

A Primer on Vendor Oversight for Clinical Project Managers ^{HS}

Update on Regulatory Expectations

This article delves into the newly illustrated focus of regulatory inspectors on the relationship between sponsors and monitors and on recommendations to build quality risk management into the clinical trials process.

HS Home Study article

LEARNING OBJECTIVE

After reading this article, participants should be able to discuss the increased regulations related to sponsors and monitors, and describe best practices for building quality risk management into the clinical trials process.

DISCLOSURES

Laurie Halloran, BSN, MS, CCRA, discloses that she has no actual or potential conflict of interest in relation to this article.

Several recent, highly quoted U.S. Food and Drug Administration (FDA) Warning Letters have resulted from focused sponsor/monitor inspections of well-established pharmaceutical companies and their outsourcing partners.¹ Coupled with very public criticism of FDA's oversight abilities by the Office of Inspector General (OIG)² and other governing bodies, the letters have galvanized sponsors to take a close look at their ability to withstand such regulatory scrutiny internally, and to develop proactively their internal capabilities and infrastructure to better manage their outsourced clinical development programs. Since virtually every biopharmaceutical and medical device sponsor uses contract research organization (CRO) services in its development activities, this should be a priority for companies of all sizes and stages.

This article delves into the newly illustrated focus of regulatory inspectors on the relationship between sponsors and monitors and on recommendations to build quality risk management into the clinical trials process. The discussion also includes some of the best practices being adopted to address these new pressures in leading sponsor organizations.

What the Regulations Say

Both FDA regulations and the International Conference on Harmonization's (ICH's) guidelines on good clinical practice (GCP) mandate sponsor oversight (see Figure 1) of all clinical research activities where transfer of regulatory obligations has occurred with external parties through contractual obligation. They also require careful selection and training of qualified individuals to manage the delegated activities. However, the importance of these seemingly simple concepts has grown significantly as the dynamics of developing products in a global environment, coupled with the increased complexity of protocols, medicine, regulations, and the heightened financial constraints of all development stage companies, has become the new norm.

What the Regulators are Doing

Traditionally, sponsor companies and their monitoring partners anticipated that there would be a relatively high likelihood of a regulatory inspection upon submission of a new marketing application (New Drug Application, Biologics License Application, or Pre-Market Approval). The focus on proactive preparation would be only for the most likely sites, where historically,

Figure 1 FDA and ICH Guidelines on Sponsor Obligations

- Drug accountability and disposition
- Obtaining information from the investigator (FDA Form 1572)
- Clinical protocol
- Financial disclosure information (Part 54) (21 CFR Part 11 in the *Code of Federal Regulations*)
- Selecting monitors
- Investigator brochure
- Secure compliance from or terminate noncompliant investigators
- Halting study in case of unreasonable risk to subjects
- Recordkeeping and record retention
- FDA inspection access
- Investigational New Drug safety reports (21 CFR §312.32 in the *Code of Federal Regulations*)

selection was based on highest enrollment or other qualitative risk perception. Several sites would be targeted for each application, with the expectation that if significant violations were identified at some sites, FDA could perform sensitivity analysis excluding those sites before moving forward with the application review. The data at other sites was assumed to be reliable, and if data at those key sites held up under sensitivity analysis, the application could be approved.

Then, in Warning Letters to both Pfizer and Johnson & Johnson, FDA¹ cited significant issues with lapses in decision-making, oversight, and the corrective and preventive actions required of all sponsors (see Figure 2), which could result in harm to subjects.

These lapses are of the sort that always raise the scrutiny, criticism, and focus from the broader approach of recent inspections undertaken by FDA and the European Medicines Agency (EMA) of sponsors and monitors to ensure that clinical research is being conducted under the utmost care and rigor by all stakeholders.

