Second Edition

Malaysian Guideline *for* Good Clinical Practice (GCP) Inspection

National Pharmaceutical Regulatory Agency
(NPRA)
Ministry of Health Malaysia

MALAYSIAN GUIDELINE FOR
GOOD CLINICAL PRACTICE (GCP) INSPECTION

National Pharmaceutical Regulatory Agency

Ministry of Health Malaysia

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This Guideline is adapted from:

1. EMA. (2007). *Annex I to Procedure for conducting GCP inspections requested by the EMEA: Investigator Site*. (INS/GCP/3/I)
2. EMA. (2007). *Annex II to Procedure for conducting GCP inspection requested by the EMEA: Clinical Laboratories* (INS/GCP/3/II)
3. EMA. (2012). *Annex III to Procedure for conducting GCP inspection requested by the EMEA: Computer Systems*. (INS/GCP/3/III-Rev 1)
4. EMA. (2007). *Annex IV to Procedure for conducting GCP inspections requested by the EMEA: Sponsor and/or Contract Research Organization (CRO)*. (INS/GCP/3/IV)
5. US FDA. Code of Federal Regulations, *Title 21 Parts 11: Electronic records; electronic signatures*. (21CFR11)
6. US FDA. Code of Federal Regulations, *Title 21 Parts 50: Protection of human subjects*
7. US FDA (2014) *Guidance for Industry Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*
8. CANADA. Health Canada. (2008). *Classification of observations made in the conduct of inspections of clinical trials.* (GUIDE-0043)
9. MHRA (2007). *Guidance for formulating responses to GCP inspection findings version 1.*

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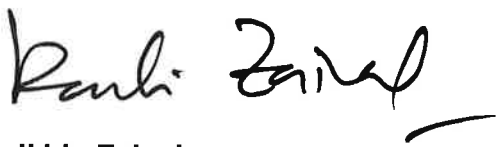
FOREWORD

Clinical research has been identified as one of the entry point projects in National Economic Transformation Program since 2010. With increasing number of clinical trials conducted in Malaysia, concerted effort is of the utmost important to ensure GCP compliance to protect the rights, safety and well-being of trial subjects as well as to ensure the integrity of clinical trial data.

GCP inspections are carried out by NPRA inspectors to verify the conduct of trials in accordance to Malaysian Guideline for Good Clinical Practice, ethical standards and other regulatory requirements. The First Edition of Malaysian Guideline for GCP Inspection was developed in 2010. It is now revised to serve as the latest guidance for the coordination, preparation, conduct and reporting of GCP inspections.

This guideline is intended to provide comprehensive information on GCP inspections at the clinical trial sites, sponsor site and/or contract research organisation site. The revised guideline also addresses observations or non compliances identified during the inspection including classifications, corrective and preventive actions involved. The examples listed in the guideline merely served as illustrations and should be interpreted on a case to case basis.

Finally, I would like to extend my appreciation and congratulations to the working committee for their contribution in this second edition of the Malaysian Guideline for GCP Inspection.



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INC Research
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ABBREVIATION

ADR	Adverse Drug Reaction
CRF	Case Report Form
CRO	Contract Research Organisation
CTIL	Clinical Trial Import Licence
CTR	Clinical Trial Report
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Council of Harmonisation
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
IVRS	Interactive Voice Response System
NPRA	National Pharmaceutical Regulatory Agency
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Drug Reaction

1.0 INTRODUCTION

The National Pharmaceutical Regulatory Agency (NPRA) has the responsibility for the inspections and investigations in all clinical trials pertaining to medicinal products for human use.

Following the decision made by Ministry of Health on the National Medicines Policy, there should be an established requirement for compliance with Good Clinical Practice for all clinical studies pertaining to medicinal products for human use to determine whether the clinical studies were conducted in accordance with applicable regulatory requirements which include regulations, ethical standards, the Malaysian Guidelines for Good Clinical Practice and the Declaration of Helsinki.

The Drug Control Authority (DCA) had endorsed Guideline for Good Clinical Practice inspection in accordance with the regulation 29 under Control of Drugs and Cosmetics Regulation 1984 in the 221 meeting on the 29th October 2009. The Malaysian Guidelines for Good Clinical Practice Inspection will integrate the principles of GCP as described in the Malaysian Guidelines for Good Clinical Practice, regulations and also to ensure that the clinical trials are carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki. This may include but may not be limited to conducting clinical trials in accordance with the approved protocol, that the data generated are accurate; that subjects enrolled in clinical trials are not subjected to undue risks and that the trial is conducted in accordance with the generally accepted principles of GCP.

Clinical trials may be inspected while the trial is still on-going, when subjects were currently enrolled in a trial or completed. An inspection may also be conducted when triggers by a complaint or there is a suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct.

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

The objectives of a GCP Inspection are to:

- Ensure the rights, safety and well-being of study subjects have been protected
- Determine whether the trial was conducted in accordance with applicable regulatory requirements, ethical standards and Malaysian Guidelines for Good Clinical Practice
- Determine whether the data submitted in the dossier are credible and accurate
- Assure the integrity of scientific testing and study conduct
- Take corrective action to ensure compliance and enforcement actions when deemed necessary

2.0 TERMS AND DEFINITIONS

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 should be considered adverse drug reactions. 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.

Regarding marketed medicinal products, ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable 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.

Approved Training in Good Clinical Practice
Training which is approved by the National Committee for Clinical Research. The content of the training must incorporate the curriculum as stipulated by the committee.

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 object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

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

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

contract.

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

Compliance
The state of conformity of a regulated party or a product with a legislative or regulatory requirement or a recognised standard or guideline.

Direct Access
Permission to examine, analyse, verify and reproduce any records and report 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 subjects' identities and sponsor's proprietary information.

