High Standards

Sponsors are increasingly seeking to reduce the costs of conducting clinical trials while adhering to strict regulations. One way of achieving this aim is by obtaining an unbiased assessment of a trial through a third party quality oversight programme

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Cost control is vitally important in a recessionary economy – and clinical trials are no exception. Sponsors are seeking ways to rein in clinical trial spending and, with some estimates putting monitoring at nearly 30 per cent of the clinical trial budget, it is little wonder that they are eager to ensure that their clinical trials are done right the first time (1).

The rise of third-party quality oversight is both a reaction to a weak economy and a directed response to FDA pressure on sponsors to ensure the integrity of clinical data. Costly delays in time-to-market can result if sponsors are unable to quickly and authoritatively respond when FDA and other regulatory investigators ask: "How do you know that your CRO is doing what they are supposed to be doing?"

Quality oversight helps companies identify and resolve clinical trial issues in real-time, so that they can avoid costly rework and reanalysis. Because it becomes a part of the clinical trial process, over time it reduces the total cost of quality.

Cost of Quality

What is the cost of quality? Contrary to popular belief, the term does not refer only to the cost of good quality (prevention and appraisal expenses) but it also refers to the cost of poor quality – that is, the cost of failure. The American Society for Quality defines the cost of quality as the combined costs of (2): investing in the prevention of nonconformance to requirements; appraising a product or service for conformance to requirements; and failing to meet requirements (2).

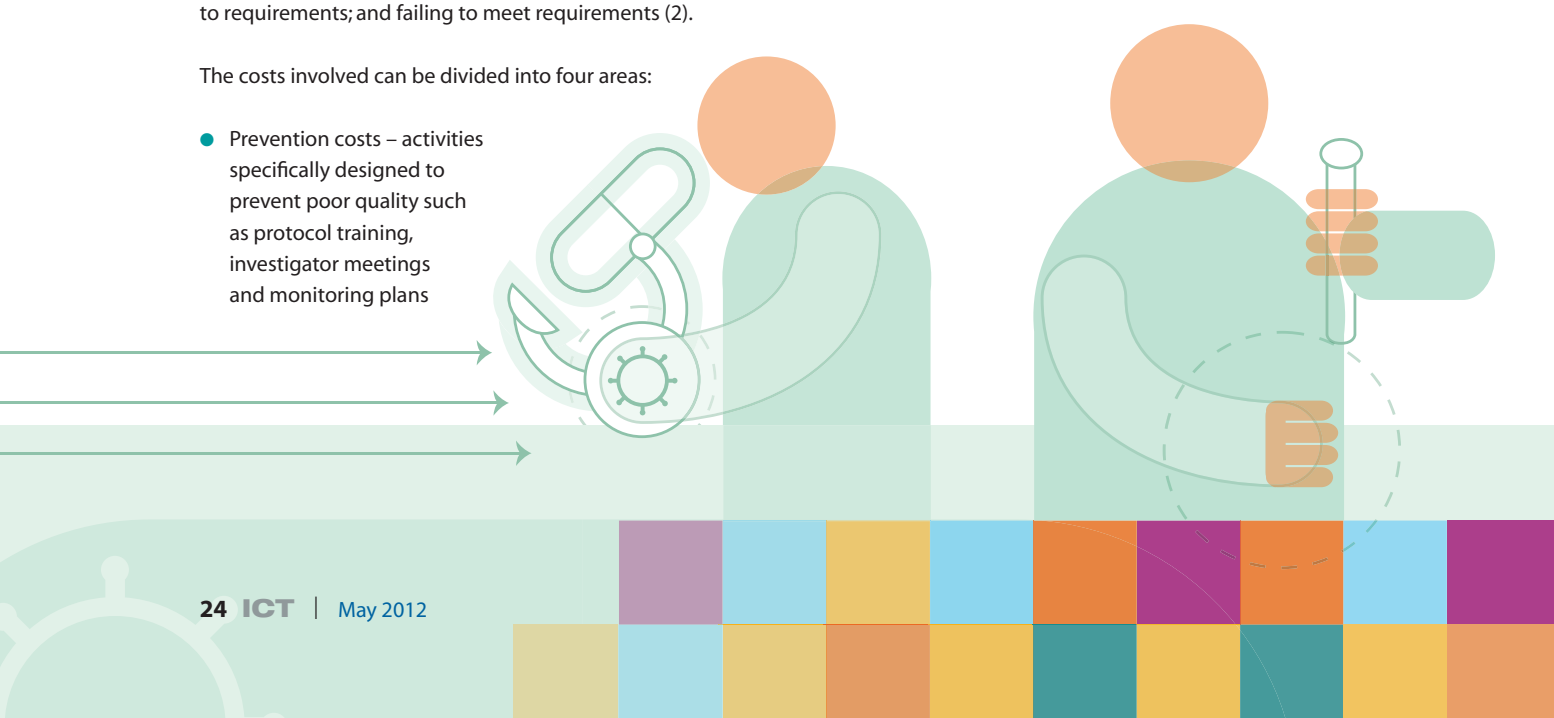
The costs involved can be divided into four areas:

- Prevention costs – activities specifically designed to prevent poor quality such as protocol training, investigator meetings and monitoring plans
- Appraisal costs – associated with measuring, evaluating or auditing clinical trials to assure conformance to quality standards and performance requirements. This includes the costs of in-process and final inspection/test, process audits and costs associated with running a clinical quality assurance department
- Internal failure costs – resulting from a clinical trial not conforming to requirements. Examples of internal failure costs are rework, re-inspection, re-testing, replacing subjects, hiring external rescue specialists and, most important, the opportunity costs associated with delays in product registration
- External failure – after a product has gone to market. There should not be external failure costs associated with clinical trials

How Can the Total Cost of Quality Be Lowered?

One might assume that the cost of poor quality and the cost of good quality are inversely proportional – one is raised in order to lower the other. This is not necessarily the case. The Six Sigma philosophy dictates that building quality into the clinical trial process can lower the cost of good quality without increasing the cost of poor quality.

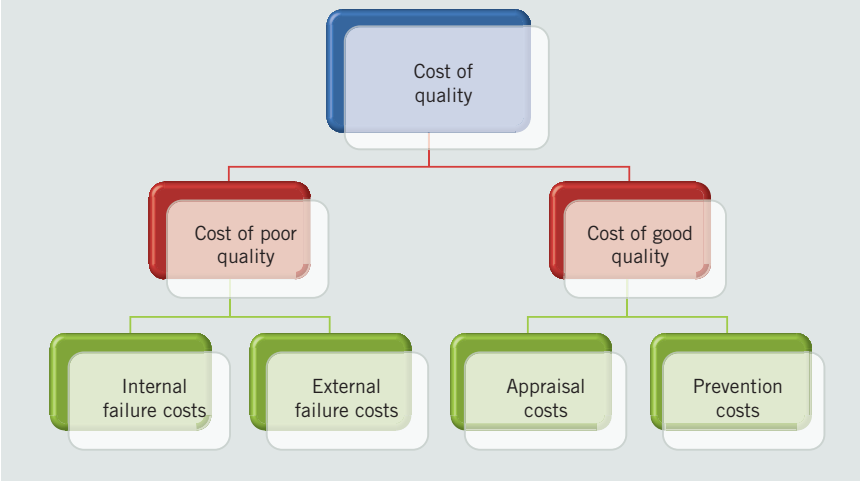
The reason is that, over time, clinical trials with better process performance will have significantly lower prevention and appraisal costs, and therefore will have a lower cost of quality. So how does one build quality into clinical trials? By implementing a quality oversight programme.



What is Third-Party Quality Oversight?

Third-party quality oversight provides an unbiased and objective assessment of the vendor CRO work effort. Sponsors utilise many processes to evaluate the quality of their clinical trial data; however, the bias that may exist in a long-term relationship between a sponsor and its clinical trial CRO makes it more difficult for the sponsor to adequately assess the vendor CRO's performance. Third-party quality oversight eliminates this bias and provides reliable information in real time.

Figure 1: Total cost of quality



Quality oversight is not a bolt-on, quality product. An optimally structured quality oversight programme should not result in any duplication of effort on the part of the sponsor. Quality oversight is about processes and adherence to contractual and regulatory requirements, not co-monitoring or re-auditing the study.

Quality oversight does not duplicate the function of clinical quality assurance (QA). There are four distinguishing characteristics between the two. 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, the value of clinical QA lies in the assurance of the integrity of the clinical data, whereas the value proposition of quality oversight is that it provides an assessment of how a CRO is doing its job according to the contractual relationship.

