GUIDANCE ON GCP COMPLIANCE INSPECTION

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Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the first edition of this document.

2. APPLICATION - Guideline for Regulators.

This document applies to the GCP inspectorate of DRAP to explain the procedure of GCP Inspections for clinical trials regulated by DRAP at any stage.

3. PURPOSE

This document guides the GCP inspectorate and officers of DRAP involved in Clinical Trials Oversight activities to overview the GCP Inspection Framework of the Drug Regulatory Authority of Pakistan.

This guidance applies to all Clinical Trials regulated by DRAP:

4. CONTEXT OF THE GUIDELINES

Clinical trials regulated by DRAP must comply with the protocol, applicable Clinical Trials and Clinical Research Material Regulations, Rules of DRAP, ICH Good Clinical Practice (GCP) Guidelines, and Standard Operating Procedures.

DRAP reserves the right to amend any part of these guidelines whenever deems fit.

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5. Glossary

Acronyms

ADR:	Adverse Drug Reaction
CRO:	Contract Research Organization
DRAP:	Drug Regulatory Authority of Pakistan
GCP:	Good Clinical Practice
ICH:	International Conference on
WHO:	World Health Organization

Definitions

Adverse Drug Reaction

"Adverse drug reaction" or "ADR" means a response to medicines or therapeutic goods which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or the restoration, correction, or modification of physiological function. A response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected;

OR

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: 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 modification of physiological function (see the ICH Guideline) for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Audit

A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and whether the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Clinical trials (Phase)

A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism, and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is impossible to draw distinct lines between the phases, and diverging opinions about details and methodology exist. Brief descriptions of the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, are given below:

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).
Clinical trial application	The clinical trial application (CTA) is the dossier that includes all documentation about the conduct of clinical trials in country according to the regulation. The dossier includes a cover letter, CVs of investigators, protocol, and an investigator's brochure or product information, etc. (Protocol and Investigator's brochure should be in accordance with ICH-GCP guidelines).
Contract Research Organization (CRO)	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
Drug Regulatory Authority of Pakistan (DRAP)	DRAP is the National Regulatory Authority in Pakistan to regulate the Control of Therapeutic Goods. Regulates all activities related to import, procurement of raw and packing materials, production and import of finished drugs, export, sales, pricing, etc.
Essential Documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (See Section 12 of these guidelines)
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 the rights, integrity, and confidentiality of trial subjects are protected.
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. Informed consent should be in accordance with Section 4.8 of the ICH-GCP Guidelines, and should be in English, National (Urdu) & Local language. (See Annexure-III).
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 organizations (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (ies).

Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. Principle Investigator will be responsible for whole Clinical Studies / Trial.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout these Guideline the term protocol refers to protocol and protocol amendments. The protocol should be in accordance with section 6 of the ICH-GCP guidelines.
Registered Product	Any product approved or permitted to be marketed in the country by DRAP
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Sponsor-Investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
Sub investigator	Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions, (e.g., associates, residents, research fellows). See also Investigator.
Trial Site	The location(s) where trial-related activities are actually conducted.
Unregistered Product	Any product that is not registered or permitted to be marketed in the country by the DRAP.

6. INTRODUCTION

These guidelines as outlined are drawn in conformity with the legal requirements of the Bio- Study Rules 2017 notified vide S.R.O. 697 (I)/2018 dated 5th June 2018. It is required that all the Therapeutic Goods and Health Products used in Pakistan are registered/enlisted with the Drug Regulatory Authority of Pakistan (DRAP) and any Clinical Trial using registered or unregistered products must receive written approval (i.e. license for Clinical Trial Site & Clinical Studies) from DRAP, under the Bio-Study Rules 2017 for this purpose.

These guidelines set out the procedures that should be followed by the inspectorate for conduct of inspection of clinical trials in Pakistan at any stage.

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 organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

7. OBJECTIVES OF GCP INSPECTIONS

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

7.1. Objectives of Protocol-Specific 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.

7.2. 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.

8. GCP INSPECTION CRITERIA

Compliance to the following standards will be determined during GCP Inspections:

(i) Protocol

(ii) Applicable Clinical Trial and Clinical Research Material Rules/regulations*

(iii) ICH Good Clinical Practice Guidelines (GCP)

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

** Examples:*
Bio-study Rules 2017, Conduct of Clinical Trials Guidelines

9. TYPES OF GCP INSPECTIONS

GCP Inspections can either be routine, triggered, or can be conducted in response to an application.

9.1. Routine GCP Inspections

Routine GCP Inspections are announced and applied to the ongoing clinical trials.