Drug
Includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for medicinal purposes.

Drug Control Authority (DCA)
An authority set up under the Control of Drugs and Cosmetics Regulations 1984 and as such its responsibility, role and mandate are defined by law.

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

Independent Ethics Committee (IEC)
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific 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 favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in Malaysian Guideline for GCP.

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

Inspector
Any person appointed to be an inspector under Section 3 of Dangerous Drugs Act 1952, Section 31 of Poisons Act 1952, Section 21 of Registration of Pharmacists Act 1951, Section 6A of Medicines (Advertisement and Sale) Act 1956, Section 3 (1) and Section 3 (2) of Sale of Drugs Act 1952.

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

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

Investigation
Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that non-compliance has occurred and that enforcement measures may be necessary (e.g. product quality complaints, reports from other regulatory authorities, reports of adverse reactions).

Observation
A deviation or deficiency noted by an Inspector during an inspection.

Product
a. A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose.
b. A drug to be used as an ingredient for a preparation for a medicinal purpose.

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

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

3.0 CONDUCT OF GCP INSPECTION

3.1 Categories of GCP Inspection

The inspection of clinical trials usually will be initiated in close collaboration with the Center for Product Registration, NPRA. These inspections may be routine or may be triggered by issues arising during the assessment of the dossier or by other information such as previous inspection experience. The inspections may be requested during the initial review of a product registration, but could arise post-registration (e.g. inspection of studies conducted or completed as part of the condition of a product registration or because of concerns arising about the studies previously submitted).

Description of the inspection categories are as follows:

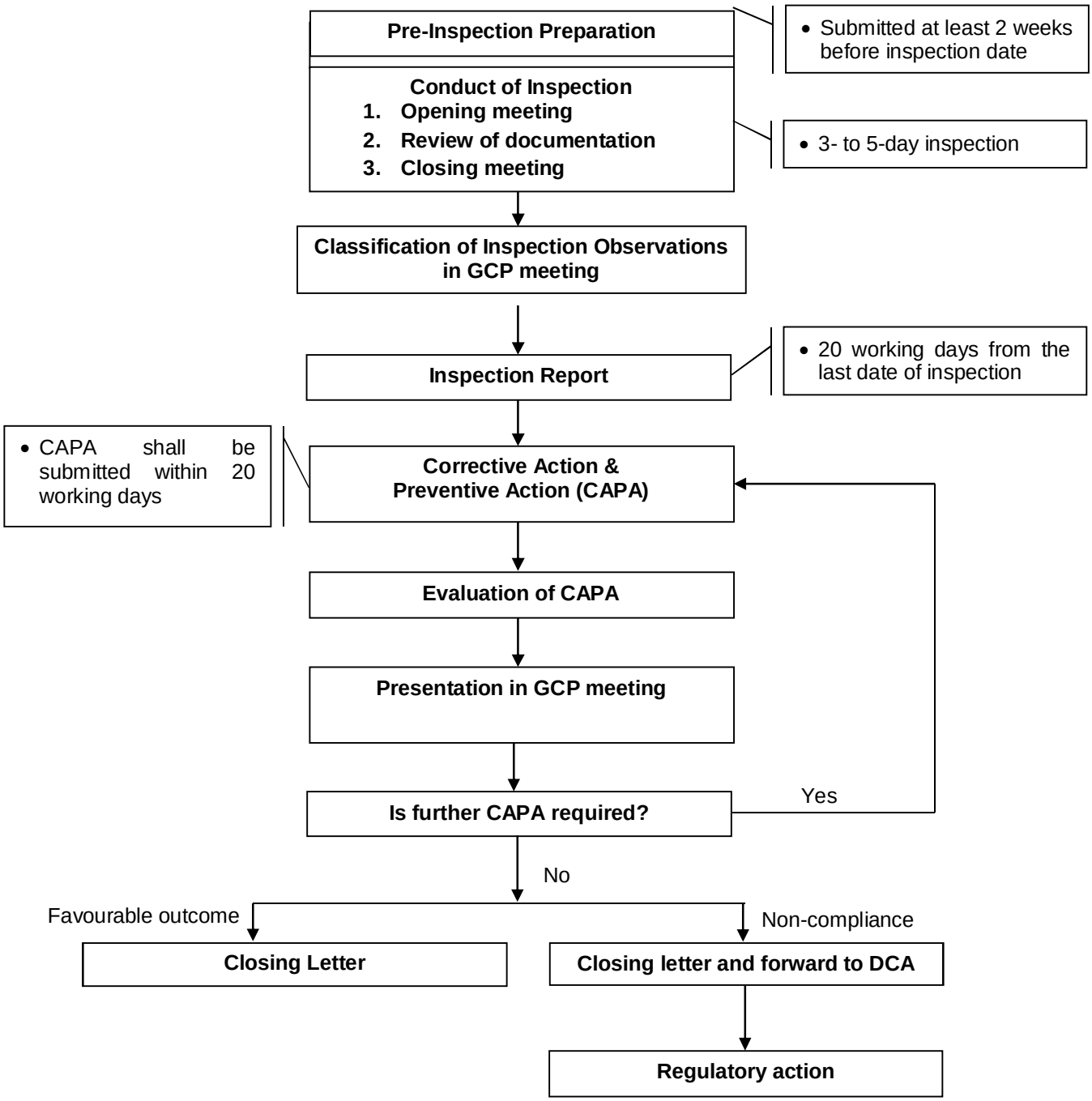
Routine inspection

Routine inspections are inspections carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements. These routine inspections should have a random element in that not all applications for product registration to the NPRA would necessarily give rise to a GCP inspection. However clinical trials and sites should be selected based on a set of criteria to ensure that a range of different situations are covered (e.g. origin of pivotal data, target population, type of product, application to the NPRA, etc.).

