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Programming Function Vendor Management in a Pharmaceutical Company

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ABSTRACT

In recent years, the pharmaceutical industry has seen a significant rise in outsourcing clinical trials to Contract Research Organizations (CROs). The oversight of these diverse CROs, with their varied practices can lead to inconsistent deliverables. This created a need for more consistent and effective CRO oversight. In this paper, we describe a CRO oversight process that was implemented by a pharmaceutical company programming function. The paper highlights various key steps of this framework from Partnership Initiation to Study Wrap-up. Overall, this framework stands as a robust solution to enhance the quality and uniformity of CRO oversight in the evolving landscape of clinical research.

INTRODUCTION

In a pharmaceutical or biotech company, we inevitably face the need to outsource some of our work to vendors, given limited internal resource. When this happens, what are our own responsibilities? Should we simply let it fly on its own or should we ensure things go smoothly by checking every details? We would like to share our practice and suggestion based on our experience working with various CROs.

WHAT DOES THE GUIDELINE SAY

Here we quote the guidelines that are relevant, they are: ICH E9 Chapter 5.8 Integrity of Data and Computer Software Validity, ICH E6 Chapter 3.9 Sponsor Oversight, ICH E6 Chapter 3.11 Quality Assurance and Quality Control, and ICH E6 Chapter 3.16.2 Statistical Programming and Data Analysis.

In summary, the sponsor takes the ultimate responsibility, no matter the clinical study are in-housing or outsourcing. Therefore, it is recommended to treat outsourcing study the same mindset as in-housing study. For example, whatever quality control and documentation are required in sponsor's company, the same should apply to outsourcing study as well.

As a lead statistical programmer (LSP), it is recommended to ask yourself a few basic questions when your study is decided to be outsourced: do you trust this vendor by working with them together to meet the same requirement as your in-housing study? Whether outsourcing this study to this specific vendor would bring additional risk in any sense that would hurt to achieve the goal of this study? If there is, is the risk manageable? What could you do to manage the risk?

VENDOR OVERSIGHT IN STUDY VARIOUS PHASES

As sponsor, we should establish a clear process in managing vendor's overall performance. Vendor management can be treated as a risk management system which should cover all phases within a clinical study. In details, we will share our practice in all phases throughout clinical studies which includes the following

Partnership Initiation Phase

During this phase, LSP is usually involved in vendor selection meeting and vendor audit trip.

1. Vendor selection meeting. In this meeting, multiple vendors presents their solutions with Q&A session. You need to make a decision which vendor you would like to pick after these time-limited meetings. It is suggested to evaluate vendor’s overall capability based on the following criteria
    a) Vendor company's overall background, which includes company size, reputation, and company age. These information tell you whether this specific vendor will provide a stable and continuous partnership service. After all, the support we need from vendor sometimes expands beyond the study closure, sometimes all the way to product submission which could be years after. It is

recommended to abstain company's reputation and past performance through colleagues before the meeting.

b) Capabilities of vendor leadership team: this represents whether vendor can support and solve complex problems, whether vendor have the capabilities of managing their team well and provide you an alternative when some unfortunate situation happens and a change to team member are necessary.

c) Vendor's SOP and process: this represents the basic requirement that are guaranteed vendor team will attain (more details will be covered in vendor audit trip session).

d) Capabilities of vendor's actual team member that are directly involved, e.g. lead programmer and individual programmers: this is the actual team that you will be directly working with. Sometimes in the vendor selection meeting there is no chance to directly communicating with them. In this case ask for their CV, training records, or another interview session, which would provide some useful information. Ask for alternative members if deems necessary.

2. Vendor audit trip: it is highly suggested to conduct a vendor audit trip (which is usually organized by QA or vendor management team), if it is a vendor that you or your company encounter with for the first time. The contents of the audit trip usually cover systematical review of vendor's SOPs (e.g. master SOP, functional SOPs, QA SOPs, as well as IT system SOPs), and interview for team member's knowledge of relevant SOPs. SOPs represent what basic requirement vendor will do for your study. Team member's awareness represents whether they are able to perform relevant tasks according to SOP and whether they are compliant with SOP in their past studies. There are all critical matters to make judgement on how they will perform in your study and whether there is any risk/gap that you need to pay attention to for rest of the study. In case there is no such trip, you could always ask to review vendor's SOP and interview vendor team members of your function.

Study Start-up Phase

At this phase, a kickoff meeting would be nice to fully establish the common knowledge ground between you and the vendor's team. Consider covering the following in the meeting: study info training, process discussion, deliverable lists, rough timeline, and any other requirements. These are suggested to be communicated thoroughly, so to avoid misunderstanding and knowledge gap that could result in a bigger problem in later phases, where it would be harder to be managed if not possible.

Another recommendation is to have a proactive quality risk management. I.E. the sponsor should define and assess proactively what are critical data and processes associated with the protocol.

At this phase, it is also suggested to develop an adaptable vendor oversight plans which are agreed upon among internal team, and which incorporate buffers for unexpected events and avoid the trap of over-reliance on predictions.

Study Ongoing Phase

At this phase, study data is getting accumulated and SAP and table shell is being generated, and usually accumulated issues and questions comes out. The goal of this phase is to establish a smooth working model so that sponsor's work and vendor's work adding up are sufficient. It is suggested to accumulate more detailed timeline, status update, and conduct issue discussion. It is also suggested to have a regular link with vendor, more frequency is better than less, at least in the beginning. The frequency can always be deducted when needed.

