Advanced Clinical

INSIGHT BRIEF

Building a Successful Clinical Oversight Function: Lessons Learned and Best Practices

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Introduction

Clinical oversight—the documented demonstration of oversight of obligations transferred by a pharmaceutical company to a CRO—contributes to global trial success by ensuring the protection of trial participants as well as the integrity of the data collected. Global regulators are increasingly seeking more formal documentation of sponsor oversight activities during inspections. By taking an active role in clinical oversight processes and following consistent documentation strategies, sponsors can minimize the risk of inspection findings that can cause delays, fines, and even impact regulatory approvals. As our industry shifts to conducting more decentralized trials, clinical oversight strategies and activities are more important than ever. When sponsors choose to outsource this critical function, the pros and cons must be carefully considered.

Overview of Clinical Oversight: Regulatory Environment

The current global landscape for clinical oversight includes a range of regulations, as illustrated in Table 1. These include the R2 update to the International Council for Harmonization Guideline for Good Clinical Practice (ICH E6 R2), which expanded sponsor oversight responsibilities to include the requirement to implement an end-to-end, risk-based monitoring approach. This is required to cover all aspects of clinical research to assess trends, identify gaps, isolate outlier data, and then plan appropriate mitigations to address the issues. European Union regulations state that sponsors are responsible for ensuring that the conduct of their clinical trials and the final data generated comply with Directives 2001/20/EC and 2005/28/EC.

The sponsor is, of course, ultimately responsible and accountable for all of its clinical trials. Clinical oversight is aimed at providing the sponsor with an updated and constant overview of CRO performance, deliverables and results, ensuring the sponsor's ultimate ownership and accountability, and maintaining tangible evidence of this sponsor oversight.

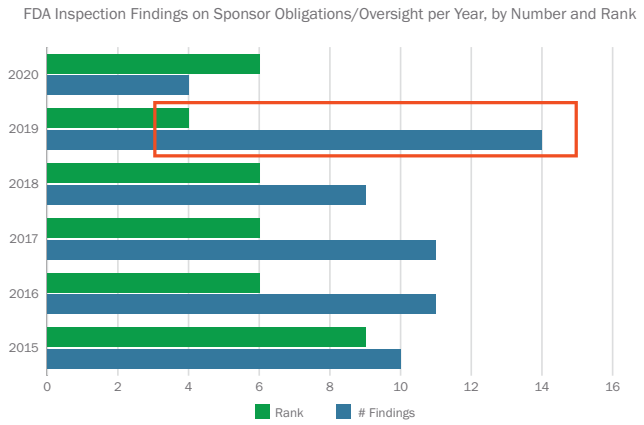
Table 1: Current landscape: Clinical oversight and global regulations

Regulation	Details
Good Clinical Practice (GCP), International Conference for Harmonization E6 (R2) Guideline for Good Clinical Practice, ICH E6 (R2)	**5.1.1** "The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements" **5.2.1** "A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor"
E6 (R2) Addendum	The sponsor should 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)
European Commission Directive 2005/28/EC	A sponsor may delegate any or all of its trial-related functions to an individual, a company, an institution or an organization. However, in such cases, the sponsor shall remain responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with Directive 2001/20/EC as well as this Directive.

The sponsor is required to maintain inspection readiness during the trial, and to proactively identify, correct, and prevent issues as these arise rather than waiting for them to be found during regulatory inspections post-submission. This includes being present at sites, avoiding "absentee sponsor syndrome," and supporting the CRO as a partner with common goals and transparency. It is important to ensure global consistency and standardization across sites and CRAs.

There is increasing scrutiny by regulators of sponsors' oversight efforts with tangible evidence of this oversight being required. Over the last few years, there has been a trend of increased findings from U.S. Food and Drug Administration (FDA) inspections (Figure 1), and this trend would likely have continued without a pause in inspections due to COVID-19.

Figure 1: FDA inspection findings on sponsor obligations/ oversight per year, by number and rank[1]



Clinical oversight resides within the clinical trial team, embedded within the sponsor project management team. This oversight falls outside of standard, day-to-day project and study management activities and is separate from Quality Management Systems (QMS), site audits and vendor audits (Figure 2).

