PharmaSUG 2024 - Paper LS-351

A Framework for Risk-Based Oversight for Fully Outsourced Clinical Studies

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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). Estimates suggest that 75% to 80% of the biopharmaceutical industry's R&D costs are outsourced, highlighting the prevalence of this practice[1,2,3]. These trials, spanning various therapeutic areas, are entrusted to multiple CRO partners. The oversight of these diverse CROs, with their varied practices, and the siloed approach by Therapeutic Area (TA) functional leads from the sponsor, can lead to inconsistent deliverables. This created a dire need for more consistent and effective CRO oversight. In this paper, we describe a new approach to CRO oversight that was implemented by a pharmaceutical company. The new approach involved the creation of a new group that was responsible for overseeing all outsourced studies, regardless of therapeutic area. This new group created a framework for risk-based oversight plan. The paper highlights various key steps of this framework from Partnership Initiation to Study Closure. The paper provides insights on different methods, trackers and tools used to aid the oversight of CRO work. It also provides references for Management mental models for outsourcing success. 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

Envision managing multiple boats, all sailing to the same destination but navigating via different routes. Now think of working with multiple vendors with different reporting styles and conventions and add siloed sponsor oversight to the complexity of this situation. Nevertheless, our common goal is to ensure seamless regulatory submissions but taking a diverse array of routes may lead to a turbulent journey to our destination.

"You do not rise to the level of your goals. You fall to the level of your systems." - James Clear

In his book Atomic Habits, James Clear encapsulates the idea that achieving success is not solely dependent on setting ambitious goals, but rather on implementing effective systems or processes to support those goals. Following the same theory, this paper presents a framework for consistent risk-based vendor oversight in clinical studies outsourced to multiple vendors, thereby achieving the goal of smooth, consistent, and compliant regulatory submission.

ESTABLISHMENT OF A CENTRALIZED GROUP FOR OVERSEEING ALL OUTSOURCED STUDIES

"The word "silo" does not just refer to a physical structure or organization (such as a department). It can also be a state of mind. Silos exist in structures. But they exist in our minds and social groups too. Silos breed tribalism. But they can also go hand in hand with tunnel vision."
- Gillian Tett, The Silo Effect: The Peril of Expertise and the Promise of Breaking Down Barriers

In fully outsourced clinical studies, all functions, including clinical operations, data management, medical writing, and statistics and programming, are outsourced. However, this paper primarily focuses on Biometrics, with a particular emphasis on statistical programming within the outsourcing model. The framework begins with the creation of a centralized group of relevant sponsor professionals, tasked with supervising all outsourced studies. This centralized group comprises of subgroups dedicated to each function, actively engaged in overseeing the lifecycle of their respective functions. These subgroups create function specific risk-based quality management plans and strategies for consistent vendor oversight. The statistical programming subgroup has exposure to all the vendors and the leads

interchangeably oversee different vendors to understand their different data mapping strategies and reporting styles and conventions. This group also works closely with the Therapeutic Area Leads and Data Standards team.

With the creation of this group, we are trying to collapse the silos in oversight of multiple vendors among different Therapeutic Area Leads. Beyond excelling in individual function oversight, the group's mission is to cultivate a stronger sponsor-vendor alliance and actively dismantle departmental and mental silos that can foster cognitive tunneling and impede collaborative success.

PARTNERSHIP INITIATION PHASE

"If you want to build a ship, don't drum up people to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea." - Antoine de Saint Exupéry

PARTNERSHIP KICK-OFF MEETINGS AND PROCESS WORKSHOP

The very first step in the Partnership Initiation Phase between the sponsor and preferred vendor is hosting a Partnership Kick-off Meeting. This meeting is organized to review the sponsor's reporting procedures and to assess the vendor's capabilities including resources, tools, and methodologies. The meeting is then followed by a deeper dive in the form of a Process Workshop. Prior to the workshop, Subject Matter Experts (SMEs) from the sponsor review the vendor's Standard Operating Procedures (SOPs) to identify any potential process gaps. This workshop then serves as a platform for the sponsor and vendor to conduct a detailed review of their reporting and analysis practices, which includes examining relevant working instructions and guidelines from both parties. Upon the workshop's conclusion, designated SMEs from both the sponsor and vendor are nominated to collaborate on developing the Sponsor-Vendor Alliance Handbook and Task Allocation Matrix.

