HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

13 SEP 2022

CLINICAL TRIALS GUIDANCE

GUIDANCE ON GCP COMPLIANCE INSPECTION FRAMEWORK

GN-IOCTB-11 Rev. No. 003

HSA
Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

CONTACT INFORMATION

For further information, please contact:

Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01, Helios
Singapore 138667

Email: HSA_CT@hsa.gov.sg
Website: www.hsa.gov.sg

REVISION HISTORY

Guidance Version (Version Date)

GN-CTB-3-001A-001 (02 May 2017)

GN-IOCTB-11 Rev. No. 002 (01 Mar 2021)

GN-IOCTB-11 Rev. No. 003 (13 Sep 2022)

SUMMARY OF AMENDMENTS

- Clarified the role of the local sponsor and global sponsor during a GCP Inspection (Section 5)
- Clarified the timeline for receipt of GCP Inspection Report (Figure 1, Section 8.7.3)
- Inspectee to ensure access to trial records (Section 7.4)
- Ad-hoc interim meeting may be conducted during the GCP Inspection (Section 8.5)
- Considerations for grading of GCP Inspection Findings (Section 8.7.2)
- Remote / hybrid GCP Inspections (Section 9)
- Other minor editorial changes

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to the industry on the overview of the GCP Inspection Framework of the Health Sciences Authority (HSA).

1.2. Background

Clinical trials regulated by HSA must comply with the protocol, applicable clinical trials and clinical research material regulations, ICH E6 Good Clinical Practice (GCP) Guidelines and standard operating procedures.

The GCP Compliance Inspection framework was launched in Sep 2009

1.3. Scope

This guidance applies to clinical trials regulated by HSA, namely:

(i) Clinical trials of Therapeutic Products[1] and Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)[1,2] that are subject to the requirements for a Clinical Trial Authorisation (CTA) or a Clinical Trial Notification (CTN);

(ii) Clinical trials of Medicinal Products[3] that are subject to the requirements of a Clinical Trial Certificate (CTC).

[1] Therapeutic Product and CTGTP are defined in the First Schedule to the Health Products Act.

[2] Class 1 and Class 2 CTGTP are defined in the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

- Class 1 CTGTP means a CTGTP that —
  (a) is the result of only minimal manipulation of human cell or tissue;
  (b) is intended for homologous use;
  (c) is not combined or used with a therapeutic product or a medical device; and
  (d) is assigned by HSA as a Class 1 CTGTP due to a lower health risk to a user of the product.
- Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.

[3] Medicinal Product is defined in the Medicines Act.

1.4. Definitions

(i) GCP Inspection

Inspections are defined by the ICH E6 GCP as 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 and 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).

(ii) Remote GCP Inspection

A GCP inspection conducted virtually or at a distance, supported by technology for communicating, sharing, reviewing, accessing systems, without the GCP inspectors being physically present at the sites, where the activities subject to a GCP inspection have taken place or where the GCP inspection would routinely be hosted.

(iii) Hybrid GCP Inspection

A GCP inspection performed using a combination of on-site and remote means.

2. OBJECTIVES OF GCP INSPECTIONS

GCP Inspections may either be protocol-specific or systems inspections. Examples of clinical trial systems that may be inspected include informed consent, investigational products, pharmacovigilance, biological samples, monitoring etc.

2.1. Objectives of Protocol-specific GCP Site Inspections

(i) To safeguard the rights, safety and well-being of trial participants;

(ii) To verify the quality and integrity of the clinical trial data submitted to the Regulatory Authorities;

(iii) To assess compliance to the protocol, applicable regulations, guidelines and standard operating procedures.

2.2. Objectives of Systems GCP Inspections

(i) To safeguard the rights, safety and well-being of trial participants;

(ii) To verify the quality and integrity of the clinical trial data submitted to the Regulatory Authorities;

(iii) To assess compliance to the protocol, applicable regulations, guidelines and standard operating procedures;

(iv) To assess whether a system is suitably designed, controlled, maintained and documented to fulfil the objectives for which it has been set up;

(v) To identify areas for quality improvement.

