

The Global Guideline for GCP Audit

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Background

ICH GCP has been adopted by three regions and implemented since 1996. The details on GCP auditing are not provided in ICH GCP and there is no global guideline for GCP audit. JSQA thought that the global guideline for GCP audit was necessary to harmonize GCP auditing for the quality assurance of global clinical studies.

JSQA looked at ENGAGE (The European Forum for Good Clinical Practice) Auditing Guideline (1998 and 2005), ICH Proposed Guideline for GCP compliance and Quality System Auditing (1993), ISO 9000 Quality management systems-Fundamentals and vocabulary (2000), ISO 19011 Guidelines for quality and/or environmental management auditing (2002), etc. to get the benefits of them.

JSQA completed the “JSQA Guideline for GCP Auditing” and announced it at 1st GQAC in 2005 as a poster session.

JSQA published “JSQA Guideline for GCP Auditing” on QA Journal of SQA in 2007 (QAJ 403) in order to promote the global discussion for the harmonization of GCP audit.

JSQA proposed the global discussion for Global Guideline for GCP Audit among SQA, BARQA and JSQA in November 2007 at the BARQA annual conference. The global project members were identified and had the kick-off meeting in April 2008 at the 24th SQA annual meeting. The global project members had meetings in October 2008 at 2nd GQAC in Edinburgh and in April 2009 at the 25th SQA annual meeting to discuss the guideline.

This guideline was completed based on the global discussions among SQA, BARQA and JSQA. The guideline includes the mission and the organization of a sponsor’s auditing department and establishes the principles for planning, performing, and reporting audits. The guideline is expected to be a basic principle along with ICH GCP for not only sponsor’s auditors, but also independent auditors and auditors of Contract Research Organizations (CROs) to conduct an audit in the various situations of each country and sponsor.

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1 Scope of the Guideline

The objective of this Guideline is to outline the mission and the organization of a sponsor's auditing department and the principles for planning, performing and reporting audits, all of which should be considered when the auditor who belongs to the sponsor performs an audit of a clinical trial performed by the sponsor. This Guideline is expected to be a basic principle along with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) [1] for a sponsor's auditor to conduct an audit in the various situations of each country and sponsor.

2 Definitions

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). (*ICH GCP [1]*)

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place. (*ICH GCP [1]*)

Audit Checklist

A working document for recording audit observations.

Audit Findings

The result of the auditor's evaluation of audit observations according to the reference documents.

Audit Observations

A record of the facts observed during auditing and supported by objective evidence.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit. (ICH GCP [1])

Audit Trail

Documentation that allows reconstruction of the course of events. (ICH GCP [1])

Auditee

Organization being audited. (ISO 19011 [2])

Corrective and Preventive Action (CAPA)

Corrective Action is action taken to eliminate the causes of an existing nonconformity, defect, or other undesirable situation in order to prevent recurrence. Preventive Action is action taken to eliminate the causes of a potential nonconformity, defect, or other undesirable situation in order to prevent occurrence.

Clinical Trial/Study System

A system for performing a clinical trial established at a sponsor's organization, participating medical institution, and other trial-related centers (i.e. the organization, structure, procedures, facilities and equipment, etc.).

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements. (ICH GCP [1])

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity. (ICH GCP [1]) 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 subject's identities and sponsor's proprietary information. (from the definition of "Direct Access" of ICH GCP [1])

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical trial. (ICH GCP [1])

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken. (ICH GCP [1])

Effectiveness Verification

The means by which effectiveness of corrective and/or preventive action implementation is verified by a documented and systemic process

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (*ICH GCP [1]*)

Objective Evidence

Data supporting the existence or verity of something.

NOTE: Objective evidence may be obtained through observation, measurement, test, or other means. (*ISO 9000 [3]*)

Quality Assurance

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). (*ICH GCP [1]*)

Quality Control

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for the quality of the trial-related activities have been fulfilled. (*ICH GCP [1]*)

Quality Management

The coordinated activities to direct and control an organization with regard to quality.

