

Vendor Audit: What it is and What to Expect from it

Parag Shiralkar, Sumptuous Data Sciences, LLC
Nagadip Rao, Eliassen Group;

ABSTRACT

Audits are primary instruments to assess the processes, procedures, and practices of an organization. It is common in pharmaceutical industry to utilize multiple contracted service providers or 'Vendors' to support various clinical trials activities for the sponsor. Likewise, the sponsors get audited by regulatory agencies. All audits in pharmaceutical industry are geared towards ensuring that the organization follows good clinical practices or GCPs and other regulatory requirements for data management and reporting. The primary objective of 'vendor audits' is to ensure that there is sufficient risk management and mitigation procedures executed on sponsor side to ensure integrity of clinical data management and reporting processes. These audits can be conducted pro-actively to support the vendor selection process or can be done re-actively to investigate the practices of the sponsors and providers. Typically, the audit conduct is done by assessment of provider's quality management system, technological platform, and personnel records.

This paper provides an overview of vendor audit from sponsor as well as vendor perspective. It also discusses typical nature of audit findings and possible resolution approaches.

INTRODUCTION

An audit according to GCP is "a **systematic and independent examination of trial-related activities and documents** to determine whether the evaluated trial-related activities were conducted, and the data recorded, analyzed and accurately reported according to the protocol, sponsor's SOPs, GCP and the applicable regulatory requirements". Periodic audit of contracted organizations and partners, providing services, supporting various aspect(s) of clinical trials is an integral part of sponsoring client's quality assurance program.

As a contracted service provider in pharmaceutical industry, we generally experience three types of audits from clients or potential clients.

1. **Pre-qualification audit:** These audits are undertaken prior to business being awarded to potential new service provider, to evaluate vendor's ability to meet sponsors expectation and industry standards. Vendor pre-qualification audits focus on new vendor capability, systems and processes followed. Vendor qualification audits are guided by 21 CFR 312.52 and ICH 5.5.2 which regulates transfer of obligations between contract research organization and sponsors.

2. **Re-qualification and in-process audits:** These audits are also known as Quality Assurance (QA) audits, refer to periodic formal review of by sponsor's quality assurance departments to examine vendor's organizational structure, review procedures followed, and selected documentation related service performed by vendor for sponsoring organization. The purpose of Vendor QA audit is to assesses potential risk and make sure vendor continues to meet sponsor's expectations.

3. **Extension of regulatory audit from sponsor to vendor:** In general, sponsors pharmaceutical companies are audited by regulatory bodies for compliance of processes. When sponsors use vendors for key processes impacting the drug development process, the regulatory audit process is extended to vendor. Such audits are extension of audit from regulatory bodies to sponsors.

In this paper author provides an overview of vendor quality assurance audit procedure, including expectations of sponsor's auditors, audit findings, and how to appropriately respond to audit findings.

AUDIT PURPOSE AND PROCESSES OVERVIEW

PURPOSE OF AN AUDIT

In general sponsor biotech and pharmaceutical companies outsource the certain set of services to vendors. Such outsourcing decision is based on lack of availability of resources with the sponsor organization. As an example, for a small to mid- size pharmaceutical company, having in-house skill sets and resources required to execute all functions associated with data life cycle is not possible. This includes technical infrastructure, processes, as well as human resources to perform various activities related to data acquisition, database management, data management, biostatistics, statistical reporting, and medical writing. Since these are essential functions, small to mid-size sponsor companies are often require bundling these services and outsource those to external vendor often referred as clinical research organization (CRO). In case of larger pharma companies, the same outsourcing for data cycle may come from meeting the requirements triggered by rapid fluctuations in the demand for technical and human resources.

While sponsor companies are required to outsource services, it is extremely critical for them to ensure that they are associating with a 'right vendor'. Beyond the legal, and financial compliance requirements, the sponsors need to ensure that the vendors meet necessary regulatory and reporting requirements when it comes to qualification of vendor. Secondly, sponsors need to ensure that they can accurately understanding of extent of risk they are taking by associating with certain vendor. Such qualification and risk assessment is done by sponsor through a formal audit process. Given the right regulations imposed by pharmaceutical industry regulatory bodies around the world, audit process in pharmaceutical industry is much more rigorous.

