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## GUIDELINES ON GCP INSPECTION

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NATIONAL MEDICINE REGULATORY AUTHORITY  
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# GUIDELINES ON GCP INSPECTIONS

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## 1. INTRODUCTION

Good Clinical Practice (GCP) inspection is necessary to ensure the protection of the rights, safety and wellbeing of study subjects and to assure the integrity of scientific testing and study conduct. It helps to determine whether the trials are conducted in accordance with GCP guidelines, ethical standards and other applicable regulatory requirements. This includes attention to the safety and integrity of trial subjects as well as good data quality.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting recording and reporting of clinical trials. An internationally aligned regulatory framework will strengthen health authority at the competitive and vibrant global clinical research market while ensuring utmost safety of the trial participants.

As defined by the ICH E6 GCP, an inspection is the act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the trial site, at the sponsors and/or CRO's facilities, or at other establishments deemed appropriate by the regulatory authority.

All clinical trials including bioavailability and bioequivalence studies, be designed, conducted, recorded and reported in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with ICH GCP and the applicable regulatory requirements.

## 2. PURPOSE

The purpose of this document is to provide guidance to all the stake holders involved in the trial particular for investigators on the overview of conduct of the GCP inspections by the National Medicines Regulatory Authority (NMRA).

## 3. BACKGROUND

Regulation 22 (2) of National Medicines (Clinical Trials) Regulations No. 2145/2 of 14.10.2019 stipulates that any site involved in a clinical trial may be subjected to the GCP inspection by the Authority.

Clinical trials that require regulatory approval of the NMRA as stipulated in Clinical Trials Regulations need to undergo regulatory review by the Clinical Trials Evaluation Committee (CTEC) and have ethics clearance from a NMRA recognized ethics review committee prior to getting the letter of authorization for the conduct of such trial. The trial must comply with the relevant approved protocol, applicable clinical trial regulations, relevant ICH guidelines and standard operating procedures. Compliance with these requirements provides an assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are accurate and credible.

Selection of trial sites for GCP inspection in multi-centre clinical trials would be based on following criteria's.

- i. Nature of intervention
- ii. Inclusion of vulnerable populations to trial
- iii. Trial sites with more patients
- iv. Facilities in the trials site
- v. Nature of IMP
- vi. Trial sites with more deviation to standard guidelines
- vii. Trial Sites to which a complaint has been received

#### 4. SCOPE

This guidance applies to:

- (i) Clinical trials which require a letter of authorization from NMRA, as stipulated in Clinical Trials Regulations No. 2145/2 of 14.10.2019.
- (ii) Bioequivalence and bioavailability studies conducted as a requirement for marketing authorization in Sri Lanka.

#### 5. OBJECTIVES OF GCP INSPECTIONS

NMRA may conduct GCP inspections typically under the following circumstances:

- To verify the accuracy and reliability of data that has been submitted
- To investigate a complaint about the conduct of the study at a particular site;
- Upon termination of the clinical site;
- During ongoing clinical trials to provide real-time assessment of the investigator's conduct of the trial and protection of human subjects;
- Serious adverse events notification
- Monitoring on safety handling of investigational products and other related items
- On request by the investigator

GCP inspections may be conducted in two ways:

- i. **Protocol specific inspections** — This type of inspection ascertain whether the trial protocol meet the standards of GCP

Objectives of this type of inspection are;

- To ensure the rights, safety and well-being of study subjects have been protected
- To determine whether the dossier data submitted to regulatory authority are credible and accurate
- To assess compliance to the protocol, applicable regulatory requirements, ethical standards, guidelines and standard operation procedures

- ii. **System specific inspections** – clinical trial systems that may be inspected include informed consent, process of obtaining the consent, handling of investigational products, pharmacovigilance, biological samples and monitoring etc.

Objectives of system specific inspections are;

- To ensure the rights, safety and well-being of study subjects have been protected
- To determine whether the trial is conducted in accordance with applicable regulatory requirements and ethical standards
- To assure the integrity of scientific testing and study conduct
- To assess whether a system is suitably designed, controlled, maintained and documented to fulfil the objectives for which it has been set up
- To determine whether the investigational medicinal products and trial related materials are being imported, distributed, stored and use in accordance with applicable GMP, GDP and GXP standards.
- To identify areas for quality improvement

## 6. TYPES OF GCP INSPECTIONS

An inspection may be conducted at investigator site (trial site) which is already approved by NMRA, any laboratory used for clinical trial analyses and facility of the sponsor. Contract research organizations/facilities, acting under arrangements with a sponsor or investigator to perform some or all of the functions of the sponsor or investigator, may also be subject to inspection.