The Issues of Current Concern

In a presentation at the Association of Clinical Research Professionals' 2011 Global Conference & Exhibition on FDA inspections and Warning Letters, Leslie Ball, MD, acting director of the Office of Scientific Investigations in FDA's Center for Drug Evaluation and Research, focused on a recent industry

survey³ that gives insight on the reasons for the agency's current concerns.⁴ It is recognized that the increased level of clinical research outsourcing, coupled with the globalization of clinical trials—especially within emerging regions with rapidly expanding, highly skilled resource requirements—forms the “perfect storm” for potentially inadequate sponsor oversight of CROs.

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It takes years to develop the wisdom needed to manage the complexity of a clinical trial, and a different set of skills to manage the relationships and expectations associated with an outsourced one. Deborah Manzo, global head of clinical trial operations at Novartis Vaccines & Diagnostics, says, “Having the ability to either learn from the experience yourself or from hearing about another situation builds wisdom. Sometimes a person can have 10 years experience and does not ‘get it,’ [while] others have five years and are head and shoulders above.”

In her presentation, Ball also mentioned the complex challenges brought by inadequate performance, coupled with a lack of accountability by CROs,

Figure 2 Violations Leading to Sponsor/CRO Warning Letters

- Failure to recognize a systemic problem with clinical trial
- Failure to investigate in a comprehensive manner, commensurate with risk
- Inadequate training of investigators and site staff regarding study responsibilities (requirements of a protocol, supervision, data collection and storage, handling of investigational product, etc.)
- Insufficient or delayed follow-up/correction of identified deficiencies
- Inadequate vendor oversight (lack of clarity in responsibility/accountability of third parties)
- Inadequate due diligence in mergers/acquisitions
- Poorly designed protocol
- Insufficient training/implementation of new technologies
- Failure to adequately document corrective and preventive actions

who are increasingly charged with executing overly complicated protocols.⁴ These complexities, when combined with insufficient sponsor oversight and training of possibly both

cal investigator was cited for lack of oversight, and when the investigator protested, he was told that his study coordinator had signed the FDA 1572 form and all of the consents with his

building in quality risk management throughout the entire development process.

Recent position presentations by the FDA are readily available via the Clinical Trials Transformation Initiative (CTTI) website,⁶ but will be summarized here for clarity and coherence. Quality risk management (QRM) within the good manufacturing practice sector has been a recognized standard⁷ for several years, but it has been recently suggested as applicable in the GCP environment, as well.⁸

The International Organization for Standardization's (ISO's) quality loop (see Figure 3) is readily adopted for use when the system is contained within a single sponsor-oriented team, but we find that frequently the sponsors who outsource the management and execution of their clinical trials do not have an opportunity to look at their integrated activities using a systematic approach. Since it is almost impossible to prepare for a sponsor/monitor inspection with a reactive approach, we suggest that sponsors conduct a gap analysis specifically focused on the outsourced clinical trial model within

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the CRO's team, as well as those at the research sites, are of notable concern to the agencies that look to these organizations to provide the data proving both safety and effectiveness before approving a product for broader distribution.

For example, at a recent study initiation visit for a complex immunotherapy for head and neck cancer, one clinical research associate from a CRO I accompanied couldn't pronounce some of the pre-existing conditions excluded from the protocol, and skipped a deeper explanation of some of the key protocol procedures stating she had only four hours scoped to conduct the visit. Clearly in this specific situation, the priority was not to educate the researchers at the site sufficiently to perform the clinical trial procedures precisely, it was to stay within the scope of the allowed timeframe for the visit.

