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Agile Sponsor Oversight of Statistical Programming Activities

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ABSTRACT

Agile sponsor oversight of a Contract Research Organization (CRO) for Statistical Programming involves a dynamic, collaborative, and flexible approach to monitoring and managing the CRO's work. Key characteristics of this method include constant communication, iterative processes, adaptive planning, proactive risk management, stakeholder engagement, and an unwavering focus on the quality of deliverables. In our discourse, we will explain in detail how oversight might be planned, conducted, and documented and highlight how the principles of agility can significantly contribute to its successful execution. A differentiation will be made between the concepts of sponsor oversight and vendor qualification, and it will be described how agile oversight aligns with risk-based principles, providing the flexibility to modify plans as necessary. Additionally, the paper will shed light on the dark sides of oversight and cover the essential qualities and skill sets required in personnel responsible for overseeing Statistical Programming activities.

INTRODUCTION

We worked as Statistical Programmers for a pharmaceutical company for many years before our management decided to shift Clinical Development from an in-house to a fully outsourced model. It was a challenging journey, involving both organizational changes and the relocation of teams across continents. While completing ongoing studies internally, we began collaborating with preferred providers, establishing expectations, interfaces, and processes, and started encountering discrepancies between the theory of performing oversight and its practical implementation. This transition began about a decade ago, and since then, we've gained considerable experience in overseeing CROs while at the same time now also working as a CRO ourselves. This paper reflects our current thinking on the topic, but we acknowledge it may not be the definitive answer. Nonetheless, we hope it offers some helpful insights for others.

REGULATORY FRAMEWORK

Ever since the release of the INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) (ICH, 2016) with its emphasis on sponsor oversight and its request to *"ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)"*, pharmaceutical companies have been working on getting their oversight activities up to speed. How well they are doing in that regard is tested regularly either internally or during regulatory inspections.

In that context it is also beneficial to gain a clear understanding of the distinction between Vendor Qualification and Sponsor Oversight. While these two concepts are closely related and can overlap, we believe that there are specific aspects that are clearly attributable to one OR the other.

ICH E6(R2) (ICH, 2016) outlines as one of the principles of ICH GCP that *"Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)."* This principle applies not only to internal personnel but also to external individuals involved in the conduct of the clinical trial.

In addition, according to the PHARMACEUTICAL QUALITY SYSTEM Q10 (ICH, 2008) guideline, before outsourcing operations, it is essential to assess the suitability and competence of the external party. This involves defining responsibilities and communication processes for quality-related activities and incorporating them into a written agreement. These steps occur prior to the commencement of the CRO's work and are integral components of the vendor qualification process.

Table 1 illustrates examples of activities typically involved in vendor qualification and those that (do not) constitute sponsor oversight.

Vendor Qualification	Sponsor Oversight
• Review of SOPs • Review of CVs of vendor's team members • Assessment of electronic systems used for suitability and compliance • Identification of gaps that need to be addressed before the start of activities	• Review of the quality of deliverables and providing feedback • Following up on issues till they are resolved • Escalation of issues if needed • NOT assessing if CRO follows its own processes (this is part of audits)

Table 1. Vendor Qualification versus Sponsor Oversight

PRINCIPLES OF AGILE OVERSIGHT

The Agile Manifesto, also known as the Manifesto for Agile Software Development, was published by the Agile Alliance in 2001 (Agile Alliance, 2001). It outlines twelve principles that form its core. We explore how these principles are relevant to the CRO & Sponsor oversight framework and how they are already deeply embedded in oversight processes, even without anyone consciously recognizing their origins. The principles are listed verbatim as originally published. For the topic at hand the term 'software' should be replaced with the more appropriate term 'Statistical Programming deliverable(s)':