3. GCP INSPECTION CRITERIA

Compliance to the following will be determined during GCP Inspections:

(i) Protocol

(ii) Applicable clinical trial and clinical research material regulations*

(iii) ICH E6 Good Clinical Practice Guidelines (ICH E6 GCP)

(iv) Applicable Sponsor / Contract Research Organization (CRO) / Vendor / Site Standard Operating Procedures (SOPs) for clinical trials

** Examples:*

Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations, Health Products (Clinical Research Materials) Regulations, Medicines (Medicinal Products as Clinical Research Materials) Regulations, Health Products (Medical Devices) Regulations

4. TYPES OF GCP INSPECTIONS

GCP Inspections can either be routine, triggered or conducted in response to a pre-marketing approval application.

4.1. Routine GCP Inspections

Routine GCP Inspections are done announced and apply to ongoing clinical trials.

4.2. Triggered GCP Inspections

Triggered GCP Inspections may be triggered as a result of requests or complaints or reports to HSA on suspected violations of the regulations. Such types of inspections may be done announced or unannounced and apply to ongoing or completed clinical trials.

4.3. Pre-marketing approval application GCP Inspections

Pre-marketing approval application GCP inspections are usually done announced and apply to completed clinical trials.

5. TYPES OF INSPECTEE

The inspectee for a GCP Inspection may either be the Principal Investigator (PI) and/or the local Sponsor.

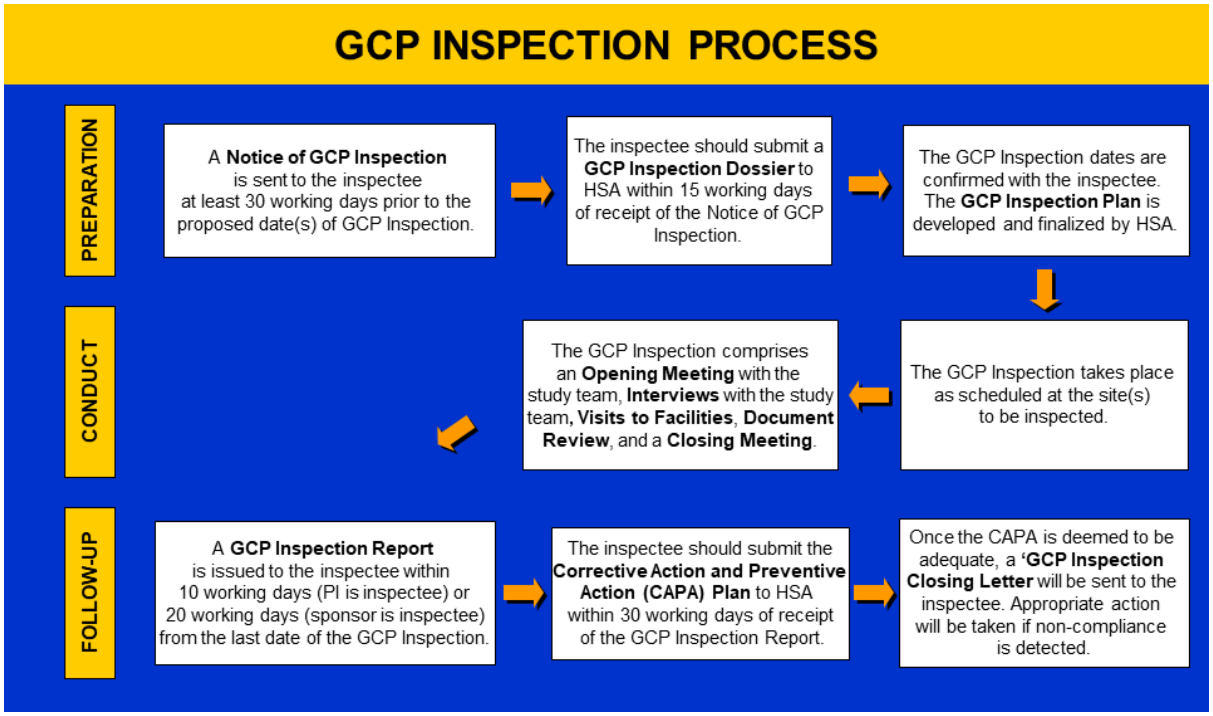
**NB:*

The local sponsor is responsible for all sponsor responsibilities as specified in the applicable clinical trials and clinical research materials regulations and ICH E6 GCP guidelines. For clinical trials where a Contract Research Organisation is the local sponsor, the global sponsor should provide the necessary support to the local sponsor for the Sponsor Inspection.

