Veeva

WHITE PAPER

ICH GCP E6(R3) Implications on Fully Outsourced Sponsors and Studies

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More than 20 fully/heavily outsourced sponsors contributed to this whitepaper.

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I. Introduction

Rapid advancements in drug development are driving scale, complexity, and cost in clinical trials, increasingly requiring an adaptable and rigorous approach to trial oversight. The upcoming **ICH E6(R3)** guideline – targeted for release in 2025 – addresses this shifting landscape while building on the established principles of Good Clinical Practice (GCP) outlined in ICH E6(R2).

While the core principles of GCP remain the cornerstone of the guideline, R3 ushers in a new era of proactive, risk-based approaches with an unwavering focus on data quality. The emphasis on a more holistic approach requires fully outsourced sponsors in Europe – especially small and medium biopharmas – to look closely at how they can adapt and thrive under the new guidelines.

This whitepaper is the result of discussions led by a cross-industry working group. The goal is to explore the intricacies of ICH E6(R3), analyze its implications for outsourced sponsors, and provide valuable insights to ensure a smooth transition to the new guidance. This work is especially important against the backdrop of increased hybrid inspections, whereby inspectors request direct access to clinical operations systems used to execute and document sponsor oversight throughout the trial.

II. Key Changes for Fully Outsourced Sponsors

The transition from ICH E6(R2) to R3 will significantly impact sponsors who outsource most of their clinical trials. This section highlights the key changes.

Essential records vs. documents: R3 introduces a critical shift that emphasizes capturing and maintaining "essential records" rather than solely focusing on "essential documents." Essential records encompass a broader range of information, including not only formal documents but also electronic data, communication logs, and other process-related materials which facilitate the ongoing management of the trial and allow the evaluation of the trial conduct.

This expanded definition requires a more comprehensive approach to operational data management and oversight within an outsourced setting. Sponsors must ensure their contracts with CROs clearly define ownership, access, and retention procedures for all essential records throughout the trial lifecycle. Sponsors will also need their own clinical systems, such as an electronic trial master file (eTMF) and clinical trial management system (CTMS), to ensure study oversight documentation and operational data are accessible throughout an inspection.

Direct Access to Essential Records

R3 mandates that sponsors and investigators have direct access to all essential records, regardless of format or location. This ensures transparency and facilitates real-time monitoring and oversight throughout the trial.

Focus beyond the outcome: R3 requires more than the final documented outcome of a process. Instead, it emphasizes capturing the rationale and decision-making trail leading to that outcome. In an outsourced context, this means sponsors must have clear visibility into CROs' decision-making processes. Sponsors should establish mechanisms to review and understand the rationale behind critical decisions made by the CRO, ensuring alignment with the overall trial objectives and risk management plan.

Proactive quality by design: While R2 advocated for a risk-based approach to quality management, R3 pushes for a more proactive "quality-by-design" philosophy. This new approach integrates quality considerations into the trial's design and operational plan. Sponsors working with CROs will need to ensure their partnerships foster a collaborative environment where quality is prioritized from the outset. Joint planning sessions that integrate quality risk management into trial design and ongoing communication throughout the trial lifecycle will be crucial for success under R3.

Strengthened sponsor oversight: R3 places a greater responsibility on sponsors to ensure quality throughout the outsourced trial. The guideline mandates clear documentation and oversight of all delegated activities. Sponsors will need to strengthen their oversight capabilities to effectively monitor CRO performance and ensure compliance with R3 requirements. This may involve developing qualified personnel, establishing robust risk management plans, implementing rigorous vendor management practices, and investing in technology.

Embracing these principles will empower fully outsourced sponsors to navigate the clinical trial landscape with confidence and be compliant.

III. Barriers to Effective Study Oversight

Study oversight requires complex orchestration between sponsors and CROs to ensure a safe, effective, and compliant trial. But, both process and technology barriers can hamper effective oversight, creating inefficiency and risk. Following are some of the most common challenges, and how they impact both sponsors and CROs.

IIIA. Process Challenges

Lack of timely issue management: Monthly review meetings are common for CROs and sponsors to discuss study progress and flag issues. CROs require significant time and resources to prepare for these meetings, and data often lags behind. As a result, sponsors don't have a real-time view of trial progress or potential issues, undermining their ability to make timely, data-driven decisions.