Triggered inspection

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

3.2 Flow Chart of GCP Inspection



3.3 Conduct of GCP Inspection

An inspection shall be conducted based on an established inspection plan. The plan will be based on the type and scope of the inspection.

Initiation of Inspection
NPRA generally will contact the licence holder before an inspection arrives at the inspection site. However, unannounced inspection may be occurred for triggered inspection. For announced inspection, an announcement letter containing the date of inspection, objective of inspection, duration of inspection, name of inspectors, inspection schedule and pre-inspection documents to be submitted to NPRA would be issued to the inspectee for all types of inspections. Under normal circumstances, the inspectee shall be required to submit the pre-inspection documents before the agreed inspection date.

Opening meeting
The inspection begins with an opening meeting between the inspectors and representative(s) of the inspectee. The lead inspector shall chair the meeting and highlight the objectives of the meeting which includes (but not limited to):

- Introduce the inspectors
- Highlight the scope and the objectives of the inspection
- Explain the regulatory framework for the conduct of the inspection
- Inform the delegation of duties among the inspectors
- Explain the methods and procedures to be used during the inspection
- Confirm that the resources, documents and facilities needed by the inspector(s) are available
- Confirm the time and date for the closing meeting and interim meetings, if any.

This shall be followed by a presentation from the representative of the inspectee on the current activities, workload and function of each department for the conduct of the clinical trial. An attendance will be kept by the inspectors.

Conduct of inspection
The inspection activities will be detailed in the agenda. During the inspection, the inspector(s) reserve the right to make adjustments to the inspection plan in the agenda to ensure all the inspection objectives are achieved.

Inspector(s) shall be granted direct access to all source data/documents, books, records and reports in hardcopy or softcopy that are relevant to the inspection. Direct access is defined as permission to examine, analyse, verify and reproduce any records and reports that are important to the inspection process. If the inspectors are denied direct access to the documents and/or facilities which the inspector has legal access, these refusals will be documented and included in the inspection observations. Refusals may result in the data not being accepted by the DCA for registration of products.

For each type of site to be inspected as well as for the archiving, the following appendices provide detailed items that may be checked during the inspection

- Appendix I: Conduct of Inspection At Investigator Site
- Appendix II: Conduct of Inspection At Clinical Laboratories
- Appendix III: Conduct of Inspection on Computerised Systems
- Appendix IV: Conduct of Inspection At Sponsor Site And/Or Contract Research Organisations

Every item listed should be checked, if applicable, how data was generated, collected, reported, analysed or modified.

Inspectee shall ensure that its management and other key personnel are available during the inspection in the event that their input is required by the inspectors. The inspectee shall also make available a room for document examination as well as assist in any other inspection related activities.

Closing meeting
The lead inspector shall be the chair for the closing meeting and should be participated by the representatives of the inspectee(s). In this meeting, all observations will be shared with the inspectee(s) verbally. At the end of the session, representatives from the inspectee will be given the opportunity to clarify on the observations made by the inspectors. Attendance will be kept by the inspector and an acknowledgement will be obtained from the representatives of the inspectee(s) on the evidences collected during the inspection.

3.4 Inspection report and CAPA

All observations will be classified as per definitions in *Section* 6.0 and presented as a written inspection report. The inspectee(s) shall receive a written inspection report detailing the observations within 20 working days from the last day of inspection. The inspectee(s) should provide a written Corrective And Preventive Actions (CAPA) in response to the observations within 20 working days from the date of the inspection report. If the assessed CAPA(s) is/are deemed unsatisfactory by the committee, additional CAPAs may be requested and shall be resubmitted to the inspector no later than 20 working days. Inspectors will issue a closing letter to the site after review the CAPAs.

4.0 OUTCOME OF GCP INSPECTION

4.1 Favourable Outcome

Once all observations have been satisfactorily addressed with the necessary CAPAs, the lead inspector shall propose for the inspection to be closed in the GCP Meeting. The inspection report will be forwarded to the Center for Product Registration. A letter would be issued to notify the inspectee(s) that the inspection has been closed.

4.2 Non Compliance

When the CAPAs are not satisfactorily addressed or the findings are remained, the lead inspector shall propose the non-compliance issues in the GCP meeting. The non compliance issues will be forwarded to the Center for Product Registration for consideration. A letter would be issued to notify the inspectee(s) that the inspection has been forwarded to Center for Product Registration.

If DCA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with GCP or applicable regulatory requirements, or has repeatedly or deliberately submitted to DCA false information in any required report, DCA may decide to take regulatory actions against the CTIL/CTX holder, Product Registration Holder and/or investigator. Regulatory actions comprise of administrative actions and disqualification of investigator to use investigational product.

Administrative Actions
On the basis of the inspectee's response, NPRA may schedule a triggered/verification inspection to confirm the adequacy of CAPA. In the event that the CAPA responses are found to be unsatisfactory, the inspector will propose in the GCP Meeting to seek the opinion of DCA. The DCA may decide to take regulatory actions against the CTIL/CTX holder, Product Registration Holder and/or investigator. Until the CTIL/CTX holder, Product Registration Holder and/or investigator takes appropriate corrective action, DCA may:

- Reject the registration of product where the overall clinical trial data contain elements of fraud, manipulation and intentional misrepresentation of data.
- Withhold approval of new studies that are related to the inspectee
- Excluding data generated from the site with GCP violation
- Direct that no new subjects to be recruited to the affected ongoing study
- Terminate ongoing studies when doing so would not endanger the subjects

Disqualification of investigator to use Investigational Product

DCA may disqualify the investigator from involvement in any part of the application of CTIL/CTX for clinical trial purposes if the DCA determines that:

- The investigator has fraud, manipulation and intentional misrepresentation of data or repeatedly or deliberately failed to comply with Malaysia's regulatory

requirements, Malaysian Guideline for Good Clinical Practice or other established guidelines, or

- The non-compliance adversely affects the rights, safety and well-being of the human subjects in a clinical trial.