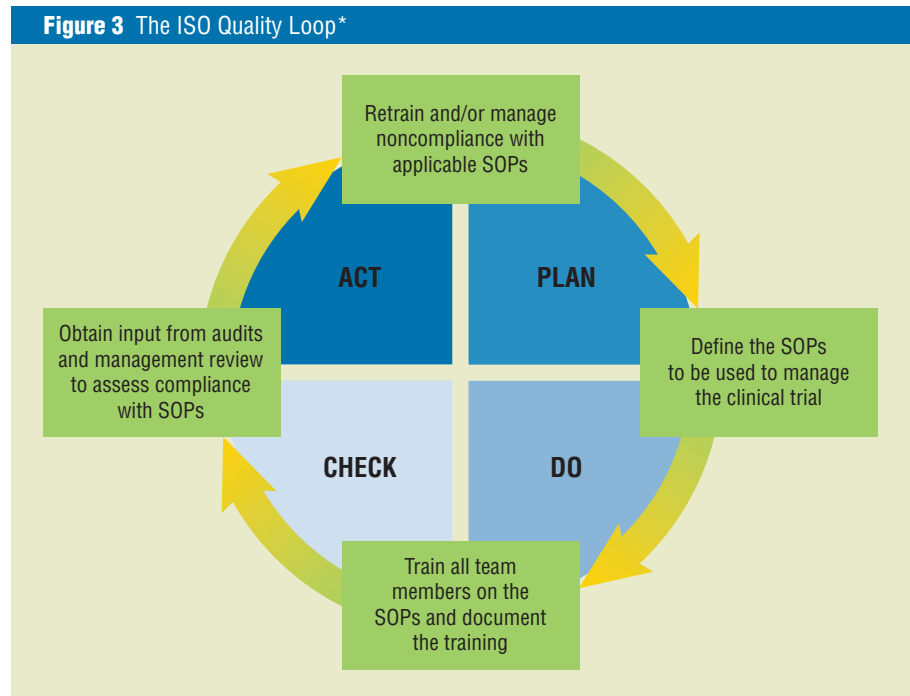
Layer on the growing recognition that there is often excessive delegation of trial-related duties to others by principal investigators, especially at the most research-naïve institutions, and the political pressure on the FDA to improve/intensify its oversight function, and there should be little surprise that the focus of regulatory inspections has turned toward the complex relationship between sponsors and the parties with whom they contract to shepherd the majority of their products to market.

These concerns are not just theoretical. During his presentation at the 2011 Drug Information Association conference, David LePay, MD, PhD, of the FDA GCP program, used an example from a Warning Letter in which a clini-

cal investigator had difficulty making the link between the findings and the concept, which had not been recognized or rectified through the entire clinical trial by either the sponsor or the monitor.⁵

A Systematic Approach to Quality Risk Management

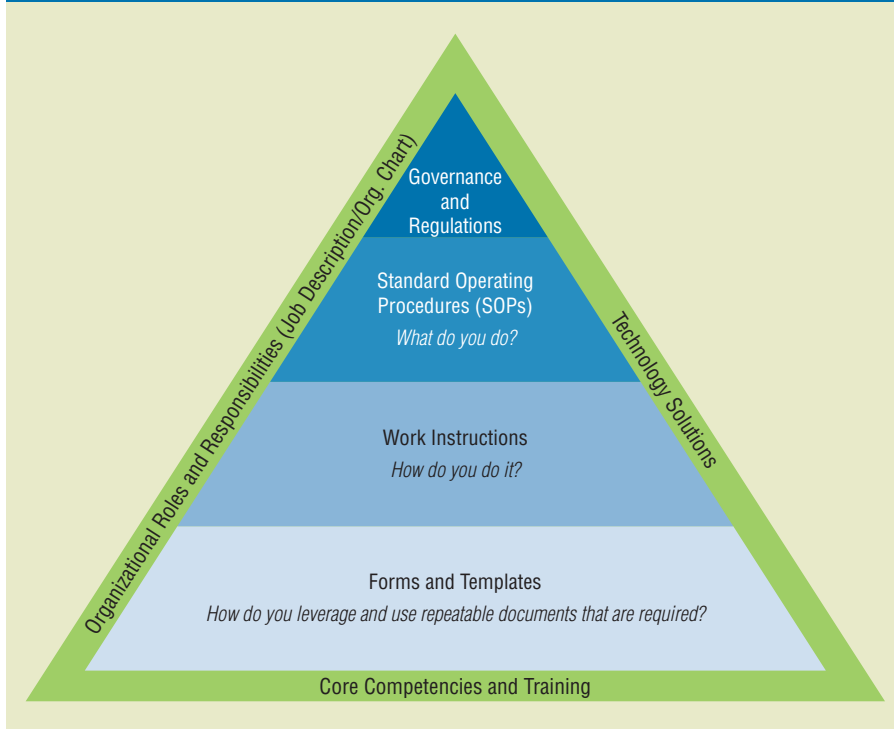
The FDA has recently been clear and consistent that it wants to see sponsors set quality expectations for outsourced work, and should be evaluating those vendors on quality with respect to deliverables. These themes complement those of EMA, with its focus on



