

Monitoring Clinical Trials with a SAS Risk-Based Approach

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ABSTRACT

With global regulatory encouragement, the life sciences industry is gaining momentum to embrace a risk-based approach to the monitoring of clinical trials. Typical to pharmaceutical organizations, there is wide variation regarding the level and speed of adoption, methodologies used, and technology employed to enable the process. The industry has a rich history of leveraging SAS® to ensure safety and efficacy of clinical trial data used for regulatory submissions, and SAS is well suited to extend its analytical approach to the operations side of clinical trials as well. This paper addresses the challenges related to aggregating critical data sources from both biometric and operational systems in order to assess study risk related to patient safety, data quality and the overall integrity and performance of the clinical trial. Analytical methods will be shared for identifying risk indicators through the application of business rules, visualization techniques, and advanced analytical models.

INTRODUCTION

In 2013, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) finalized drafts of recommendations for the pharmaceutical industry to embrace a more risk-based approach for the monitoring of clinical trials. These and other regulatory agencies have significant influence on the industry, especially when they support and encourage innovation and the use of improved technologies to advance the effectiveness of clinical trials. It should be noted that the FDA's "Guidance for Industry"¹ and the EMA's "Reflection Paper"² on this topic are not setting a mandatory regulation for monitoring trials using a risk-based approach. Rather, they are providing a path forward after withdrawing a 1988 FDA guidance for monitoring clinical investigations that suggested on-site monitoring was an effective way of ensuring quality data. In 1988, the effort of recording and checking data was a manual and primarily paper-based process, but with the development of electronic data capture (EDC) systems and other electronic medical recording systems, it was clearly time for a change in regulatory recommendations.

Some key points of these recommendations include:

- Improve the quality and integrity of clinical trial data
- Ensure patient safety
- Leverage technology and analytics to improve processes and reduce inefficiencies
- Understand and communicate risks associated with clinical trials to ensure trial safety and effectiveness

Pilot studies through industry groups such as TransCelerate Biopharma Inc. (TransCelerate) and the Clinical Trial Transformation Initiative (CTTI) have shown that employing risk-based monitoring (RBM) and a centralized review of data, uncovers more errors, even fraud, versus what can be captured through traditional source data verification (SDV) techniques performed by a monitor at investigator sites. In addition, patient safety has the potential to be improved since certain signals, like an increase in adverse events, can theoretically be detected sooner.

Regulators emphasize the need to maintain data quality and patient safety with RBM. Pharmaceutical sponsors and contract research organizations (CROs) have additional interests related to investment and potential cost savings with new process changes. On-site monitoring ranges from 15% - 35% of the cost of a trial and can serve as an incentive for an upfront investment in new methods, processes, training, and technology. Some CROs have been reluctant to adopt RBM, concerned about losing a major channel of revenue, but the industry as a whole is gradually adopting the risk-based approach.

Adopting RBM is challenging. It requires business process transformations, changes in technology, and perhaps even organizational restructuring. Organizations new to RBM have pilot examples available today but will have to determine the best approach that aligns with their business model for executing or overseeing clinical trials. The adoption of RBM doesn't mean the end of on-site monitoring, but it requires a balanced approach between central and on-site monitoring where certain factors still require SDV. From a technology perspective, there is no standard "out of the box" risk-based monitoring solution, so organizations need to align potential technology with their goals for approaching RBM.

Various terms are used to indicate methods of monitoring clinical trials that are not on-site methods (i.e., risk-based, data-driven, central, central statistical, and remote). For the purpose of this paper, the term risk-based monitoring or RBM will be used to indicate the general method of collecting data centrally across all sites in a study and assessing important study parameters used to determine data quality, patient safety, and clinical trial efficiency.

DATA SOURCES AND DATA PREPARATION

As with most business or analytical processes, one must start with the data. A crucial component of making risk-based monitoring successful is to bring together essential data elements that include clinical data (i.e., patient response) and operational data (i.e., site performance) from both past studies and the incoming study data. Leveraging the historical data along with current trial data enables the broadest perspective on overall risk.

DATA ACCESS

With many operational systems migrating to hosted environments (cloud based, 3rd party hosted, etc.), it is likely the data will not only be diverse but scattered. Source systems for electronic data capture (EDC), laboratory results (Lab), clinical trial management systems (CTMS) and integrated voice response systems (IVRS) are all examples of data sources that may require web services, FTP/HTTP methods, APIs or other import/export methods to access the remote data.