Inability to analyze and react to trends: Issues that surface during review meetings are not easily reportable. In the best-case scenario, issues are defined and documented one by one in the eTMF for a given trial. However, this process doesn't give sponsors the ability to analyze trends across multiple studies or CROs, making it difficult to identify common issues or take broad corrective action.

Inadequate documentation: Following oversight processes and procedures alone is not sufficient — sponsors must be able to show regulators proof of study oversight. Even when sponsors have a clear oversight plan, the distributed nature of the work across sponsors and CROs makes it very difficult to clearly document actions and the resulting mitigations.

IIIB. Technology Challenges

eTMF is helpful, but not sufficient: eTMF stores essential study documents, including the oversight plan, to help inspectors evaluate the conduct of a study and the quality of data. However, with R3's emphasis on essential records, eTMF is no longer sufficient to fully satisfy regulatory requirements. While eTMF is an effective document management tool, it doesn't adequately demonstrate proof of ongoing management of sponsor oversight, such as actions taken on specific issues.

Fragmented record-keeping systems: While eTMF provides one centralized system for study documentation, other types of records that demonstrate trial oversight are often widely distributed across various technologies. This may include email, shared drives, Word documents, SharePoint, and other systems. As a result, sponsors lack a single source of truth for reviewing information, decision-making, execution, and recording the outcome. Current practices around managing emails, for example, may fall well short of regulatory requirements.

Cumbersome and incomplete metadata: Sponsors typically do not have full visibility into the complete library of relevant records and associated metadata, often as a byproduct of fragmented technology. Sponsors will need to migrate inspectable records generated by the CRO at the end of the study, but these migrations are cumbersome. In many cases, the sheer volume of metadata is not fully anticipated by the sponsor due to the lack of visibility.

Inspectors require direct access: R3 requires inspectors to have direct access to all requested trial-related records. This requirement stipulates that the sponsor should make the clinical oversight system readily available for inspections. Read-only and study documentation are not sufficient. This also means that "paper" legacy systems for keeping records will be harder to maintain since they do not allow direct access for inspections.

IV. How to Adapt Sponsor Oversight Processes for ICH GCP E6(R3)

Although eTMF has introduced common ways of working for essential documentation management across sponsors, there is no common approach to trial oversight. A lack of defined standards creates ambiguity as to whether a sponsor's essential records are really inspection-ready. In this section, we'll share best practices for building an oversight plan curated from the working group's collective experiences.

Build an oversight plan

Establish oversight governance

Create and document evidence of oversight tasks and study data reviews

Evaluate vendor performance

IVA. Build an Oversight Plan

Effective sponsor oversight begins with a well-structured oversight plan that delineates the essential records to be reviewed, the frequency of those reviews, and the roles responsible for conducting them. The following steps are critical in constructing a comprehensive oversight plan:

- **Define essential data and review parameters:** Identify the specific set of data (essential records) that require review. Determine the frequency of these reviews and assign responsibility to qualified individuals. Emphasize both the quantity and quality of resources, ensuring the team possesses substantial oversight experience and expertise.

- **Adopt a risk-based approach:** Tailor the oversight strategy based on the type of trial, its phase, and the associated risks. This ensures that higher-risk areas receive appropriate attention. As applicable, co-define acceptable ranges, previously referred to as quality tolerance limits (QTLs), for in-scope activities with relevant CROs or for site-relevant activities.
- **Adaptive planning:** Define processes to continuously adapt oversight planning and actions based on emerging risks.
- **Collaborate with the CRO:** Engage the CRO early in the process to align on expectations and responsibilities. This collaboration is crucial for seamless oversight.
- **Establish key performance indicators (KPIs):** Develop KPIs that will help identify oversight issues. These may include metrics for study progress, deviations, monitoring visit report (MVR) timeliness, quality issues, and time taken to resolve issues.
- **Prepare a contingency plan:** Ensure that a contingency plan is in place to address unexpected issues that may arise during the trial.