Clinical trial sites may be inspected before the regulatory approval, while the trial is on-going, when subjects are currently being enrolled in a trial or completed on a routine basis or sometimes when triggered by a complaint or there is a suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct.

Inspections are generally announced. However unannounced inspections may be possible.

The legal framework does not distinguish between academic versus commercial trials, be they run through a clinical research facility or other. Therefore, NMRA applies the same standards to all GCP related inspections.

### *i. Routine GCP inspections*

Routine inspections are inspections carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements. These inspections are announced prior and apply to ongoing clinical trials.

The inspections should have a random element in that not all applications for a letter of authorization to conduct clinical trials to the NMRA would necessarily give rise to a GCP inspection. However, clinical trials and sites selected are 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, and application to the NMRA etc.)

The duration of the inspection and the number of inspectors present on an inspection will vary depending on the complexity of the clinical trial and activities conducted at the site. Typically, they are scheduled for 3-5 days.

### **ii. Triggered GCP inspections**

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 when a 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 announced or unannounced and apply to ongoing or completed clinical trials.

### **iii. GCP inspections relevant to premarketing approval**

These inspections are usually done announced and apply to completed clinical trials.

## **7. GCP INSPECTION PROCESS**

### **7.1 Type of inspectors**

GCP inspectors attached to Clinical Trials Regulatory Division will perform the inspection. A member of the CTEC may accompany the inspection team as an external expert.

The inspection team will be constituted considering the phase/ type of trial, the investigational product, and other variables considered relevant on a case-by-case basis.

The inspectors should have valid GCP certification and continuous qualification as well as a letter of appointment from the Authority to perform the inspection.

### **7.2 Type of inspectees**

The inspectees in a GCP inspection may either be the principal investigator and/or the sponsor.

### **7.3 Notification of inspection**

In general, the inspectees of a clinical trial will be notified 4-5 weeks prior to the proposed announced inspection date and asked to confirm availability. The notification will identify the study to be inspected, if applicable and the proposed sites, including any investigator site/s.

In relation to for cause or triggered inspections, the NMRA may provide a shorter notice period.

The following information may be requested from the inspectees to be submitted to NMRA

- Participant status per trial site (number randomised, drop-out rate, and number of serious adverse events reported per site) at trial initiation or during the trial
- Copies of company standard operating procedures along with amendments e.g. (monitoring procedure, informed consent procedure, serious adverse event reporting procedure, drug supply procedure).
- Trial-specific document such as Trial Master File (TMF), a copy of the current protocol and protocol amendment and informed consent form, source data verification guidelines, product handling instructions, laboratory manual, randomisation code breaking procedure, monitoring plans and reports.
- Updated CV of principal investigator.
- Arrangements for direct access to any computerised systems upon which trial data or essential documents are stored.
- Any other documentation deemed necessary by the inspectors.

An inspection plan, outlining the units to be inspected and the schedule of meetings to be held with the investigator and/or sponsor will be provided prior to the inspection.

In accordance with the regulations, the trial master file comprising the essential documents which enable both the conduct of the trial and the quality of the data produced to be evaluated must be available by direct access and shall provide the basis for the GCP inspection.

### **7.4 Pre – inspection preparation**

The inspection dates will be confirmed with the inspectee and he will be required to submit the above data to NMRA within 14 days of the receipt of the notice of GCP inspection, along with relevant essential documents. The inspection plan is developed and finalized by NMRA before the inspection.

## 7.5 Conduct of GCP inspection

Inspections usually consist of an opening meeting, document review, interview sessions, visit to site facilities and a closing meeting as indicated in the inspection plan.

An opening meeting will be conducted with study staff by the inspectors, where the inspectors will explain the GCP inspection plan, and also confirm that the resources, essential documents and facilities required for the inspection are available. If resources such as access to a photocopier, printer etc. are required, this shall be communicated to the inspectee prior to the date of inspection.

The inspectee is required to present general overview of the clinical trial at this meeting, information regarding the recruitment of subjects, informed consent process, investigational product management, safety reporting, biological sample handling etc. During inspection the inspectors may interview study staff to determine how the trial is conducted and may also visit facilities used to conduct clinical trial being conducted.