SAS provides a number of access methods to virtually any type of data. Direct database access engines and data step code provide basic data access, while SAS Clinical Data Integration (SCDI) provides an interactive graphical user interface for integrating clinical and non-clinical data. SCDI enables automation and repeatable processes for integrating data, metadata management across trials, and generation of code.

An advantage of prevailing EDC and lab software is that the data already conforms to Clinical Data Integration Standards Consortium (CDISC) data standards. For clinical data that is not CDISC formatted, SCDI can provide the mapping to those standards. Pre-built processes can also be deployed that take incremental form updates from the EDC, map the data into the appropriate CDISC domain, validate the data against the standard, and make the data ready for analysis and visualization. Where other systems provide some edit checks within their individual systems, SCDI can automate data quality and data transformation routines for all of the aggregated data, ensuring the integrity, validity and accuracy of clinical trial data.

TYPE OF DATA NEEDED

A comprehensive and centralized monitoring approach brings together two distinct areas of clinical trials: 1) the operational aspect that focuses on trial execution and performance; 2) the clinical aspect that focuses on subject safety and data quality. Adoption and maturity of RBM practices may vary, but ideally all possible data sources are included in the risk assessment, making sure key variables that contribute to the evaluation of safety, data quality, and trial performance are included.

Access to historical trial performance can be essential in the practice of risk-based monitoring. Data from past studies can be used to set a baseline for what to expect in similar new studies. In a SAS Global Forum 2014 paper, Andy Lawton of Boehringer Ingelheim discussed how SAS was used throughout the process for producing their risk reports in risk-based monitoring trials³. When determining risk for new studies, he emphasizes the value of past study data, saying, “SAS is the primary tool to model the historical data, this forms an essential basis for understanding risk and setting the appropriate threshold / trigger for when to take action.”

Leveraging the historical data along with current trial data enables the broadest perspective on overall risk of a study. The graphic (Figure 1) demonstrates the process of including both operational and biometric (clinical) data as well as including the historical study and site performance data.

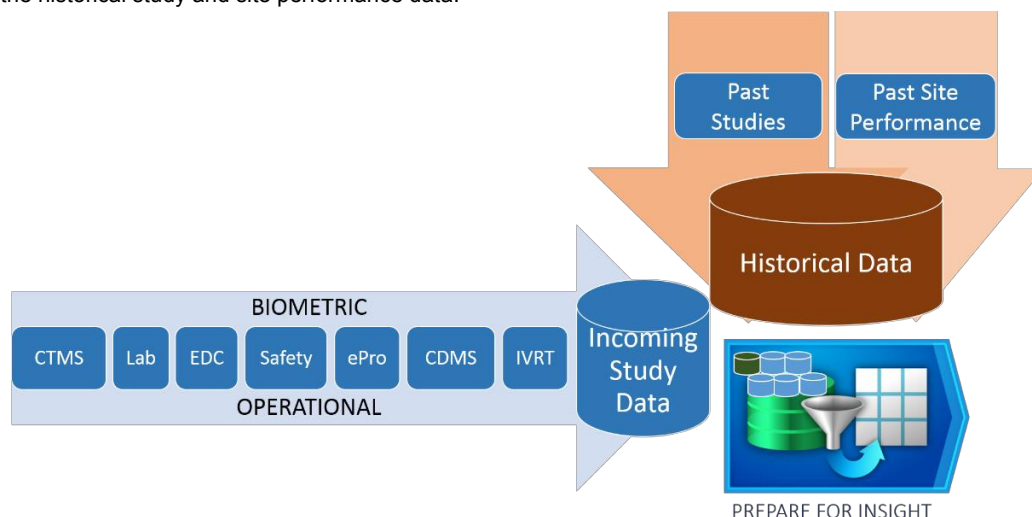


Figure 1 – Information Management Process for Risk-Based Monitoring

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DATA PREPARATION

The data management process includes automating the collection and update frequency of the data, reconciling data from various data sources, and preparing the data for analytics that will drive risk assessment. The data preparation component is not to be taken lightly, as this activity is critical to having quality data to effectively implement remote and central monitoring.