Clinical oversight outsourcing models: Roles and assumptions

Historically, sponsors may have approached clinical oversight as being the responsibility of the CRO and may have utilized Quality Management Systems and audits as the only oversight mechanism. Oversight models typically involved a reactive process.

Figure 2: Where does clinical oversight reside?

Monitoring Visit: CRO CRAs	Oversight Visit: Sponsor Oversight Leads	Quality Site Audit: Sponsor QM
Focus on **site's** study execution	Focus on **CRO monitor**	Focus on **site** process and performance
Review source **data** against CRF	Review **process** used by CRO monitor to verify data	Audit **data** to verify integrity
Ensure **site** staff is in compliance with protocol, IRB, regulations, guidelines, etc.	Evaluate **CRA monitor** to ensure compliance with systems, SOW (contract), SOPs, regulations, sponsor expectations, etc.	Evaluate **site** to verify compliance with regulations, guidelines, etc.

In contrast, currently, sponsors and CROs typically go into projects with a partnership mentality, with shared goals of increasing collaboration and transparency. Inspection readiness is part of day-to-day activities, with oversight enhancing and elevating the CRO-sponsor relationship and the overall quality of the trial. Sponsors and CROs work together to proactively mitigate risks, resolve issues, and conduct risk management collaboratively during the trial.

A lack of clinical oversight poses several risks. If oversight cannot be proven, there is a risk of inspection findings, which in turn may delay a regulatory submission or threaten a drug's entry to the market. In addition, if trends or issues are found during the trial such as deviations, informed consent issues, safety trends or IP problems, they can be more easily addressed. In the current and highly competitive site landscape, sites typically prefer to work with sponsors who are engaged and accessible. Finally, thorough oversight provides an opportunity for a deeper partnership with the CRO team through transparent and collaborative issue resolution.

Oversight in Governance

Components of governance include the documentation of oversight, issue escalation, and quality and continuous improvement (Figure 3). All these strengthen the partnership between sponsor and CRO. Governance meetings offer another mechanism to demonstrate careful sponsor oversight. These set infrastructure and expectations, while ensuring quality and continuous improvement, and may be executive-level or operational meetings.

Figure 3: Components of clinical trial governance

Oversight in governance has multiple elements, including:

- Study team interactions to facilitate initiation, execution and completion of the study
- Ensuring accountability between the various teams
- Review of contract/budget status and adherence
- Risk mitigation for program milestones
- Evaluating team performance and dynamics through tracking milestones, ensuring that the CRO continues to meet sponsor requirements
- Establishing an attendee list, agenda, and keeping minutes for trial master file (TMF) reviews
- Setting expectations for escalation, decision making and communications
- Reviewing subcontractor performance

Overall, quality is the central element in oversight (Figure 4).

Figure 4: Elements of effective clinical oversight

Clinical Oversight Best Practices

Given the critical importance of clinical oversight, sponsors may consider bringing this function fully in-house. This decision requires full buy-in and support from senior management and the sponsor because change management is required. Collaboration with CRO partners is also important, including them in implementation planning and clarifying roles and expectations. There are also budget considerations for oversight costs, including the need for a dedicated oversight functional area and dedicated personnel with strong monitoring experience and a proven ability to partner with the CRO's CRAs. A system is also required to automate oversight activities, tracking and reporting.

Clinical oversight workflow

Clinical oversight focuses on identification of trends and risk management activities through global oversight processes with a focus on clinical activities. There are three key factors in this workflow. One is the TMF review, including post-CRO quality control (QC) reviews, inspection readiness viewpoint and identification of trends. The second involves oversight visits conducted with the CRO's CRAs at the site to identify global study trends and issues during the course of the trial. The third is the monitoring visit report (MVR) and inspection readiness review, as specified in the clinical monitoring plan, to identify trends.

The oversight infrastructure includes:

- Oversight plan or process documents, which describe how oversight activities will be executed, including conducting oversight visits at select site initiation and interim monitoring visits based on selection criteria. This should include accompanying each monitor at least once during the course of the trial
- Oversight visit report templates
- Oversight trend tracking (manual or via a system)
- CRO MVR review checklist/guideline and tracking
- TMF review trend tracking (manual or via a system)

Sample selection criteria to consider include:

Clinical oversight focuses on identification of trends and risk management activities through global oversight processes with a focus on clinical activities.