Based on the inspection report, the response/ CAPAs taken by the CTIL/CTX holder/ investigator, recommendation from the Center for Investigational New Product and/or Center for Product Registration, DCA will make the final decision based on above regulatory action.

An investigator who has been determined to be ineligible to use investigational product may be reinstated as eligible. The investigator shall apply to DCA for reinstatement as eligible after reattend the NCCR approved GCP course and pass the GCP examination. DCA may reinstate the investigator after determined the investigator has presented adequate assurances that the investigator will comply to the GCP and applicable regulatory requirements in clinical trials that involved investigational products.

5.0 REFUSAL OF INSPECTION

Inspector(s) have the right to enter any sites involved to carry out inspections, take samples, require the production of books and documents, and to take copies of, or copies of entries in, such books and document which inspector(s) reasonably believes would furnish evidence of the inspection and observations without any redaction. Obstructing an inspector(s) intentionally during the conduct of inspection may lead to non-acceptance of studies for registration purposes.

Circumstances that would constitute delaying, denying, limiting or refusing an inspection are as below:

Delay of inspection
Delay may occur for many reasons, some of which are beyond the control of the facility. Delay scheduling pre-announced inspections, delay during an inspection and delay producing records without reasonable explanation are considered obstruction of inspection.

Denial of inspection
DCA interprets the word deny to include active behavior by the owner, operator or agent of a medicinal product facility to prevent GCP inspectors from conducting an inspection or to prevent GCP inspectors from completing an inspection. This includes statements or physical actions intended to avoid inspection or to mislead, deceive or impede the GCP inspectors.

Limiting of inspection
Any personnel who prevents GCP inspectors from conducting an inspection to the extent allowable under the applicable regulatory guidelines may be reviewed as limiting inspection.

Limiting access to facilities
Preventing GCP inspectors to have reasonable access to an area of the site that the inspector is entitled to inspect may be considered limiting an inspection.

Limiting photography
Photographs are an integral part of GCP inspection because they present an objective and contemporaneous representation of facility conditions. Impeding of resisting photography by GCP inspectors may be considered a limitation if such photographs are determined by the inspectors to be necessary to effectively conduct that particular inspection.

Limiting access to or copying of records
Ability to have direct access and copy records is a critical aspect of GCP inspection. Not allowing GCP inspectors access to or copying of records may be considered limiting an inspection.

Refusal to permit entry or inspection
Refuses to permit entry or inspection include active and passive behavior and non-action by the owner, operator or agent of a drug facility/institution/site that results in GCP inspectors not being able to enter or fully inspect the facility.

Refusal to permit entry to any inspection site would be written in the inspection report.

6.0 CLASSIFICATION OF INSPECTION FINDINGS

The classification of the inspection findings is intended to help classify the severity of observations noted during inspections of clinical trials. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity). The inspection findings should be classified as critical, major and minor as per the following definitions.

Observations classified as major may be upgraded to critical when accompanied with an arrow up sign (↑), depending on the quantity and/or nature of the deviations.

Critical

Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.
Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required
Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents, fraud, manipulation and intentional misrepresentation of data.
Appendix A - Examples of observations that are considered critical

Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.
Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or legal action required
Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.
Appendix B – Examples of observations that are considered Major

Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.
Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.
Appendix C – Examples of observations that are considered Minor

FORMULATING RESPONSE TO INSPECTION FINDINGS

Only observations in the inspection report require responses. The observation should be reviewed to determine the issue that the inspector has raised. The inspector is likely to have cited evidence to support the observation and this has the potential for correction and prevention. The finding issue applies to (at least) the cited evidence.

On reviewing the evidence, the inspectee should decide whether the evidence supporting the issue can actually be corrected (e.g. corrective action), prevented (e.g. preventive action) or whether the problem requires documentation only (e.g. in a file note, deviation record etc). Response to inspection findings shall be submitted in both hard copy and soft copy according to the template outlined in Appendix D – Response To Inspection Observation.

Analysis of the Finding
The inspectee should ensure the finding is reviewed to determine the root cause. The following may be used as guidance to determine the root cause.

- Is the finding systematic (could other trials be affected) or isolated?
- What was the cause of the finding?
- Was it a genuine error or oversight?
- Was there a lack of training (individual/ all)?
- Was there no documented procedure?
- If there was a documented procedure, was it not followed or was it inadequate?

Corrective Action
Provide an explanation for the corrective action, eg. Note file, correction records,etc

Preventive Action
Preventive action should include details of any planned amendments to referenced documented systems/ procedures. It may also require training to be undertake and methods to assess the effectiveness of the preventive action.

Timescales
Both corrective and preventive actions, together with suitable timescales should be provided.

Findings relating to other parties (e.g. CRO, Sponsor, Trial Sites)
Some of the findings in the report may be related to the systems/ procedures of another party involved in the clinical trial. A response along the lines of “The point raised has been noted and has been brought to the attention of the related party” is not sufficient. The inspectee is expected to liaise with the related party to generate a comprehensive response for the finding.

APPENDIX A: EXAMPLES OF OBSERVATIONS THAT ARE CONSIDERED CRITICAL

General

- Use of a prohibited substance(s) without having received prior authorisation.

Prohibition

- Clinical Trial Import Licence and Clinical Trial Exemption (CTIL/CTX) is not obtained, as required and in accordance with Controls of Drugs and Cosmetics Regulation 1984 and Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia.

