



European Forum for Good Clinical Practice Audit Working Party

REVISION OF THE ENGAGE¹ AUDITING GUIDELINE. AN OPTIONAL GUIDELINE FOR GCP COMPLIANCE AND QUALITY MANAGEMENT SYSTEMS AUDITING

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INTRODUCTION

With the evolution in the perception of quality management in clinical research that has taken place since its publication in 1997, the ENGAGE Guideline now appears somewhat anachronistic. In addition, many independent Quality Management departments have now been active for ten or more years and there has been a resultant increase in experience and expertise in the area of GCP compliance auditing.

New ISO Guidelines, the 9000:2000 series have been published in which there has been a trend away from a system based on quality standards to one based on quality management. ISO has moreover recently published the new guideline, 19011:2002 for the auditing of both quality and environmental management systems. ISO has now provided definitions, which were not available at the time that the first ENGAGE document was written, for some of the terms included in the glossary. It has also included several new terms and ideas with which auditors need to become familiar.

Because it is so widely recognised, referred to, used, and applied, the term “quality assurance” has come to mean many different things to many different industries, Organisations, and people. The actions of the Pharmaceutical Industry are bound by the requirements of GCP and the regulatory authorities, which affects the interpretation of the guidelines. In clinical research in particular, the definition and scope of the activities of the “quality assurance function” is determined by the Organisation management’s perception of quality, the structure of the Organisation and the functional responsibilities assigned to the unit. Unfortunately, the terms “quality assurance”, “quality control”, “auditing” and “inspection” are often used incorrectly. This may be due to the evolutionary application of related GLP/GMP concepts and terms to the GCP arena, as well as the structural and organisational differences in the companies who apply such terms and definitions. One should however, try to stop using the term “quality assurance” when what is really meant is “quality management”.

Taking into consideration all the above factors, the Audit Working Party of the EFGCP took the decision to re-examine and modify the ENGAGE auditing guideline with the aim of bringing it more into line with today's concepts.

The objective of this document is therefore to promote common GCP audit methodology. It is based on internationally accepted quality standards including ISO 19011:2002. Priority has been given to the terminology to facilitate the understanding of the document and the process of harmonisation. Definitions related to the Note for Guidance on GCP CPMP/ICH/135/95 (ICH GCP) and ISO standards are used when possible. New definitions from ISO 19011:2002 and ISO 9000:2000 have been incorporated but these have been related to existing ICHGCP concepts where feasible.

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

¹ European Network of GCP Auditors and other GCP Experts

1. GLOSSARY

Audit: a systematic, independent and documented process for obtaining audit evidence objectively to determine the extent to which audit criteria are fulfilled. (ISO 19011:2002, 3.1)

NOTE: ICH GCP interprets this requirement as "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). (ICHGCP 1.6)

Audit Certificate: a declaration of confirmation by the auditor that an audit has taken place. (ICHGCP 1.7)

Audit client: the Organisation or person requesting an audit. (ISO 19011:2002, 3.6)

NOTE: This may be the auditee or any other Organisation that has the regulatory or contractual right to request an audit. Management may also confer the right to plan and execute audits to the auditing function.

Audit conclusion: the outcome of an audit provided by the audit team after consideration of the audit objectives and audit findings. (ISO 19011:2002, 3.5)

NOTE: See also **Audit report**

Audit criteria: the set of policies, procedures or requirements used as a reference for the audit. (ISO 19011:2002, 3.2)

NOTE: See also **Compliance**

Audit evidence: records, statements of fact or other information, which are relevant to the audit criteria and verifiable. (ISO 19011:2002, 3.3)

NOTE: Audit evidence can be qualitative or quantitative.

Audit findings: the results of the evaluation of the collected audit evidence against audit criteria. ISO 19011:2002, (3.4)

NOTE: Audit findings can indicate either conformity or nonconformity with audit criteria or opportunities for improvement.