- Principal Investigator (PI) and site: Insufficient PI oversight reported; research-naïve PI/key staff/site; PI/lead CRC turnover; PI/country new to sponsor
- Deviations: Recidivism related to protocol deviations; major/significant informed consent form findings; serious adverse event (SAE) reporting timeline deviations; concern of possible underreporting of deviations and SAE/adverse event (AE) reporting
- Data: Trends in significant delays of data entry; trends in significant delays in query resolution
- Enrollment: High enrollment; high screen failure rate
- Action/issue resolution: Non-resolution of action items above a certain threshold
- CRA: CRA turnover; sponsor and/or CRO identification of a CRA requiring close oversight
- CRO Site Quality Indicators; CRO request for an oversight visit

Alternative Models to Manage Clinical Oversight Challenges

A sponsor's decision to work with a partner on clinical oversight offers multiple potential benefits. These include the ability for: ownership of oversight to remain with sponsor without needing to increase internal headcount; the team to be branded as part of the sponsor's organization and as members of the sponsor project team; the sponsor to "in-source" the infrastructure and processes involved in oversight without having to build these internally; instant access to expertise for small biotech/pharma companies and a cost-effective solution for larger pharma firms; and a built-in, global, oversight team by bringing on people from different regions, for example, under a Functional Service Provider (FSP) model.

Three examples of challenges involved in partnering on clinical oversight are:

Challenge 1: Sponsor oversight of a third-party provider (this is the most significant challenge)

Solution 1: The oversight team is branded as part of the sponsor organization; this team functions as the sponsor, represents the sponsor at the sites, and executes the work, and the internal sponsor project teams have decision and implementation authority

Challenge 2: Role clarity: It is important for all involved to understand where the oversight function fits (for both the internal sponsor team and the CRO)

Solution 2: Secure senior management buy-in, assign an internal sponsor champion, and drive change management, including training and implementation

Challenge 3: Need to maintain and improve the sponsor's existing strong, positive relationship with current CROs

Solution 3: Roll-out and training for new oversight program including partnership messaging, and roles and responsibilities clearly defined in the oversight plan and with the CRO

To summarize, partnering on clinical oversight is a realistic option that requires a significant investment. For large pharma firms running hundreds of trial sites, clinical oversight is costly and time consuming and partnering may offer savings. For emerging biotech companies, sufficient internal expertise may not exist to manage oversight effectively, making partnering a promising alternative.

Future Implications for Clinical Oversight

The COVID-19 pandemic has impacted most areas of clinical research. As industry shifts to conducting more decentralized trials, clinical oversight strategies and activities will be more critical. Process changes have included greater use of home health vendors, processes, execution, revised site documentation and practices, and the need for remote access to electronic medical records. These risks and mitigations specific to COVID-19 are likely to remain for the foreseeable future.

On the regulatory front, changes are expected with ICH E6 (R3), which is likely to focus on diversity in both trial design and data sources. In this context, oversight provides sponsors with an additional mechanism for evaluation of innovative technologies and new processes to add to risk-based approaches.

> **As industry shifts to conducting more decentralized trials, clinical oversight strategies and activities will be more critical.**

In conclusion, a clinical oversight model can be created for any size client from emerging biotech to global pharmaceutical companies. No matter the size of company, a formal process must be put in place including plans, standard operating procedures and processes, and thorough documentation of output. Clinical oversight focuses on inspection readiness including risk management and monitoring of trends.

Clinical oversight can be carried out in-house by companies that have the necessary time, expertise and resources to execute and manage the oversight process for all their trials. For sponsors that would prefer to avoid this step, the oversight function can be executed by an experienced partner through an FSP model to design and deliver a strong oversight program.

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- Executive-level, clinical research professional who has been in the industry for over 25 years.
- Program Director of Advanced Clinical University – developed the program to train individuals in clinical research.
- Provides leadership, policy making, infrastructure development and regulatory guidance to internal clinical operations teams.
- Key role in establishing risk-based monitoring infrastructure.
- Leads the company's formal program governance function.

References

[1] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations