Salve 1

The ENGAGE Guideline

OPTIONAL GUIDELINE FOR GOOD CLINICAL PRACTICE COMPLIANCE AND QUALITY SYSTEMS AUDITING

In conformity with the Note for Guidance on GCP CPMP/ICH/135/95 (ICH GCP)

ENGAGE

European Network of GCP Auditors and other GCP Experts

Supplement to the EFGCP News, September 1998

INTRODUCTION

THE OBJECTIVE OF THIS DOCUMENT IS TO HARMONIZE AND PROMOTE COMMON GCP AUDIT METHODOLOGY

This document is based on internationally accepted quality standards.

Priority has been given to the terminology to facilitate the understanding of the document and the process of harmonization. Terminology related to the ICH GCP Guideline and ISO standards is used whenever possible. Excerpts of the ICH GCP Guideline relating to audits are attached for reference.

Whether auditing trials, systems or processes, the basic audit methodology remains similar. This document can therefore be considered as a guideline for the conduct of all types of Good Clinical Practice compliance and quality systems audits.

In this document CPMP/ICH/135/95 official terminology and formal text are printed in italics to differentiate established definitions from those created for the purpose of this auditing guideline. Terms mentioned in the glossary are marked with an asterisk (*) in the text, when used for the first time.

1. GLOSSARY

Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs) ( ), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) (1.6)

Note : this also includes the SOPs of CROs .

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place (1.7).

Audit plan

A plan setting out the specific practices, resources, activitics and time lines relevant to a particular audit or a group of related audits (e.g., those associated with a particular protocol or system).

Audit Report

A written evaluation by the sponsor's auditor ( ) of the results of the audit (1.8).

Note : this includes the CROs auditor.

Audit Schedule

Overall planning of essential audits (system audits and trial specific audits) prepared by the audit group and agreed upon as defined by management policies.

Audit Trail

Documentation that allows reconstruction of the course of events (1.9).

Auditee

The audited party.

Auditor

A person qualified by training and experience to conduct audits.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements (1.15) .

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity (1.16).

Direct Access

Permission to examine, analyse, verify, and reproduce any records and reports 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(1.21).

Finding

see Observation.

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 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) (1.29).

Objective evidence

Qualitative or quantitative information, records or statements of fact pertaining to the quality/accuracy of data, or to the protection of trial subjects, or to the existence and implementation of a (regulatory and/or quality) system element, which is based on observation, measurement or test and which can be verified and can not be rejected as wrong.

Observation

A statement of fact made during an audit and substantiated by objective evidence.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (1.46).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (1.47).

Quality system

The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

System audit cycle

Ongoing review of systems which is part of the audit schedule and allows the implementation of continuous improvement. The system audit cycle is a conceptual model that allows a long-term quality approach and leaves to the organisation the choice of defining which systems will be part of the audit schedule.

2. AUDIT APPROACH

ICH GCP requires that a system of Quality Assurance* and Quality Control* be implemented and maintained. Auditing is an integral part of this quality strategy. The careful choice of systems to be audited or specific trial audits to be performed is part of the audit approach. The audit approach consists of the ongoing review of systems through the system audit cycle* and the performance of selected trial specific audits. Both types of audits* (systems and trials) are included in the audit schedule* and conducted in accordance with the audit plan*.

3. PREPARATION OF THE AUDIT

3.1 Audit assignments

Depending on resources and activities, audits are assigned to auditors* as defined in Standard Operating Procedures.

3.2 Working documents

The auditor(s) review(s) the applicable standards, regulations, guidelines, SOPs and/or protocol or project specific requirements.
Working documents (e.g., checklists, forms, etc.) are prepared as needed.

3.3 Audit plan contents

Standard Operating Procedures (see ICH GCP 5.19.3) should allow for audit plans* to be flexible in their design in order to permit changes.
The plan communicated to the auditee* should include:

- the audit objectives and scope;
- identification of the responsible individuals;
- identification of reference documents (such as the applicable quality system* standard, regulatory requirements, and the auditee's quality manual or standard operating procedures);
- identification of auditor(s);
- the date(s) and place(s) where the audit is to be conducted;
- identification of the organizational units to be audited;
- description of facilities which need to be made available to the auditor(s) to perform the audit;
- the expected time and duration for each major audit activity;
- the schedule of meetings to be held with the auditee and/or auditee management;
- arrangements for translations and indication of audit language, if required;
- confidentiality* requirements and confidentiality statements, if required;
- audit report* distribution.

If the auditee objects to the audit plan, any objections should immediately be made known to the auditor(s). They should be resolved between the auditor(s) and the auditee before performing the audit.