Thirdly, clinical QA is traditionally conducted as an assessment at one point in time and does not provide a continuous assessment over the course of the trial. Quality oversight, however, is performed over the full course of the trial. Therefore it represents simultaneous information exchange 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 utilises an independent organisation, providing a totally objective assessment of the CRO work effort.

Clinical Trials Transformation Initiative

The FDA and Duke University have joined together in a public-private partnership, the Clinical Trials Transformation Initiative (CTTI), to identify practices that increase the quality and efficiency of clinical trials. Due to growing concern about the effectiveness and efficiency of monitoring practices, the CTTI has made monitoring the focus of its first project (3). The organisation states that:

"Little empirical evidence exists to determine which practices best achieve the goals of trial monitoring…across a range of clinical trial settings. This lack of information is concerning, especially given the contention by some in the clinical research field that cumbersome monitoring practices contribute to more work and higher costs for clinical studies."

Figure 2: Six Sigma and cost of quality

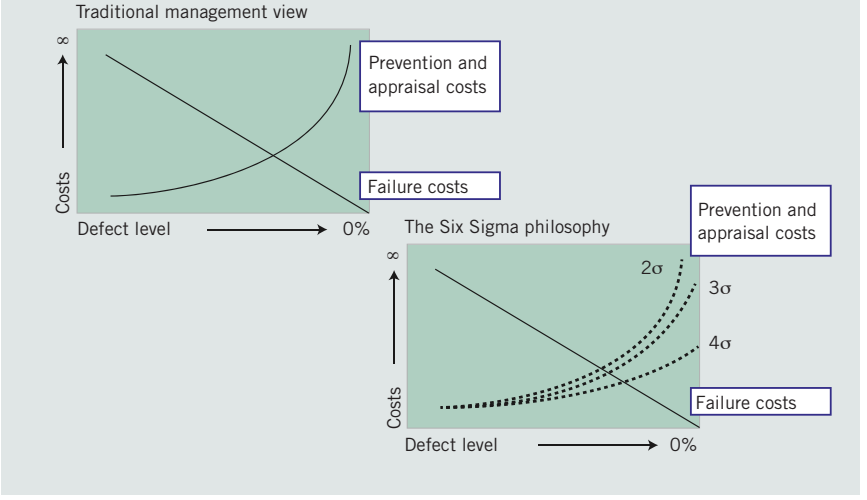


Image: www.isixsigma.com

The CTTI's primary recommendation was to "build quality into the scientific and operational design and conduct of clinical trials" (4). The results showed that to build quality into trials the "primary focus should shift from *post-hoc* monitoring/inspection to incorporation of quality into the scientific and operational design of a trial." CTTI believes that sponsors should "focus on what is important [including] unbiased ascertainment and analysis of study outcomes." The study also found that the "sponsor should institute metrics to prospectively ensure the quality of critical data."

Third-party quality oversight is the obvious answer. Both unbiased and metrics-driven, it incorporates quality into the clinical trial from the outset, while providing real-time results. Corrective and preventive actions (CAPA) can be put into effect immediately, giving the sponsor assurance that they have done everything possible to build quality and safety into their clinical trial.

Optimal Quality Oversight Programmes

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, independent role. Choosing a CRO that is large enough to handle the project with its own in-house professionals and regionally-based quality oversight assessors, but that does not compete with the larger CROs for any projects, is key. The CRO performing the quality oversight must be collegial with the vendor CRO, not competitive.

A Quality Oversight Plan and Team

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. From an operational perspective, the quality oversight team should be comprised of senior clinical research associates with significant experience in this type of activity. Only the most experienced, uniquely qualified CRAs should act as quality oversight assessors. 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.

Regular Reports

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 discovered at sponsor clinical trial sites, and should be used to drive CAPA and provide management with real-time metrics regarding CRO performance. 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. Regardless of format, the quality oversight report should utilise a detailed template that targets key areas of assessment in evaluating CRO performance and compliance.

Conclusion

Third-party quality oversight can help sponsors control clinical trial costs by lowering the cost of poor quality and by protecting against a delay to market due to regulatory concerns. Ensuring quality in clinical trials makes good business sense, no matter whether in a recessionary economy or boom.

References

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2. Campanella J (ed), *Principles of Quality Costs: Principles, Implementation, and Use, Third Edition*, ASQ Quality Press, pp3-5, 1999
3. Visit www.trialstransformation.org/projects/effective-and-efficient-monitoring/
4. Visit www.trialstransformation.org/Monitoring%20Project%20Results%20and%20Recommendations%20FINAL.pdf

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