All the essential documents concerning a clinical trial must be available for inspection. A TMF for a clinical trial must contain all documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The TMF must be established from the onset of the trial and kept updated on an ongoing basis as the trial completes different stages. All the essential documents contains a minimum list of documents generated before, during and after the trial, which must be stored in the Trial Master File with the sponsor and investigator, respectively. If certain documents are assessed not to be of relevance to the TMF, it must include a reason for omitting these documents in a timely manner.

The inspectee must ensure that a list of source data is available with a description of where source data etc. can be found. Source data may be both electronic and on paper. A list of such data includes medical records, laboratory reports, diaries, dispensing logs, ECG print-outs, Case Report Forms (CRF), X-ray images, radiological reports, etc. The list of source data must be prepared before the trial is initiated. It must be signed and dated by the principal investigator or by a person whom the principal investigator has assigned this task. The list must be available in the Trial Master File.

The activities and documents examined during common type of GCP inspection undertaken by the NMRA are outlined below:

### Protocol specific inspections may include:

- Trail Master File
- Legal and administrative aspects
  - Communication with the ethics Committee
  - Communication with the Regulatory Authority
  - Other Communications
- Organisational aspects
  - Implementation of the trial at the investigator site
  - Facilities and equipment
  - Management of biological samples
  - Organisation of the documentation
  - Monitoring and auditing
  - Use of computerised systems

- Informed consent of trial participants
- Details of impartial witness if any
- Review of the trial participant data
- Adverse event reporting
- Management of the investigational medicinal product(s)
- Protocol deviations
- Other, as required

