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Adaptive Monitoring: Risk-Based Monitoring and Beyond

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In August 2011, the FDA and EMA issued a guidance and reflection paper, respectively, encouraging biopharmaceutical companies to consider risk-based monitoring (RBM).[1,2] Since then, there has been an exponential increase in interest in RBM. However, the industry is cautious about implementing RBM plans that regulators might determine, after the fact, to be inadequate. Given the lack of specific regulatory guidance or industry consensus about how to implement RBM, this caution is justified.

Figure 1. Types of SDV Systems

Partial SDV verifies less than 100% of source data, the defining feature of RBM.

Declining SDV starts by verifying 100% of source data at a site and then reduces the percentage if the site meets specified quality levels.

Random SDV randomly selects elements to verify and is best used to examine low-importance data that otherwise would not be verified at all.

Tiered SDV divides data into levels based on perceived importance and assigns different percentages of SDV to each tier. In practice, most RBM plans utilize a tiered approach, at least implicitly, by performing a very high percentage of SDV on primary and secondary endpoints and safety data, and lower percentages on noncritical data.

Triggered SDV verifies data when observed values for that data or other indicators deviate from the acceptable range.

Targeted SDV precisely selects data points for SDV based on rules and analytical methods.

Mixed SDV combines two or more of the above approaches.

Nevertheless, the benefits of RBM are so substantial that we would be foolish not to move forward. Recently, the TransCelerate Biopharma consortium of pharmaceutical companies published a white paper that describes a wide variety of RBM techniques.[3] This flexibility is necessary, given differences in sponsor priorities, individual studies, and limitations in the capacity of different electronic data capture (EDC) and clinical trial management systems (CTMS) to generate the measures necessary for implementing many features and to do so in a timely manner.

This article discusses RBM as one element of a more comprehensive system: "adaptive monitoring." RBM is typically viewed as an "open loop" system that focuses on establishing and possibly adjusting monitoring plans, without much attention to the question of what corrective actions should be taken based on the monitors' observations. In contrast, adaptive monitoring is a "closed loop" system that considers RBM as just one element — albeit a very important one — in a comprehensive approach to detecting and correcting problems and optimizing the adaptive monitoring system itself as a study progresses.

The adaptive monitoring system discussed in this article been refined over the past eight years. It has been used successfully to monitor and manage trials in a variety of indications and phases, with sample sizes ranging from 50 to 13,000 subjects. It goes beyond risk-based principles and can be tuned to achieve both efficiency and data quality.

Figure 2. Centralized Techniques that Supplement SDV

Statistical Monitoring utilizes statistical principles to identify patterns and outliers that might indicate problems and trigger SDV.

Rules-Based Analytic Monitoring searches the study database for violations of rules that might indicate problems and trigger SDV. For example, a rule might be that no study subject's blood pressure should be the same at four consecutive visits.

Beyond risk-based elements, other important data-driven and algorithmic components enable the study team to customize the system to meet the unique needs of each study.

While adaptive monitoring is flexible, changes must be implemented systematically. This is true both for pre-specified corrective actions triggered by deviations from AQLs and changes based on an evolving understanding of trial trends and issues. If a problem is observed, it is important to look for it elsewhere, not only at the same site but also at other sites. The monitoring process must be managed based on objective results as measured during the study by specific risk indicators that correlate with site performance and data quality.

The guidance and literature on RBM reflect a variety of approaches, with source data verification (SDV) the single most important differentiator. Figure 1 defines terms commonly used to describe various SDV methods. Figure 2 defines two analytical methods that can be used to supplement SDV. Figure 3 defines measures commonly used in RBM and/or adaptive monitoring.

Figure 3. Definitions of RBM and/or Adaptive Monitoring Measures

A given measure can have different uses in different studies and, in a given study, multiple functions, which might change over time.

Measure. An observed or calculated value (e.g., 7.2, yes/no, high/medium/low) related to site performance.

Metric. A measure.

Indicator. A metric that, in a specific study, provides a meaningful signal about some aspect of site performance that affects the likelihood of study success or failure.