Audit plan: a description of the activities and arrangements for an audit. (ISO 19011:2002, 3.12)

NOTE: This can apply to the specific practices, resources, activities and time lines relevant to a particular audit or a group of related audits (e.g. those associated with a particular protocol or system). See also **Audit programme**

Audit programme: a set of one or more audits planned for a specific time frame and directed toward a specific purpose. (ISO 19011:2002, 3.11)

NOTE: This includes the System Audit Cycle

Audit Report: a complete, accurate, concise and clear record of the audit. (ISO 19011:2002, 6.6.1)

Audit scope: the extent and boundaries of an audit. The scope typically includes a description of physical locations, organisational units, activities and processes, as well as the time period covered. (ISO 19011:2002, 3.13)

Audit team: one or more auditors conducting an audit, supported, when appropriate, by technical experts. (ISO 19011:2002, 3.9)

NOTE: One auditor of the audit team is appointed as audit team leader; the audit team can include auditors-in-training.

Audit Trail: documentation that allows reconstruction of the course of events. (ICHGCP 1.9)

NOTE: For Computer Systems, Title 21 Code of Federal Regulations Part 11.10(e) requires the use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

NOTE: See also **Record** and **Document**

Auditee: the Organisation being audited. (ISO 19011:2002, 3.7)

Auditor: a person with the competence to conduct an audit. (ISO 19011:2002, 3.8)

Competence: is defined as demonstrated personal attributes and demonstrated ability to apply knowledge and skills. (ISO 19011:2002, 3.14)

Compliance (in relation to trials): Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, applicable regulatory requirements (ICHGCP 1.15) and compliance with contractual requirements. (ISO 19011:2002, 6.2.2 (b))

Confidentiality: Prevention of disclosure to other than authorised individuals of a sponsor's proprietary information of a subject's identity. (ICHGCP 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 authority, 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. (ICHGCP 1.21)

Document: information and its supporting medium. (ISO 9000:2000 3.7.2)

Information: meaningful data. (ISO 9000:2000 3.7.1)

Inspection: See **Regulatory Authority Inspection** below.

Quality Assurance: the part of quality management focused on providing confidence that quality requirements will be met. (ISO 9000:2000 3.2.11)

NOTE: ICH GCP interprets this requirement as "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)". (ICHGCP 1.16)

NOTE: To be compatible with current concepts, the word "ensure" should be replaced with "assure". Hence the aim of Clinical Quality Assurance should be to give assurance to management (and ultimately to the Regulatory Authorities) that the processes are reliable and that no major system failures are expected to occur that would expose patients to unnecessary risks, violate their legal or ethical rights or result in unreliable data.

Quality Control: the part of quality management focused on fulfilling requirements. (ISO 9000:2000 3.2.10)

NOTE: ICH GCP interprets this requirement as "the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial have been fulfilled". (ICHGCP 1.47)

NOTE: To be compatible with current concepts, the word "assurance" should be replaced with "management". See also **Quality Management System** below.

Quality Improvement: the part of quality management focused on increasing the ability to fulfil quality requirements. (ISO 9000:2000 3.2.12)

Quality Management: the co-ordinated activities to direct and control an Organisation with regard to quality. (ISO 9000:2000 3.2.8)

Quality Management System: a management system to direct and control an Organisation with regard to quality. (ISO 9000:2000 3.2.3)

NOTE: The description of the Quality Management System should cover the organisational structure, responsibilities, procedures, processes and resources for implementing quality management.

Quality Planning: the part of quality management focused on setting quality objectives and specifying necessary processes and related resources to fulfil the quality objectives. (ISO 9000:2000 3.2.9)

Record: a document stating results achieved or providing evidence of activities performed. (ISO 9000:2000 3.7.6)

Regulatory Authority Inspection: The act by a regulatory authority(ies) of conducting 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). (ICHGCP 1.29)

NOTE: This review may also include clinical development or pharmacovigilance activities.

