice (GCP) Inspection