At this stage, risk assessment should be basically established. Pay attention to the following questions and ask yourself whether there is a risk you should concern.

a. How does vendor's programming function do quality control for all deliverables, e.g. CSR tables, and submission packages?
b. How does vendor's programming function raise data issue that are concerning programming function?
c. Whether vendor's programming function have sufficient documentation for audit of various purposes (e.g. regulatory's or sponsor's)?

d. How dose vendor programming function document day-to-day issues and resolution (usually documented at 'issue and decision log') that are not covered by formal documents like SAP or Table Shell?
e. How seamless are vendor programming function collaborating with their own data management team, and biostatistician team?
f. Does vendor have an appropriate escalation route that effectively identify and solve problems?

Study Delivery Phase

AT this phase, pay more attention to the risk identified in previous phases and how it is resolved. Theoretically, most of the risk should be resolved at this stage. Any major risk that still exists requires more attention or escalation.

At part of the team, LSP is responsible for reviewing vendor's dry run(s) and final deliverables. Other than regular review, LSP should focus more to those that are function-specific documentations, e.g. data specification, Pinnacle 21 reports, data issue report log and issue and decision log. It is also recommended to pay more attention to those that are not established in SAP or in TFL. LSP are responsible to raise concern to project team if derivation rule is deviated from SAP, PROTOCOL or common sense.

It is also recommended to pay attention to how vendor's programming function raise data issue that are concerning programming (e.g. those that results in error/working in program log, Pinnacle 21 report, or etc.). In theory, all issues should be resolved and good quality should be established upon reaching DBL. Every efforts should be made to avoid fixing data issues or have major change to TFL after DBL, where you will have the final review.

Study Wrap-up Phase

Vendor's involvement does not end in study delivery phase. In some cases, vendor is required to provide minor updates and ad-hoc analysis. Change after DBL are sensitive to clinical trial, it would be necessary to ensure these changes and decision log are well documented and archived by vendor. LSP should also consider archiving the final full deliverables in sponsor's storage system according to company's SOP. In this phase, it is also recommended to have a lesson learn session for the next collaboration to come.

PRACTICAL WORKING EXPERIENCE AND SUGGESTIONS

In the actual project implementation, we encountered more specific and complex problems. To address these cases, we have provided practical experience and suggestions as a reference (Figure 1). It is important to emphasize again that success begins with detailed planning. The following figure (Figure 2) presents a commonly used list of deliverables. This list can help us avoid many disputes with the vendor.

Issues	Suggestions
Study preparation phase	
Multiple reputable vendors, each with a strong leadership team, employ a variety of data mapping strategies, reporting styles, and conventions.	Focusing on their ability and willingness to consistently implement sponsor's processes and procedures across the portfolio of work.
Study startup phase	
Fewer connections were made until the dry run began.	A dedicated programming-specific kick-off meeting is recommended to align the expectations and goals for both sides. Ensure to provide a comprehensive list of deliverables and schedule regular catch-up meetings
Study ongoing phase	
Programming work was progressing slowly and seems unable to delivery as expected	Identify the root cause of the situation and escalate it to the vendor's leadership team and sponsor project team. If a resolution is still not achieved, consideration should be given to bringing the project in-house or outsourcing again.
Study delivery phase	
Failure to address the findings from the sponsor.	Should the issue persist, escalate it to the vendor's leadership team. If a resolution is still not achieved, consideration should be given to bringing the project in-house or outsourcing again.
A significant number of errors and warnings were present in the SDTM/ADaM P21 validation report for the delivered datasets.	Poor CDISC compliance. It is suggested that the vendor adds the P21 validation report, along with an explanation of errors/warnings, to the delivery list for each dry run.
Study wrap-up phase	
Any programming errors in the top-line tables	Escalate the issue to vendor's leadship team and sponsor project team, monitor the vendor to promptly correct errors in order to minimize the impact on subsequent work.

Figure 1. Suggestions for common issues in outsourcing model

Deliverable List	Comments
Study documents	
Protocol	Source of ADaM datasets & TFLs generation
SAP & Mock Shell	
CRF & CCG & CRF Specification	Source of SDTM annotation
Rawdata	
EDC Data	Support sponsor perform the third-line programming QV
Non-EDC Data & DTA	
Programming materials	
SDTM Annotated CRF	
SDTM Programming Specification	Source for SDTM Define & cSDRG
SDTM DefineXML	Usually delivered after TLFs finalization
Clinical Study Dataset Review Guide	
SDTM Datasets	
ADaM Programming Specification	Source for ADaM Define & ADRG
ADaM DefineXML	Usually delivered after TLFs finalization
Analysis Dataset Review Guide	
ADaM Datasets	
Combined & Individual TFLs	
Programming management documents	
SDTM Pinnacle21 Reports	With explanations for error/warnings; Compliance of SDTM standards
ADaM Pinnacle21 Reports	With explanations for error/warnings; Compliance of ADaM standards
Data Issue Tracking Log	Document any data issues found during the preparation of deliveriables
Programming QV Tracking Log	Document the QV information, including QV status, QV findings, path for QV code and signature.
Programming Decision Log	Document any decisions made by study team, especially not specified in protocol or SAP.

Figure 2. Programming deliverable list for reference

CONCLUSION

In conclusion, vendor management for programming function is essentially a risk management that involves identification, assessment, planning, monitoring, and reacting to threats. Due to diverse vendor practices, vendor management could be complex and challenging. Our framework for risked-based oversight in outsourcing studies offers a practical and strategic approach. It serves as a foundation for sponsors to navigate this complex environment, promoting a more cohesive and thriving approach to outsourcing studies, ultimately ensuring patient safety, data integrity, and regulatory compliance.

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