



Quality First—Implementing Quality in Times of Change

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Building quality into an organization, such as a pharmaceutical company or a contract research organization (CRO), requires recognition of economy change indicators in addition to having the right people and processes to be successful. Quality Assurance (QA) can contribute greatly to the success of an organization by ensuring that the processes in place incorporate the federal, state, and country/local requirements as well as providing smart concepts for streamlining and achieving best practices.

Building quality into any system takes time. One way to make quality a part of your ongoing business is to design and monitor it. A checklist like the one presented below can be designed into your quality system by identifying upfront critical parameters that could affect your business early on to minimize the chance that they will occur.

An example of risk parameters that QA could monitor based on the analysis of the work conducted before, during, and after a clinical trial includes the following:

Step 1. Prior to Accepting Work on a Clinical Trial

QA Assessment/Questions

If contracting to vendors such as CROs and central laboratories, prior to signing the contract, contact QA to ascertain whether the CRO been audited prior to use.

Points to consider/Questions to ask:

Audits are needed to assess suitability of the vendor.

Example of Questions to Ask:

- Has the vendor been audited within the past 2 years?
- If the vendor was audited, were there significant findings associated with the audit?
- Were all audit findings resolved and corrective action accepted by QA so that the report could be closed out?

Note: The industry standard for re-audit is every 2 years. However, this depends on use, business, and regulatory risk. Also, any issues detected while working with a vendor need to be fed back to QA.

QA Assessment/Questions

An independent review by a quality unit should be conducted to look at the vendor's processes and procedures to determine whether there are any gaps which may have an effect on the vendor's performance in the study as well as regulatory risk for the company.

Note: It is important to assess whether there is sufficient documentation in place to demonstrate that audits were conducted and resolved and that training records have been reviewed and found to be acceptable.

Points to consider/Questions to ask:

Critical factors to identify include:

- Do procedures exist for all work that will be performed?
- Have all individuals to be involved in the study met their training requirements?
 - Does the vendor's team list identify everyone working on the study?
 - Are there job descriptions, CVs, and training records for individuals working on the study and is the individual's job background appropriate for the work being performed on the study?
- Is any of the work going to be further subcontracted to another vendor?

QA Assessment/Questions

Prior to signing the final contract, it is important for individuals from the sponsor and CRO to discuss issues which could affect the client deliverables, procedures used on the study, and overall regulatory impact on the study. Often, the decision on whether to waive or combine the prestudy and site initiation visit are frequent areas which need to be addressed. In addition, there are times in which the sponsor may request that telephone visits/assessments be conducted.

Points to consider/Questions to ask:

Examples of questions to ask prior to signing the contract for clinical services:

- Is there a plan to waive or conduct via phone any pre-study site qualification visits or site initiation visits?
 - Is there sufficient documentation/reason documented to justify waiving the visit?
 - Has the investigator site been used for the same indication within the last six months?
 - Does the vendor have procedures to support conducting visits by phone or waiving visits?
- Are there policies in place for home-based CRAs? Will documents be stored or destroyed according to set procedures?
- Who will be conducting translation of relevant clinical trial documents? What are the processes for back-translation?

Step 2. After Signing the contract and Before the Sponsor/CRO has Begun Work on the Study

QA Assessment/Questions

Conduct a GCP/GMP/GLP assessment early in the study to assess vendor compliance.

Points to consider/Questions to ask:

Areas to assess for a GCP assessment include:

- Have any modifications been made to sponsor-approved documents without sponsor approval which would include:

- Monitoring visit reports or other templates
- Change in procedures used by the vendor
- Change in computerized systems used for the trial
- Current status of study team member's adherence to required regulatory and study-specific training.
- Documentation of list of procedures (including version dates) used to conduct work on the study. This should be a living document.
- Signed documents by sponsor and CRO prior to performing work include:
 - Data Management Plan
 - Clinical Monitoring Plan
 - Safety Management Plan

Tip: The sponsor/CRO should have a list of procedures that will be used on the study for all services that are contracted along with a written plan for services such as project management, monitoring, data management plan, safety monitoring plan.

QA Assessment/Questions

Request from the sponsor/CRO the following documents on an ongoing basis during the study.

Points to consider/Questions to ask:

Request updated documents, for example:

- Trial Master File (TMF) Structure/and or access to documents (if applicable) including whether electronic

files are maintained and location of files.

- Recent changes in procedures associated with work performed on study.
- Team Member List, including CVs, JDs, and training records.
- Company Organogram.
- A list of regulatory inspections/ sponsor audits and whether major or critical issues were noted.
- Ongoing trackers and access to the TMF for ensuring that the TMF and investigator site files contain the required essential documents as per ICH GCP and applicable regulatory requirements.

Tip: The above documents should be reviewed on an ongoing basis. Changes in any of these areas could indicate areas which need to be audited or followed up closely. Too frequent changes in personnel can indicate issues within the company and can have an effect on the management of the study.

QA Assessment/Questions

Sponsors should ensure that they are reviewing the CRO and their own internal deliverables on a timely basis (for example, monitoring visit reports).

Points to consider/Questions to ask:

Review of Monitoring Visit Reports:

- Do the monitoring visit report templates contain all the required information including an area to indicate what was not able to be covered during the visit, and have these templates been reviewed by the sponsor?