4. CONDUCT OF THE AUDIT

4.1 Opening meeting

The purpose of an opening meeting is to

- introduce the auditor(s) to the auditee;
- review the scope and the objectives of the audit;
- provide a short summary of the methods and procedures to be used to conduct the audit;
- establish or confirm the official communication links between the auditor(s) and the auditee;
- confirm that the resources, documents, and facilities needed by the auditor(s) are available;
- be informed of any national, departmental, or other practices which affect the implementation of quality systems or Good Clinical Practice compliance by the auditee;
- confirm the time and date for the closing meeting and any interim meetings of the auditor(s) and the auditee's management;
- clarify any unclear details of the audit plan.

4.2 Collecting information

Sufficient information to fulfill the audit objective(s) should be collected through the examination of documents with direct access*, interviews, and observation of activities and conditions in the audited areas. Findings* suggesting non-compliance* or quality concerns should be noted and an audit trail* followed to determine the full extent of any problem identified. Information gathered through interviews should be cross-checked by acquiring the same information from other independent sources.

During the audit, the auditor(s) may adjust the audit plan to ensure the achievement of the audit objectives.

4.3 Audit observations

All audit observations should be documented. After all activities have been audited, the auditor(s) should review all observations to determine which are to be reported as noncompliance and/or quality system deficiencies. The auditor(s) should then ensure that these are documented in a clear, concise manner and are supported by objective evidence*. All reported observations* should be identified with reference to specific requirements of the standard(s) or other related documents against which the audit has been conducted.

Audit findings should be reviewed by the auditor(s) with the auditee(s) and appropriate management, which should acknowledge all findings of non-compliance.

4.4 Closing meeting(s) with auditee(s)

At the end of the audit, the auditor(s) should hold a meeting with the auditee(s) and those responsible for the functions concerned. The main purpose of this meeting is to present audit findings to the auditee(s) to ensure that the results of the audit are clearly understood and that there are no misunderstanding by either the auditor(s) or the auditee(s).

The auditor may also make recommendations to the auditee for improvements; however, it is the responsibility of the auditee and/or the auditee s management to determine the extent, the way, and means of actions to be taken to improve the system(s).

5. THE AUDIT REPORT

The content of the audit report should reflect the execution of the audit.
It should be dated and signed by the auditors and contain the following items, as applicable:

- the scope and the objectives of the audit;
- the audit methodology (procedures, activities), the identification of audit team members and auditee's representative, audit dates, identification of the specific organization audited, and adherence to the audit plan;
- identification of the reference documents against which the audit was conducted;
- observations (unsubstantiated verbal statements should be identified as such);
- recommendations for corrective and/or preventive action(s) may be included (acknowledgement should be given if deficiencies have already been recognized and corrective actions initiated);
- the audit report distribution list.

6. AUDIT CERTIFICATE

The Audit Certificate is a document indicating

- the audit (type, identification number);
- the audited system, clinical trial, or organization;
- the audit dates;
- the name and affiliation of the auditors.

The Audit Certificate is prepared and used in accordance with Standard Operating Procedures and may include, if applicable, the date of release of the audit report and other information.

Audit Certificates may be incorporated as an Appendix to the clinical study report (see 16 Appendices of the ICH Guideline 'Structure and Content of Clinical Study Reports" adopted in the EU as CPMP/ICH/137/95 note for Guidance on Structure and Content of Clinical Study Reports).

Since it is recognized that not every clinical study will be subject to an independent audit, Audit Certificates* for systems audits can be used to demonstrate the independent assessment of the systems or part of the systems.

7. CORRECTIVE ACTION AND FOLLOW-UP

7.1 Auditee's responsibility

The auditee is responsible for determining, initiating, and completing corrective action needed, and for communication thereof to the auditor(s) and management.

7.2 Follow-up

Corrective action and subsequent follow-up audits, if required, should be completed within a time period agreed to by appropriate management and the auditee in consultation with the auditor(s).

The auditors should keep the appropriate management informed of corrective action activities and follow-up audits.

8. AUDIT RECORD RETENTION

Standard Operating Procedures should describe the retention of audit records, taking into account the applicable regulatory requirement(s).

When available, the audit certificate is an Essential Document and as such should be retained by the sponsor.

9. CODE OF CONDUCT AND CONFIDENTIALITY STATEMENTS

The code of conduct and confidentiality statements may differ depending on the regions and company policies. The principles of the conduct of auditors are addressed in this auditing guideline and the ICH GCP Guideline.

Excerpts from the Note for Guidance on GCP (CPMP/ICH/135/95) (ICH GCP)

2. The Principles of ICH GCP
2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

5.1 Quality Assurance and Quality Control
5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.2 Contract Research Organisation
5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should always implement quality assurance and quality control.

5.19 Audit
If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose
The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors
(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.
(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e)When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance
5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institutions's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).