Technical expert: a person who provides specific knowledge or expertise to the audit team. Specific knowledge or expertise is that which relates to the Organisation, process or activity to be audited, language or cultural guidance. A technical expert does not act as an auditor in the audit team. (ISO 9000:2000 3.9.11)

2. AUDITING PRINCIPLES

Adherence to these principles is a prerequisite for providing a reliable and relevant audit outcome. These principles relate to auditors:

1. **Ethical Conduct:** Trust, integrity, confidentiality and discretion are essential to auditing. Actions that may influence the results of an audit should be avoided.
2. **Impartial reporting:** The obligation to describe truthfully and accurately the audit activities.
3. **Due professional care:** The application of diligence and judgement in auditing. Reasonable care in all matters and the completeness of the audit report avoiding errors that may jeopardise any of these auditing principles.

Two further principles relate to the audit process:

4. **Independence:** Auditors cannot audit work where a conflict of interest would arise. They must maintain an objective state of mind throughout the audit process to ensure that the findings and conclusions will be based only on the evidence.
5. **Evidence:** The rational basis for reaching reliable audit conclusions based on audit criteria.

3. THE 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 management strategy.

The Organisation's internal quality management system incorporates quality risk management in order to develop a strategic audit programme. On the basis of the analysis of the quality system for a given system or sub-system – this can be a trial, a clinical development program, or a system used by these – the Quality Assurance function will determine the impact and likelihood of a possible or potential system failure and its impact on the proper functioning of the system. This aims to assure management that the rights, safety and well being of the patients are protected as well as the integrity of the data.

The audit programme can include audits with a variety of objectives. Depending upon the size, nature and complexity of the Organisation to be audited, the audit programme can include one, a few or many audits, and joint or combined audits. The way in which audits are assigned to auditors is determined by the structure and arrangement of the Organisation's resources and activities, and may be defined in SOPs.

The Organisation's top management should grant the authority for managing the audit programme and provide the resources necessary to conduct the audits. Those responsible for managing this programme should utilise a "Plan-Do-Check-Act" cycle² to define it. Some of the key actions to be addressed are:

- a. establish the objectives and extent of the audit programme;
- b. establish the responsibilities, resources and procedures;
- c. ensure the implementation of the audit programme;
- d. monitor, review and improve the audit programme;
- e. ensure that appropriate audit programme records are maintained;
- f. ensure that audit findings are adequately followed-up and, where appropriate, the audited Organisation profits from the experience.

The audit programme should be monitored and reviewed by management to ensure its ongoing effectiveness in meeting the needs of the Organisation. Management should make adjustments to the audit programme when needed in order expedite improvements.

4. PREPARATION OF THE AUDIT

4.1. Audit assignments

Depending on the structure and arrangement of the Organisation's resources and activities, audits are assigned to audit team members as defined in the Organisation's SOPs.

4.2. Audit objectives, scope and criteria

The audit objectives should define what is to be accomplished by the audit. The audit scope describes the extent and boundaries of the audit. The audit criteria are used as a reference against which conformity is determined and may include applicable policies, procedures, standards, regulations, management system requirements, and contractual requirements.

4.3. Feasibility of the audit

The feasibility of the audit should be determined, taking into consideration such factors as the availability of sufficient and appropriate information for planning the audit, adequate co-operation from the auditee, and adequate time and resources.

Where the audit is not feasible, an alternative should be proposed to the audit client, in consultation with the auditee and in full respect of the governance principles.

4.4. Governance

The SOPs of the Organisation initiating or requesting an audit should describe a process for resolving any conflicts of interest between auditor, auditee and or audit client for all aspects of the auditing function.

Depending on the organisational structure an escalation process to the Organisation's senior management should be defined.