1. ***Our highest priority is to satisfy the customer through early and continuous delivery of valuable software.***
   Every sponsor hopes that this is the CRO's guiding principle. However, it can also be seen as showing how committed the Statistical Programming team (including external as well as internal personnel) is to provide high-quality deliverables to the study team, ensuring a successful regulatory submission.
2. ***Welcome changing requirements, even late in development. Agile processes harness change for the customer's competitive advantage.***
   For various reasons, the study team might find the need for changes at a late stage. This could happen because of overlooked reviews earlier on or due to unforeseen circumstances. Regardless of the cause, it's crucial to objectively assess these changes, evaluate their impact, and come to an agreement on the necessary actions to be taken.
3. ***Deliver working software frequently, from a couple of weeks to a couple of months, with a preference to the shorter timescale.***
   Some contracts may plan for delivering the entire submission package at the study's conclusion. However, this approach has several disadvantages. First of all, it limits sponsor oversight since there's no continuous involvement. Secondly, it sets the stage for last-minute change requests. These issues can be avoided by scheduling multiple review rounds of predetermined deliverables throughout the study's duration.
4. ***Business people and developers must work together daily throughout the project.***
   Perhaps not on a daily basis throughout all project phases, but it certainly proves beneficial during critical submission phases. It's most important to identify and communicate within the team on an ongoing basis any circumstances specific to the study to ensure they don't get overlooked during routine work.
5. ***Build projects around motivated individuals. Give them the environment and support they need, and trust them to get the job done.***
   During vendor qualification, one of the aspects assessed is whether required processes and systems are in place. The sponsor relies on the CRO to adhere to these processes once qualified.
6. ***The most efficient and effective method of conveying information to and within a development team is face-to-face conversation.***
   Effective communication is essential, making it a logical decision to schedule regular meetings with the CRO to address timelines, progress, updates, and any issues that may arise.
7. ***Working software is the primary measure of progress.***
   High-quality deliverables are the best measure of progress.

8. ***Agile processes promote sustainable development. The sponsors, developers, and users should be able to maintain a constant pace indefinitely.***
   The sponsor should at least plan to promote sustainable development, despite the fact that in reality, heightened pressure to meet or exceed deadlines may place prolonged strain on both the team creating the deliverables and the team overseeing the process.
9. ***Continuous attention to technical excellence and good design enhances agility.***
   Attention to detail enhances agility, allowing for more efficient and effective adaptation to changing circumstances or requirements. Which can happen a lot.
10. ***Simplicity – the art of maximizing the amount of work not done – is essential.***
    Focus the oversight on the essential deliverables and don't get lost in detail that won't have a meaningful impact overall.
11. ***The best architectures, requirements, and designs emerge from self-organizing teams.***
    Teams with power can decide and keep making progress consistently. This applies to Statistical Programming, too.
12. ***At regular intervals, the team reflects on how to become more effective, then tunes and adjusts its behavior accordingly.***
    We acknowledge the value of well-organized lessons learned sessions. Let's remember to ensure they are utilized effectively for meaningful improvements.

ICH E6(R2) (ICH, 2016) emphasizes managing risks in clinical trials and agile oversight offers flexibility in responding to emerging risks promptly. The goal of agile oversight within the framework of ICH E6(R2) (ICH, 2016) is to uphold the quality standards established for clinical trials. By proactively identifying and addressing risks in a timely manner, agile methods help ensure that the trial proceeds smoothly and that reliable data are generated. It allows for quick adjustments and encourages collaboration among stakeholders.

HOW TO PLAN AND CONDUCT OVERSIGHT

To set up the framework for oversight, it's important to establish Standard Operating Procedures (SOPs) or similar regulated processes. These guidelines will direct team members involved in oversight. Sponsors often have a preferred provider and establish written agreements with the vendor that outline points of interaction, expectations for deliverables, responsibilities (often defined using responsibility matrices), and other details.

It's best practice to create an oversight plan at the start of a project to clarify internal expectations regarding the extent and focus of oversight activities. It is very useful to have an oversight plan template available that can be adjusted to address each project's requirements. Oversight plans should, at a minimum, include a list of providers and their delegated tasks, contact details, preferred modes of communication, as well as tasks that must be performed and tasks that are optional based on the level of complexity and observed quality. To improve consistency among reviewers in terms of the focus and level of detail applied, creating checklists that categorize tasks by type of deliverable may be considered.

At the beginning of the project, having a kick-off meeting with the CRO team is important for building relationships, setting clear expectations for deliverables and timelines, and defining communication methods, with escalation procedures if necessary. It is essential that by the end of the kick-off meeting as well as after any subsequent study meetings, all stakeholders are aligned, and decisions are documented and accessible to everyone. Keep in mind that team members may have varying backgrounds and levels of experience.

Usually, Statistical Programmers are involved in reviewing Statistical Analysis Plans and corresponding table shell documents, Study Data Tabulation Model (SDTM) annotated Case Report Forms (CRFs), dataset specifications and their implementation as well as reviewing dataset metadata such as data reviewer's guides and SDTM or (Analysis Data Model) ADaM define.xml files.