NOTE: Direction and control with regard to quality generally includes establishment of the quality policy and quality objectives, quality planning, quality control, quality assurance and quality improvement. (*ISO 9000 [3]*)

Quality Management System

Management system to direct and control an organization with regard to quality. (*ISO 9000 [3]*)

Quality Policy

Overall intentions and direction of an organization related to quality as formally expressed by top management. (*ISO 9000 [3]*)

Reference Documents

Documents which are used to evaluate compliance (e.g., trial protocols, sponsor's Standard Operating Procedures, Good Clinical Practice, and the applicable regulatory requirement(s)).

Risk Assessment

A systematic process of organising information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (*ICH Q9 Quality Risk Management*)

Risk Management

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. (*ICH Q9 Quality Risk Management*)

Root Cause

Is the most basic cause of any undesirable condition or problem, which when eliminated or mitigated will prevent or significantly reduce the effect of the condition or problem.

Root Cause Analysis

A class of problem solving methods used to identify the root causes of problems or events. The practice of RCA is predicated on the belief that problems are best solved by attempting to correct or eliminate root causes, as opposed to merely addressing the immediately obvious symptoms. By directing corrective and preventive measures at root causes, the likelihood of problem recurrence will be minimized.

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of clinical trial. (*ICH GCP [1]*)

3 Mission of a Sponsor's Auditing Department

A quality management system is established to define quality policy and implement quality management. Quality Control (QC) and Quality Assurance (QA) are implemented in accordance with the quality policy. As part of implementing Quality Assurance, a sponsor's audit is generally performed to accomplish the following missions:

1. To evaluate compliance with the reference documents so as to ensure the reliability of trial data and protection of the subject's rights.
2. To evaluate the effectiveness of the clinical trial system and provide an opportunity for the sponsor to improve it.

It is expected that the results of an audit will be utilized by the auditee as essential information for the improvement of the clinical trial system or by the sponsor's chief executives as material for making a business judgment about the quality of clinical trials. To accomplish the above objectives, the sponsor is expected to establish an independent auditing department and to ensure that the auditor(s) is(are) appropriately qualified by education and training.

4 Auditing Department

It is useful for the sponsor to establish an independent auditing department so as to ensure systematic and continuous conduct of audits. To ensure that a sponsor's auditing department functions effectively the sponsor should fulfil the conditions specified in paragraphs 4.1 to 4.4 below, specify the roles and responsibilities of the auditing department, and establish written SOPs for the performance of audits. It is possible for a sponsor to define the responsibilities of a department manager and assign the manager if necessary.

4.1 *Independent Auditing Department*

The auditing department should be independent of the auditees so as to ensure the credibility of its audits. Auditing is part of Quality Assurance and involves independent and objective evaluation of clinical trials. The auditing department fulfils part of the Quality Assurance responsibilities of the sponsor.

4.2 *Qualified Auditors*

The sponsor should establish an auditing department with qualified auditors so as to ensure the proper conduct of audits as part of implementing Quality Assurance. Each auditor's qualification should be documented to verify that he/she is a suitable person to properly conduct audits, e.g., records of education/training and business experience.

4.3 *Qualifications of Auditors*

The sponsor should specify the qualifications of auditors in auditing procedures and should only appoint appropriate individual(s) as auditor(s) based on consideration of his/her education/training, business experience, and ability. For example:

Knowledge: Necessary laws and regulations, GCP, relevant guidelines, the Declaration of Helsinki, clinical and pharmaceutical knowledge, SOPs, computerized system validation, etc.

Skills: Communication, writing, language, etc.

Nature: Tenacity, power of observation, analytical capability, decision, sense of ethics, maturity, etc.

4.4 *Responsibilities of Auditors*

The sponsor should specify the roles and responsibilities of the auditor before starting to conduct an audit so as to ensure fair and smooth performance of the audit. The auditor is responsible for maintaining the confidentiality of information obtained during an audit, planning (designing and updating) and conducting the audit, and reporting the audit results.

5 Planning of Audits

Before conducting an audit, the auditor (including the auditing department manager) should establish a written audit plan (such as an annual plan, a monthly plan, and a plan specific to each trial or audit) based on the results of the risk assessment according to the written auditing procedures.