4.5. Selecting the audit team

When the audit has been declared feasible, an audit team and team leader should be selected, This process should be described in the Organisation's SOPs taking into account the competence needed to achieve the objectives of the audit. The process of assuring the overall competence of the audit team should include the identification of the knowledge and skills needed to achieve the objectives of the audit and the selection of the audit team members such that all of the necessary knowledge and skills are present in the audit team. If there is only one auditor, the auditor should perform all applicable duties of an audit team leader.

² Walter Shewhart and W. Edwards Deming's PDCA Cycle

If not fully covered by the auditors in the audit team, the necessary knowledge and skills may be satisfied by including technical experts. A technical expert does not act as an auditor and should operate under the direction of an auditor.

Auditors-in-training may be included in the audit team, but should not audit without direction or guidance.

4.6. Document Review

Prior to the audit activities the auditor(s) review the applicable standards, regulations, guidelines, SOPs and/or protocol or project specific requirements. This review should take into account the structure of the Organisation and the objectives and scope of the audit.

If the documentation is found to be inadequate the audit team leader may inform the audit client and the auditee prior to the audit. Depending on the nature of the deficiency further resources should not be expended until such concerns are resolved. Deficiencies in the auditees' written procedures and documentation are documented in the audit report.

4.7. Preparing the audit plan

In order to provide necessary information to the audit team, auditee and audit client, an audit plan should be prepared according to the Organisation's SOPs (see ICH GCP 5.19.3). The plan should facilitate scheduling and co-ordination of the audit activities.

The audit plan should be sufficiently flexible to permit changes, such as changes in the audit scope, which can become necessary as the audit activities progress.

The audit plan should include or describe:

- a) the audit objectives;
- b) the audit criteria and any reference documents;
- c) the scope, including the identification of the organisational and functional units and processes to be audited;
- d) the dates and facilities where the audit activities are to be conducted;
- e) description of facilities which need to be made available to the auditor(s) to perform the audit;
- f) the expected time and duration for audit activities, including meetings with the auditee's management and audit team meetings;
- g) the roles and responsibilities of the audit team members and any accompanying persons;
- h) the allocation of appropriate resources to critical areas of the audit.

The audit plan can also include, as appropriate:

- i) the identification of the auditee's representative for the audit;
- j) the working and reporting language of the audit where this is different from the language of the auditor and/or the auditee;
- k) the audit report topics (including any methods of nonconformity grading), format and structure, expected date of issue and distribution;
- l) logistic arrangements (travel, on-site facilities etc.);
- m) matters related to confidentiality;
- n) the need to have direct and unrestricted access to original documents and records containing source data.

The plan should be reviewed and discussed with the audit client and presented to the auditee before the on-site audit activities begin.

Any objections by the auditee should be resolved among the audit team leader, the auditee and the audit client. Any revised audit plan should be agreed among the parties concerned before continuing the audit (See also Section 4.4 Governance).

4.8. Assigning Work to the Audit Team

Responsibility for auditing specific management system processes, functions, sites, areas or activities will be assigned to each team member. Such assignments should take into account the need for auditor independence, competence and effective use of resources as well as different roles and responsibilities of auditors, auditors-in-training and technical experts. Changes to the work assignments can be made as the audit progresses to ensure the achievement of the audit objectives.

The audit team members should review the relevant information related to their audit assignments and prepare work documents necessary for those assignments.

4.9. Preparing work documents

Work documents should be prepared and used by the audit team for the purpose of reference and recording the proceedings of the audit and can include:

- a) checklists and audit sampling plans;
- b) forms for recording information, such as supporting evidence, audit findings and records of meetings.

The use of checklists and forms should not restrict the extent of audit activities which can change as a result of information collected during the audit.