Application for Authorisation

- Misrepresentation or falsification of data submitted to obtain authorisation to conduct clinical trials.

Authorisation

- Clinical trial ongoing after authorisation suspended or cancelled.
- Importation of a clinical trial drug when authorisation is suspended or cancelled.

Amendment

- Information contained in the application for amendment falsified, misleading, or deceptive.
- Failure to notify NPRA after amendment was implemented in cases where the clinical trial endangered the health of trial subject or other person.
- Failure to stop a clinical trial during a suspension or cancellation.

Good Clinical Practices

- Evidence of fraud such as “fabricating” subjects, falsification of study data.

Records

- Sponsor withholding data (e.g. for purpose of deception).

- Failure to report SUSARs which occurred inside and/or outside Malaysia.
- No records in respect of the use of a drug in a clinical trial.
- No records with respect to the enrolment of clinical trial subjects.

Additional Information and Sample(s)

Providing false, misleading or deceptive sample(s) of the drug or additional information relevant to the drug or the clinical trial.

APPENDIX B: EXAMPLES OF OBSERVATIONS THAT ARE CONSIDERED MAJOR

Interpretation

- Voting members of the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) were not independent of the qualified investigator and/or the sponsor of the clinical trial. (↑)
- Approvals of clinical trials without a quorum of members with the required representation.
- Major changes to previously approved protocol that increase health risks to subjects, were given expedited approval only.

Application for Authorisation/CTIL/CTX

- Information contained in the application was incomplete or incorrect. (↑)

Authorisation/CTIL/CTX

- Failure to disclose all Malaysian clinical trial sites for clinical trial that requires CTIL/CTX or which requires notification to NPRA.
- Failure to provide all necessary information, not previously provided in the application, prior to the importation of a drug at a clinical trial site.

Notification

- Failure to notify NPRA when changes made to the chemistry and manufacturing information or to the approved protocol. (↑)

Amendment

- Implementation of an amendment without obtaining authorization from IEC/IRB.
- Failure to implement IEC/IRB approved amendment at a clinical trial site. (↑)

Good Clinical Practices

- Approved investigator does not have the qualifications to conduct the clinical trial. (↑)

- Medical care and decisions related to the trial are not under the supervision of the qualified investigator. (↑)
- Failure to obtain IEC/IRB approval of the protocol and/or the informed consent forms prior to initiation of a clinical trial. (↑)
- Protocols not amended, informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the clinical trial drug which endanger the health of the clinical trial subject or other person. (↑)
- Failure to obtain IEC/IRB approval prior to implementation of amendments to protocol or informed consents forms. (↑)
- Informed consent not obtained from subjects before enrolment in the trial or after major amendments to the informed consent form. (↑)
- Informed consents not administered properly or not signed and dated. (↑)
- Inadequate source data to substantiate clinical trial results. (↑)
- Clinical trial was not conducted in accordance with the protocol. (↑)
- Sponsor did not notify the qualified investigator of SUSARs that occurred at other sites. (↑)
- Qualified investigator did not notify the sponsor and/or IEC/IRB in a timely manner of SUSARs. (↑)
- No procedures in place for reporting new safety information to the qualified investigator.
- Significant clinical endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms. (↑)
- Inadequate systems in place for drug accountability.
- Storage or handling controls in place for drugs were inadequate.
- Source data was not verified for quality, completeness and integrity.
- System(s) and/ or procedure(s) that assure the quality of every aspect of the clinical trial were not implemented.
- The informed consent did not contain all of the required information. (↑)
- Inadequate monitoring of the clinical trial site by the sponsor.

- Individuals involved in the conduct of the clinical trial are not qualified by education, training or experience to perform their respective tasks.
- Incomplete documentation of protocol deviation.
- Lack of documentation that sponsor was informed of protocol deviations.

Records

- No security procedures in place for electronic records or electronic signatures.
- The electronic data system was not validated.
- Sponsor has no or incomplete records of all adverse events which occurred inside or outside Malaysia. (↑)
- Incomplete records respecting the enrolment of clinical trial subjects.
- Incomplete records concerning shipment, receipt, use, disposition, return or destruction of the drug. (↑)
- Quantities of drug not accounted through the various stages of shipment, receipt, disposition, return or destruction of the lot of the drug. (↑)
- No signed/dated qualified investigator undertaking for each clinical trial site prior to the commencement of his/her responsibilities.
- Copies of the protocol/amendments and informed consents approved by the IEC/IRB does not retained for each clinical trial site.
- Absence of IEC/IRB 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. (↑)
- No edit trails for changes to electronic records in order to identify who made the changes or when.
- No provisions for retention of records as required by the Malaysian Guidelines for Good Clinical Practice.
- Incomplete records in respect of the use of a drug in a clinical trial.

Suspected Unexpected Serious Adverse Reactions (SUSARs) Reporting

- Sponsor failed to report SUSARs to NPRA. (↑)
- Sponsor did not comply with the prescribed timeline for reports of SUSARs.
- Sponsor did not submit, within the prescribed timeline, an assessment of the importance and implication of any findings made.

Discontinuance of a Clinical Trial

- Sponsor did not inform NPRA that the clinical trial was discontinued in its entirety or at a clinical trial site within 15 working days after the date of the discontinuance.
- Sponsor did not provide NPRA with the reasons for the discontinuance and its impact on the proposed or ongoing clinical trials.
- Sponsor did not inform all qualified investigator(s) of the discontinuance of a trial, the reason for the discontinuation or did not advise them in writing.
- Sponsor did not stop the importation of the drug as of the date of the discontinuance.
- Sponsor, after having discontinued a clinical trial, resumed importing the drug without having submitted the required information to NPRA.
- Clinical trial ongoing at one or more sites after Sponsor stated that the trial was discontinued at those sites. (↑)

APPENDIX C: EXAMPLES OF OBSERVATIONS THAT ARE CONSIDERED MINOR

Application for Authorisation/CTIL/CTX

- Sponsor did not maintain copies of previous investigator's brochures pertaining to the clinical trial drug.

