Audits in GCP and Beyond

Methods and Experiences

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2.1 Audit Schedule

The audit schedule is a plan that includes all QA activities of a development project, covering all studies from phase 1 to 3 throughout the clinical program from project initiation to application for approval.
The initial audit schedule serves to plan individual audit activities and, ideally, will be set up and amended at the same time as the CDP. Information from previous audits and other sources may also be included.
In order to plan the audit activities in parallel to the clinical activities, it is recommended to include the studies' milestones in the audit schedule, i.e., start and end dates of the program's studies and planned date of application for approval.

Essential information for each planned study to set up the audit schedule
- Timing and scope of the clinical study within the project
- Time schedule for the individual study
- Projected number and geographical distribution of the investigator sites
- Number of patients
- Study phase
- Parameters and/or procedures critical with regard to quality
- Complexity and risk-benefit ratio of the study
- CROs/vendors involved

Close co-operation and regular communication between the QA and clinical development personnel during the preparation of the CDP are vital as these data serve as a basis for the audit schedule.
The audit schedule specifies which clinical studies in the development program will be audited, and which specific audit activities should be carried out. The planned audit activities usually include document audits (i.e., study protocol, patient information, Informed Consent Form, Case Report Forms, Investigator's Brochure, clinical study reports and other documents such as the Clinical Expert Report or the Integrated Safety Summary [ISS]), investigator site audits, Trial Master File (TMF) audits, and audits of external service providers (i.e., Contract Research Organisations, central laboratories). In addition to these study-related audit activities (horizontal auditing) primarily aiming to safeguard the interests of the participating subjects and to ensure the data integrity of a specific clinical study, aspects relevant to the overall project, such as data management or archiving may be audited within the framework of system audits (vertical auditing).
The criteria for the selection of studies to be audited vary from company to company. Studies typically audited are either those of particular significance for approval or those allowing validation of the methods used, i.e., first-in-human studies, dose-finding studies, phase-III comparative studies and systems such as monitoring or data management. Nowadays, most companies use a risk-based approach when selecting the studies to be audited, applying predefined criteria like:

- "Proof-of-concept" study
- Study on the evidence of principal efficacy (pivotal)
- Study on the evidence of principal safety (pivotal)
- At least one study from each clinical phase
- Outsourced study

The first draft of the audit schedule includes all planned audit activities for the project and provides information about the audit subject, resources required and estimated budget required. The QA representative presents this draft audit schedule to the responsible project team for information.

The audit schedule is then discussed within the QA department and synergies between different project audit schedules determined and potentially applied during system audits.

For example, a CRO involved in multiple projects will be targeted for a more system-based CRO audit rather than conducting a study-specific audit at the CRO.

After the project audit schedule has been revised and agreed upon within the QA department, the final version is presented to the project teams.

Parallel to the Clinical Development Plan, the audit schedule has to be reviewed and up-dated regularly. Additionally, relevant audit findings and their Corrective and Preventive Actions (CAPA) might also lead to adjustments of the audit schedule. As part of the project audit schedule and to put the audit plan into practice, individual study audit plans are created. Each audit plan of an individual clinical study should include the following information:

- Number, type, and scope of the audits within the study
- Estimated resource needs for each audit activity
- Budget planning
- External auditor support (taking the required budget into account), as necessary
- Names of auditors, if possible
- Time schedule

2.2 Competence and Responsibilities of the Project Auditor

When integrating QA into a clinical project and development program, the role of a "project auditor" is best assigned to the contact person for all QA aspects of a specific project. The project auditor takes a leading role in establishing and updating the audit schedule and is responsible for the execution of the plan. The project team will benefit from having a single point of contact for all QA related questions. Although QA resources should not be used for questions the project teams can solve themselves via review of respective procedures or guidelines, the auditor is a resource providing guidance for more complex questions.

The project auditors exchange their experience to avoid duplication of work and to make use of synergy effects. Within the clinical development project, the project auditor ensures that all auditors involved follow the same procedures, contribute to the harmonisation of methods and standards, and thus ensure a uniform quality policy.

An "audit manual" may also be helpful; it is compiled by the project auditor and up-dated regularly.

The audit manual includes the study documents that are important for the auditors, e.g.:

- Study protocol
- Amendments
- Study-specific monitoring guidelines
- Study-specific operating procedures
- Information on findings from audits that have already been carried out during the project

In addition to their oversight role, project auditors themselves also conduct selected audits for the project in order to ensure immersion and deep understanding of the project.