5.1 *Establishing the Goals of Audits*

One or more objectives are generally established for a trial audit based on the importance of the trial with regard to submissions to regulatory authorities, the type and complexity of the trial, the level of risk to the trial, and any problem(s) identified previous. The most important part of audit planning is to specify the goal(s) of the audit. By establishing the goal(s) of an

audit, the subjects and methods of the audit will be determined and the consistent conduct of the audit will be ensured. One or more objectives may be chosen from the following examples:

- Evaluation of the compliance of any organization involved in a clinical trial (pre-qualification).
- Evaluation of the compliance with regulatory requirements and human subject protection.
- Confirmation of the appropriate conduct of a trial, the credibility of data obtained, and the condition of record keeping at a participating medical institution(s) through direct access.
- Confirmation of the conduct of monitoring.
- Confirmation of the credibility of a clinical trial/study report.
- Early detection and correction and prevention of any existing problems or potential problems with a system and/or process.
- Early detection and correction and prevention of any existing problems or potential problems occurring at an institution entrusted with trial-related duties.

5.2 Designing and Updating the Audit Plan

Planning is essential to systematically, effectively, and efficiently conduct an audit with consideration of resource management in the auditing department. Audit plans, such as an annual plan, a monthly plan, and a plan specific to each trial or audit, should be established based on consideration of the goal(s), contents (e.g. subjects and methods), and timing of an audit, the progress of the targeted trial, and other relevant factors. The audit plan should be updated in accordance with progress of the trial or auditing activity. Prior to conducting an audit, the auditors and the auditee will discuss and adapt the audit plan, as necessary.

5.3 Determining the Subject[s], Timing, and Method[s] of an Audit

The subject(s) (e.g., a medical institution, CRO, system, clinical trial/study report, computerized system validation, and database), timing (e.g., before the start of the trial, during the trial, after the completion of the trial, or periodically), and the method(s) (e.g., sampling, interview, or tour) of an audit should be determined based on the goal(s) established for the audit.

5.4 Information in the Audit Plan

An audit plan should provide the following information, although the contents may vary depending on the type of the plan (e.g., annual plan, monthly plan, or plan for a specific trial or audit).

- The goal(s) of the audit.
- The subject(s) of the audit.
- The scope of the audit.
- The timing of the audit.
- The name(s), title and address of the auditor (s)(and the auditing department manager).
- The reference documents required.
- The person(s) to whom the audit report will be submitted.
- Timelines for the audit(s) and report(s) (if possible)

6 Conduct of an Audit

Auditing is performed by the auditor in accordance with a written audit plan and procedures, and involves the examination and evaluation of information obtained through investigation of the audit trail (e.g. essential documents and SOPs) and a trial site(s) (e.g. facilities and equipment), as well as interviews with the auditee, etc. It is important to specify reference documents that auditees comply with before performing an audit so as to ensure fair conduct of audit. The auditor evaluates conformity and compliance with these reference documents. The auditor should inform the sponsor about the conduct of an audit in advance.

6.1 Explaining the Auditing Procedures

To efficiently collect accurate information through auditing, the auditor should give the auditee a prior explanation about the conduct of an audit (e.g. the goal(s) and method(s) of the audit).

When providing an explanation for the auditee, the auditor should confirm the subject(s) (i.e. materials and facilities that will be audited), the schedule, and the contact person(s) for the audit so that both the parties obtain the necessary and full understanding about the audit.

6.2 Conducting an Audit and Collecting Information

There are two types of sponsor's audit, i.e., auditing of internal trial-related department(s) and auditing of external establishment(s) involved in the trial concerned, e.g., a medical institution, laboratory, and/or CRO. To ensure the smooth conduct of an audit of an external institution, such as a participating medical institution, laboratory, or CRO, it is important to properly perform a preliminary internal audit.

When conducting an audit, the auditor should collect audit observations by reviewing the documents subject to the audit and interviewing the auditee etc. Based on audit observations collected, the auditor should confirm and document whether or not the audit observations are compliant to GCP, all applicable regulatory requirement(s), SOPs, the study protocol, and any other relevant documents and procedures.

Utilization of an audit checklist and a sampling method is useful for the standardization and efficient conduct of auditing activities.