DEVELOPMENT OF SPONSOR-VENDOR ALLIANCE HANBOOK

The Sponsor-Vendor Alliance Handbook serves as a charter for the operational alliance between the sponsor and vendor. This handbook is used as a guide for all activities conducted pursuant to the Master Services Agreement (MSA) and any current MSA amendments.

The objective of the handbook is to describe how sponsor and vendor will work together with the expectation of high-quality services in compliance with sponsor and/or applicable vendor standards, and industry regulations. The handbook outlines the governance structure to support planning, execution, and review of the studies. It also defines the quality and issue escalation pathway for early identification, escalation and resolution of issues impacting the Alliance and deliverables. It also describes the Key Performance Indicators (KPIs) and metrics used to measure performance and quality including criteria, targets, thresholds, and documentation. Furthermore, resourcing and training requirements are also listed.

The handbook defines the rules and mandates for the entire cycle of outsourced clinical trials conduct. The Biometrics section of the handbook describes the process of Randomization code allocation and code breaking if applicable. It specifies the minimum information included in the SAP. It provides a list of deliverables like the Study level datasets, specifications, and other components of the submission package. It also clarifies whether sponsor or vendor Standard Operating Procedures (SOPs) pertaining to layouts will be followed and specifies the version of Implementation Guides and other regulatory guidance documents. Additionally, the handbook also mentions the transfer frequency and file format of the deliverables e.g., xpt, pdf files, etc. The process of validation is also outlined. For e.g., independent double programming validation is generally implemented for all the Statistical Programming deliverables, with the vendor readily providing proof of validation upon sponsor request. This comprehensive handbook ensures consistent quality and regulatory compliance throughout the entire outsourced clinical trial process, ultimately paving the way for successful regulatory submissions.

Partnership communication channel

“Communicate everything you can to your associates. The more they know, the more they’ll care. Once they care, there’s no stopping them.” - Sam Walton, Walmart founder

Preferred mode of communication is also stated in the handbook. Study kick-off meeting followed by weekly meetings (or frequency as deemed necessary) are planned between the sponsor and vendor project teams. In the kick-off meeting, the sponsor provides the overview of the study, explains the study design, endpoints, and other necessary details from the protocol. The discussion also covers an update on the protocol amendments or any expected amendments to happen in future. This keeps the study team vigilant of any reporting changes due to protocol amendments. In the recurring meetings the study teams discuss the status, timelines, ongoing issues, and any other risk factors. Yearly Governance meetings are designed to go over KPIs, milestones, and any other items of concern. The Alliance fosters collaboration between the vendor and sponsor Statistical Programming/Data Standard teams if required, regarding the SDTM domains and variables, the definition of algorithms (if applicable), or other components to be applied to the generation of the SDTM or ADaM data sets. Hence, Ad hoc meetings are encouraged for issue resolution or potential risk mitigation.

TASK ALLOCATION MATRIX

The Task Allocation Matrix (TAM) document outlines the tasks required for the assigned functional deliverable and assigns roles using the RACI model (Responsible, Accountable, Consulted, Informed). This model clarifies the involvement of each member throughout the Biometrics tasks, from protocol review to CSR finalization. By defining who is responsible, accountable, consulted, and informed for each task, the RACI matrix helps prevent confusion, duplication of effort, and misunderstandings about roles and responsibilities between the sponsor and the vendor.

STUDY EXECUTION PHASE

"Sir, I'm afraid that the quality of this airline is partly measured by on-time departures. And unfortunately, on-time departures are measured by when we left the gate, not by wheels-up."
- Marcus Buckingham

Before entering the Study Execution Phase, sponsor should ensure that all statistical programming deliverables needed for regulatory submissions are covered in work order/budget for the study. Sponsor should be able to reconcile the deliverables with the Biometrics TAM. To ensure that we adhere to the rules and achieve the desired quality, it is imperative to regularly refer to the Alliance Handbook and TAM during the study execution phase.

