

Standard Operating Procedure

Audit Management

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1 ABBREVIATIONS

ASST-PG23:	Azienda Socio Sanitaria Territoriale – Papa Giovanni XXIII
CAPA:	Corrective and Preventing Actions
CRO:	Clinical Research Organization
DM:	Data Manager
FROM:	Fondazione per la Ricerca Ospedale Di Bergamo
GCP:	Good Clinical Practice
ICH:	International Conference on Harmonisation
QAM:	Quality Assurance Manager
PI:	Principal Investigator
PM:	Project Manager
SOP:	Standard Operating Procedure
TMF:	Trial Master File

2 SCOPE

The aim of this Standard Operating Procedure (SOP) is to define the process for planning and documenting an audit and the relevant responsibilities.

3 FIELD OF APPLICATION

This SOP applies to clinical trials sponsored and/or supported by Fondazione per la Ricerca Ospedale Di Bergamo (FROM) or sponsored by Azienda Socio Sanitaria Territoriale – Papa Giovanni XXIII (ASST-PG23) or to systems/process to be applied to clinical trials.

4 RESPONSIBILITIES

Quality Assurance Manager (QAM)

- Ensures that trial related activities are compliant with the FROM SOPs, GCP and applicable regulatory requirements (by means of audits).
- Prepares the CAPA (where applicable) to be completed by the auditees.
- Reviews and approves the CAPA when completed by the auditees.
- Follows-up the corrective/preventive actions to be undertaken as a consequence of an audit/inspection.
- Defines the CAPA “closed” when all corrective/preventive actions have been implemented.
- Archives the audit documentation.
- Acts as reference person in case of audit by an external auditor or inspection by a Competent Authority.
- Performs the cause analysis of critical findings and identifies corrective and preventive actions with the collaboration of the involved parties.
- Drafts the Annual Audit Plan for clinical trials.

Auditor

- Performs audits to verify that the clinical trial activities are compliant with SOPs, GCP and applicable regulatory requirements.
- Issues the audit agenda, audit report and audit certificate.

Principal Investigator(PI)/Project Manager (PM)/Data Manager (DM)

- Primary contact for the trial specific audit.
- Coordinates the corrective/preventive actions for trials of competence.
- Collaborates in case of trial audits or inspections.
- Archives the audit certificate(s) in the TMF.
- Performs the cause analysis of critical findings and identifies corrective and preventive actions with the collaboration of the QAM and any other involved party.

Operational Director

- Appoints the QAM and the Auditor.
- Approves the Annual Audit Plan according with Medical Director.

Medical Director

- Ensures that the relevant auditee takes appropriate corrective measurements in case of critical findings emerged during the trial related audits.
- Approves the Annual Audit Plan according with Operational Director.
- Notifies AIFA about critical deviations occurred in any Phase I clinical trial.

Auditee

- Completes the CAPA with the preventive and correctives actions to be taken, the relevant responsibilities and deadlines.
- Implements the preventive and correctives actions as defined in the CAPA.
- Takes appropriate corrective measurements with a matter of urgency in case critical findings.

5 PROCEDURE

According to GCP regulation the sponsor should implement and maintain a quality assurance system and appoint individuals, who are independent of clinical trials/systems, to conduct audits.

“Quality Assurance” consists of all those planned and systematic actions that are established to ensure that the trial is performed and data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

“Audit” is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were performed, and the data were recorded, analysed and accurately reported according to protocol, SOPs, GCP, and the applicable regulatory requirements.

The Clinical Quality Assurance is an integral part of all clinical trial-related activities but the personnel involved in the audit activities (i.e. auditor) must have no direct involvement in any aspect of clinical trial conduct. Both roles have to be qualified and trained according to Ministerial Degree dated November 15th, 2011 (CRO minimum requirements) in case they are involved in Phase I trials.

5.1 Audit

The two main audit categories are:

- *Trial specific audit* performed across a single trial irrespective of the trial stage of development. This type of audit is described in the SOP **Types of Audit (CQA02)**.
- *System/process audit* aimed to verify the performance of specific processes within systems or an organization (e.g. SOP process, archives, laboratories). It includes service provider's audit to ensure that they are able in terms of resources, facilities and processes to conduct the activities delegated by FROM. This type of audit is described in the SOP **Types of Audit (CQA02)**.

These audits can be conducted at FROM/ASST-PG23 or external facilities.

The QAM is responsible for drafting an Annual Audit Plan including the audits to verify the compliance with the clinical trial quality system in place. The plan has to be approved by the Operational Director and Medical Director. The Operational Director is also responsible for the auditor's identification and appointment with the support of the QAM.

5.2 Audit Documentation

5.2.1 Audit Agenda

At least one month before the planned audit date the auditor contacts the auditee to agree on the audit date(s). Once the date is confirmed the auditor prepares an Audit Agenda, including the logistics information about the audit, the scope, documents to be available during the audit, the personnel to be interviewed, the facilities to be visited and the audit timetable.