5. CONDUCT OF THE AUDIT

5.1. Opening meeting

The purpose of an opening meeting, is to:

- a) introduce the participants, including an outline of their roles;
- b) confirm the audit objectives, scope and criteria; and clarify any unclear details of the audit plan;
- c) provide a short summary of the methods and procedures to be used to conduct the audit, confirm the audit timetable and other relevant arrangements with the auditee ;
- d) establish or confirm the official communication links between the auditor(s) and the auditee and confirm of the language to be used during the audit;
- e) confirm that the resources, documents and facilities needed by the auditor(s) are available;
- f) confirm the time and date for the closing meeting and any interim meetings of the auditor(s) and the auditee's management;
- g) be informed of any local practices which affect the implementation of quality systems or Good Clinical Practice compliance by the auditee;
- h) confirm any relevant work safety, emergency and security procedures for the audit team;
- i) confirm matters relating to confidentiality;
- j) provide an opportunity for the auditee to ask questions;
- k) discuss sampling techniques applied to select audit evidence.

5.2. Collecting information

During the audit, information relevant to the audit objectives, scope and criteria, including information relating to interfaces between functions, activities and processes, should be collected by appropriate sampling and should be verified. If appropriate, an audit trail should be followed to determine the full extent of any problem identified. Only information that is verifiable may be audit evidence. This is particularly true for information gathered through interviews. This should be crosschecked by acquiring the same information from other independent sources. It is recognised however that the use of unsubstantiated verbal statements cannot always be avoided, especially in the context of misconduct, and in such cases they should be identified as such.

The audit evidence is based on samples of the available information. There is therefore, an element of uncertainty due to the sampling technique applied.

The sources of information chosen may vary according to the scope and complexity of the audit and may include the following:

- a) interviews with employees and other persons;
- b) observations of activities and the surrounding work environment and conditions;
- c) documents such as policies, objectives, plans, procedures, standards, instructions, contracts with third parties and validation documentation;
- d) all "essential documents" (ICH definition) associated with the conduct of a clinical study;
- e) any kind of records, such as laboratory journals/registries, hospital or medical charts, inventory logs, QC reports, minutes of meetings, audit reports or audit certificates, etc.;
- f) computerised databases, data summaries, analyses and reports;
- g) any relevant information from external parties and suppliers;

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

5.3. Generating audit findings

All audit evidence should be documented. After all activities have been audited, the auditor(s) should review all the evidence and evaluate it against the audit criteria to generate the audit findings. These can indicate either conformity or non-conformity with the audit criteria, or opportunities for improvement.

The auditor(s) should then ensure that the supporting audit evidence is documented in a clear, concise manner. Depending on the Organisation's structure and SOPs, non-conformities may be graded.

If included in the audit plan, individual audit findings of conformity and the supporting evidence should also be recorded.

5.4. Preparing audit conclusions

The audit team should confer prior to the closing meeting:

- a) to review the audit findings, and any other appropriate information collected during the audit, against the audit objectives;
- b) to agree on the audit conclusions, taking into account the uncertainty inherent in the audit process;
- c) to prepare recommendations, if specified by the audit objectives, and;
- d) to discuss audit follow-up, if included in the audit plan.

If there is only one auditor, the auditor should go through the same process.

5.5. Closing meeting(s) with auditee(s)

At the end of the audit, the auditor(s) should hold a closing meeting to present the audit findings and conclusions in such a manner that they are clearly understood and acknowledged by the auditee and to agree, if appropriate, on the time-frame for the auditee to present a corrective and preventive action plan.

Participants in the closing meeting should include the auditee, and may also include the audit client and other parties.

Non-conformities should be reviewed with the auditee to obtain acknowledgement that the audit evidence is accurate, and that the non-conformities are understood.

Depending on the type of audit and the SOPs of the Organisation, the method of reporting, including any grading of non-conformities could be discussed and information provided about any appeal system on the conduct or conclusions of the audit.

Every attempt should be made to resolve any diverging opinions concerning the audit evidence and/or findings, and unresolved points should be recorded.

If specified by the audit objectives, recommendations for improvements should be presented. It should be emphasised that recommendations are not binding.