Good Clinical Practices

- Delegation of tasks incomplete, signature log incomplete.
- Correction of data not initialled and/or dated.
- Minor errors in transcribing data from source documents to case report forms.
- Drug is not manufactured, handled or stored in accordance with the applicable good manufacturing practices.
- Source data stored in unsecured location. (↑)

Labelling

Labelling of the products not complying with requirements of the Controls of Drugs and Cosmetics Regulation 1984 and Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia.

APPENDIX D: RESPONSE TO INSPECTION OBSERVATIONS

Name of Trial Site/Sponsor/CRO	
Address	
Date of Inspection	

No	**Finding** *(Follow the sequence in inspection report)*	**Response**
1.		Corrective Action: Preventive Action:
2.		Corrective Action: Preventive Action:
3.		Corrective Action: Preventive Action:
4.		Corrective Action: Preventive Action:
5.		Corrective Action: Preventive Action:
6.		Corrective Action: Preventive Action:
7.		Corrective Action: Preventive Action:
8.		Corrective Action: Preventive Action:
9.		Corrective Action: Preventive Action:
10.		Corrective Action: Preventive Action:

The inspectee shall provide all the evidences described in the CAPAs in the appendixes. Please submit the CAPAs in both softcopy and hardcopy form.

APPENDIX I : CONDUCT OF INSPECTION AT INVESTIGATOR SITE

1.0 ORGANISATIONAL ASPECTS

1.1 Implementation of the trial at the site

Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts)
- Documentation of delegation of responsibilities by the principal investigator.
- Systems for QA and QC
- SOP system where available
- Disaster plans, e.g. handling of defective equipment and consequences
- Staff - qualification, responsibilities, experience, availability, training programmes, training records, CV
- Numbers of clinical trials being performed and their nature
- Proportion of time allocated to clinical trial work

Inspect the conditions of implementation of the study at the site

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

The inspector should also inspect the dates of the first inclusion/selection of a patient at the site inspected and the last visit of the last patient.

1.2 Facilities and equipment

The aim is to verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the trial. The inspection may include a review of the following:

- Equipment used
- Facilities
- Their suitability for the protocol requirements and the characteristics of the study being inspected

1.3 Management of biological samples

The aim is to examine, conditions and documentation regarding the management of biological samples, if applicable:

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

1.4 Organisation of the documentation

The aim is to determine whether the general documentation (according to Malaysian Guidelines for GCP), is available, dated, signed and if applicable how it is archived at the trial site.

Also it should be determined if the following trial subjects' documents are available, completed and archived at the trial site:

- Source documents (patient's charts, X-ray,etc.)
- Informed consent documents
- Case Report Form (CRF)

- A sample of data should be verified from the study report and or CRF to the source documents

1.5 Monitoring and auditing

The following points should be examined, if available:

- 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, where these have been requested from the sponsor. Actions required by the monitor. Monitoring visits log. Monitoring plan/SOPs
- Audit certificates – if available (from sponsor file)

1.6 Use of computerised systems

If computerised systems have been used for the trial, it will be necessary to ascertain their validation status.

The elements to evaluate during inspection of computerised systems used in clinical trials are established in a separate document. 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, online laboratory data, ECG recording, etc.)

2.0 INFORMED CONSENT OF TRIAL SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with Malaysian GCP Guidelines from an appropriate sample of subjects/patients (including the subjects/patients whose medical records are reviewed), or the subjects' legally acceptable representative, prior to their entry into the study. This needs to include the patients whose medical records are reviewed.

It will be necessary to check:

- The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC/IRB

- The information sheet actually used and approved by the IEC/IRB, in order to determine whether it includes all the elements required by the Malaysian Guidelines for GCP and current regulations
- The centre practice for giving a copy of the informed consent to the patient
- Consent for access to medical records by the authorities

3.0 REVIEW OF THE TRIAL SUBJECT DATA

The aim is to check whether the investigator team conducted the clinical trial according to the approved protocol and its amendments by source data verification. In the source data verification, it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to Malaysian GCP Guidelines(signed and dated by the authorised person who did it and providing justification, if necessary).

For a number of subjects that will be determined within the inspection plan, (the sample might include the first and last patient enrolled etc) the following should be checked:

3.1 Characteristics of the subjects included in the clinical trial

The aim is to determine whether the inclusion of the subjects in the trial was performed in accordance with the approved protocol and/or that protocol violations are documented and also described in the study report.

It should be checked whether:

- Subjects included in the clinical trial existed and participated in the clinical trial
- Subjects' participation was recorded in their medical records
- Subjects included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present. Appropriate medical records must support these criteria

3.2 Subjects' visits calendar

The aim is to determine whether the subjects' visits calendar established in the protocol was followed. This check will include a review of the dates when the trial visits took place in order to evaluate whether they were done on the correct dates.

3.3 Efficacy and safety assessment data

The aim is to verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the trial and whether adequate data management procedures were in place. All data related to endpoints should be compared with source documents, if applicable.

This check will also include whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC/IRB and authorities in accordance with current regulations.

In the safety data verification, it will be necessary to evaluate the premature discontinuation of treatment and drops outs.

3.4 Concomitant therapy and intercurrent illness

Whether concomitant therapy and intercurrent illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

4.0 MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT(S)

The aim is to verify whether all the activities related to the Investigational Medicinal Product(s) have been done according to the protocol.