VENDOR OVERSIGHT CHECKLIST AND REVIEW UTILITIES REPOSITORY

The sponsor develops a comprehensive Vendor Oversight Checklist (Gawande) for each statistical programming component. This tool is extensively used during the study execution phase to ensure timely compliance and quality assurance of deliverables. It includes checks for each deliverable, ranging from annotated Case Report Form (aCRF) to reviewer's guide, and is regularly updated to align with the latest/preferred guidance. For example, according to Metadata Submissions Guidelines (MSG) v2.0, the aCRF bookmarking should include a sub-bookmark for Running Records for unplanned events (forms). This tool guarantees that all deliverables follow specified version of the guidance.

Study execution phase comprises of a meticulous review of deliverables coupled with the development and use of SAS/Python/R utilities for review automation. The vendor oversight checklist is utilized for each deliverable. In parallel various other review utilities are used to check data fitness and integrity. Some examples are: VIMO macro (Valid, Invalid, Missing Outlier) for getting an overview of quality of the data, Subject Grid macro, which displays the grid of subjects present in each dataset, Data Compare macro – to check the data difference between two deliveries, Subject visit date macro, which reports the subjects who have multiple visit dates within each visit identifier[4,5]. Numerous additional utilities can be developed to automate and ease the review process.

There can be scenarios when a sponsor is working with multiple vendors, each vendor may adhere to their own Standard Operating Procedures (SOPs) for analyzing and reporting clinical data as per their Alliance Handbook. This may result in deliverables with different reporting styles and conventions. Hence, it is recommended that a unified single version of Vendor Oversight Checklist is used across all vendors. It is also encouraged that regular internal meetings are conducted with the Data Standards team and TA

leads to discuss any discrepancies or difference of opinions in the data mapping or reporting conventions. For e.g., in one of these meetings, decision is made to remove the duplicate aCRF forms, arising due to multiple visits, and only unique forms should be retained in an aCRF. These decisions are then incorporated in the Vendor Oversight Checklist which keeps the checklist evolving throughout. And these decisions can then be easily disseminated across all vendors by using a common Vendor Oversight Checklist.

The framework also emphasizes the continuous performance monitoring through use of common study status tracker between the sponsor and the vendor, the collaborative improvements from vendors are also sought during the recurring partnership meetings. And now at this stage of the framework, when the Handbook and TAM is used as a compass to navigate and common vendor checklist is used across multiple vendors, it resonates with the famous saying –

We may have all come on different ships, but we are in the same boat now. - Martin Luther King Jr.

STUDY CLOSURE PHASE

"You can't connect the dots looking forward; you can only connect them looking backwards. So, you have to trust that the dots will somehow connect in your future. You have to trust in something - your gut, destiny, life, karma, whatever. This approach has never let me down, and it has made all the difference in my life." - Steve Jobs

In the Study Closure Phase, the sponsor ensures the regulatory submission package is complete, performing a final reconciliation against the TAM and Vendor Oversight Checklist for submission readiness. To promote continuous improvement, a comprehensive closure meeting, leveraging partnership review techniques from the Alliance Handbook, is held between the sponsor and vendor. Both parties collaboratively review Key Performance Indicators (KPIs) to capture key takeaways and lessons learned, incorporating them into the Vendor Oversight Checklist for future studies. This iterative approach, akin to connecting the dots in hindsight, allows the sponsor to leverage past experiences to enhance future CRO oversight practices.

MENTAL MODELS FOR OUTSOURCING MANAGEMENT MASTERY

While outsourcing clinical trials to Contract Research Organizations (CROs) offers several benefits, it also introduces unique management challenges. One critical aspect is vendor oversight, where sponsors need to ensure the quality and progress of the study without the same level of direct control they have with in-house teams. To navigate this landscape successfully, sponsor managers need to adopt specific mental models that shift their perspective from "seeing all the trees all the time" to "seeing the forest for the trees."