SOPs = standard operating procedures

*Adapted for this article from www.iso.org/iso/iso_catalogue/management_standards/understand_the_basics.htm.

Figure 4 Systematic “Company Way” of Selecting and Managing Vendors



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their organizations and their outsourcing partners; this identifies the risks on the overall scale, allowing for a corrective and preventive plan to adopt the best practices of an integrated system (see Figure 4).

Although the fundamentals of adapting the QRM approach for GCP cannot be addressed here due to space limitations, these concepts will be examined in a future article in *The Monitor*. What this article addresses is the overview of a systematic approach sponsors

can take to ensure that the key areas of regulatory scrutiny are addressed in the relationship between themselves and their vendors, so that the execution of the well-written protocol by a team comprised of both sponsor and CRO representatives meets the quality expectations of regulatory inspectors (see Figure 5). These are a subset of the overall challenges, but are critical factors to consider in planning for success during the management of an outsourced program.

Figure 5 Implementing a Quality Risk Management System⁶

- Create systems that limit opportunity for errors
- Simplify protocol and outcomes assessed
- Standardize systems and formats where possible
- Use validated instruments/definitions
- Keep amendments to a minimum and check the case report forms and consent form against each change
- Think very carefully about unblinding procedures
- Insist on training and then test it
- Have a disaster plan
- Do beta-testing/dry runs
- Monitor and correct errors in real time

Focus on Vendor Oversight

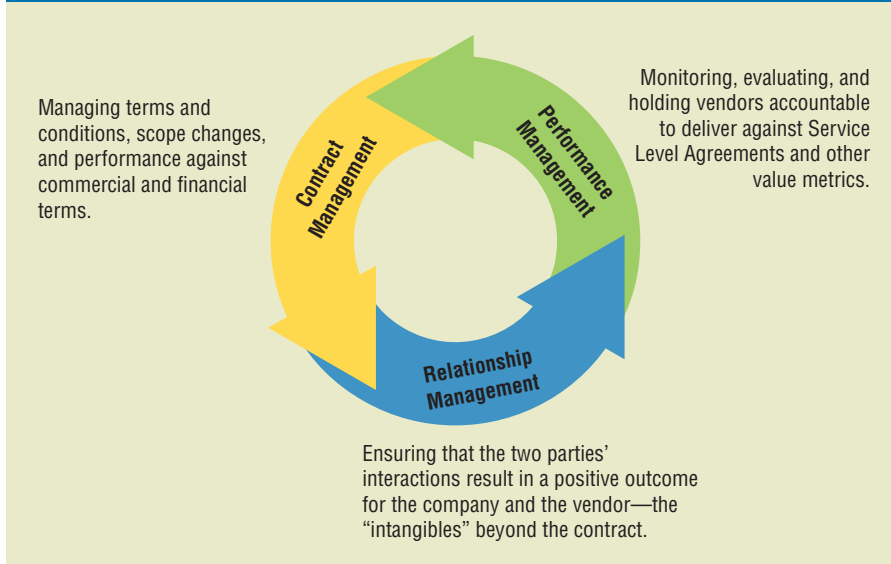
Vendor oversight can be defined using three major components: engagement/contractual, performance, and relationship management (see Figure 6). All of the components are important, because negative findings related to sponsor oversight and monitoring responsibilities that highlight gaps in one area will affect all three.