6.3 Confirmation and Evaluation of Audit Observations

The auditor should discuss audit observations with the auditee so that the absence of errors can be confirmed. The auditor should then review the confirmed audit observations and further information can be collected if required.

The auditor should examine (within the auditing department) whether the audit observations involve any violations of GCP or applicable regulatory requirements, deviations from the relevant protocol and sponsor's SOPs, or problems with respect to the reliability of clinical data and then should determine the observations to be reported as audit findings. The auditor should also examine whether any of the obtained audit observations could have an influence

on other trials, medical institutions, clinical trial/study systems, etc. When audit findings are reported, they may be graded according to the level of importance.

7 Reporting the Results of an Audit

The auditor should provide written audit results (i.e. an audit report) for the sponsor to make the auditee recognize audit findings and take the opportunity to make improvements. It will be useful to provide an opportunity for the auditor to give an explanation about audit results to the sponsor at the time of submitting the audit report. To preserve the independence of auditing, the auditor must not be directly involved in the corrective and preventive action (CAPA) process.

7.1 Preparation of an Audit Report

The auditor should prepare an audit report based on the results of the evaluation. When an auditing department manager has been appointed, the audit report should be prepared by the auditor and if necessary reviewed or approved by the manager.

The contents of an audit report will be as follows:

- Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
- The person to whom the audit report will be submitted.
- The date of issuing the audit report.
- The subject of the audit.
- The site of the audit.
- The scope of the audit.
- The name(s), title and address of the auditor (s)(and the auditing department manager).
- The name and address of the auditee.
- The date/period of the audit.
- The results of the audit, including audit findings (grading of the findings may be included).
- A list of all persons receiving a copy of the audit report.

The following information may be contained in an audit report depending on the objective(s) of the audit:

- Suggestions for improvement and advice for CAPA.
- Responses to the audit findings.
- The results of the auditor's confirmation of the auditee's response.

7.2 Persons to whom Audit Reports are submitted

The auditor should submit an audit report to the sponsor. The auditor may give a copy of the audit report to the sponsor's auditee. In such a case, the auditor should pay special attention to ensuring the confidentiality of the contents of the report and should handle the report with due caution. Concerning audit reports, ICH GCP 5.19.3 (d) states the following:

'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.’

8 Corrective and Preventive Actions

Implementation of a CAPA plan after the conduct of an audit is necessary to eliminate present and potential causes of non-conformity and prevent re-occurrence or future occurrence. Once the conduct of the audit is complete the auditor should be provided a CAPA plan to the auditee that will be utilized to remediate issues of non-compliance and potential non-compliance identified during the audit process. The CAPA plan should, at minimum, require the auditee to identify the root-cause of audit findings and describe whether corrective and/or preventive actions will be necessary to address the audit findings.

9 Completion of an Audit

Upon receipt of the preliminary responses to the CAPA from the auditee, the audit is completed. Follow-up should be performed depending on the significance of the audit findings. CAPA follow-up and subsequent effectiveness verification should be ensured by continued interaction between the auditor and auditee until mutual agreement has been met that the CAPA have been addressed.

10 Audit Certificate

The auditor (including the auditing department manager) should prepare an audit certificate at the request of the sponsor. The sponsor should attach the audit certificate to a clinical trial/study report of the targeted trial.

The audit certificate should contain the following information:

- Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
- The date of issuing the audit certificate.
- The contents of the audit (e.g., subjects and date of the audit, and date of issuing the audit report).
- The name(s), title and address of the auditor (s)(and the auditing department manager).
- The name and workplace address of the auditee.

11 Keeping Audit Records

Audit records should be kept according to sponsor’s SOPs for record keeping. The SOPs should specify the procedures for keeping or destroying audit-related records, as well as the place, subject, and duration of record keeping.

References

- [1] ICH GCP. ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice, Recommended for Adoption at Step 4 of ICH process, 1 May 1996

- [2] ISO 19011. Guidelines for quality and/or environmental management systems auditing, first edition 1 October 2002
- [3] ISO 9000. Quality management systems – Fundamentals and vocabulary, second edition, 15 December 2000

Acknowledgment

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