AUDIT PROCESS OVERVIEW

In general sponsor companies select the vendors through their due diligence process. The due diligence is undertaken through request for information (RFI) and request for proposal (RFP) followed by bid defense. Every sponsor has different set of rules, expectations, and requirements for selection of vendor. Prior to initiating association and starting the business operations, sponsors take audit of vendor processes, systems, infrastructure, and personnel. Such audit is called 'pre-qualification' audit. Upon satisfactory outcome of this audit, the vendor gets selected by sponsor for the functional operations sponsor desires. After association, the sponsor needs to take routine audit to ensure that the vendor processes promised initially are followed by vendor upon continued operations. Secondly such routine audits also ensure that the vendor has resolved or addressed the observations from prior audits. Most sponsors have a rule of auditing every service provider at least once in a span of two to three years subject to continued association with vendor. Vendor's deemed higher potential risk are audited more frequently.

The second type of audit is the 'vendor qualification audit'. This audit is usually taken for vendors where the sponsor has existing contract. This audit can be a routine audit as a quality assurance requirement, or it can trigger from a qualified quality event through business operations. Depending on cause of such audit, this audit can have a different scope and stakeholders involved. This audit can happen frequently or with predefined frequency based on mutual agreement between sponsor and vendor. The third type of audit is triggered through submission process from regulatory body. In many circumstances, the US FDA, EMA, or PMDA may request additional process specific information pertaining to vendor processes utilized in the submission of clinical data to regulatory body. This audit can be much more comprehensive in case of clinical research organizations. In subsequent sections, we will look into each audit type in more details.

AUDIT CONDUCT AND RESPONSE

PRE-QUALIFICATION AUDIT

After vendor due diligence is complete, sponsors conduct vendor pre-qualification audit. This audit includes formal validation and assessment of vendor capabilities. This audit focuses on following aspects of

business. This audit is conducted by a quality assurance personnel representing the sponsor. The goal of quality assurance personnel in this case is to evaluate all processes and procedures of the vendor before awarding business. Various processes generally assessed during a pre-qualification audit are in the following

Business Processes

A formal review of vendor's organizational setup along with project management processes is conducted. An auditor reviews vendor's work allocation processes, cost estimation and study milestone management processes. A review of project plan is done for consistency with sponsor's expectations. Vendors resourcing capabilities along with any previous regulatory remarks are reviewed. An auditor is also interested in operational quality and performance metrics assessment processes. An assessment of vendor's disaster recovery and business continuity plan is also done by auditor. Overall KPI's are evaluated including repeat business, vendor's finances along with staff retention rates etc.

QMS Processes

A vendor having robust quality management system is essential for success of partnership between sponsor and vendor. A pre-qualification audit involves evaluation of QMS related processes and related documentations like Standard Operating Procedures (SOPs), standard templates and work instruction and guidance documents, training processes and records, delivery quality management processes, personal CV, s, job description along with hiring and employee evaluation processes. Vendor policies and procedures related to data privacy and protection. Computer System Validation required as per 21 CFR part 11 compliance are also reviewed in detail along with due diligence done by vendor before deploying any new software for project execution. An auditor evaluates if QMS processes of potential vendor aligns with sponsor and in accordance with industry standards.

Personnel Qualification and Interviews

Review of vendor staff qualifications and interview of key personals is essential to ascertain qualified resources are available for project execution. Qualification of vendor staff is compared against job descriptions and their training records are evaluated. Some of the key staff will be interviewed by sponsor assess their qualifications and experience.

Infrastructure Review

Auditor evaluates building and facility infrastructure including accesses to workplace along with server room and data center security. Auditor will also review IT infrastructure related to remote work by vendor personals like VPN, remote staff accesses and monitoring processes.