Consider the relatively common example of a poorly defined scope of transferred responsibilities, lacking in critical detail around the complex decision-making process related to investigator selection and site approvals following site selection visits. If the sponsor has not clearly defined and documented how this should work contractually, a monitor's evaluation of an investigator's qualifications to perform specific protocol-related eligibility tests may not be communicated during the project kickoff meeting, and opportunities for poor decisions abound. Moreover, this critical baseline activity is not captured in historical records that can be reviewed *post facto* to determine decision-making surrounding the selection of sites.

Leading sponsor companies are starting to examine options for prospectively building in a systematic quality and oversight management of outsourcing to be used in upcoming clinical trials.

At this intersection both performance and relationship management expectations are set, first through training and evaluation of the individual monitor's abilities to make the correct assessment, and then in the escalation process between sponsors and CROs

Figure 6 The Three Major Components of Vendor Oversight



describes this preventive approach, which should be led by the sponsor’s clinical project manager with support from his or her senior clinical leadership.

The Prospective Approach

Clinical project management (CPM) at many sponsor companies has been described and institutionalized more than ever before. The CPM function should, at a basic level, have overall responsibility for the budget, timeline, team performance, and deliverables in a trial.

Standardized tools, such as Gantt charts, resource plans, communication plans, and budgets are being used widely by companies that embrace the value of project management. Project plans are not always created in great depth, but are more common now than even a year ago in many sponsor companies with outsourced clinical trials.

Two additional plans are now being added to the tool list, to be used to set

who have defined responsibilities and authorities when areas of concern are identified. These concerns must be discussed collaboratively between the parties to make the best decision regarding the inclusion of the physician.

Leading sponsor companies are starting to examine options for prospectively building in a systematic quality and oversight management of outsourcing to be used in upcoming clinical trials. The next section

Table 1 Quality Plan Excerpt*						
Metric #	KQI or KPI	Measurement and/or Quality Criteria	Target Goals	Frequency of Review	Evaluation	Tools
1. Project Management						
1.1	KPI	Completion of comprehensive either first draft or final version of the following project management plans prior to first site activated: <ul style="list-style-type: none"> • Project start-up plan • Project plan • Investigator agreement plan • Project timelines • Adherence to and continuing review of the above plans after first site activated 	100%	Quarterly	Review of project management plans’ status relating to the timing of first site activated. Ongoing alignment review after first site activated and then quarterly thereafter.	CRO portal Checklist of responsibilities
1.2	KPI	Proper training of CRO staff: <ol style="list-style-type: none"> 1. Staff trained prior to their participation in trial activities. 2. Retraining occurring as updated procedures and/or study requirements are available. 	90%	Quarterly	Training tracking spreadsheet reviewed against complete study team list and training requirements for each specific CRO role.	CRO portal eTMF Training tracker
1.3	KPI	All CRO vendor deliverables meet CRO project timelines and expectations as defined in the project plan.	90%	Quarterly	Review of CRO vendor deliverables against CRO project plan/timelines	CRO portal eTMF Project plan

*Used with permission.

Legend: KPI = key performance indicators; KQI = key quality indicators.