- Are the monitoring visit reports finalized with approval signatures and filed in the TMF as required?
- Do the monitoring visit reports carry over any noncompliance issues to the next report until resolution?
- Do the monitoring visit reports contain serious noncompliance issues that would require action on the part of the sponsor, such as an enrolment hold or suspension due to repeat protocol violations or non-reported serious adverse events?
- Do the monitoring visit reports contain documentation that the IRB or ethics committee was notified of all issues subject to reporting?

Tip: Timely review of internal deliverables can prevent issues from escalating later in the study, when corrective action will be less effective.

QA Assessment/Questions

The sponsor/CRO should ensure that quality checks are being performed as required.

Points to consider/Questions to ask:

Questions to ask include:

- How often is the TMF being reviewed and are the results documented?
- Have any internal audits been performed on the study and what were the results? Were any critical issues or findings that affect the study being conducted noted?
- What are the current systems being used to run the study, eg, Oracle Clinical, Oracle AERs, Electronic Data Capture System,

Interactive Voice Response System (IVRS).

- Are the computer systems currently being used for the study validated? If yes, when were the systems last validated?
- Are any home-grown systems being used (as opposed to off-the-shelf software) and are they validated?
- Are all systems being used 21 CFR Part 11 compliant?

Step3. After Completing the Trial

QA Assessment/Questions

The sponsor/CRO should conduct a final review of documents. Examples of some of the critical documents to review include the following:

- Final monitoring close-out report for each investigator site
- Final report by investigator to the IRB for study closure
- Close-out of queries prior to database lock
- Close-out of all sponsor/CRO audit findings with corrective and preventative action and copies of audit certificates as applicable
- AE/SAE reconciliation tracker
- Final audit or QC check of TMF prior to transfer to sponsor

Points to consider/Questions to ask:

Questions/follow-up per category:

Final Monitoring Visit reports:

- Have all adverse events been reported to the sponsor/CRO, IRB/IEC and regulatory

authorities as required and followed to final resolution?

- Was the principal investigator available for final resolution of any issues noted, and is this documented?
- Was a 100% investigational drug accountability performed and all drugs either returned to the sponsor or disposed of per protocol?
- Have all case report form pages been verified and pulled prior to study termination?
- Has the IRB/IEC been notified of site closure per local law/regulations?
- Was a final investigator site reconciliation performed to verify that all essential documents are present?
- Was a final check performed to ensure that source documents, data correction forms/queries, monitoring notes, all approved/signed informed consents and any HIPAA/Data Protection documents are present for each subject?
- Have all lab reports been reported and analyzed?

Query Process:

- Have all outstanding queries been resolved or a plan agreed to for resolving any remaining queries including database lock procedures?

AE/SAE Tracker:

- Have all SAEs been recorded on the SAE Tracker and has the tracker been compared to the clinical database tracker?

- Were any discrepancies noted in comparison of the trackers resolved?

File Transfer Process:

- Is there a process in place to ensure that all original study documentation is returned to the sponsor after close-out at the end of the study?
- Does the transfer of files include a quality check for missing documents by the CRO?
- Are the files returned to the sponsor inventoried and organized to include a list of all documents provided?

What Do We Find During Audits?

Internal process audits which focus on training requirements frequently show that although individuals have met the training requirements, they fail to meet regulatory requirements because they do not understand them. As resources for professional training courses can be expensive, QA can be utilized as a resource to teach managers how to self-audit, perform employee gap analysis on training requirements, and provide information to set up proficiency testing programs. Utilization of these types of programs can go far in giving assurance to sponsors that vendor selection is appropriate and repeat business is warranted.

As an example, QA should take the lead in ensuring that systems are in place to assure that individuals who perform key roles in the company have met the ongoing training requirements and have the relevant background. This is the number one finding in many sponsor audits.

While online test questions help in assessing an individual's understanding of procedures,

this is no guarantee since tests can be retaken and answers can be memorized. Only through conducting review of documentation, interviews, and observation of processes can the true picture of an individual's understanding be ascertained.

An area which frequently goes unnoticed, but can result in significant impact for the company, is audit or inspection readiness. QA is adept in knowing the skills necessary and documentation requirements to ensure that individuals are prepared at a moment's notice. This includes holding a question-and-answer session to provide training on routine questions asked during a sponsor audit or FDA inspection. The best way to prepare for these is to have unannounced audits/inspections and have individuals respond to questions and receive immediate feedback on their performance.

Where Else Can QA Add Value?

Another area where QA can add value is by assisting the organization in understanding root cause analysis. By really understanding the issues, by peeling back the layers like an onion, you reach the key reason why something has gone wrong. This problem-solving process is something that has to be taught. When the real issue is identified, the organization is on its way to prevent re-offending, thereby saving potential time and cost. As part of this process, it is important to gain consensus rather than rushing in to fix the problem.

It is important that QA continue to build collaboration within operational teams and management. In QA, we have the enviable position of overseeing most of the activities of the organization and can easily determine issues and trends. Our strength is assisting teams in working

together at interfaces where issues are most often found.

Summary

Conducting more audits does not improve compliance within an organization; this has been proved many times. We need to consider further ways in which QA can work with teams to improve quality. By improving the quality culture within an organization and the involvement of QA as a "change agent," the organization will be best placed to work effectively in this ever-changing environment. ■



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