Key Performance Indicator (KPI). One of a small number of indicators important for assessing site performance or data quality in a specific study.

Index. A composite indicator composed of multiple individual indicators, which are sometimes weighted for their expected importance, preferably based on objective data.

Site Performance Index (SPI). An index that provides a summary measure of site performance, including high-quality data.

Risk Factor. Any measure or consideration that affects the likelihood of successfully executing a study.

Risk Indicator. A performance or quality indicator.

Predictor. An indicator that can be used to predict, with some accuracy, some aspect of future site performance.

Indirect Indicator. An indicator that does not measure a thing but measures something correlated with that thing. For example, if it takes a site a long time to enter data, there might be a problem with the quality of that data.

Acceptable Quality Level (AQL). The acceptable range (typically from zero to a "low" positive number) for a quality indicator.

Adaptive Monitoring System Features

The following are essential features an adaptive monitoring system:

Near-Real-Time Monitoring. Timeliness is a critical element of any adaptive system. Any system, and especially RBM systems that rely primarily on paper documentation, site visits, and periodic statistical analyses, are inherently unable to quickly identify and correct problems. Adaptive monitoring systems should collect data, generate indicators, and take or recommend corrective or preventative action in near-real-time (within 24 hours). Site visits are, of course, periodic, but electronic data can be analyzed and acted upon within a daily cycle.

Usability. While RBM is complex and adaptive monitoring utilizes sophisticated algorithms, the user interface for the system must be simple and understandable to the study team. For example, it should show how an improvement in quality as measured by a site's SPI would lead to a reduction in site monitoring activity. The detailed calculations behind the change need not — and, in most cases, should not — be part of the user experience.

Quality and Economy. A primary objective of RBM and adaptive monitoring is to decrease the cost of monitoring. Equally important, if not more so, are the objectives of reducing risk and improving the quality of the data and other performance indicators. High-risk studies and high-risk sites might require more monitoring than normal. On average, however, the intelligent use of monitoring resources should reduce risk, improve quality, and save money. We must do whatever it takes to reduce risk and achieve quality, but no more. Eventually, FDA and EMA are more likely to question a brute-force 100% SDV monitoring plan than an RBM plan based on thoughtful consideration and effective management of the risks involved.

Risk Indicators. The initial monitoring plan should be based on a thorough risk assessment that considers the requirements of the protocol, the vulnerability of the population, known risks associated with the investigative product or class of drug, the operational challenges involved in executing the study, and so on. As a study progresses, experience will indicate adjustments to the risk assessment, and these adjustments should be reflected in the monitoring plan. The risk of specific sites will certainly change as they gain more experience with the protocol. Broader risk assessments may also change based on overall adverse event severity, protocol amendments, and so on.

Prior experience with a given site is invaluable, but only as a starting point in a continuously adapting process. The past does not necessarily predict the future, and a rigid plan based on experience can lead you astray. The monitoring plan must then adapt, based on a wide range of observations during the study. For example:

- A central monitor might detect a peculiarity in the lab data for a site.
- A site monitor might encounter an issue with the delegation-of-authority log.
- A statistical analysis might flag anomalies in patient-reported data at a site.
- The study coordinator might leave and be replaced with a different one.
- The medical monitor might read an article about a new safety risk in the study drug's class.

While most risk indicators should be quantitative and based on data from the CTMS and EDC systems, some should be based on qualitative measures like the occurrence of protocol deviations and serious adverse events. Risk indicators that do not depend on physical visits to the site are very useful because they can be measured frequently. Indirect measures are also very useful because of their objectivity. For example, the time required for a site to enter data is an indirect, objective measure of quality since speedy entry cannot be faked and slow entry is often correlated with quality problems. Some risk indicators should not be revealed to the sites. For example, a site can solve a missing data problem by entering fictitious data, but such data often reveals a statistical pattern that points to a problem — under time pressure, the study coordinator might enter identical blood pressure data for several study subjects, all on the same day.