HOW TO DOCUMENT AND WHERE TO STORE THE DOCUMENTS

The documentation of the performed oversight is equally important as performing the oversight. All the issues that are reported and all the documents that a Statistical Programmer reviews can be used to prove oversight.

We believe that documents generated during the conduct of a study, which may serve to document oversight of Statistical Programming activities, can be classified using the following four descriptions:

- Forms owned by the CRO which are reviewed and also approved by the sponsor. The signed forms are filed in the study's Trial Master File (TMF) by the CRO. E.g., Data transfer agreements, Approval forms of final deliverables.
- Any other documents which are created by the CRO and reviewed and approved by the sponsor. Track-changed versions of the documents may serve as proof for the sponsor's feedback and can be stored together with other study related internal business records. The approved and final versions of the documents are filed in the study's TMF by the CRO. E.g., Statistical Analysis Plans, Dataset specifications.
- Filled in forms and documents specifically created by the sponsor for the purpose of documenting oversight. These documents are filed by the sponsor in the study's TMF. E.g., Oversight Plans, Forms for documenting TMF checks.
- Supportive documents which are created by the sponsor during the performance of oversight and filed in the study-specific internal business records. E.g., Issue tracker, Internal meeting minutes.

Figure 1 illustrates the lifecycle of the aforementioned document types and their eventual storage location.

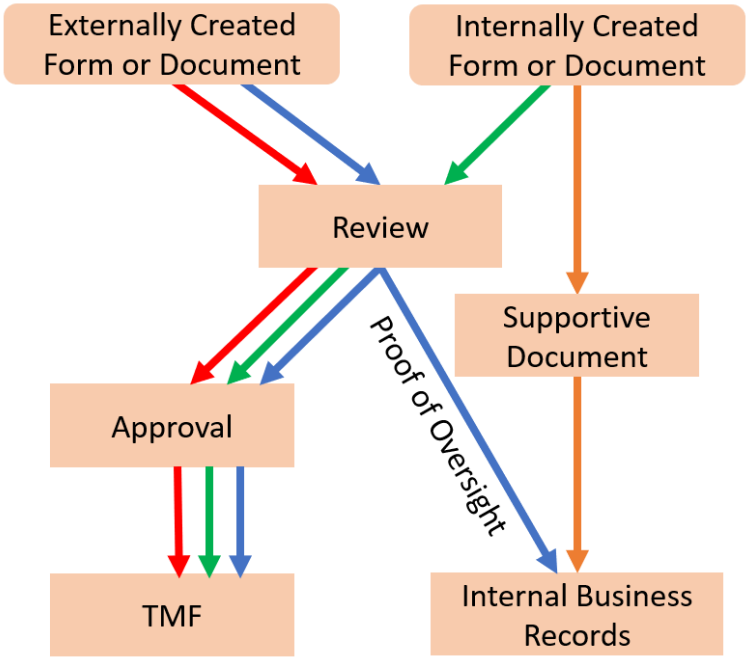

Figure 1. Sponsor Oversight Documentation

For decades, we were instructed to file only final versions of documents in the clinical trial's TMF. Nowadays, however, an increasing number of sponsors are considering filing track-changed versions of documents as well, aiming to provide evidence of their oversight of the CRO. These files are either explicitly marked with the word 'DRAFT' in their filenames or metadata or they are stored in specially dedicated folders.

POSSIBLE COMPLICATIONS AND HOW TO AVOID THEM

We have given you a lot of information on how to do oversight in the previous sections and how to apply agile oversight principles. But in real-life situations, things can get tricky.

COMMUNICATION IS KEY

Often, sponsors expect higher quality deliverables than what CROs provide. It's important to clarify that sponsors aren't responsible for quality control, so CROs can't skip or ignore this important task. Handling this situation might strain the relationship, but it's necessary to escalate if needed. However, it's crucial to remain constructive rather than assigning blame, as most CROs genuinely aim to perform well. It's common for sponsors and CROs to get stuck in lengthy, repetitive discussions on certain topics. It's key to recognize these situations early and break the cycle by engaging in direct conversation rather than relying solely on written communication through issue trackers or emails, where misunderstandings are more likely to occur.