Certain capabilities are essential for appropriate data preparation for risk analysis and reporting. While many can be accomplished programmatically, SAS Clinical Data Integration is recommended for its prebuilt components enabling the following:

- **Collect & Refresh:** automate the data collection and refresh process; determine how frequently the data will be refreshed; depending on the stage of the trial or even the type of study, the refresh/update of the data may vary: near real time, daily, weekly, monthly, etc.; the system of record for updated data should show what data is new or changed.
- **Filter & Aggregate:** aggregate the historical data and incoming study data from the relevant sources (CTMS, Labs, EDC, IVRS, ePRO, etc.); filter sources to extract appropriate data elements are relevant in determining the risk factors of trials; additional variables or a subset of variables may be used for particular studies; historical data may also contain derived information regarding past performance related to sites and/or monitors that will be included.
- **Standardize Data:** Leverage the benefit of standardized data and metadata that can be used across trials and for downstream processing.
- **Reconcile Sources:** the data integration process can also ensure reconciliation of multiple data sources, for example resolving duplicate entries for a single subject with different values coming from Labs and eCRFs.
- **Create Profiles:** during the information management process, profiles can be developed for easy viewing and exploration by study, sites, clinical research associates (CRAs), investigators, countries, and more.

A well-designed data management plan describes the procedures for collecting data, contains key elements of the study, and includes milestones dictated by the protocol. It can specify edit checks and validations to be completed within the CTMS and EDC systems as well as any that will still be completed through SDV by a monitor. In addition to setting the frequency of the data updates (daily, weekly, monthly...), another consideration is determining how much data is required for analysis. For example, when does the data reach the point where there are enough patients per site and a sufficient number of sites that have started collecting data that can be used for analysis? The matter of organizing the data as it relates to projects is also a factor, where a project might be a single study or a broader program within a therapeutic area.

ANALYSIS METHODS

Analytics for risk-based monitoring can range from simple summary statistics, noting frequencies of events or biometric measures and their variances, to more advanced predictive models that trigger alerts when a concern is uncovered by a trend in the data. Some of the analytics will be data-driven, while other algorithms may be predefined using a rules-based method.

RULE-BASED ANALYSIS

Analytical rules can be established for an individual study, a therapeutic area, or even at the portfolio view. Rules will contain defined threshold levels and can be set to include ranges of high, medium and low risk indicators. While some rules can be reused from study to study as is, others may be modified at the threshold level, where additions or deletions of rules may be needed for different studies. For example, a rule might trigger an alert when systolic blood pressure (SBP) reaches a certain level for most studies. But in a hypertension study, the rule would likely be modified to account for higher levels of SBP in patients at the start of the trial.

Made up of a consortium of pharmaceutical sponsors, the TransCelerate Risk-Based Monitoring group openly published the "Position Paper: Risk-Based Monitoring Methodology⁴" in May of 2013, with Volume I⁵ and Volume II⁶ updates in 2014. The methodology paper provides specific recommendations for measuring the risk associated with a clinical trial. These metrics have been tested in over 30 pilots and serve as a viable starting point for organizations in their adoption of RBM.

The TransCelerate team has taken into consideration risk indicators across all facets of a trial, including the biometric or clinical measures, trial design and protocol compliance as well as other areas related to the operational aspect and performance of the trial. Table 1 provides a sampling of the metrics suggested by TransCelerate in the areas of Quality, Cycle Time and Efficiency. A comprehensive list of metrics is detailed in the appendix of the TransCelerate paper in Table 8.1.3. Risk Indicators.

Indicator	Metric Examples
Quality	Average number of major/critical audit findings per audited site
Quality	Number of significant protocol deviations per site
Quality	Number of unreported, confirmed SAEs as discovered through any method
Quality	Percentage per site of unreported, confirmed SAEs as compared to

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	total SAEs as discovered through any method
Timeliness/Cycle Time	Average number of days from data entry to initial monitoring (central, off-site or on-site)
Timeliness/Cycle Time	Median number of days from patient visit to eCRF data entry
Timeliness/Cycle Time	Median number of days from query open to close
Efficiency	Average monitoring (all types) cost per site
Efficiency	Average interval between On-site Monitoring visits per site

Table 1 – Sample of TransCelerate's Suggested Metrics for Risk-Based Monitoring

Managing the algorithms or rules that generate the indicators can be accomplished in several ways. Developing them using SAS Clinical Data Integration provides a means for capturing and reusing associated metadata from study to study. SAS Business Rules Manager, an alternative option, provides a comprehensive environment to create the rules, manage associated vocabularies, deploy rules and monitor rule execution.