6. GCP INSPECTION PROCESS

The GCP Inspection Process for a routine GCP Inspection is summarized in the flowchart below:

Figure 1. GCP Inspection Process for a routine GCP Inspection



7. GCP INSPECTION PREPARATION

7.1. Notice of GCP Inspection

A Notice of GCP Inspection will be sent to the inspectee at least 30 working days prior to the proposed date(s) of the GCP Inspection.

7.2. GCP Inspection Dossier

The inspectee will be required to submit a GCP Inspection Dossier to HSA within 15 working days from receipt of the Notice of GCP Inspection, along with relevant essential documents.

7.3. GCP Inspection Preparation Checklist

For GCP Site Inspections, the inspectee will be provided with a GCP Inspection Preparation Checklist to help the trial site prepare for the upcoming inspection.

7.4. Access to Trial Records

The inspectee should ensure that access is provided to all trial records, including trial participant medical records, Investigator Site File, Trial Master File, Case Report Forms and applicable standard operating procedures, where applicable.

8. GCP INSPECTION CONDUCT

8.1. Opening Meeting

The GCP Inspection will start with an Opening Meeting, where the GCP Inspectors will explain the GCP Compliance Inspection framework, confirm the agenda, the availability of resources, access to records and facilities required for the GCP Inspection, and matters relating to confidentiality.

The inspectee would be required to present a general overview of the clinical trial being inspected at this meeting. The inspectee may refer to the Notice of GCP Inspection for further details on the information to be presented.

8.2. Interviews with Study Staff

During the GCP Inspection, the GCP Inspectors will conduct interviews with the relevant study staff. The study staff to be interviewed will be determined based on the scope and objectives of the GCP Inspection, and on any emerging observations noted during the Inspection.

8.3. Visit to Facilities

The GCP Inspectors may visit facilities used to conduct the clinical trial being inspected.

8.4. Document Review

The GCP Inspectors may review essential documents pertaining to the clinical trial being inspected.

8.5. Interim Meeting

An interim meeting may be conducted during the GCP Inspection to discuss observations noted from the GCP Inspection and provide the inspectee with an opportunity to resolve the observations during the GCP Inspection. The resolution status of the observations may be reviewed on the next business day of the GCP Inspection.

8.6. Closing Meeting

At the end of the GCP Inspection, there will be a Closing Meeting where the GCP Inspectors will present the observations noted from the GCP Inspection to the inspectee and timelines for GCP Inspection Report and Corrective Action and Preventive Action (CAPA) Plan. The inspectee will be given an opportunity to provide clarifications to the observations.

8.7. GCP Inspection Follow-up

8.7.1. Grading of GCP Inspection Findings

The GCP Inspection Findings will be graded as critical, major or other.

(i) **Critical:** Conditions, practices or processes that adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data

(ii) **Major:** Conditions, practices or processes that might adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data

(iii) **Other:** Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the trial participants and/or the quality and integrity of data

(iv) **Comments:** The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

8.7.2. Considerations for grading of GCP Inspection Findings

The impact on the goals of GCP, frequency of occurrence and corrective actions and preventive actions that may be taken will be considered in the grading of GCP Inspection Findings.

8.7.3. GCP Inspection Report

Once the GCP Inspection has been completed, it will be sent to the inspectee within 10 working days (PI is the inspectee) or 20 working days (Sponsor is the inspectee) from the last date of the GCP Inspection. It should be noted that the factual matter contained in the GCP Inspection Report relates to observations noted during the GCP Inspection.

8.7.4. Corrective Action and Preventive Action Plan

The inspectee should submit a Corrective Action and Preventive Action (CAPA) Plan to HSA within 30 working days of receipt of the GCP Inspection Report.