SHIFTING GEARS: KEY MENTAL MODELS FOR SUCCESS

"Cogito, ergo sum (I think, therefore I am)" - Rene Descartes

Below mental models might help managers thrive in this outsourced environment.

1. **Shift from Hands-on management to Strategic Oversight:** Instead of obsessing over every data point, transition to a risk-based approach, focusing on critical milestones and deliverables defined in contracts and study protocols. Trust established processes and qualified personnel at the CRO, while reserving your expertise for reviewing key documents and proactively addressing potential issues.

2. **Leverage Effective Communication and Collaboration:** Foster open and transparent communication with the CRO throughout the study. Establish regular meetings, clear communication channels, and defined escalation procedures. Remember, the CRO is your partner, not just a vendor. Invest in building strong relationships with key personnel at the CRO to facilitate smooth collaboration.

3. **Master the Art of "Zooming In and Out"**: Develop the ability to quickly assess overall study

progress based on key performance indicators (KPIs), while also possessing the expertise to delve into specific details when necessary. Utilize project management tools and dashboards to visualize progress and identify potential deviations early on.

4. Trust but Verify: While trusting the CRO's expertise is essential, verification remains crucial. Develop clear quality metrics and milestones and use focused audits and reviews to assess progress and identify potential issues.

5. Risk-Based Quality Management: By understanding inherent variations in outsourced tasks (Wheeler) and incorporating buffers for the unexpected (Taleb), you can create a more realistic and adaptable plan and handle the inevitable surprises of remote collaboration.

6. Cultivate a Proactive Mindset: Don't wait for problems to arise. Anticipate potential challenges based on your experience and industry knowledge. Proactively communicate concerns and work collaboratively with the CRO to develop mitigation strategies.

7. Embrace Continuous Improvement and Cross-Pollination: Regularly evaluate the outsourcing relationship, including communication effectiveness, data quality, and adherence to timelines. Provide and seek regular constructive feedback from the CRO and identify areas for improvement. Actively share best practices and collaborate on solutions. Recognizing the potential benefits of cross-pollination, where diverse ideas converge to create innovative solutions, sponsors should actively encourage the sharing of best practices and collaborative problem-solving[6].

"I have a degree from Harvard. Whenever I'm wrong, the world makes a little less sense." - Dr. Frasier Crane, played by Kelsey Grammer

8. Beware of Cognitive Biases: Cognitive biases among pharma managers, such as confirmation bias, the IKEA effect (overconfidence in in-house expertise), blind spot bias (an inability to recognize one's own biases), and the ostrich effect (avoidance of negative information), can impact their oversight of outsourced clinical trials.

"The best way to have a good idea is to have lots of ideas." - Linus Pauling, winner of Nobel prize in Chemistry and Peace

By adopting these mental models, sponsors can successfully navigate the shift towards outsourced clinical trials. Remember, the goal is not to micromanage every detail, but to confidently oversee the "forest" while ensuring the health and integrity of the individual "trees" through strategic oversight, effective communication, and a proactive approach.

CONCLUSION

In conclusion, our framework for risk-based oversight in fully outsourced clinical studies offers a strategic approach to address challenges associated with diverse vendor practices. By establishing a centralized oversight group, initiating effective partnerships, and emphasizing continuous improvement, our framework ensures standardized processes and enhances collaboration. The outlined mental models guide sponsors towards strategic oversight, effective communication, and proactive management. As we navigate the dynamic landscape of clinical research, this framework serves as a beacon for a more unified and successful approach to fully outsourced studies, promoting consistent quality and regulatory compliance.

"A good chess player having lost a game is sincerely convinced that his loss resulted from a mistake he made and looks for that mistake in the opening but forgets that at each stage of the game there were similar mistakes and that none of his moves were perfect. He only notices the mistake to which he pays attention, because his opponent took advantage of it. How much more complex than this is the game of war, which occurs under certain limits of time, and where it is not one will that manipulates lifeless objects, but everything results from innumerable conflicts of various wills! "
-Leo Tolstoy in "War and Peace".