Predefined risk rules will capture outliers in the data or highlight events that indicate a need for review due to an acceptable threshold that has been breached. Rules alone only provide a certain level of insight. Predictive analytical modeling goes beyond finding the known factors in the risk rules and provides the opportunity to uncover additional risks sooner, such as patient safety issues. By spotting trends (not just a threshold breach), newly identified issues can be addressed earlier in the trial.

The combined rules and predictive models provide risk scores (high, medium, low) at designated levels: site, subject, CRA, country or others. Individual risks can be rolled up into overall risk assessments within a study or across multiple studies to give trial operations staff more insight into the execution and performance of trials. Based on the type of study, thresholds can be fixed or statistically generated with alerts and triggers surfaced through reports and dashboards for all critical areas. Fraudulent activity can also be uncovered through this assessment and scoring process, adding to the increased quality and integrity of the trial.

The entire analytical process will be cyclical. A learning environment captures the results of triggers for later analysis and modeling. Actions such as phone calls, additional training or on-site visits can be incorporated into the reporting. Over time, models will improve their predictive ability to warn of potential impending risk, not just uncover alerts after the fact. The real value of this "rules plus models" approach is the ability to improve the predictive capability of understanding risk across all trials as they are started and progress.

REPORTING AND VISUALIZATION

Reporting risk associated with clinical trials may vary depending on the business requirements of the audience. Risk-based monitoring has driven the development of entire teams with representatives from Data Management, Statistics, Clinical Operations, Safety and Medical Monitoring in some organizations. Other companies still have more silo-driven requirements for reporting within their own domain. Reporting interests will include the clinical aspects such as data integrity and patient safety, and trial performance such as efficiency of the sites in recruiting or in responding to queries. SAS provides a variety of ways to generate and deliver reports, from code generated reports and graphics to desktop solutions such as JMP® Clinical (examples below) to web-based reports using SAS® Visual Analytics (examples below).

There are numerous options for presenting the results of a study's risk assessment. Geocoded maps of the sites, tables, listings, cross tabulations and graphical illustrations such as pie or bar charts are easily combined into reports of various types of risk. Individual reports or combined dashboards are easily constructed using SAS Visual Analytics, for example, and presented to Clinical Operations, Data Management, or cross-functional teams via the web or a mobile interface. For clinical research associates (CRAs), the reporting can be customized to include only the sites managed by a specific monitor, enabling them to identify and drill into problem areas within the sites for which they are responsible.

WEB AND MOBILE REPORTING EXAMPLES

In Figure 2, serious adverse event (SAE) risk is determined to be high (red), medium (yellow), or low risk (green) by thresholds suggested from the TransCelerate methodology. Using SAS Visual Analytics and displaying the results geographically, it's easy to determine if certain geographies have higher incidences of SAEs. The table (when used interactively, expands to full screen) provides details by site of individual risk measures such as number of SAEs per patient week, AEs per patient week, number of queries, time to query resolution as well as a weighted overall risk score for each site. The bar chart combines the sites at the monitor level and represents the number of SAEs per patient week. Detailed data can be further explored for countries, regions, sites, monitors or other factors where higher risks are indicated.

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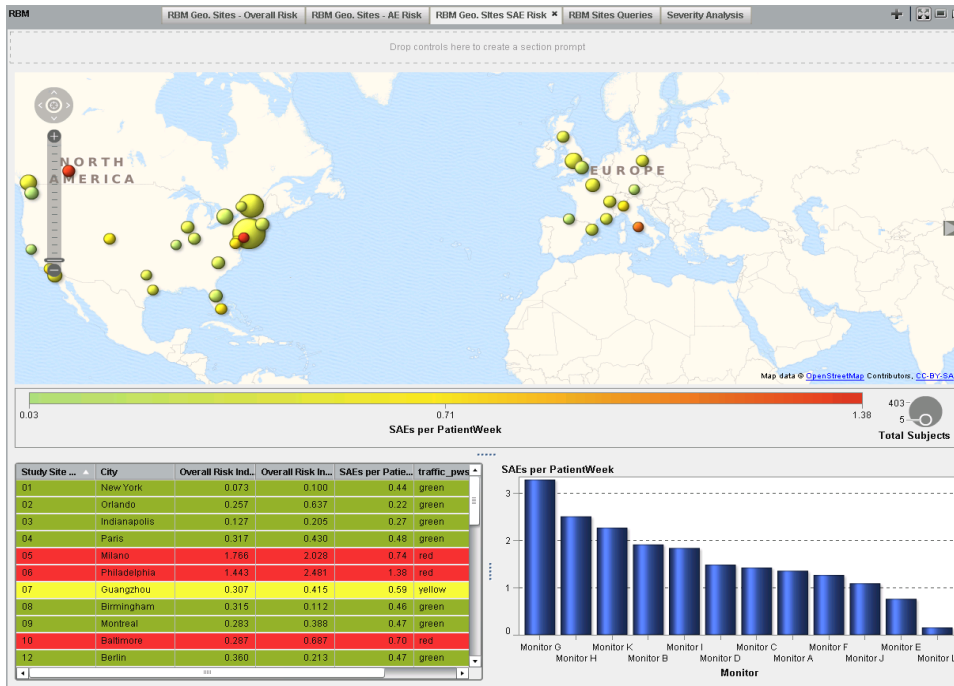


