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Risk-Based Monitoring Across Six Dimensions

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The system of performing site monitoring visits every six to eight weeks with 100% source data verification (SDV) is slow, costly and ineffective. With its August 24, 2011 draft guidance document, "Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring," the FDA has blessed risk-based monitoring (RBM) as a way to achieve better regulatory compliance and higher data quality, and do it faster and cheaper than can be done with traditional methods.

The basic concept of RBM is to focus attention on the data, documents and processes (in this article, collectively, "data") that really matter. The military strategist, Sun Tzu, wrote that to defend everywhere is to defend nowhere. The same principle applies to defending against regulatory noncompliance and erroneous data.

The central question of RBM, as in military strategy, is to decide what to defend, i.e., what data to monitor. How should a study sponsor or CRO (or site) allocate its scarce resources to ensure regulatory compliance and data quality? The military commander must assess the risk of attack across the dimensions of space, time and force. Similarly, the study manager must assess the risk of error across multiple dimensions:

- **Who.** Which sites should be monitored?
- **What.** What data should be monitored?
- **Where.** Where should monitoring be performed (on-site or remotely)?
- **When.** When should monitoring occur?
- **How.** How should the data be tested?
- **Why.** Why are the answers to the above questions correct?

Initial monitoring intensity (amount, frequency and location) should reflect the overall risk of the study. Observation, statistical analysis, and judgment can identify trends, anomalies and outliers. Over the course of the study, as perceived risks change, the intensity of monitoring should adapt accordingly, so resources are always applied to maximum effect. While decreasing cost is a major RBM benefit, in some cases, monitoring intensity can be higher than normal, e.g., for a problematic site.

The monitoring plan documents the strategy, requirements and procedures for conducting monitoring visits, setting the standards for visit frequency and level (percentage) of data review. In some cases, the level may entail 100% SDV. However, even that level of review does not guarantee data reliability; training or some other activity might be the best way to reduce risk.

Trials conducted for FDA marketing applications (NDA or PMA) generally require 100% review of critical regulatory elements (eligibility criteria, informed consent, adverse events, data related to study endpoints, etc.). However, with a risk-based model, other data fields (e.g. reimbursement, demographics) may only require a 30% or 40% level of review.

Who should be monitored?

There are four types of investigators: the proven, the plausible, the potential, and the problem.[1] Proven investigators pose relatively low risk because they have a history of successful trial conduct with the sponsor. Plausible investigators claim previous study

experience with other sponsors, so pose intermediate risk. Potential investigators are new to clinical research, so pose relatively high risk. Problem investigators have demonstrated that they should be avoided, so pose a significant risk. At the beginning of a study, rate each investigator and site for risk, based on the medical condition being studied, protocol complexity, experience with similar trials, and other factors. The situation at a site may have changed recently. For example, recent personnel turnover poses a relatively high risk.

What data should be monitored?

Data that are critical to the reliability of study findings, are essential for support of a regulatory application, or are difficult to collect accurately pose relatively high risk. Critical data that deserve the most attention relate to eligibility criteria, informed consent, primary and secondary endpoints, safety, investigational product accountability, HIPAA compliance, and data that would be the focus of an FDA inspection. Non-core data, such as logs, laboratory reference range, financial disclosure forms, and CV's pose lower risk and require less stringent monitoring. A site might be very good at data collection but lack experience with regulatory documents, so the focus of the monitoring should be adjusted accordingly.

It is important to monitor data that indicate the presence of a systemic risk, as opposed to random human error.[2] For example, if the instructions for an assessment are ambiguous, inter-rater reliability may be unacceptably low, jeopardizing the entire study. If site performance improves or diminishes, the amount of data monitored should change accordingly.

Where should the monitoring be performed?

In general, review critical data on-site to confirm data integrity. Less-critical data can be monitored remotely, eliminating travel-related costs and leveraging technology. The risk of overlooking a forged signature on an informed consent form is lower when the original document is inspected on-site. On the other hand, a remote monitor does not have to deal with possibly inefficient working environments or jet lag. If site performance improves or diminishes, the percentage of data monitored on-site should change accordingly.

When should monitoring occur?

If site performance improves or diminishes, monitoring frequency should change accordingly. Trend analysis may reveal problems; for example, slower data entry may indicate an increase in site workload. An increase in adverse events or out-of-window visits suggests the need for more monitoring; a decrease suggests less monitoring will be sufficient.

How should the data be tested?

The options for testing data at the research site are limited to variations on manual inspection. However, informed consent signatures can be compared, investigator signature dates on lab tests checked against the office calendar, etc. Site monitors with more or less expertise can be employed.

Remote monitoring does not permit inspection of original paper documents like visit worksheets, but it does facilitate automated comparisons and analyses to identify trends, anomalies and outliers. Automation can also support more efficient review and thus a higher level of data review at a lower cost.

Monitoring can affect site behavior. For example, as a site learns which data are being monitored, it might raise the quality of that data and possibly neglect other data. Or, it might lower the quality of the data being monitoring because it can count on the monitor to find any problems. Discussing data quality expectations and results with the investigator and study coordinator can help mitigate this issue.

Why are the answers to the above questions correct?

Some studies carry a higher degree of risk than others because serious adverse events are more likely, study procedures are more complex, the study has high public visibility, the drug or device class is new, or the FDA has indicated a high level of concern. Other studies are low to medium risk because the potential health effects are modest, the FDA's attitude is more circumspect, the investigator has a solid track record, or the regulatory designation is not PMA or NDA.

A study team could informally set monitoring levels based on experience, but a better approach is to form a "risk management team" that provides a wide range of perspectives, including clinical operations, medical affairs, safety, quality, data management, biostatistics, information technology, finance, and, of course, risk management. This team can tailor a statistical model based on comprehensive data from past studies plus real-time data from the current study. The model should objectively and systematically optimize monitoring to achieve the organization's risk/resource objectives. If the model does not completely capture every variable, the risk management team or the study team can use their judgment to make manual adjustments.

If resources are unlimited, frequent 100% on-site monitoring might be ideal. On the other hand, if resources are limited — as they usually are — judicious allocation will minimize risk by focusing resources where they are most useful.

Conclusion

Given the intense pressures on pharmaceutical and medical device companies, wasting valuable resources on 100% SDV is no longer feasible. The FDA has opened the door to more intelligent monitoring strategies based on risk assessment and management. Adopting RBM is essential to move the clinical research enterprise forward. Not only will RBM help us achieve better regulatory compliance and higher data quality, faster and cheaper than with traditional methods, but it will also change the very way we think about clinical research, with significant impacts across the entire process, from test article prioritization to protocol design to study conduct to FDA review. However, effective RBM requires a fundamental understanding of risk and how to manage it in clinical studies.

References

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