The Audit Agenda should be delivered at least three weeks prior to the audit to the reference person of the auditee. The Clinical Operations Coordinator, the Operational Director, the QAM and the Phase I Medical Director are copied in the relevant correspondence.

5.2.2 Audit Report

After the audit the auditor should prepare an Audit Report (example provided in the document **Audit Report-T.CQA01.01/2**) tentatively within 20 calendar days of the audit end.

The Audit Report describes audit findings and their classification (i.e. critical, major, minor) in accordance with the criteria published on the AIFA website.

Copy of the signed Audit Report is sent to the Clinical Operations Coordinator, the Operational Director, the QAM and the Phase I Medical Director.

Critical findings requiring prompt corrective actions must be immediately (i.e. before the Audit Report finalization) reported to and discussed with the Phase I Medical Director .

The Audit Report is a confidential document filed in the QAM archive. It should not be archived in the Trial Master File. The Audit Report should not be copied or released to any external party (e.g. Investigator).

5.2.3 Audit Certificate

An Audit Certificate is a declaration of the auditor that an audit has taken place.

The Audit Certificate (example provided in the document **Audit Certificate-T.CQA01.02/2**) is delivered to the PM/DM for filing in the Trial Master File. A copy of the Audit Certificate is filed by QAM along with the audit documentation.

The Audit Certificates have to be included in the Clinical Study Report as Appendix according to the ICH guideline.

5.2.4 Corrective and Preventing Actions Plan (CAPA)

The **CAPA Plan (T.CQA01.03/02)** is a tool used to track the corrective/preventing actions to be undertaken as a consequence of an audit.

The QAM prepares the CAPA Plan with findings and relevant grading as reported in the Audit Report within 10 calendar days from Audit Report release.

The CAPA Plan is sent to the concerned PM/DM for clinical trial audit and to the auditee in case of system/process audits.

Ideally the completed CAPA Plan should be remitted to the QAM within 15 calendar days of CAPA receipt with the relevant corrective/preventing actions to be undertaken, the name of the person responsible for the implementation of such actions and the planned timelines for their implementation.

The QAM reviews and approves the plan or ask for modifications in case the actions reported in the document are not deemed adequate.

If a deviation is considered significant (i.e. major or critical) the QAM with the collaboration of the PI/PM/DM and other involved parties should perform a cause analysis to identify the most suitable actions to be implemented.

The audit reference person is responsible for informing the QAM about the action implementation. If the person fails to provide updates, the QAM must be proactive in requesting the CAPA Plan update.

The CAPA Plan is considered “closed” by the QAM when all corrective/preventing actions are implemented, or upon justified QAM decision (i.e. very long period requested to implement the actions). A follow-up audit can be performed to verify the preventing/corrective actions implementation.

The CAPA plan is confidential and the original document is filed in the QAM archive. It should not be archived in the Trial Master File.

5.2.5 Audit Documentation Archive

The Audit Agenda, the Audit Certificate and relevant correspondence are archived in the TMF.

The Audit Report, Audit Certificate and **CAPA Plan (T.CQA01.03/2)** are archived by the QAM.

Audit documentation is to be maintained by FROM for a period of 25 years of the audit end.

6 REFERENCES

- Guideline for good clinical practice E6(R2) (CPMP/ICH/135/95).
- Ministerial Degree dated November 15th, 2011 – Definition of the minimum requirements which a CRO shall satisfy in order to work within clinical trials on medicinal products.

- Determina n.809/2015 del 19 giugno 2015 inerente i requisiti necessari per le strutture sanitarie che eseguono sperimentazioni di fase I di cui all'art.1 del decreto del Presidente della Repubblica 21 settembre 2001, n.439 e di cui all'art.31, comma 3 del decreto legislativo 6 novembre 2007, n.200.
- Q&A alle Determine AIFA n. 809/2015 e n. 451/2016 inerenti ai requisiti minimi necessari per le strutture che eseguono sperimentazioni di Fase I (08 luglio 2019).

7 TEMPLATE

T.CQA01.01/2	Audit Report
T.CQA01.02/2	Audit Certificate
T.CQA01.03/2	CAPA Plan

8 VERSION HISTORY

Version	Date	Reason for revision
1	30 Sept 2016	Starting document.
2	28 Feb 2020	<ul style="list-style-type: none"> • Deletion of document specific audits because not performed. • Inclusion of the PI e DM role as collaborator in the trial specific audit. • Templates of the Audit Report and Audit Certificate identified as examples to allow the auditor to use her/his own templates. • CAPA signed only at the time of closure (the first signature for the planned corrective and preventive actions has been removed). • CAPA layout changed.