Figure 2 – Reporting SAEs by Geo, Overall and Individual Risk by Site, SAEs/Patient Week by Monitor

In another SAS Visual Analytics example (Figure 3), operational performance metrics are provided that indicate the average numbers of queries per randomized subject by site using a bubble chart. With the combined clinical and operational data store, the reports can include measures across both areas, demonstrated in this report with the addition of a bar chart showing the number of deaths by site.

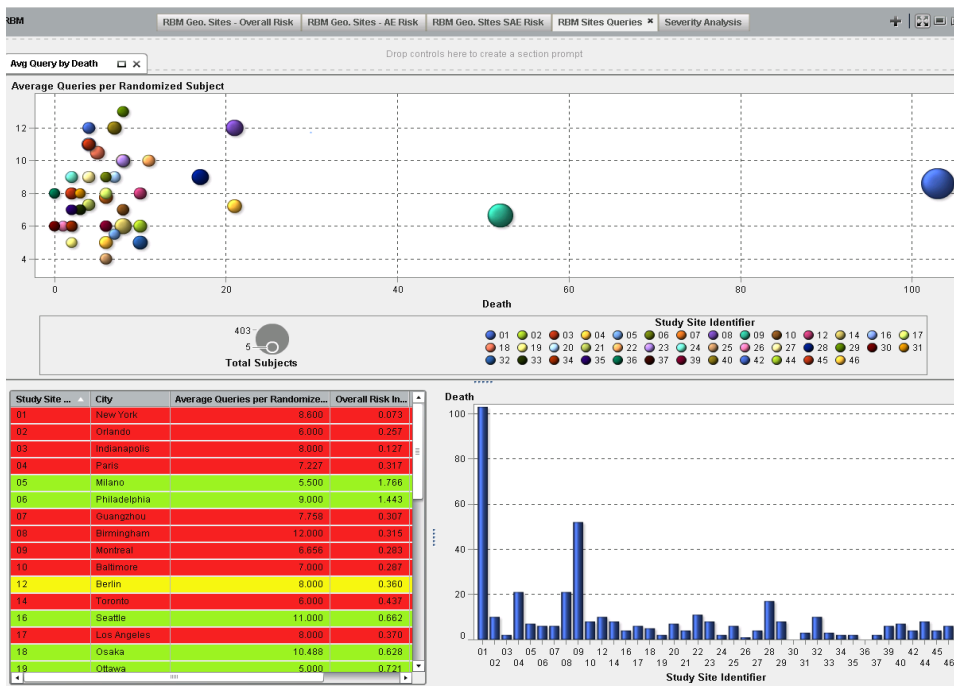


Figure 3 - Average Queries by Randomized Subject (operational) and Number of Deaths by Site (clinical)

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With risk-based monitoring, exploration of the detailed data is an important element and will aid in the discovery of patient safety issues as well as trial performance. Without having to define hierarchies in advance, a user exploring the data or creating their own reports can populate additional tables and graphs with the detailed data down to the subject level if desired (Figure 4). These detail level views, as well as the aggregated views across sites, significantly aid the remote or central monitoring process.