9.2. Triggered GCP Inspections

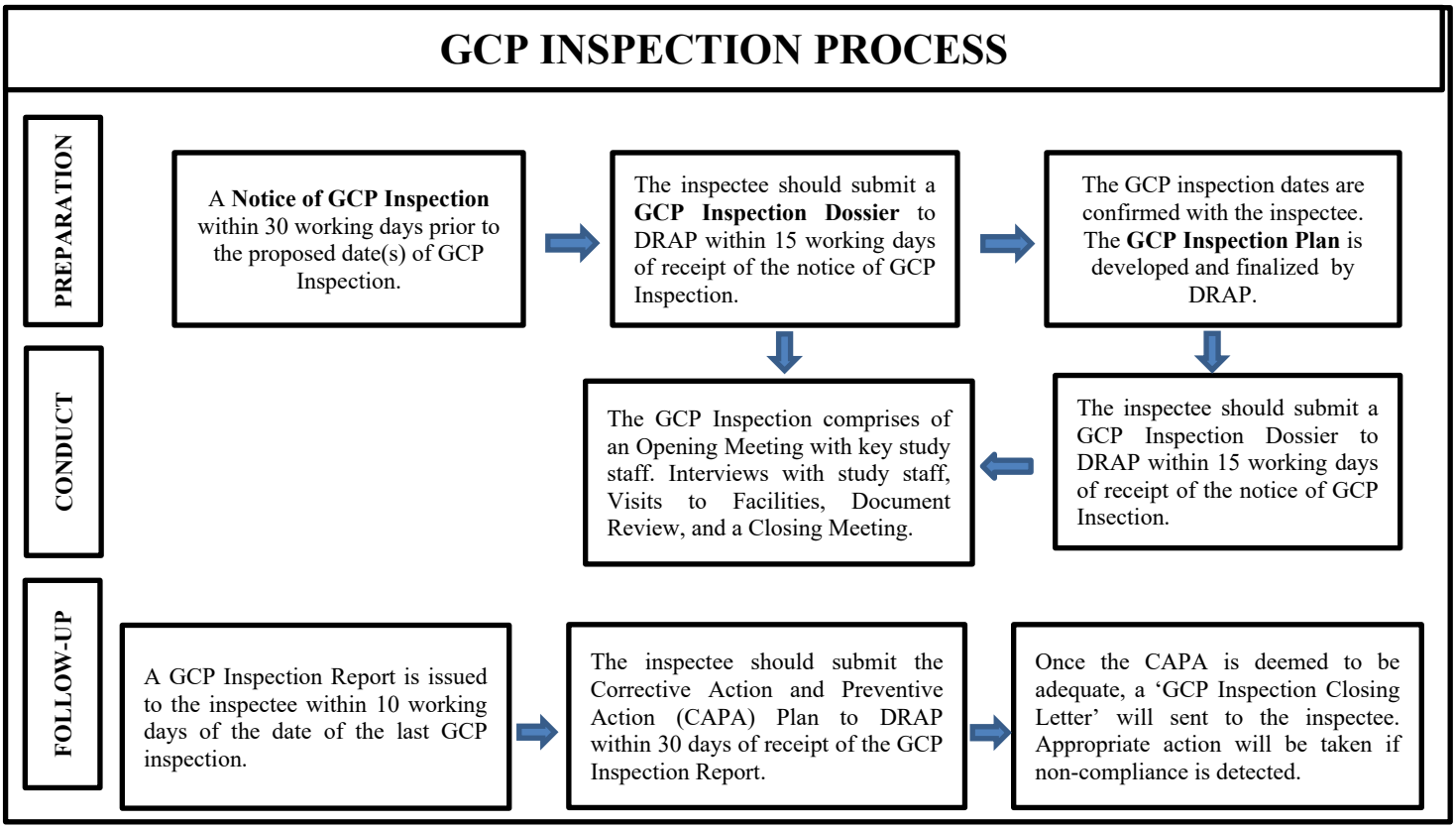
Triggered GCP Inspections may be triggered as a result of requests or complaints or

reports to DRAP on suspected violations of the regulations. Such types of inspections may be announced and applied to ongoing or completed clinical trials.

10. GCP INSPECTION PROCESS

The inspectee in a GCP Inspection may either be the Principal Investigator and/orthe Sponsor.

The GCP Inspection Process is summarized in the flowchart below:



11. GCP INSPECTION PREPARATION

11.1. Notice of GCP Inspection

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

11.2. GCP Inspection Dossier

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

12. GCP Inspection Preparation Checklist

The inspectee will be provided with a GCP Inspection Preparation Checklist to help the site prepare for the upcoming inspection.

13. GCP INSPECTION CONDUCT

13.1. Opening Meeting

The GCP Inspection will start with an Opening Meeting, where the Compliance Inspectors will explain the GCP Compliance Inspection framework; confirm the agenda; and also confirm that the resources, essential documents, and facilities required for the GCP Inspection are available.

The inspectee would be required to present a general overview of the clinical trial at this meeting. Information pertaining to trial participant recruitment, informed consent process, investigational product management, safety reporting, and biologicalsample handling may be included.

13.2. Interviews with Study Staff

During the GCP Inspection, the Compliance Inspectors will interview study staff to determine how the clinical trial is conducted and review essential documents pertaining to the clinical trial being inspected. Questions relating to study staff,

Institutional Review Board (IRB), Regulatory Authority, Investigator Site

Files, Trial Participant Recruitment, Informed Consent, Investigational Product Management, Safety Reporting, Biological Samples handling, Source Documents, Case Report Forms, record keeping, monitoring, etc. may be asked.

13.3. Visit to Site Facilities

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

13.4. Document Review

The Compliance Inspectors may review essential documents pertaining to study staff, Institutional Review Board (IRB), Regulatory Authority, Investigator Site Files, Trial Participant Recruitment, Informed Consent, Investigational Product management, Safety Reporting, Biological Samples handling, Source Documents, Case Report Forms, record keeping, monitoring etc.

13.5. Closing Meeting

At the end of the GCP Inspection, there will be a Closing Meeting where the Compliance Inspectors will present the GCP Inspection Findings and gradings to the inspectee; ensure that results of the GCP Inspection are clearly understood and acknowledged by the inspectee; and provide an appropriate time frame for the inspectee to present the Corrective Action and Preventive Action (CAPA) Plan.

14. GCP Inspection Follow-up

14.1. 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 therights, 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.

15. GCP Inspection Report

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

16. Corrective Action and Preventive Action Plan

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

17. GCP Inspection Closure

Once the CAPA is deemed to be adequate, the Compliance 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.

18. REFERENCES

i. Bio-Study Rules 2017 (DRAP)

ii. Conduct of Clinical Trials Guidelines 2021 (DRAP)

iii. ICH Good Clinical Practice (GCP) Guidelines.

DRUG REGULATORY AUTHORITY OF PAKISTAN
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