Key Performance Indicators (KPIs). EDC and CTMS systems can capture an immense amount of data. An effective adaptive monitoring system should distill this data down to 30 to 40 risk indicators, of which 10 to 15 can be considered KPIs. Based on experience within and across studies, the choice of KPIs can evolve to generate better results.

The purpose of a KPI is to identify a pattern of problems that should be corrected and prevented, not specific instances like data entry errors. KPIs can be categorized by domain, e.g., data, procedures or safety. Each domain should have adequate representation. The KPIs within a given domain indicate problems and determine corrective actions within that domain. For example, a sudden change in the range of values reported for an assessment might indicate a change in personnel, with an untrained new person performing the

assessment. Obviously, the new person should be trained immediately. The sponsor might also create new KPIs to discover such anomalies in similar assessments.

Site Performance Index (SPI) A study's SPI provides high-level assessments. Changes in the index can automatically drive changes in the monitoring plan, such as visit frequency or percentage of SDV. Changes in individual risk indicators can automatically drive other changes in the monitoring plan, such as the type of data to be verified.

The SPI should consist of about five to 10 KPIs. This number is usually sufficient to predict site performance and data quality. However, the most predictive risk indicators vary study to study and change over time, so the composition and weighting of SPI components must evolve accordingly, based on indicator correlations with observed site performance and data quality, and with an emphasis on preventing future problems, especially recurring problems. These changes can be made automatically, based on prespecified performance levels, and periodically reviewed, as well.

Acceptable Quality Levels (AQLs). Perfection is ideal but seldom possible in clinical research. 100% SDV is a failed approach to achieving perfection. A study's AQL should be high but realistic, considering factors like the complexity of the trial and the importance of each specific KPI, e.g., critical vs. non-critical data.

Patterns and Trends. Statistical analysis of patterns and trends is a powerful tool for identifying possible problems. However, sufficient data is required for the analysis to be meaningful. Standards can be established over the course of multiple studies, but most issues do not emerge with statistical significance until a study has been underway for several months, and often much longer, depending on study specifics. Analysis of patterns and trends is best used to identify and correct systematic problems like unclear instructions in the protocol.

Corrective Action. Adaptive study designs require pre-defining exactly what adjustments will be made based on pre-specified events. Otherwise, bias could be introduced into the study's results. RBM and adaptive monitoring are not subject to the same scientific restrictions, so the adjustment can be refined in near real-time as the study progresses, based on a continuous automated assessment of correlations between individual indicators and performance with a linear multivariable model.

Crossing an AQL threshold should consistently trigger immediate corrective action, as specified in the monitoring plan, such as informing the site of the problem and how to correct it. The corrective action should be tracked to completion. Its impact can be measured and thus become more predictable. If necessary, additional action can be taken. The AQL for each KPI defines the point at which the value becomes unacceptable and corrective action should be taken.

It is essential to measure the impact of corrective actions. Some actions intended to be corrective might even be counterproductive. For example, adding range checking to an EDC data entry field might reduce data entry errors, or it might lead harried study personnel to fudge the data to satisfy the constraint.

Dynamic Resource Allocation. The goal of adaptive monitoring is to employ monitoring resources where they are most useful, taking into account the relative importance of different types of data, the cost and effectiveness of different monitoring techniques, the availability of monitoring personnel, and the study's unique characteristics. Dynamic resource allocation requires flexibility to adjust the type, focus, frequency and intensity of monitoring throughout the study. In particular, centralized (remote) monitoring has emerged as a useful and cost-effective component of RBM or adaptive monitoring, when implemented in an integrated approach that appropriately blends centralized and on-site monitoring.

In a small study, it may be practical to make simple adjustments manually with a reasonable degree of precision. However, a study of any significant size and RBM complexity requires automated processing and adjustments. The role of the study manager changes from directing specific adjustments to managing the automated system for making the adjustments, while looking for ways to correct and improve the system.