It will be necessary to review the following documents:

- Instructions for the handling of Investigational Medicinal Product(s) and trial related materials (if not included in protocol or investigators brochure)
- Shipping records for Investigational Medicinal Product(s) and trial related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site), expiration dates and codes assigned to the product and the trial subject

- Documentation regarding allocation of treatment, randomisation and code breaking
- Investigational Medicinal Product(s) accountability at the site (pharmacy or investigator)
- Date and quantity dispensed or returned, identification of recipients (patients code or authorized persons). This record should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject
- Documentation about relabelling, if applicable
- Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject
- Documentation of destruction of Investigational Medicinal Product(s) (if destroyed at the site), dates and quantity. Documentation of return (if not destroyed at the site), dates and quantity
- Treatment compliance

Other activities, as appropriate:

- Check the suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.)
- Specific SOPs for this activity from the pharmacy or institution should be reviewed
- Check whether there was controlled access to the Investigational Medicinal Product(s) from reception to dispensing
- Verification of the labelling for compliance with applicable regulations

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

APPENDIX II: CONDUCT OF INSPECTION AT CLINICAL LABORATORIES

1.0 GENERAL ASPECTS

1.1 Background

Scope of work and responsibilities.

Accreditation status of the laboratory (the methods) e.g. GLP, ISO

- Fulfilment of national requirements of accreditation
- Relevance of accreditation in the context of clinical trial(s)

Proportion of work in connection to clinical trials.

1.2 Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts)
- Systems for QA and QC, including the programme for internal audits
- SOP system (distribution, availability including holidays etc., audit-trail, clinical trials, archiving etc)
- Disaster plans, e.g. handling of defective equipment and consequences
- Staff – qualification, responsibilities, experience, availability, training programme, training records, CV

1.3 Contractual arrangements

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

1.4 Facilities/ Premises

- Suitability and adequacy of premises – e.g. adequate degree of separation of work 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

- Apparatus available in good working order and complies with relevant specifications
- Quality of general supplies including tap water, analytical water, gases etc.
- Records of operation, maintenance, justification and calibration. Records of the validation for the methods used for the measuring equipment and apparatus (including computerised systems) and logbooks.
- Materials and reagents are prepared, labeled and stored under appropriate conditions and adherence to expiry dates. Labels for reagents indicate their identity, source, concentration and expiry dates
- Apparatus and materials used do not alter to any appreciable extent the samples
- Definition of source data and source documents, retrieval and archiving Data generated in automatic systems e.g. listings, graphs, record traces or computer printouts are archived

2.0 TRIAL RELATED ASPECTS

2.1 Handling of samples

Pre-examination

- Samples obtained from subjects in the clinical laboratory (date and time), identification, labelling, conditions, preparation, storage
- Documentation of receipt (date and time), identification, condition, re-labelling and storage of samples by an identifiable person
- Procedures for acceptance or rejection of samples for analysis
- Aliquotting and distribution for examination

Examination

- Compliance with protocol and specified test methods

- Traceability and identification of samples and controls
- Recording of data and acceptance and release of results
- Handling of non-conformance, repeat analysis / re-analysis and results within critical / alert ranges
- Competence, training and experience of personnel

Procedures for disaster recovery

Post-examination

- Storage (anonymisation, decoding), retrieval and destruction of samples

2.2 Material and methods

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

3.0 REPORTING

- Various systems for reporting of results may be required according to the protocol/contract e.g. report per sample (i.e. for immediate consideration in medical care of the subject) or on an integrated basis (i.e. to be used in the trial report). This will affect the procedures used by the laboratory and the inspection.

3.1 Procedures for reporting and evaluation of results and for data transfer.

3.2 Systems for alerting results that are unexpected and/or significant deviations from pre-specified limits.

3.3 Transcription of raw data into the report

- Identification of laboratory
- Unique identification and localisation of the subject
- Identification of investigator
- Date and time of sample collection, and time of receipt
- Date and time of examination and release of report
- Source of primary sample type and any comments of its quality
- Description of the examination and of its results
- If applicable, detection limit, uncertainty of each measurement and reference intervals
- Where appropriate, interpretation of results and other comments
- Identification of the person releasing the report

3.4 Attribution of review and release of the report(s) to responsible personnel.

3.5 Procedures for alterations and amendments of reports.

3.6 Procedures for complaints and corrective actions.

4.0 QUALITY ASSURANCE

4.1 Integrity of data reported by internal QA/QC and / or sponsor's QA/QC personnel, (audit certificate).

APPENDIX III: CONDUCT OF INSPECTION ON COMPUTERISED SYSTEM

The following guidelines shall be used as references for inspection on Computerised Systems:

- PIC/S Guidance on Good Practices for Computerised Systems in Regulated "GXP" Environments (PI 011-3). The hyperlink to the PIC/S site is http://www.picscheme.org/index.php
- Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, EMA, 2010
- CDISC (Clinical Data Interchange Standards Consortium) Clinical Research Glossary Version 8.0, 2009
- Code of Federal Regulations. Title 21-Food and Drugs; Part 11: Electronic Records; Electronic Signatures. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=11&showFR=1

APPENDIX IV: CONDUCT OF INSPECTION AT SPONSOR SITE AND/OR CONTRACT RESEARCH ORGANISATION (CRO)

1.0 SPONSOR OR CRO QUALITY SYSTEM INSPECTION

The aim of this kind of inspection is to evaluate the quality assurance and quality control systems established by the sponsor/CRO in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The following items should be reviewed in a sponsor/CRO system inspection:

1.1 Organisation and personnel

The aim is to evaluate if the sponsor/CRO has a well-established organisation for clinical research activities and has a sufficient number of properly qualified and trained personnel for each area.