RE-QUALIFICATION AND IN-PROCESS AUDITS

Vendor re-qualification and in-process audit also known as QA compliance audit refers to periodic formal review of by the sponsor's quality assurance departments, to examine vendor's organizational structure, review procedures followed, and selected documentation related to service performed by the vendor for sponsoring organization. The purpose of Vendor QA audit is to assesses potential risk and make sure vendor continues to meet sponsor's expectations.

Scope of Audit

A QA compliance audit assess compliance with relevant Standard Operating Procedures (SOPs), applicable guidelines/regulations, contracts, and work orders, and will include an assessment of the protection of the rights, safety, and well-being of patients/ consumers. Generally following areas will be reviewed during a typical QA audit.

- a. Service provider's organizational structure, personal qualification, employee oversight, trainings and turnover, project management processes relevant to execution of sponsor's clinical trials
- b. QMS related documents like SOP's, templates etc.
- c. Review of documentation related to relevant contract including work orders, budget and change orders etc.
- d. Documentation of selected sponsor studies for which vendor provided services
- e. Operational quality and performance metrics (quality, error rate, re-work rate and productivity etc.) and previous quality deviation management (frequency, RCA, CAPA etc.)
- f. Computer systems, data and information security and privacy safeguard processes
- g. Periodic software and computer system validation documentation
- h. Review of previous negative findings in regulatory inspections if applicable
- i. Previous audit findings and its related corrective and preventive action plan (CAPA)

Method of Audit Conduct

Most vendor audits are currently conducted remotely utilizing Zoom or MS teams with auditors requesting documents to be uploaded on cloud platforms prior to audit. An audit is an agenda driven meeting generally takes place for about 2 business days.

Gap Assessment and Comparative Assessment with Previous Audit Findings

A review of gap assessment provided by sponsor auditors during previous pre-qualification audit or previous audit and agreed upon vendors action plan along with its effectiveness and timely implementation is reviewed. Any delay in vendor's CAPA plan implementation or less than optimal action plan implementation will be notified as an audit observation. A vendor is expected to provide documentary evidence of Gap assessment CAPA implementation.

Review of QMS

Quality management system refers to comprehensive set of policies and procedure in place to meet sponsor and regulatory requirements which includes protecting rights and wellbeing of subjects and maintaining the integrity of clinical study data and analysis. GCP requires that, all data transformations need to be validated and documented. To meet these stringent guidelines, it is essential that SOP's and procedures that a vendor implements needs to meet sponsor's expectations. An auditor reviews current policies, procedure and SOP associated with QMS processes, along with expected documentary evidence of its appropriate implementation. An auditor will review various templates used by vendor e.g., study validation template to make sure it meets sponsor's standards and captures required information.

Gap Assessment of Current Processes

The Gap Assessment of current processes is done by an auditor by reviewing the record of activities performed by vendor from selected studies, to assess compliance with relevant SOPs, proper documentation and applicable guidelines related to protection of the rights, safety, and well-being of patients/ consumers. During audit of selected studies, it is expected that key personal responsible for execution of relevant clinical study activities be present and answer questions from auditors. An auditor will review CVs and training curriculum of vendor personals, who worked on selected studies activities to ascertain these activities were carried out by qualified personals. Auditors will assess if proper procedures were followed for maintaining data integrity and study result validity. A formal review of every study milestone documentation is done, including study startup activities like list of table creation and updates, documentation related to DMC, study test run, unblinding and final run of study deliverables etc. Auditors will expect evidence of study activities being executed correctly as per industry/sponsor standards in formal study documentation (Trial master file) and any missing/ incomplete or in appropriate documentation will have to be explained by accountable vendor personals. If there were any quality deviation during the

execution of study activities, the sponsor will look for documented evidence of root cause analysis and relevant CAPA.

Findings and resolutions

An audit report is formal communication of observations from an audit provided by sponsor's auditor team to the service provider. Audit observations are classified into three types based on its potential impact on study subjects' safety/well-being and quality/integrity of data produced and reported in a clinical trial.