**System Inspection may include:**

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

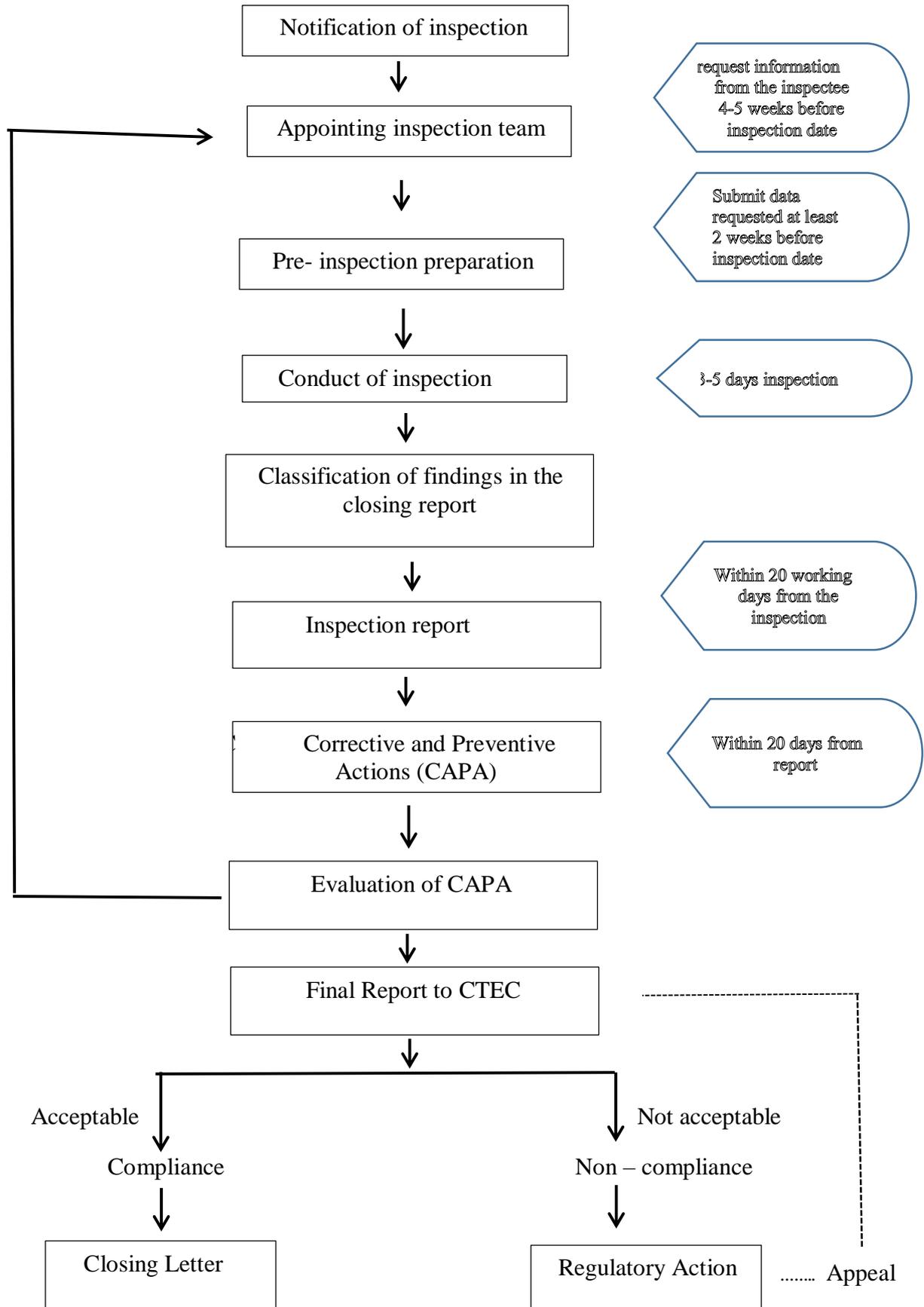
**Specific clinical trial inspection**

- Implementation and termination of the clinical trial
- Investigational Medicinal Product
- Case Report Form data verification
- Data handling and clinical trial report (CTR)
- Clinical trial documentation and archiving
- Audit trails

At the end of GCP inspection, there will be a closing meeting where the inspectors will present the GCP inspection deficiencies and grading to the inspectees, ensure that results of the inspection are clearly understood. A debriefing to the inspectee shall be provided with an appropriate time frame for Corrective and Preventive Action (CAPA) plan as described in the written report.

A written report outlining deficiencies observed during inspection is then issued to the inspectee within 20 working days from the last day of inspection. In general, written reports are issued in paper format and an electronic copy is sent to a nominated contact if requested. The inspection report shall be tabled at the subsequent CTEC meeting for discussion. The CTEC may invite the inspectee for a discussion in case of defence or clarifications as needed. Once the report is approved by CTEC, it will be submitted to inspectees. Inspectees may appeal against the recommendations within 4 weeks of submission and a final decision on the appeal shall be by CTEC.

## 7.6 Flowchart of GCP Inspection



## 7.7 Inspection reports

Once a GCP inspection is completed, an inspection report will be issued for the inspected parties and the entity responsible for the clinical trial (sponsor) or the sponsor's representative. The inspected parties may be one or more of the following: investigator, sponsor, contract acceptor (CRO), manufacturer, hospital pharmacy and laboratory. One inspection report will be issued for each GCP inspection and it will be issued to the principal investigator of the particular clinical trial.

The content of the report depends on the inspected site and the background for and scope of the inspection. The report includes data on the time and place of the inspection, inspection participants, a description of observations and a list of deficiencies from current legislation, guidelines, trial protocol and own procedures and a set of recommendations. The report will be issued within 20 working days from the inspection.

Deficiencies are classified depending on the specific circumstances of each individual inspection as below and they are evaluated relative to the deviation's risk to the safety and integrity of trial subjects as well as data quality.

## 7.8 Classification of deficiencies

Deficiencies are classified into three categories;

- Critical deficiencies
- Major deficiencies and
- Minor deficiencies

A summary for the criteria for judging deficiencies as critical, major or other are detailed below.

- ***Critical deficiency:***

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 deficiencies are totally unacceptable and may result in rejection of data and/or regulatory actions. The observations may include fraud, a pattern of deviations classified as major deficiencies, absence of source documents, and poor quality data.

- ***Major deficiency:***

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. They are serious deficiencies and are direct violations of GCP principles. The observations may include a pattern of deviations and/or a cluster of minor deficiencies and may result in rejection of data and/or regulatory actions.

- ***Minor deficiency:***

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

- **Comments:**

The observations that have been made during the inspection and alerts that might lead deficiencies and information on how to improve quality or reduce the potential for a deviation to occur in the future.

- **Clarifications:**

Issues arising from the inspection, which do not fit the definitions of above classifications but **may** require clarification from the sponsor company or trial site. These may become graded **finding** deficiencies depending on the nature of the clarification.

### **7.8 Corrective Action and Preventive Action Plan**

The inspectee must provide a response to the deficiencies outlined in the inspection report within 20 working days of receipt of inspection report and should include a proposal for corrective and preventative actions and a timeline for completion of those actions.

### **7.9 GCP Inspection closure**

The responses are reviewed by the inspection team to determine whether or not they are acceptable. Once the CAPA is deemed to be adequate, the NMRA will send a GCP inspection closing letter.

