Quality Assurance in Multi-Site Studies

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Introduction

Subcontracting study components among multiple Contract Research Organization (CRO) sites presents the need to identify and overcome obstacles to reach successful and compliant project completion. Multiple sites present multiple challenges. Subcontracting requires dealing with personnel with a wide range of knowledge levels, varied personnel structures and philosophies, cultural differences, and unfamiliar standard operating procedures.

Issues that may appear obvious and immediate in one organization can easily be overlooked during the transfer of authority for completion of a specific study component to another organization. Critical issues that may differ among organizations include:

- Distribution and reporting mechanisms for protocol amendments
- Protocol and SOP deviations documentation and communication
- Quality Assurance (QA) differences between sites regarding the appropriate level and type of audit activities
- Reporting procedures for contributing scientist reports

BSI routinely contracts to perform study roles including study management and/or sponsor or CRO QA or QAU. Our experience has led to the observation of inconsistencies when dealing with multiple CROs and sponsors. In this Poster, we present methods that may help in attempting to manage these differences, with an emphasis on the role of QA. Those methods include a phased and logical approach to scheduling, judicious application of QA Site Audits, active and well documented in-study communication, and study tracking by QA with scheduled reporting to Study Directors and Management. We have presented this from the perspective of an FDA GLP study; however, the principles will apply across studies subject to other regulations.

Study Development

Successful launch of any study requires careful planning and scheduling. This is particularly true of multi-site studies. We have found that the subcontracting of individual study components is best accomplished using a phased approach as the study Protocol is developed. As development proceeds, suitable subcontractors can be identified and initial interest contacts made. Cost estimates may then be requested from interested CROs through Requests for Proposals or less formal processes. As the estimates are received and evaluated, QA site audits are scheduled and performed to confirm that the proposed study sites are capable of performing the contracted activities in compliance with applicable regulations.

Contracts with CROs are not finalized until the protocol nears completion, availability of test and control articles has been confirmed, methods of analysis are available and suitably validated, and the availability of in-life sites has been determined. If the study is terminal and an on-site CRO pathologist will be required, pathologist availability will also be confirmed before contracts are signed.

These are all possible bottlenecks to any study or project and inattention to any of these can delay studies and activate delay penalty clauses in executed contracts.

Figure 1
Scheduling Issues

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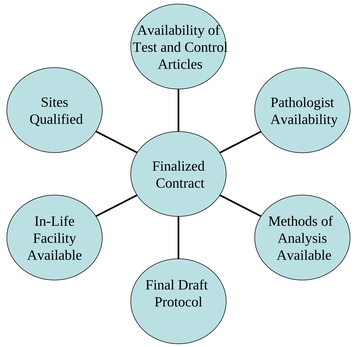


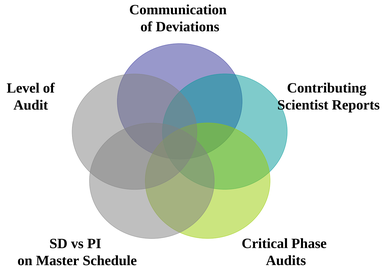
QA Site Audits – An Opportunity

The objective of a QA site audit is to confirm the capability of the organization to conduct the study activity in compliance with the appropriate regulations. However, the site audit may also allow an opportunity for QA to provide insight into questions that could arise during the execution of the subcontracted study component. Those insights could be critical to avoiding misunderstandings or missteps that could compromise compliance. Examples of potential issues that might benefit from clarification include:

- What is the mechanism for reporting possible protocol deviations and when will deviations be forwarded to an off-site Study Director?
- Will the CRO forward all SOP deviations to the Study Director and when will that occur?
- What are the SOP requirements for preparing and forwarding Contributing Scientist Reports?
- For CROs with internal QA capabilities, what is the required level of QA audit for study data and reports; how are critical study phases selected for audit?

Clarification of these questions can be obtained through on-site review of CRO SOPs or by conversations with CRO personnel during the site audit.

Figure 2
Issues to be Clarified



Communication

Lack of effective and timely communication has resulted in critical study failures such as failures to amend protocols in a timely fashion and failure of Study Directors to address circumstances that may affect the quality or integrity of data. Training of QA and study personnel defines critical information that should be communicated and identifies the study personnel to whom it should be communicated. Data collection forms, visit logs, and other form and phone log templates are prepared and reviewed for confirmation of adequate definition of communication. Consideration should also be given to various types of critical study communication such as:

Among Sites

Communication between the Study Director and CRO Investigators will be documented in order to demonstrate the Study Director's control of the study. Documentation of Study Director communication with investigators is most often in the form of email printouts and phone logs supported by trip reports and site visit logs, as appropriate.

QA communication

CRO with no internal QAU

- QA Plan provided by lead QA for Investigator agreement
- QA Audit Reports routed to CRO Investigator and Management and Study Director and Study Director Management

CRO with internal QAU

- Requirement for critical phase inspections confirmed through direct QA to QA communication
- Routing of QA Audit Reports from CRO to Study Director and Study Director Management predetermined
  - Confirmation of distribution by return signature
  - Copy to Study Director QA

Protocol amendments and deviations

Approved amendments provided to all sites.

Deviations communicated by the CRO to the Study Director as they occur.

Study Tracking

21 CFR Part 58.35(b)(4), 40 CFR Part 160.35(b)(4), and 40 CFR Part 792.35(b)(4) require that Quality Assurance periodically submit to Management and the Study Director written status reports on each study. In our experience, this is best accomplished by maintaining an active status spreadsheet on each project, with separate worksheets for each Protocol. This status report is updated as events occur, providing up-to-date tracking and is issued to Management and the Study Directors or Monitors each quarter. The document is structured as shown below:

Project specific
- •Includes all Protocols

Coversheet
- •Lists all QA activities since the last status report by Protocol
- •Lists all outstanding activities and issues

Listing of all QA activities, independent of Protocol, by date

Protocol specific worksheets
- •Regulatory status
- •Description of each activity
- •Status of each activity
- •QA Personnel involved
- •Date reported
- •Identity of Study Director/Monitor
- •Identity of CROs
  - •Function
  - •Status
  - •Investigator
  - •QA Plan of projected activities

Summary

A review of records of regulatory inspections and Form FDA 483 items indicates that failures to effectively communicate are a root cause for many of the objectionable inspectional observations described, especially in studies that are distributed across multiple testing facilities or sites. Effective study planning combined with QA methods that decrease the probability of errors caused by lapses in communication can pay large dividends. In this Poster, we have attempted to describe some methods and practices that we have used to address these communication issues.

Our experience indicates that addressing communication problems through these procedural and documentation measures coupled with continuous education of QA and study personnel contribute to a successful study.

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