Study Management. "Adaptive monitoring" understates the role of an adaptive monitoring system. Data quality is just one aspect of site performance and monitoring just one tool for managing a study. Adaptive monitoring is also useful for managing other study objectives, such as subject enrollment and regulatory compliance. It can also trigger actions other than adjustments to the monitoring plan. For example, high scores can trigger rewards like a congratulatory telephone call from the study manager. Low scores can trigger retraining personnel, amending the protocol, or recruiting additional research sites.

By aggregating SPIs across sites, the overall health of a study can be measured and tracked. Normally, scores improve as sites learn how to deal with the challenges specific to each study.

System Requirements. Full implementation of adaptive monitoring requires near-real-time capabilities often lacking in current EDC and CTMS systems:

- Capture direct and indirect measures of data quality within 24 hours after events in the field (when something happens, *not* when source data is entered and certainly not after entry into the EDC system).
- Assure proper tests and procedures, e.g., EKGs, have been performed.
- Interpret reporting of screen failures and adverse events (or lack thereof) for evidence of proper use of inclusion/exclusion criteria and appropriate and timely reporting of safety information.
- Update and track KPIs.
- Identify anomalous trends and patterns that might indicate problems at a site or with a study.
- Pinpoint specific issues that can be addressed specifically.
- Collect and process substantial performance- and quality-related data without visiting the sites.
- Continuously and automatically adjust the monitoring plan, down to the specific data to review at a specific site visit.
- Automatically recommend corrective actions for the site to perform.
- Record, track and measure the effect of corrective actions.

The Adaptive Monitoring Process

The steps in the adaptive monitoring process are as follows:

1. Identify and assess risk factors.[a]
2. Specify risk indicators and set AQLs.[a]
3. Specify the starting frequency and intensity of field monitoring.[a]
4. Specify an initial target SPI.[a]
5. Continuously measure and evaluate risk indicator scores.[b]
6. When a problem is detected, generate one or more corrective actions, informing the study coordinator, site monitor, or other person what needs to be corrected and exactly how it should be corrected.[b]
7. Update SPI scores.[b]

8. Update the SPI calculation based on the indicators that the system identifies as most predictive of a strong SPI.[b]
9. Assess SPIs to allocate monitoring resources across sites and adjust the monitoring plan for each site.[b]
10. Analyze patterns and trends.[c]
11. Based on this analysis, take corrective action, whether pre-specified and triggered or manual, where appropriate.[c]

Notes:
a. Manual process
b. Automatic or mostly automatic process
c. Manual and automatic process

Adaptive Monitoring and the CRA's Role

With conventional, 100% SDV monitoring systems, monitor productively is usually measured by the number of source data fields verified per day. This metric is useful for scheduling site visits but misses the point of monitoring: The purpose of monitoring is not to verify X number of data fields; it is to ensure high quality data. The true measure of monitor performance (in the data quality domain) is whether the monitor's sites produce data of high quality.

We know that 100% SDV does not consistently accomplish this objective. Why not? With traditional monitoring:

- It is hard to motivate site monitors to spend day after day carefully reviewing thousands of data fields, especially when they know that much of the data just doesn't matter. It is easy for site monitors to grow bored and lose focus.
- Feedback on data quality is slow and imprecise, with corrective action often ineffective and not followed up. Lack of improvement by the sites further demotivates the site monitor.
- Sites know they can rely on site monitors to catch any errors, so the sites can relax their own, internal quality standards.

In contrast, with adaptive monitoring:

- It is much easier to motivate site monitors to focus on activities that matter, vary from day to day, and are more likely to extend beyond SDV to training and other site management activities. With some of the time saved with adaptive monitoring, site monitors can employ their initiative and creativity to help sites improve their performance.
- Feedback on data quality is quick and precise, with effective corrective action and good follow up. Improvement by the sites further motivates site monitors.
- Sites quickly perceive that their level of quality matters. Low quality quickly generates corrective actions; high quality quickly generates positive feedback, reduces the length of monitoring visits, and changes their content to more productive activities.