Review:

- Organisational charts that identify the key personnel in each area
- The independence of the quality assurance unit
- The job description, qualifications and training of the individuals involved at any stage of the clinical trial process

1.2 Facilities and equipment

The aim is to identify and evaluate the facilities used for archiving or investigational medicinal product(s) storage as well as the equipment used. Special attention should 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 Sponsor/CRO Operating Procedures

Procedures should be reviewed in order to verify their compliance with GCP standards and applicable regulations.

Implementation and termination of the clinical trial

The aim is to evaluate the procedures established for the implementation and termination of the clinical trial.

Review the procedures for:

- Document preparation(format and content and distribution of protocol, protocol amendments, informed consent documents, investigator brochure, CRF and any other trial documents)
- Investigators selection and training.
- Regulatory compliance(obtaining EC approval/favourable opinion and necessary authorisations, providing notifications and reports as required by GCP and local regulations)

Monitoring

The aim is to evaluate the system established for monitoring clinical trials.

Determine if procedures include:

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

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

Investigational Medicinal Product(s)

The aim is to determine if sponsor procedures for different stages of the investigational medicinal product cycle are according to the current GMP, GCP and applicable regulations.

Determine if these procedures establish provisions for:

- Quality control requirements
- Manufacturing, packaging and labelling
- Supplying, accountability, returns and destruction
- Randomisation and code breaking

Sample management

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

Safety and adverse events reporting

The aim is to verify procedures for reviewing and communicating findings that could adversely affect the safety of subjects and the reporting of serious adverse events to regulatory authorities, investigators and IECs/IRBs, where applicable.
Review procedures for:

- Expedited Adverse Drug Reaction reporting to regulatory authority(ies), investigators and IEC/IRB, where applicable
- Serious adverse events notification by investigators
- Management of the serious adverse events reported by investigators
- Safety updates and periodic safety reports
- Validation of computer systems used
-

Data handling and clinical trial report

The aim is to evaluate the system established by the sponsor/CRO for handling the data obtained during the clinical trial and reporting it in the clinical trial report.
Determine if the procedures establish:

- Data handling, data analysis and their control procedures
- Clinical trial report preparation according to ICH standards
- Validation of the computerised systems used
- Audit trails (for paper and computer systems)

Documentation archiving

The aim is to 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 Malaysian Guidelines for GCP) is available, complete and maintained in good conditions during the period of time established.

Determine if procedures include:

- System for archiving and retrieval of documents
- Controlled access to the archives

Sponsor audit and quality assurance system

The aim is to determine if the sponsor/CRO has established an audit system, as part of its own quality assurance system in order to evaluate its activities related to clinical trials.

It should be determined if the procedures include:

- Audits of key clinical trial processes including monitoring, data management, safety reporting, clinical study report production, archiving and computer system validation activities
- Audits of contractors/sub-contractors

The inspectors should 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 non-compliance
- Audit trails
- Procedures for generation and implementation of audit programme(s)/plan(s)

Delegation of duties

The aim is to verify the procedures for contracting/subcontracting of trial-related duties. Inspectors should examine the procedures related with:

- Pre-selection and ongoing assessment of contractor/subcontractors
- Documentation of duty delegation and its time recording
- Handling contract amendments

- Contracts should be reviewed (either specific ones or a sample)

2.0 SPECIFIC CLINICAL TRIAL INSPECTION

The aim of this type of inspections is to verify if the trial has been conducted, data has been generated, documented and reported in compliance with the protocol, GCP principles and sponsor procedures. The procedures and requirements applicable at the time of the trial should be considered, and compared where relevant to those applying at the time of the inspection.

The specific clinical trial inspections could also be conducted to answer questions listed in the request for a GCP inspection.

The aspects that should be checked include:

2.1 Implementation and termination of the clinical trial

The aim is to determine if all legal and administrative aspects of the clinical trial have been accomplished.

Review:

- Distribution of sponsor's duties or functions
- Information given to investigators and/or specific training
- Investigator selection and agreements
- Fulfilment of regulatory requirements(IEC/IRB approval/favourable opinion and necessary authorizations)
- Submission and approval of amendments
- Critical dates: IEC/IRB approval/favourable opinion, regulatory authorisation (where required) initiation of the study, patient enrolment period, closing of the trial sites, termination of the study

2.2 Monitoring

Inspect :

- Monitoring plan/SOPs (availability, content and compliance to it)
- Frequency and extent of the monitoring activities made
- Monitors' qualifications

- Monitoring visit reports and the review of the reports by sponsor/CRO
- Corrective actions induced by monitoring visits

2.3 Investigational Medicinal Product(s)

Inspect the documentation about:

- Manufacturing, packaging, labelling and quality control
- Supplying, accountability, returns and destruction (investigational medicinal product(s) tracking system)
- Randomisation and code breaking
- Blinding
- Shipment
- Condition of shipped product on receipt and during storage

2.4 Safety and adverse events reporting

Inspect:

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

2.5 Case Report Form data verification

A selected number of CRFs should be checked to verify:

- Adherence to the protocol as well as data accuracy, completeness, legibility and timeliness
- CRF corrections
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well as with investigational medicinal product(s) delivery

2.6 Data handling and clinical trial report (CTR)

Inspect:

- Data tracking system from CRF to the database

- Validation of computer systems used
- Data Management
- Statistical analysis as established in the protocol
- Clinical trial report content
- Quality control applied
- System for review of CTR, including signatures

2.7 Clinical trial documentation and archiving

Determine if all essential documents listed in the Malaysian Guidelines for GCP are available during the inspection.

2.8 Audit

Determine:

- If the clinical trial was audited and audit reports exist
- Qualification of the auditors