## **8. REGULATORY ACTIONS**

Based on deficiencies of the GCP inspection, NMRA may proceed to suspend or cancel the letter of authorization for the trial in terms of regulation 12 or 13 of Clinical Trials Regulations No. 2145/2 of 14.10.2019, if the inspectee fails to address the deficiencies, especially the critical and major deficiencies within the stipulated timelines.

In terms of section 125 of National Medicines Regulatory Authority Act No. 05 of 2015, an inspector Inspector(s) describes in point 7 have the right to enter any site/s involved in a clinical trial to carry out inspections, examine and open any receptacle or package that he believes to contain any article, take samples, examine any book/s , documents or record including electronic data found in any place and to make copies or take extracts and seize and detain for such time as may be necessary an article. Refusal or impair the inspector by not providing information / documentation or obstructing an inspector(s) intentionally during the conduct of inspection may lead to non-acceptance of trial for letter of authorization or suspend or cancellation of the letter of authorization.

NMRA may not wait for CAPA to suspend or cancel a letter of authorization in cases of deliberate misconducts such as fraudulent documentation or continuation of the clinical trial can have an adverse impact on study participants.

## **9. ABBREVIATIONS**

CAPA – Corrective and Preventive Actions  
CRO – Clinical Research Organization  
CTEC – Clinical Trials Evaluation Committee  
CTRDR – Clinical Trials Regulatory Division  
CV – Curriculum Vitae

ERC – Ethics Review Committee

GCP – Good Clinical Practice

ICH – International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use

NMRA – National Medicines Regulatory Authority

TMF – Trial Master File

## **10. DEFINITIONS**

### **Clinical Trial**

Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions may include but are not restricted to substances such as drugs, cells and other biological products, vaccines, surgical procedures, radiological procedures, or any other item claimed to have therapeutic benefit. The terms “clinical trial” and “clinical study” are synonymous

### **Compliance**

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

### **Contract Research Organization (CRO)**

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

### **Ethics Review Committee (ERC)/Ethics Committee**

An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non- medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics review committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

### **Good Clinical Practices (GCP) Guidelines**

Identified ethical and scientific quality requirements which are internationally recognized and which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety, and well-being of the study participants are protected, and the results of the clinical trials are credible;

### **Deficiencies**

A deviation or shortages noted by an Inspector during an inspection

### **Principal Investigator (PI)**

A doctor or dentist, as the case may be, having specialized in the area of study and specified in an approval as the person responsible for the conduct and supervision of a clinical trial at a particular trial site.

## **Protocol**

A document that states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

## **Sponsor**

An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

## **Study Participant**

An individual who participates in a clinical trial, either as a recipient of the investigational product under investigation or as a control. The individual may be a healthy person who volunteers to participate in a trial, a person with a condition unrelated to the use of the investigational product, a person (usually a patient) whose condition is relevant to the use of the investigational product.

## **Trial Master File**

A TMF is the collection of documentation that allows the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with GCP to be evaluated. It is also essential to allow the trial to be effectively managed by the sponsor as it allows the appropriate individuals access to the necessary trial documentation.

## **Essential Documents**

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

## **Impartial witness**

A person who is independent of a clinical trial, cannot be unfairly influenced by those involved with the trial, attends the informed consent process if the subjects or their legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

## **Protocol amendment**

In clinical trials, a written description of one or more changes to, or formal clarifications of, the study protocol.

## **Source data**

The data as any 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 may be both electronic and on paper.

## **11. RELATED LEGISLATION AND DOCUMENTS**

- National Medicine (Clinical Trials) Regulations 2145/2, 14th October 2019
- ICH E6 (R2) Good Clinical Practice (GCP) Guidelines
- Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, FDA Inspections of Clinical Investigators, June 2010, USFDA
- Clinical Trials Guidance (guidance on GCP compliance inspection framework), 02<sup>nd</sup> May 2017, Health Sciences Authority (HAS), Singapore
- ISO 14155 : 2020 Clinical investigation of medical devices for human subjects - Good clinical practice)
- GCP Inspection checklist , Central Drugs Standard Control Organization
- Guideline for GCP inspections , National Pharmaceutical Regulatory Agency, Malaysia

## **12. FEEDBACK**

Staff and stakeholders may provide feedback about this document by emailing [pathmaperuma.a@nmra.gov.lk](mailto:pathmaperuma.a@nmra.gov.lk)

## **13. APPROVAL AND REVIEW**