8.7.5. GCP Inspection Closure

Once the CAPA is deemed to be adequate, the GCP Inspector will send a GCP Inspection Closing Letter. It is important to note that the GCP Inspection Closing Letter should not be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

9. REMOTE / HYBRID GCP INSPECTIONS

9.1. Overview

The COVID-19 pandemic has resulted in regulatory authorities adapting their GCP inspection approaches to ensure continued regulatory oversight of clinical trials. Remote / hybrid GCP inspections were undertaken amidst hospital restrictions to protect public health. HSA has similarly embarked on conducting remote / hybrid GCP inspections since the COVID-19 pandemic.

Remote / hybrid GCP inspections helped to ensure that regulatory oversight of clinical trials regulated by HSA is maintained, allowed greater flexibility in the scope of the GCP inspection, and protected the health and safety of GCP inspectors and inspectees in the context of a public health emergency.

Experience gained from the remote / hybrid GCP inspections had identified potential technological and logistical challenges, including access to electronic systems and file sharing portals, and availability of interviewees due to differing time zones, but had also identified areas where there has been more suitable use of remote approaches to inspection.

Moving forward, remote / hybrid GCP inspection approaches may be incorporated into regular GCP inspections in the post-pandemic era, if they are deemed to be appropriate based on the scope of the GCP inspection and will not compromise the objectives of the GCP inspection.

9.2. Considerations for remote / hybrid approaches

The considerations for remote / hybrid GCP inspections may include the following:

(i) Trial site or staff restrictions in the context of a public health emergency;
(ii) Differing time zones of inspection attendees;
(iii) Scope and objectives of the inspection;
(iv) Complexity of the activities being assessed;
(v) Operational feasibility of a remote / hybrid GCP inspection;

(vi) Availability of technology and access to electronic systems and file sharing portals to enable stable and secure remote communication, sharing, access and review of essential documents in accordance with institutional data policies.

9.3. GCP inspection activities that may be more amenable to being conducted remotely

In general, the following GCP Inspection activities may be more amenable to being conducted remotely:

(i) Meetings;

(ii) Interviews;

(iii) Review of documents that are made accessible remotely via electronic systems in compliance with institutional data policies.

9.4. Logistical arrangements

The inspectee may expect to receive a request for exploratory feasibility and logistical assessment if a remote / hybrid GCP inspection is being considered, prior to receiving formal notice of GCP inspection.

The inspectee should ensure the following in order to facilitate the smooth running of the remote / hybrid GCP Inspection, where applicable:

(i) All required attendees are able to participate in the remote / hybrid GCP Inspection in accordance with the GCP Inspection Agenda;

(ii) Remote access is provided to the GCP Inspectors for the electronic systems used for the clinical (e.g. Investigator Site Files, Trial Master Files, Case Report Forms, Standard Operating Procedures etc.) from GCP Inspection notice to closure;

(iii) Arrangements are made for the GCP Inspectors to complete the necessary training requirements in order to access the electronic systems used for the clinical trial;

(iv) A secure file sharing portal is established for document sharing, with downloading functions enabled for the GCP Inspectors; and

(v) In situations where the inspectee is unable to use the proposed video conferencing software, the inspectee should propose using an alternative video conferencing software to facilitate communication with the GCP Inspectors during the conduct of the remote / hybrid GCP Inspection, including:

a) Enabling screen sharing, virtual visits, and break-out rooms; and

b) Disabling the recording function.

9.5. Duration of remote / hybrid GCP inspection

The duration of the remote / hybrid GCP inspection may be adjusted, depending on the logistical arrangements.

9.6. Framework

Generally, the objectives, scope, criteria and process for remote / hybrid GCP inspections are similar for on-site GCP inspections.

10. REFERENCES

(i) Health Products (Clinical Trials) Regulations

(ii) Medicines (Clinical Trials) Regulations

(iii) ICH E6 Good Clinical Practice (GCP) Guidelines

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

CONTACT INFORMATION:

Innovation Office & Clinical Trials Branch

Health Products Regulation Group

Health Sciences Authority

11 Biopolis Way, #11-03, Helios

Singapore 138667

Email: HSA_CT@hsa.gov.sg

Website: www.hsa.gov.sg

HSA
Health Sciences Authority