Third-party quality oversight: designing an optimal programme

John Wilson explains how sponsors can gain more confidence in clinical trial data through quality oversight.

Pharmaceutical and medical device clinical trial sponsors are ultimately responsible for the integrity of the data generated by their third-party vendors. This is the central issue that necessitates the application of quality oversight to today's clinical trials. Nowhere is this more evident than in the case of recent US Food and Drug Administration warning letters issued to top-quality pharmaceutical firms for failure to oversee the activities of their vendors. This article focuses on the US but should also be useful to companies in other markets.

Problems don't have to reach warning letter status to attract the attention of regulatory authorities. FDA investigators are asking how sponsors oversee the activities and assure the quality of their clinical vendors. This is a legitimate question and one that third-party quality oversight answers.

Why third-party quality oversight?

Third-party quality oversight provides an unbiased and objective assessment of the vendor contract research organisation work effort. The bias that may exist in a long-term relationship between a sponsor and its clinical trial CRO makes it difficult for the sponsor to adequately assess the vendor CRO's performance. Third-party quality oversight eliminates this bias.

What quality oversight is not

Quality oversight is not an additional quality product, but rather a directed response to pressure from the FDA to ensure the integrity of clinical data. The principles apply to vendor oversight of medical device and *in vitro* diagnostic clinical trials as well as to pharma trials.

An optimally structured quality oversight programme should not result in any duplication of effort on the part of the sponsor. The sponsor must keep in mind that quality oversight is about processes and adherence to contractual and regulatory requirements. It is not about co-monitoring or re-auditing the study.

Quality oversight v clinical QA

There are four distinguishing characteristics between quality oversight and clinical quality assurance.

Firstly, clinical QA addresses quality across the entire spectrum of a sponsor's work. Quality oversight is focused only on the work that is contracted to a third party. Secondly, clinical QA assures the integrity of the clinical data, whereas quality oversight provides an assessment of how a CRO is doing its job. Thirdly, clinical QA is conducted as an assessment at one point in time. Quality oversight is performed over the course of the trial and allows for real-time corrective and preventive action. Finally, clinical QA is provided by the sponsor as a function within the organisation. Quality oversight involves an independent organisation, thus providing a totally objective assessment of the CRO work effort.

Optimal quality oversight programmes

Good business practices, to say nothing of current good clinical practice, dictate that when work is assigned to a vendor, that work should be performed consistent with sponsor expectations and contractual obligations. Exactly how this is determined differs from sponsor to sponsor, therefore, specific quality oversight activities, metrics and report formats can vary; however, there are some common denominators among optimal quality oversight programmes.

A driving principle of an optimal quality oversight programme is that the vendor CRO does not feel threatened by the CRO performing the quality oversight. This is where a small boutique firm can play a unique role. Choosing a CRO that is large enough to handle the project with regionally based, global quality oversight assessors, but that does not compete with the larger CROs is key. The CRO performing the quality oversight must be collegial with the vendor CRO, not competitive.

A quality oversight plan is critical. The plan, developed in consultation with the sponsor, should list the key processes for assessment and should outline the methods and timelines utilised in performing those assessments. Based on a risk analysis, what is most important for the trial? What primary and secondary endpoint data should be considered? Are all contractual obligations of the vendor CRO identified and measured?

The CRO performing the quality oversight should have extensive experience in good manufacturing practice as well as GCP in order to bring GMP quality methodology to the clinical process. The quality oversight team should be comprised of senior clinical research associates with significant experience in this type of activity. In addition, the quality oversight assessor must have a demonstrated ability to interface with more junior CRAs in a non-threatening manner.

Quality oversight assessors should observe, critically assess, and provide objective and unbiased feedback on the vendor CRO's clinical research associates' level of knowledge, experience and training for the specified trials. They should incorporate immediate onsite CAPA only when there is a need to ensure patient safety and provide clarification on protocol-specific guidelines and monitoring plans. To ensure consistency, the quality oversight provider should conduct a thorough internal review of all quality oversight reports to assure the sponsor that the visits are carried out in a methodical and consistent manner.

Two reports that provide hard metrics should be readily available. The first report, an internal report compiled on a regular basis, should contain a comprehensive, quantifiable analysis of high risk issues, and should be used to drive CAPA and provide management with real-time metrics. The second report, for use during FDA inspections, should be used to demonstrate to the FDA exactly what the sponsor, through third-party quality oversight, did to ensure that the CRO provided its services according to contractual and regulatory requirements.

What the future holds

The outsourcing of clinical trials is here to stay and a well-structured and appropriately conducted quality oversight programme will maximise the value of those partnerships.

Quality oversight fits the stated mission of the FDA's Clinical Trials Transformation Initiative: "To identify practices that through broad adoption will increase the quality and efficiency of clinical trials." Ideally, quality oversight will be accepted as a critical trial process by a large number of firms, thus increasing its positive impact.

Quality oversight, when applied in a structured, methodical manner, is aligned with the FDA's call for industry to be more innovative in its clinical trial work. A trial-specific, formal quality oversight plan could be an important component for any prospective trial review conducted under the agency's pilot initiative for adaptive clinical trials.

With the FDA placing increased scrutiny on outsourced relationships, a solid, metrics-driven quality oversight report can greatly facilitate the inspectional process, particularly when FDA investigators ask "How do you, sponsor, know that the CRO is doing what they are supposed to be doing?"

A longer version of this article is available on the RA Pharma website at http://bit.ly/oyuXAy and on the RA Medtech website at http://bit.ly/purldB.

John R Wilson, Jr, PhD, MPH, is senior vice president at Beaufort LLC, a clinical research organisation based in Norfolk, Virginia, US. Among other things, Beaufort offers quality oversight services.
Website: www.BeaufortCRO.com.
Email: jwilson@BeaufortCRO.com.