As project auditors are known to the teams and are aware of the details of the project, they are the ideal contact for all quality-related aspects of the project. They also proactively initiate advisory and training efforts, which may translate into intensified training for monitors or investigators, or into suggestions for revisions of Standard Operating Procedures (SOPs). They may not only support the project teams in implementing corrective actions but also in identifying the root cause of audit findings and providing advice for preventative actions (CAPAs).

Furthermore, project auditors have the responsibility to assess project-associated quality problems that have already or are likely to occur, including potential consequences. They suggest corrective actions in co-operation with the audit team, QA management, and the project team, as necessary. Thus they continuously analyse the audit findings and categorise them as "insignificant", "quality-relevant", or even as "high regulatory risk" to the course of the project. This analysis forms the basis to assess deviations and to provide suggestions for correction. An example for a corrective action is to organise a risk-management team to counter serious misconduct or suspicion of fraud (see chapter 22). The timely communication of these quality-relevant aspects is essential for the further course of the project.

In case of external inspections (i.e., regulatory authorities or in the event of a 'due diligence'), the project auditor is responsible for supporting and advising the project team, for preparing and organising the inspection, and for its smooth conduct and follow-up.

In order to meet these responsibilities, project auditors should have several years of experience in auditing and extensive QA expertise. They should have excellent organisational skills, be good team players, and effective communicators (within the QA team, in co-operation with the other project team members, and executive management). These attributes will allow project auditors to be efficient, constructive contributors towards enhancing the quality of clinical development programs.

Even as part of the project team, the independence of project auditors must be guaranteed. They should not be involved in any operational procedures for Quality Control (QC). In this respect there may be challenges of clear delimination.

3. Discussion

In contrast to roles in project management or controlling, many pharmaceutical companies' QA departments have the tendency to consider, plan and conduct audits purely at a task-oriented study level. However, in more and more

competence) [17]. ISO/IEC 17025 was established in 1999 by the International Organization for Standardization to combine the general quality management principles of the ISO 9000 series with a deep focus on the analytical competence of the laboratory. The special requirements of medical-diagnostic laboratories have been taken into account when the ISO 15189 standard was introduced in 2009 to serve as an adoption of the ISO 17025 for these types of laboratories.
In European countries, the accreditation of medical laboratories according to ISO/IEC ISO 15189 or ISO/IEC 17025 requires the examination of the laboratory by a national accreditation body (e.g., Deutsche Akkreditierungsstelle (DAkkS) for German laboratories). In contrast, American laboratories historically maintain an accreditation by the College of American Pathologists (CAP) [18]. All these laboratory accreditation programs ensure and document that an adequate quality management system is in place and that the capability of the laboratory meets the required quality standards. Maintaining the accreditations requires regular inspections by representatives of the accreditation bodies, i.e., every 15–18 months. According to the CAP guidelines, the laboratory is obliged to perform self-inspections between these regular inspections. CAP surveys four areas—personnel, safety, technical process, and proficiency testing—and rates these from unsatisfactory to excellent.

3. Pre-analytical Procedures, Infrastructure, and Logistics

It is often considered that the laboratory's responsibility starts with the receipt of the samples, but almost all central laboratories as well as some local laboratories are involved in the definition of pre-analytical procedures, the generation and provision of sample collection kits, and the set-up of the respective instructions in a "Laboratory Manual" (see Box 1).

The Laboratory Manual instructs on

- Sample type
- Sampling materials (laboratory kits)
- Sample-collection procedures
- Sample processing
- Packaging materials
- Storage & transport conditions (temperature/humidity).

Since the applicable pre-analytical procedures depend on the specific assays performed in the laboratory, the source of information is of great importance [19]. A common practice is the use of the information usually provided by the manufacturer of reagents in the package inserts or information leaflet. However, if the required information is not available, the laboratory should perform its own evaluations. If the laboratory contributes to the definition of pre-analytical procedures, e.g., provides specimen collection kits or issues a laboratory manual, these tasks should be subject to the audit. In this case, it is mandatory that the batch numbers as well as the expiry dates of each single item of the specimen collection kits are recorded at the laboratory to enable the traceability of a sample to the respective sample-collection device. Moreover, a proper quality-control step should assure the integrity and completeness of the specimen collection kits and the laboratory manuals.