IVB. Establish Oversight Governance

Governance is a crucial component of an effective clinical trial oversight process. It ensures that oversight issues are identified, addressed, and resolved in a systematic and transparent manner. Governance involves establishing a robust framework for regular discussions, decision-making, and documentation. The following steps outline the key elements of oversight governance:

- **Form an oversight governance team:** Establish an oversight governance team that goes beyond the traditional study team by incorporating members with diverse, cross-functional expertise. This might include representatives from clinical operations, data management, quality assurance, regulatory affairs, and other relevant departments. Define clear roles and responsibilities within the governance team to ensure that each member understands their duties and contributions to the oversight process.
- **Create dedicated oversight roles:** To complement the cross-functional oversight governance team, consider allocating the responsibility of study-level oversight to an oversight manager or study/trial operations manager (SOM/TOM).
- **Schedule regular oversight governance meetings:** Weekly meetings ensure continuous monitoring and timely identification of issues and allow for quick adjustments and proactive management of potential problems. A well-structured agenda should include a review of study progress, deviations, quality issues, and other relevant KPIs. Ensure that all team members have access to the agenda and relevant documents prior to the meeting.
- **Identify and document trends:** Use continuous data reviews and oversight tasks to identify patterns that may indicate systemic problems or recurring challenges in the trial. Regular trend analysis helps identify the root causes of recurring problems and develop preventive measures.

- **Update oversight risk assessments:** Update the oversight risk assessments regularly based on identified trends and new information. This ensures that the oversight plan remains adaptive and responsive to emerging risks.
- **Document decisions:** Thoroughly document all decisions made during oversight governance meetings. This includes the rationale behind each decision, the data reviewed, and the anticipated outcomes.
- **Engage the CRO on issues:** Communicate identified oversight issues with the CRO promptly. This ensures that the CRO is aware of the issues and can take appropriate actions to resolve them. Continuously monitor the CRO's progress in resolving oversight issues. Evaluate the effectiveness of the resolution actions and ensure that they meet the predefined quality and timeliness standards.

Ensure that there is documented evidence that oversight governance processes have taken place. This includes minutes of oversight meetings, decision logs, communication records with the CRO, and evidence of issue resolution. It should be easily accessible and auditable to demonstrate compliance with regulatory requirements and internal standards.

IVC. Create and Document Evidence of Oversight Tasks and Study Data Reviews

Continuous data review and oversight tasks are pivotal to maintaining trial integrity.
The key steps include:

- **Distribute oversight tasks:** Assign oversight and data review tasks to specific study team members, ensuring clarity in roles and responsibilities.
- **Review CRO data:** Review the CRO's data regularly, focusing on records that pose the highest risk to the trial.
- **Document task completion:** Maintain documentation as evidence of oversight task completion. This includes tracking deviations and maintaining communication logs.
- **Record oversight issues:** Document any oversight issues that arise, noting the specific data reviewed to inform decision-making.
- **Track evidence of oversight records in validated systems:** Establish a clear record to maintain data integrity, demonstrate regulatory compliance, create audit trails, and improve transparency and accountability. This can also help identify cross-study trends or areas of improvement.

IVD. Evaluate Vendor Performance

Effective vendor evaluation ensures vendors meet required performance standards and contribute positively to the success of the clinical trials they are involved in. A dedicated vendor evaluation team plays a crucial role in this process, ensuring thorough and consistent assessments. Below is a detailed approach to forming and utilizing a vendor evaluation team:

- **Define vendor evaluation team:** Assemble a vendor evaluation team that includes representatives from clinical operations, procurement, quality assurance, regulatory affairs, and data management. This ensures a comprehensive evaluation from multiple perspectives. Clearly define the roles and responsibilities of each team member in the evaluation process. Train team members to effectively evaluate vendor performance, emphasizing the importance of both the quantity and quality of resources, including their oversight experience and expertise. The vendor evaluation team can be an agile team or a dedicated function, sometimes referred to as outsourcing management (OM) function. OM functions are typically a combination of procurement, project management office (PMO), and a clinical operations team representative.
- **Define performance KPIs:** Establish clear and measurable KPIs for vendor performance. These KPIs should reflect critical aspects of the vendor's responsibilities, such as data quality, adherence to timelines, regulatory compliance, responsiveness, and cost management.
- **Continuous vendor performance review:** Conduct vendor performance reviews on a regular basis. The frequency of these reviews should be based on the complexity and volume of trials the vendor is involved in. Use the predefined KPIs to assess vendor performance. Based on findings from the performance reviews, implement corrective and preventative actions (CAPAs) as necessary. Maintain thorough documentation of all discussions and decisions made during performance review meetings. This includes specific performance issues, agreed-upon actions, and timelines for improvement.
- **Vendor engagement and improvement:** Establish a continuous feedback loop with the vendor. Provide constructive feedback based on performance reviews and work collaboratively on improvement plans. If performance issues are identified, develop and implement improvement plans in collaboration with the vendor. These plans should outline specific steps, responsibilities, and timelines for addressing issues.
- **Vendor performance assessment:** Conduct retrospective evaluations of how the CRO performed related to ways of working, proposed governance charters, and KPIs/acceptable ranges to understand what forward-looking mitigation measures should be put in place.

With this study oversight framework in place, the next section will focus on best practices sponsors can adopt to improve the quality and efficiency of the process.

V. Key Success Factors to Optimize Oversight Quality and Efficiency

Preparing for ICH GCP E6(R3) may require a mindset shift for sponsors, who are ultimately responsible for a study's execution. Even in instances where they can delegate duties to CROs, they cannot delegate oversight. Sponsors will need experienced personnel who can establish and execute oversight tasks and leverage clinical systems to keep essential records for inspections.

Additional keys to success are outlined below.

Define study oversight: Oversight is often confused with supervising CRO performance, rather than overseeing GCP compliance, proactively mitigating risks to patient safety and data integrity, and reacting in a timely manner. Ideally, vendor oversight should drive service excellence and mitigate risks through practices, processes, and tools designed to get full value from vendors throughout the partnership. Optimal vendor oversight should create visibility into GCP compliance, vendor contracts, relationship objectives, quality of work, and performance tracking. The goal is efficient and compliant delivery of contracted products and services, guaranteeing timely action and escalation when issues arise. Sponsors should define the scope of outsourced activities and establish clear transition points, which are crucial to ensure proper oversight and integration between outsourced and in-house activities.

Create an oversight model focused on people, process, technology, and data: A sponsor's internal capabilities and strategic vision may shift over time, so sponsors will benefit from a scalable oversight model built for the long term. Sponsors should begin by defining when study activities will be outsourced. Then, oversight should include cross-functional internal processes that account for global vs. local nuances. Change management is critical as internal sponsor teams will require support if outsourcing needs or regulations shift over time. Sponsors should invest in the right clinical systems and infrastructure - beyond study documentation - to achieve optimal oversight. Technology enables real-time monitoring of study progress, early identification of potential issues, and efficient communication between study partners. Automation can support timely and streamlined data ingestion from multiple external and internal sources as well. By leveraging advanced analytics and automation, sponsors can make data-driven decisions, reduce operational costs, and improve oversight.

Embed a culture of oversight: Study oversight should be embedded in the design of quality processes across the entire multi-disciplinary team. While clinical operations may lead the process, every team involved in the trial needs to be accountable and document records accordingly. This collaborative approach ensures comprehensive oversight and reduces the risk of errors or delays. While CROs can provide valuable expertise and resources, sponsors must ensure that CROs have the necessary tools, information, and support to execute the trial effectively. Strong collaboration at the outset can help avoid potential issues and ensure both parties achieve their common goals.

VI. Conclusion

More than 20 heavily outsourced sponsor and CRO organizations headquartered in Europe contributed to the guidance in this whitepaper, and this working group will continue to share, update, and refine guidance as ICH GCP E6(R3) is finalized. As the guidance nears its 2025 release date, fully outsourced sponsors have a narrow window of opportunity to revisit their approach to study oversight.

Sponsors may need to update ways of working with CROs, adopt new technologies, or manage change within their organizations to ensure compliance. More importantly, sponsors should recognize this new guidance as an opportunity to create a proactive, risk-based approach to executing safe, effective, and successful clinical trials, while ensuring oversight for their outsourced studies.