The quote from Leo Tolstoy's "War and Peace" aptly reminds us that effective oversight is a continuous process, requiring a holistic perspective and ongoing refinement. Much like his poignant observation, countless "moves" – decisions, protocols, and interactions – contribute to the final result. Focusing solely on the oversight misstep that led to an escalation, as with a lost chess game, ignores the symphony of preceding choices that shaped the trial. Our framework serves as a foundation for sponsors to navigate this complex environment, promoting a more cohesive and thriving approach to fully outsourced studies, ultimately ensuring patient safety, data integrity, and regulatory compliance.

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ACKNOWLEDGMENTS

The authors gratefully acknowledge Prafulla Girase and Kelly Cook for their support.

RECOMMENDED READING

"*Books are the bees which carry the quickening pollen from one to another mind.” - James Russell Lowell*

While the phrase "quickening pollen" might send shivers down the spine of someone with seasonal allergies, James Russell Lowell intended it to evoke a far more positive image: the fertile cross-pollination of ideas that books facilitate. The framework presented in this paper is a product of cross-pollination, drawing inspiration from concepts found in various books unrelated to clinical trials or outsourcing. Authors recommend the following books, not traditionally associated with clinical trials, as a testament to the diverse sources that can contribute to innovative and effective frameworks:

1. Atomic Habits by James Clear

This book emphasizes the importance of developing good habits and systems to achieve success. It argues that achieving goals is not simply about setting ambitious goals, but rather about implementing effective systems or processes to support those goals.

The concept of creating systems and processes can be applied to managing outsourced studies. By establishing a clear framework and protocols for oversight, sponsors can ensure consistent and effective monitoring of CRO work, ultimately leading to smoother study execution and regulatory compliance.

2. The Checklist Manifesto by Atul Gawande

This book advocates for the use of checklists to improve decision-making and reduce errors in various fields, including medicine and aviation. It highlights the power of checklists in capturing essential knowledge and ensuring consistent performance.

Implementing a standardized checklist for CRO oversight can help ensure that sponsors consistently

cover all critical aspects of deliverables and data quality. This can help mitigate the risk of overlooking essential elements and promote consistent oversight practices across different studies and vendors.

3. Understanding Variation by Donald Wheeler

This book explores the concept of variation and its impact on different processes. It emphasizes the importance of understanding both natural and assignable variation to effectively manage processes and improve quality.

When working with CROs, sponsors encounter inherent variations in deliverables and processes due to different working styles and methodologies. Understanding these variations allows sponsors to set realistic expectations, focus on critical deviations, and develop appropriate risk-based monitoring strategies.

4. Fooled by Randomness by Nassim Nicholas Taleb

This book discusses the role of randomness and uncertainty in various aspects of life, including decision-making and risk management. It highlights the limitations of human knowledge and prediction in the face of random events.

The unpredictable nature of clinical trials, coupled with the added layer of outsourcing, introduces elements of randomness and uncertainty. By understanding these limitations, sponsors can develop more adaptable oversight plans that incorporate buffers for unexpected events and avoid the trap of over-reliance on predictions.

5. War and Peace by Leo Tolstoy

This classic novel explores the complexities of human nature and the challenges of leadership and decision-making in the context of war. It emphasizes the importance of learning from mistakes and adapting strategies based on unforeseen circumstances.

Tolstoy's quote about the complexities of war serves as a powerful metaphor for the challenges of oversight. The quote reminds us that effective oversight requires a holistic perspective and a commitment to continuous improvement. Similar to the intricate strategies and dynamic nature of warfare depicted in the novel, effective oversight of outsourced clinical trials requires a comprehensive and adaptable approach. Sponsors must learn from past experiences, both successes and failures, to continuously improve their oversight practices and navigate the complexities of working with external vendors.

We encourage fellow professionals to explore these titles for their valuable insights and consider adopting a similar interdisciplinary approach in their endeavors.

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