Selected Major Activities	Major Measurement and/or Quality Criteria
Project Management	Completion of project management plans prior to first site activated
	Proper training of CRO staff
	All CRO vendor deliverables meet timelines as defined in the project plan
Regulatory Affairs/Study Start-up	Regulatory approval received prior to first-patient-in for each country
	CRO meets projected submission dates for country submissions
	CRO meets requirements of each competent authority
Clinical Operations	Completion of and adherence to a clinical management plan
	Initial regulatory documents received
	Ethical approval current (no patients enrolled without)
	Quality of CRO monitoring reports
	Follow up documentation is sent according to standard operating procedures/clinical management plan

expectations that begin contractually, and include both performance and relationship management. The use of both quality plans (see Tables 1 and 2) and oversight plans (see Tables 3 and 4) facilitates a proactive approach between sponsor and vendors to discuss and define expectations at the engagement (contractual) stage, set them at the kickoff stage, and manage them throughout the entire program. In this manner, both minimum performance and the relationship are clearly defined and not only managed by all parties, but documented for future inspection retrieval and stored to create institutional knowledge that is transferrable to future projects.

As in all planning activities, the focus must be on the dialog that the tools foster, because the results of the discussion are the valuable outcomes,

Activity	SPONSOR Oversight Activity/Responsible Person(s)	Frequency	Documentation
Vendor Set-up			
Study Contract, Change Orders, Invoices, and Deliverables (work complete)	<p>Clinical operations will develop, finalize, and approve study tasks, assumptions and budget.</p> <p>Change orders will evolve as there are changes in study tasks, assumptions, task units required, and timelines.</p> <p>Set up time or frequency to re-visit/review the contract (if applicable for lengthy contracts).</p> <p>Clinical operations study team members review invoices and work complete:</p> <ul style="list-style-type: none"> • In accordance with company process, collaborate with sponsor finance department as needed. • Review invoices for monthly direct costs and pass through expenses against the contract. • Review units of work complete and remaining on the contract. 	<p>Initially and as required by ongoing management identification of tasks and units complete</p> <p>Direct units – monthly; pass through invoices as received</p>	<p>Executed contract</p> <p>Acknowledge change in scope notification form with estimated budget</p> <p>Signed/dated invoices to indicate review and approval in accordance with signing authority</p>
Timelines	<ul style="list-style-type: none"> • Sponsor management approved study timelines define program goals. • CPM routinely reviews timelines to ensure on-time completion of study. If actual timelines deviate from approved timelines, mitigation and escalation plans should be outlined in project management plan. • Working timelines with vendors can be more aggressive than company timeline. • Risk to company timeline is to be escalated to line management and sponsor management. 	<p>Initial and monthly review of high level timelines and milestones.</p> <p>CRO-SPONSOR review of MS project timelines quarterly or biannually as needed</p>	<p>Sponsor approved timeline</p> <p>CRO project management plan minutes</p>
Key Vendor Staff	Sponsor to approve key vendor staff	Initially and upon changes in key staff	Signed sponsor CV approval form

*Used with permission: Carol Lewis-Cullinan.

Table 4 Oversight Plan Examples	
Project Execution	Examples of Sponsor Oversight Activity/Responsible Person(s)
Project Management	CRO will develop draft or final plan following sponsor review and approval and prior to first site activated; update as required
Meetings and Communications	CPM will be responsible to ensure: <ul style="list-style-type: none"> • Meeting frequency per the contract • Vendor sets proper agenda for meeting
Project Plans	CPM will review and approve project plans that may include: <ul style="list-style-type: none"> • Project management plan • Feasibility plan and start-up plan, if applicable • Communication plan and escalation plan
Clinical Trial Materials	CPM will: <ul style="list-style-type: none"> • Coordinate clinical trial materials requirements with clinical protocol and materials management
Trial Master File Structure	CPM will: <ul style="list-style-type: none"> • Provide sponsor with the trial master file structure or review and approve the file structure
Status Reports as Management and Oversight Tools	CPM will review and acknowledge status reports, which may include: <ul style="list-style-type: none"> • Site activation tracker • Regulatory status: Ministry of Health submissions, approvals

not the completion of the tool. Quality plans and oversight plans are not the solutions, but they can help to organize the structured interaction and facilitate the capture of decisions for future reference. However, use of these tools assumes a level of skills and knowledge that must be in place so that the discussion can be led by the sponsor's management joined by management representatives from every vendor. If these critical factors are not considered and so-called CPM professionals are not actually trained and experienced in outsourced study management, they will likely not provide adequate oversight unless their managers are involved at a detailed level.

