Over the past few decades, the complexity of clinical trials has increased dramatically as has the obligation on sponsors to ensure that the study participants are adequately protected and the integrity of the study data is maintained to the highest standards. These obligations have commonly been translated as a need for frequent on-site visits and 100% Source Data Verification (SDV). Although 100% SDV is by no means ubiquitous, most approaches to meeting obligations on data quality are inherently dependent upon on-site monitoring and source data verification as the primary mechanisms to detect issues with data quality and site non-compliance.

The Limitations of On-Site Monitoring

Because of the emphasis on the Clinical Research Associate (CRA) as the key person for detection of non-compliance and scientific laxity, the frequency of CRA visits to investigator sites has become a surrogate marker for site quality and data integrity. The rationale has been, the more often the visit, the more certainty there is of a site’s conformance to the protocol and the greater the accuracy in the reported data. In actuality, visit frequency is probably only an indicator of sponsor due diligence, not necessarily of effectiveness in ensuring that the site will correctly interpret and execute the protocol. Furthermore, source data verification often only assesses the site’s attention to detail, not its clinical competency.

On-site monitoring is costly, and the dependence on the CRA to detect data quality issues and non-compliance leads to an interesting paradox: reducing monitoring will certainly reduce cost, but it is accompanied by a proportional decrease in source data verification, reducing the ability of the CRA to detect the very non-compliance they are looking for. In recognition of this limitation, most reduced SDV monitoring plans are a calculated compromise between reduced monitoring costs and the risk of failing to detect an issue. This paradox substantially limits the possible reductions in on-site monitoring and introduces risk which many sponsors are not willing to accept.

On-site monitoring by CRAs has another limitation: each CRA has a very narrow perspective and can only make comparisons between the sites in his or her purview or between individual data points that are maintained in his or her memory (not to mention the natural variability in skills from one person to another). There is generally a minimal cross site perspective, except for the smallest trials, and no comprehensive cross trial perspective.

In combination, these limitations prevent dramatic reductions in SDV and suggest that an alternative may be needed to reduce costs and improve detection of data errors. In recognition of this, the FDA guidance document was published to make clear that they support alternative approaches to monitoring, with specific support for centralised, risk-based monitoring. The guidance states, “Several publications suggest that data anomalies (e.g. fraud, including fabrication of data and other non-random data distributions) may be more readily detected by centralised monitoring techniques than by on-site monitoring.”

There is growing evidence to show that centralised monitoring may be more effective in detecting non-compliance and data fabrication than even 100% SDV. There are also certain critical deviations that only become apparent when viewing the summary data with a broader perspective than can be held by any single person operating in the field. One method of risk-based monitoring is described below, including real-life examples of the errors that have been detected, demonstrating the viability of this alternative solution.
A Risk-Based Monitoring Model

With Case Report Forms (CRFs) now being completed electronically, it is possible to import CRF data into a central repository, along with the full complement of operational, quality, efficacy and clinical safety data from all sites, across multiple studies. With respect to risk-based monitoring, software algorithms can scan the data for specific, scientifically-designed triggers that suggest something is amiss. The key is to determine which metrics (and there are a multitude to choose from) correlate with increased site risk and to monitor the incoming data for those risks. The metrics should be designed to detect deviations in real time, impartially and with absolute accuracy. It should be recognised that there are subtle different types of risk, and different metrics are needed to monitor each type of risk; a given site may perform normally in some areas, but not in others.

The system can then be instructed to compare and contrast data from across sites and indicate outliers above a pre-determined threshold or results that don’t fall into the expected pattern. It is then a matter of knowing what to make of the findings. A number alone—or a point on a graph—has little meaning until it is put into context by somebody with a deep understanding of the underlying data. For example, if a site has a higher than expected adverse event reporting rate, is that evidence of exemplary attention to detail or a worrying example of unusual behaviour? The answer, in our experience, is that it depends but is not infinitely variable. In other words, there are specific, well-defined characteristics which indicate concern and other well-defined characteristics which give comfort that the site is a high performer. A clear definition of those characteristics is needed to ensure that the resulting assessment of risk is consistent and repeatable across studies and analysts.

The next critical step is to use the finding to direct a course of action. With clear information on a site’s specific risk, CRAs can be instructed to visit the site and take specific corrective action. This means that the CRA’s efforts are targeted toward those sites that are at risk (but only when needed), and focused on the problems at hand, often down to a patient level, making very efficient use of their time.

Surfacing the Big Issues

Our experience is that the combination of automation, analytical and visualisation tools, human intelligence, and established processes for corrective actions has proven to be very effective and efficient at uncovering major sources of risk that could, and would, jeopardise the integrity of the data, and hence of the trial itself. These include:

- Fraud and fabrication of data.
- Unreported or inaccurately reported data.
- Protocol deviations, ranging from mild to severe, that can be related to poor training, questionable competency, or a simple misunderstanding of the protocol.

The following graphs illustrate some real-life examples. The first relates to an analysis of blood pressure readings in a mid-sized diabetes study where our automated system flagged several sites for reduced variability. Figure 1 shows the results for one of those sites, 507, which had unusually low data variability and strong evidence of number preference. They also had mathematically and clinically improbable heart rate data (not shown), highly suggestive of fabrication.

Figure 2 shows an analysis for adverse event reporting rates in the same study. Once again site 507 was identified as a site of concern due to an unusually low reporting rate.

The combination of a low adverse event reporting rate, low blood pressure variability and potentially fabricated heart rate data meant that site 507 was classified as extremely high risk. Identification and analysis of the site took less than 15 minutes and a subsequent CRA visit revealed systemic failings at the site.

Figure 3 shows a patient recruitment analysis used to detect sites which are unusually successful or underachieving. The analysis clearly identifies site number 123450197 with an unusually high randomisation rate and high subject volume—a signal that it was doing something out of the ordinary. Review of other risk analyses related to this site (not shown) clearly demonstrated that the site was conducting inappropriate prescreening and corrective action was initiated.
Benefits of a Centralised Process

When a risk-based monitoring system incorporates a centralised, real-time overview of the data with well-entrenched risk detection and mitigation strategies, the result is one of the industry’s most effective tools for managing a clinical trial, proactively. Such a system:

• Identifies problems early so that they can be remedied quickly, protecting patients and preserving the overall integrity of the study.
• Improves the efficiency of CRAs, as they concentrate on the sites that need help and allow competent sites to proceed without unnecessary interference.
• Dramatically improves the reliability and verifiability of study data, avoiding unpleasant surprises upon regulators’ review.
• Has the potential to reduce overall monitoring costs in most studies.

Despite the relative immaturity of risk-based monitoring, preliminary data suggests that this solution is providing equal or superior results to the classic 100% SDV process. Many companies are shifting to this more efficient model with several large studies well underway using the methodology.

Given that the FDA “encourages greater reliance on centralised monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring,”4 the path is clear for companies to take full advantage of what technology can offer. With the proper system, risk-based monitoring is an effective way to meet the growing challenge of ensuring that the study protocol is being correctly interpreted and executed, resulting in proper patient care and valid study results whilst simultaneously reducing clinical trial costs.

For more information go to:
http://www.iconplc.com/technology/iconik/

References
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