Adaptive monitoring focuses site monitor attention on improving quality and provides the supporting tools: goals, metrics, corrective actions, and a tracking system. Adaptive monitoring also enlists the sites in helping site monitors achieve their mutual goals. It yields quick and precise indicators of site monitor performance. If necessary, study managers can take corrective action, such as training, to improve performance and justify increased compensation and promotion.

Table 1 outlines the differences in the site monitor's job with traditional vs. adaptive monitoring.

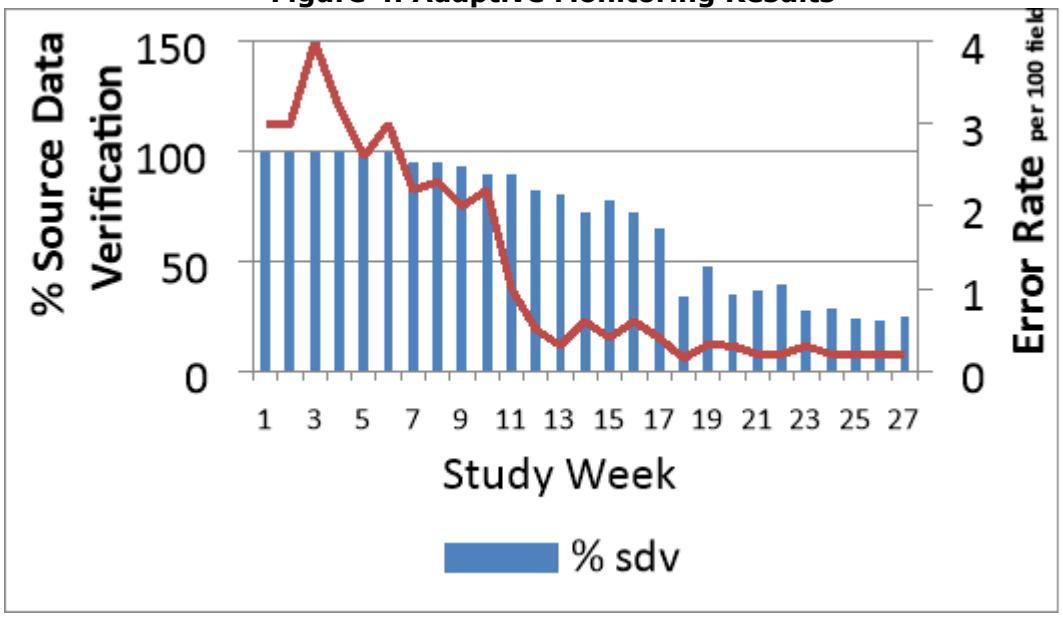
Table 1. Site Monitor Jobs

Traditional	Adaptive Monitoring
100% SDV	Varying levels and scope of SDV
Fixed site visit intervals	Variable site visit intervals
Less variety	More variety
Responsibilities mostly limited to checking data	Responsibilities include more mentoring, coaching and site management
Focus on finding and correcting errors	Focus on finding, correcting and preventing errors
Simple measures of performance	Complex measures of performance
Limited opportunities for advancement	More opportunities for advancement
Focus on activity	Focus on results
No guidance from performance goals and measures and corrective actions	Quick and precise guidance from performance goals and measures and corrective actions

Adaptive Monitoring Results

Figure 4 shows the dramatic effect of using an adaptive monitoring system to both reduce both SDV percentage and increase data quality in a 3,400-subject global study. While the results in this study were spectacular, impressive results have been achieved in 100% of more than 20 studies.

Figure 4. Adaptive Monitoring Results



Conclusion

Adaptive monitoring requires adjustments for CRAs that may not at first be comfortable or welcome. However, the transition to adaptive monitoring will transform the CRA's role, enabling CRAs to use their time more productively and shift the focus from checking and reporting after the fact to adjusting activities to meet quality goals. Perhaps the greatest shift in the CRA's role will be from passive to active, from checking data and correcting errors to managing toward goals required for the success of a study. As a result, CRAs will be better prepared to advance to higher levels of responsibility.

References

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