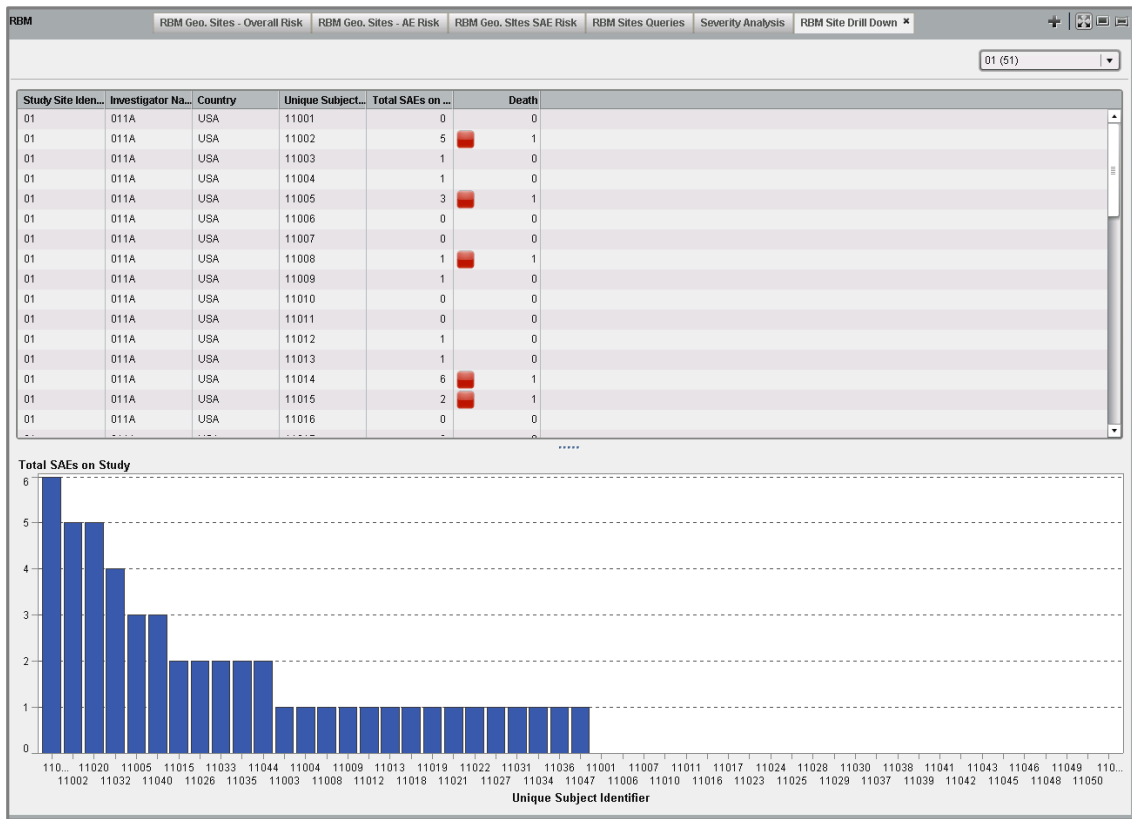


Figure 4 – Detailed View of SAEs at the Subject Level

JMP CLINICAL EXAMPLES

JMP Clinical is another SAS offering that provides capabilities to a number of users managing trials with a risk-based approach. Unique to JMP Clinical is a set of predefined methods for both risk-based monitoring and the detection of fraudulent data. These methods are based on the Clinical Data Interchange Standards Consortium (CDISC) data formats (Figure 5). Medical monitors are a common example of users of JMP Clinical and will benefit from the addition of the RBM and fraud components that can quickly assess risk, explore data, and perform advanced analysis. The example in Figure 6 demonstrates one of the fraud detection capabilities for finding suspect sites based on the data distributions using a weekday-holiday algorithm.