- a. Critical observations: A critical audit findings are those deviations that will adversely impact the rights, safety, or well-being of the subjects and/or the quality and integrity of data. A critical finding in an audit is not acceptable and a service provider receiving critical finding(s) is considered to have failed audit. A data with incomplete source documentation, code with multiple hardcoding instances without appropriate note to file. Receiving critical observation amounts to an audit failure.
- b. Major observations: A major audit findings results from deviations that might potentially impact safety/well-being of subjects and/or quality and integrity of clinical trial data. An example of major audit finding is inaccurate QC documentation. Major observation can might lead to a failed audit.
- c. Minor observations: Any observation that does not impact patient safety/well-being or quality of data/clinical trial integrity is communicated as minor observations in an audit report. It is to be noted that multiple minor observations potentially can become a major observation of the consequence of it may potentially impact patient safety or data integrity. A good example of minor observation would be incomplete employee training record.

A CAPA needs to be implemented by the vendor upon receipt of audit report. A CAPA is a formal document containing vendor audit observations remediation plan along with implementation timeline. It is to be noted that a sponsor would expect documentary evidence of appropriate and timely execution of CAPA.

REGULATORY AUDIT

While supporting regulatory submissions and even reporting of clinical trial results and progress, the sponsor companies are frequently audited by regulatory bodies. For US FDA, these are managed through the forms FDA 482 (notice of inspection) and FDA 483 (Observation of inspection). The audits from regulatory bodies are to ensure that the sponsor is conducting the clinical trial processes with integrity and as per the regulatory guidance and requirements to ensure patient safety. In clinical data operations these audits means ensuring that the processes utilized in clinical data processing, management, and analytics are validated thoroughly. Since in many cases such processes are owned by CROs and vendors, the regulatory audit gets extended to evaluate the vendor processes. These audits include following aspects.

Instance Driven Process Documentation Request

The clinical data submission process goes through various milestones which requires interaction with and approvals of regulatory bodies. This includes but not limited to the FDA -Advisory committee meeting, Real time Oncology Reporting (RTOR), Periodic data and status reporting requirements from FDA. For EMA this includes periodic reporting as well as GDPR specific reporting requirements. There are similar reporting events from other regulatory bodies like PMDA, MHRA and Health Canada. These reporting events may trigger routine questions and potentially an audit from regulatory bodies. In many circumstances such audit could be remote audit requesting gathering of necessary and sufficient information related to conduct of clinical trial by sponsor. In some instances, such audit can get into more detailed assessment of processes.

Personnel Interviews

Personnel qualifications and employee records is an important component of the regulatory audits. This includes the resume, training files, and job descriptions of each individual responsible for conducting clinical trial operations processes. Conducting interviews gives necessary confidence to the regulatory personnel about qualification and experiences of the staff performing clinical operations.

Necessary and Sufficiency Documentation -Development and Fulfillment

In many circumstances, the clinical trial does not go as planned. The sponsor needs to thoroughly document the discrepancies and anomalies in the data and processes to ensure that the trial is conducted with integrity and to ensure patient safety. Such documentation evidenced through documents like 'note to file' and the content of such document can initiate a requirement for regulatory audit. As a result of these audits regulatory bodies may request additional documentation and related evidence from sponsor and vendors.

CONCLUSION

Pharmaceutical industry is one of the most highly regulated industries, in order to protect rights and well-being of subjects and integrity of data and analysis, audits are integral part of our business. It is essential that we understand regulatory requirements and how it impacts to programming processes so we can pass the audits. Programming teams needs to be prepared for audit by ensuring timely and appropriate documentation of programming activities. Our documentation should be in accordance with the current sponsor standards and follow QA guidelines.

REFERENCES

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Parag Shiralkar
Sumptuous Data Sciences, LLC
Monmouth Junction, New Jersey, USA,
Email: Parag.shiralkar@sumptuous-ds.com

Nagadip Rao
Eliassen Group: Biometrics and Data Solutions
300 Atrium Drive, Suite 301 Somerset, NJ 08873
Email:Nrao@eliassen.com

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