If this service is not provided, the receipt of the samples at the laboratory should mark the onset of the laboratory audit.
By considering the pre-analytical procedures, it becomes obvious that variables influencing sample integrity are not limited to the sampling itself but also comprise the logistic process as well as factors like geographical regions and their climate, annual seasons, transit times/shipping days, and import/export requirements [20].
Due to many interfaces between the acting parties (sender, courier(s), airline(s), recipient) and the lack of comprehensive documentation that would allow full traceability of sample handling during shipment, auditing the path of the sample from being obtained to its arrival at the laboratory is often found to be quite difficult. This subsequently results in uncertainties of possible causes if samples cannot be analysed due to weak quality of the samples received by the laboratory. It should be emphasised that auditing the "chain of custody" for the samples is at least as important for the assessment of the analytic quality as the laboratory audit itself. The audit of the logistics process (transport, storage) becomes more complex and vulnerable to failures in multi-national trial settings requiring cross-border transports. Therefore, it should be considered to qualify not only the laboratory but also the courier at an early stage of trial preparation as part of the sponsor's vendor-selection process (see 3.1).
Invalid laboratory results often stem from mistakes occurring during the different pre-analytic procedures performed at the investigator site or during transport, which should be evaluated as part of the audit (Box 2; Fig. 3) [19].

Potential failures during pre-analytical procedures

- Improper sampling, e.g.,
  - Hemolytic blood sample
  - Use of incorrect tubes
- Sample mix-up, e.g.
  - Missing sample label,
  - Incorrect label text and subject ID
- Incorrect preparation, e.g.
  - Centrifugation time or speed
  - Delayed processing
  - Fractioning of sample
- Incorrect packaging, e.g.
  - Not shock-resistant boxes
  - Use of sealed container for dry ice shipment
  - Unconditioned cool container
  - Insufficient cooling capacity of gel packs
- Inadequate storage at investigator site, e.g.,
  - No storage capacity with required conditions
  - No temperature control in storage area
- Documentation, e.g., lacking or inadequate
  - Laboratory requisition form
  - Packaging slip
  - Pro-forma invoice
  - IATA dangerous goods declaration
  - Other export/import documents
  - Labeling of transport box(es)
  - Airway bill

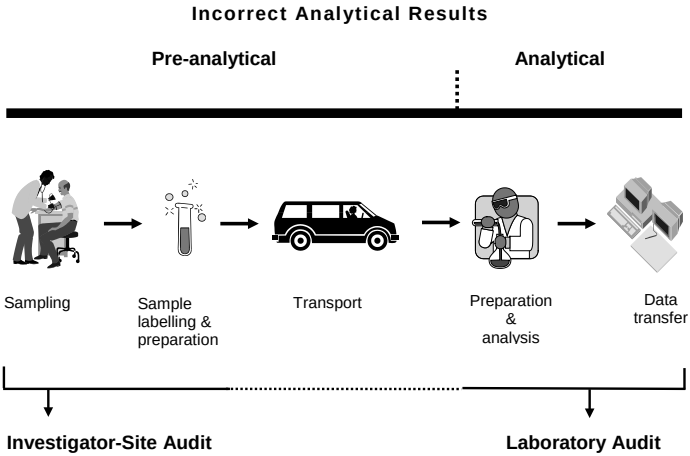

Fig. 3. Possible reasons for incorrect analytical results and allocation to audit types. Possible reasons for determining the incorrect laboratory results, which may have been caused at any stage during the entire procedure from sampling to the submission of the laboratory report to the sponsor/investigator, should be checked by audits. Depending on the delegation of responsibilities for the transport of samples, this procedure has to be part of the investigator-site or the laboratory audit.

Although sample handling by the laboratory (e.g., documentation of sample identification, registration, preparation and analysis) is standardised and well documented, it must be assured during the laboratory audit that the specific requirements of the clinical trial are mastered.
The organising skills (organisation of analytical procedures and sample handling) should be audited with special care. The correctness and timeliness of the laboratory work has a direct impact on the clinical part of the trial, (e.g., assessment of trial subjects' eligibility), thus directly affecting the recruitment rate. It has to be scrutinised if the processes at the interfaces between investigator site(s), courier service(s), and laboratory(s) are established and tested or must be newly set up for the trial.
In addition to the preparation of the sample, the analytical tests, the premises, the personnel (capacity, qualification, and training) and the technical equipment as well as the management of samples and data should be part of the audited infrastructure of the laboratory.

3.1 Sample Transport

Recently, not only the number of global trials increased but also the need for accelerated analytics since patient-selection criteria based on laboratory parameters have been established as standard when innovative approaches and personalised healthcare principles are applied. In this setting, it becomes essential that all laboratory samples are analysed and evaluated with the same methods and technical equipment and the sponsor decides more often in favour of a highly specialised central laboratory. As a consequence, shipments