CAREFULLY PLAN THE TIMING AND CONTENT OF DELIVERABLES

As previously discussed, having planned only for a single final delivery can result in critical issues being identified only at a late stage, leading to delays. Therefore, it's essential to carefully plan and establish expectations regarding timelines, standards, and frequency and content of deliverables. However, issues may still arise, necessitating adaptation. For instance, dry runs could be conducted in batches rather than as a single delivery as initially intended, and additional deliveries may need to be included for specific specialty data, such as PK or immunogenicity data. Occasionally, source data and/or current specifications are omitted from deliverables. For instance, only SDTM datasets may be included without the raw data used to generate them, or ADaM datasets and TLFs may be provided without the corresponding or with inconsistent SDTM versions. Dry-run deliverables should also include both ADaM and SDTM datasets as SAS transport files (.xpt). This facilitates the use of tools for checking for compliance with CDISC standards as well as technical requirements. It helps to identify issues such as variable names exceeding 8 characters or labels surpassing 40 characters for .xpt files, problems with special characters when converting SAS datasets to .xpt files, and identification of missing required variables or incorrectly named expected variables according to CDISC standards. It's crucial to establish in advance that all these components are required for a delivery in order to perform meaningful oversight.

STAY UP TO DATE WITH REGULATORY REQUIREMENTS AND APPLICABLE STANDARDS

Not staying up to date on current standards and regulations can cause problems with electronic data submissions. Issues related to the submission package structure, file naming conventions, sizes, and formats might occur. CROs should provide ready-to-submit materials, and sponsors should be able to spot any problems. Train your team to stay current - it's challenging but necessary for successful submissions.

Reviewer’s guides (RG) often lack quality. These guides are meant to support regulatory agency reviewers and make their assessments easier. However, many RGs contain only generic content from PHUSE templates rather than project-specific and relevant information.

At times, inconsistencies across a deliverable in terms of formatting, terminology, or derivations (e.g., duration of AEs, duration of effect, handling of incomplete and missing dates/times) are observed simply because they were created by different personnel. It is understood that often the workload needs to be split between Statistical Programmers but nonetheless everyone should follow the same pre-defined standards.

AGREE UPFRONT ON A PROCESS FOR PROVIDING FEEDBACK AND STICK TO IT

Documenting and tracking oversight feedback can be challenging if there's no predetermined process between the CRO and the sponsor. It's crucial to ensure that no comments are overlooked and that all are addressed until resolved. For instance, using a user-friendly issue tracker can be helpful. Relying solely on email or oral discussions without meeting minutes or without recording issues in a tracker is not

recommended, as important details can be lost or forgotten easily. Documenting everything in writing is important, especially considering potential personnel changes on both sides of the project, as it helps to maintain continuity.

FIND THE RIGHT PEOPLE TO CONDUCT OVERSIGHT

Statistical Programmers usually get into their line of work because they enjoy writing computer code, not because they want to watch others do it. As a result, not every Statistical Programmer automatically has the skills and motivation needed for overseeing Statistical Programming activities.

Whether a Statistical Programmer is a good fit for an oversight role depends on a few factors, like their personal skills and their role-specific experience. It is helpful to have previously worked with SDTMs as well as ADAMs and if the candidates have produced statistical outputs themselves or have been involved in regulatory submissions before. If they understand the regulatory requirements and know how to implement them, they're well-suited for ensuring electronic submission packages are of high quality. It is also helpful if they are good at managing expectations and timelines and are skilled at communicating complex ideas in simple terms.

Sometimes, overseeing a project means making important decisions that can change the project's direction so the person performing the oversight has to be able to take over responsibility and provide guidance to the team producing the deliverables. They also need to be able to judge when it is necessary to consult other team members such as the Biostatistician or Medical Director, and when it is appropriate for them to make decisions independently.

To be able to do all that you do not necessarily need extensive experience in Statistical Programming in the pharmaceutical industry. It can be beneficial, but what is equally important is the ability to quickly grasp a project's design, scope and potential pitfalls that require special attention. A good candidate needs to understand data structures and needs to know how to apply predefined standards and diligently check for consistency from start to finish. Being detail-oriented, having strong communication skills, and occasionally having the patience to perform monotonous tasks are also important qualities.

CONCLUSION

Effective agile sponsor oversight in clinical trials relies on open, honest, and clear communication between sponsors and CROs. This collaborative approach is vital for ensuring alignment towards a common goal: the successful submission and approval of clinical trial data. By embracing this cooperative mindset and working together for a shared objective, both sponsors and CROs can manage the complexities and potential risks of a clinical trial with greater efficiency, ultimately benefiting patients and advancing healthcare outcomes.

REFERENCES

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