It is however, the responsibility of the auditee and/or the auditee's management to acknowledge the findings of non-compliance and determine the extent, the way and means of actions to be taken to improve the system(s).

6. PREPARATION, APPROVAL AND DISTRIBUTION OF THE AUDIT REPORT.

6.1. Preparation of the audit report

The audit report should provide a complete, accurate, concise and clear record of the audit, and include or refer to the following items as applicable:

- a) the audit objectives and scope, particularly identification of the organisational and functional units or processes audited and the time period covered;
- b) identification of the audit client;
- c) identification of audit team leader and members;
- d) the dates and places where the audit activities were conducted;
- e) the audit criteria;
- f) the audit evidence (unsubstantiated verbal statements should be identified as such);
- g) the audit findings;
- h) the audit conclusions.

The audit report may also include or refer to the following, as appropriate:

- i) the audit plan;
- j) a list of auditee representatives;
- k) a summary of the audit process, including the uncertainty and/or any obstacles encountered that could decrease the reliability of the audit conclusions;
- l) confirmation that the audit objectives have been accomplished within the audit scope in accordance with the audit plan;
- m) any areas not covered, although within the audit scope;
- n) any unresolved diverging opinions between the audit team and the auditee;
- o) agreed follow-up action plans, if any; including recommendations for corrective and /or preventive action(s) if specified in the audit objectives; (acknowledgement should be given if deficiencies have already been recognised and corrective actions initiated);
- p) a statement of the confidential nature of the contents;
- q) the distribution list for the audit report.

6.2. Approving and distributing the audit report

The audit report should be issued within the agreed time period. If this is not possible, the reasons for the delay should be communicated to the audit client and a new issue date should be agreed.

The audit report should be dated, reviewed and approved in accordance with the Organisation's procedures.

The approved audit report should then be distributed to recipients designated by the audit client.

The audit report is the property of the audit client. The audit team members and all report recipients should respect and maintain the confidentiality of the report.

6.3. Conducting audit follow-up

The conclusions of the audit may indicate the need for corrective, preventive or improvement actions, as applicable. Depending on the Organisation's SOPs, such actions are usually decided and undertaken by the auditee within an agreed time frame and are not considered to be part of the audit. The auditee should keep the audit client informed of the status of these actions.

The completion and effectiveness of corrective action may be verified as part of a subsequent audit.

The audit programme may specify follow-up by members of the audit team, which adds value by using their expertise. In such cases, care should be taken to maintain independence in subsequent audit activities.

7. COMPLETING THE AUDIT

In some Organisations, depending on the SOPs, the audit is only considered complete when all activities described in the audit plan have been carried out and an appropriate audit response has been received. The audit response may be distributed together with the approved audit report. If the audit response does not address the audit findings or conclusions, a mechanism should be in place to escalate this to management.

Documents pertaining to the audit should be retained or destroyed by agreement between the participating parties and in accordance with the Organisation's SOPs and applicable statutory, regulatory and contractual requirements.

Unless required by law, the audit team and those responsible for managing the audit programme should not disclose the contents of documents, any other information obtained during the audit, or the audit report, to any other party without the explicit approval of those responsible for quality management within the Organisation. If disclosure of the contents of an audit document is required, the audit client and auditee should be informed as soon as possible.

8. AUDIT CERTIFICATE

The Audit Certificate is a document prepared and used in accordance with the Organisation's SOPs and may include, if applicable:

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

Since it is recognised 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.

SUPPORTING DOCUMENTS

European Network of GCP Auditors and Other GCP Experts. *The ENGAGE Guideline: Optional Guideline for Good Clinical Practice Compliance and Quality Systems Auditing*. Supplement to *The EFGCP News*, September 1998.

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) 1 May 1996.

ISO 9000:2000 *Quality Management Systems - Fundamentals and Vocabulary*. ISO December 2000

ISO 19011:2002 *Guidelines for Quality and/or Environmental Management Systems Auditing*. ISO 2002