The two tools can be used together or separately. They have been developed collaboratively and shared with a group of clinical operations executives in the Boston area that meets regularly to share best practices. Currently, they are being tried by the lead developers with their current programs to proactively institute new practices in preparation for future inspection readiness.

For programs that are already ongoing, a retrospective approach can be

used if there is concern that oversight has not been consistent through the organization. An example of this type of corrective action will be discussed next.

The Retrospective Approach

The typical engagement process for clinical trial vendors is managed by multiple individuals within a sponsor company of any size, and will include clinical project managers and potentially up to a dozen other individuals from various areas, including legal, finance, executive management, procurement or outsourcing, and quality assurance (QA), just to name the simplest outsourcing team construct. The standard request-for-proposal process is the beginning, and a final scope of work (SOW) and master service agreement (MSA) is the end of the engagement/contractual phase, whereby the work of the functional team is initiated and the project team begins to coalesce.

In many large pharmaceutical companies, vendors are audited by QA as a matter of routine every other year, but

the inner workings of a preferred vendor are not known by the project manager until the project is ready to begin. In small companies, vendors may never be audited prior to use, especially if the company is financially constrained, because the resources and/or expertise are not in place, or the board member or executive who insisted the vendor should be engaged immediately because of prior experience with them has engendered enough trust or temerity that no questions are asked. If the vendor is audited, the information learned in the audit may be of significant value to the operational team, but only if shared.

Until very recently at most companies, the complete documentation that would serve to define governance after execution of the MSA/SOW might have been a standard operating procedure on vendor selection and management, and perhaps a project plan, which might have been comprehensive, or merely created to serve as a placeholder to "check the box." Meeting minutes documenting CPM, vendor oversight, and identification and correction of performance issues with vendors from the earliest stage onward could be voluminous, or could just be an agenda with handwritten notes stuck in the files (or nothing!). Likewise, oversight and quality plans were not widely in use until recently, so how decisions at every level were made for an ongoing trial, except for reportable safety events, might not have been considered at all, or at best would have been determined only through coordinated excavation within the files.

If gaps existed in how outsourced projects were managed in those earlier days, no one can really say, because the specifics of vendor governance and oversight typically were not "pressure tested" unless there was a regulatory inspection. Thus, our second major suggestion to better understand the potential gaps that could be seen in a regulatory audit is a very focused, "inspection readiness" exercise to look at the outsourcing of a clinical trial using a systematic approach. Initiating this type of

vendor oversight-focused gap analysis would not only highlight potential risks on a current trial, it could serve as a risk mitigation plan for future trials.

Using the recently released FDA *Compliance Program Guidance Manual* as a tool to conduct the gap analysis would be useful for highlighting the areas of concern. It could also provide invaluable insight for leveraging investments in time and resources to train inexperienced managers. Alternatively, the sponsor could utilize the tools mentioned above for a retrospective check, with the goal of augmenting the existing infrastructure and creating the company's standard toolkit to better manage all vendors going forward.

Conclusion

There has been a stronger focus and an increase in sponsor/monitor inspections in recent years that point to a significant increase in scrutiny by regulatory agencies of this key relationship and the methods by which quality is assessed

throughout the relationship. Meanwhile, sponsors are now more likely to be formally addressing risk management, and those on the leading edge are looking into their internal practices in order to find and close performance gaps through a systematic retrospective analysis of their internal oversight and quality practices in regards to their existing vendor relationships. Prospectively, sponsors are developing quality plans and oversight plans to clearly define their expectations of how this relationship will be more closely managed. How will you initiate this in your organization?

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