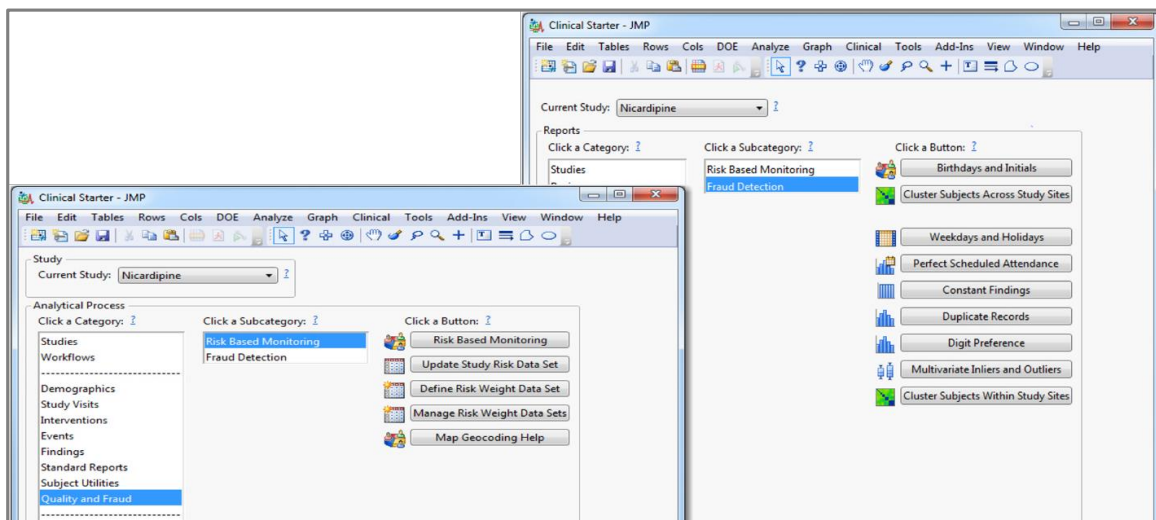


Figure 5 – JMP Clinical Menus for Risk-Based Monitoring and Fraud Detection Analyses

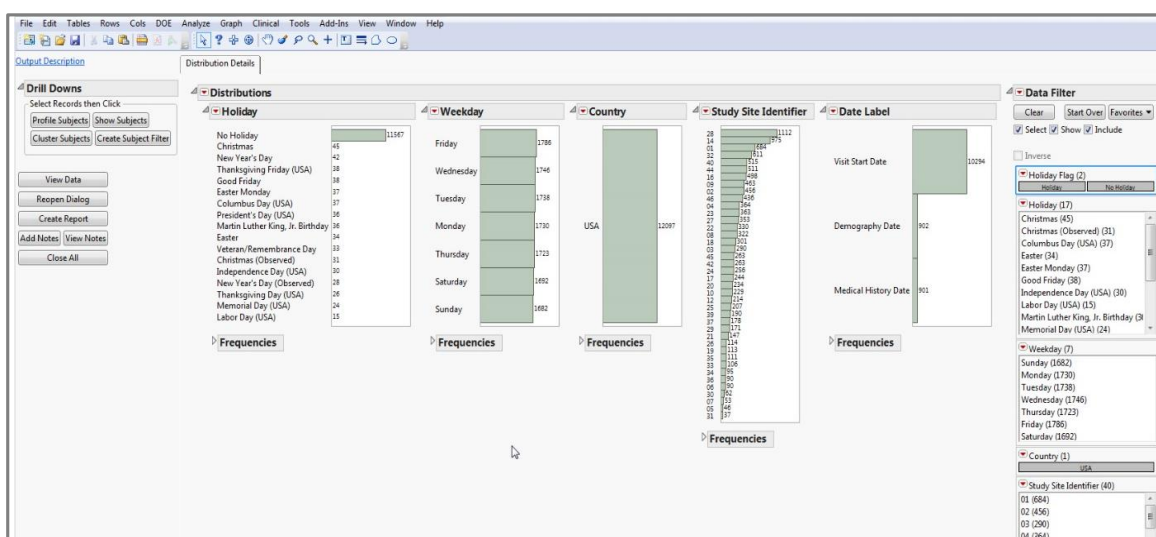


Figure 6 – Variation of Visits on Holidays and Weekends at the Site Level

CONCLUSION

Regulators support risk-based monitoring, and the industry will continue to adopt and mature RBM methods as the effectiveness of central monitoring practices becomes evident. Organizations new to RBM will face challenges in processes, technology and personnel responsibilities. Technology vendors such as SAS support the effort with solutions and methods to manage the data, assess risk factors, drive workflow processes, and provide reports to a wide range of users involved in the RBM process.

Risk-based monitoring represents just one opportunity for leveraging a combined data store of clinical and operational data and using analytics to improve the operations of clinical trials. With historical clinical data and site performance data in place, predictive modeling and simulations can lead to significant improvements in other areas of trial operations. Protocol development, site selection, recruitment, and an improved understanding of risk in the broader compound portfolio are all areas for advancements. Figure 7 provides a suggested roadmap for leveraging the same data collected for RBM for other purposes across clinical operations.

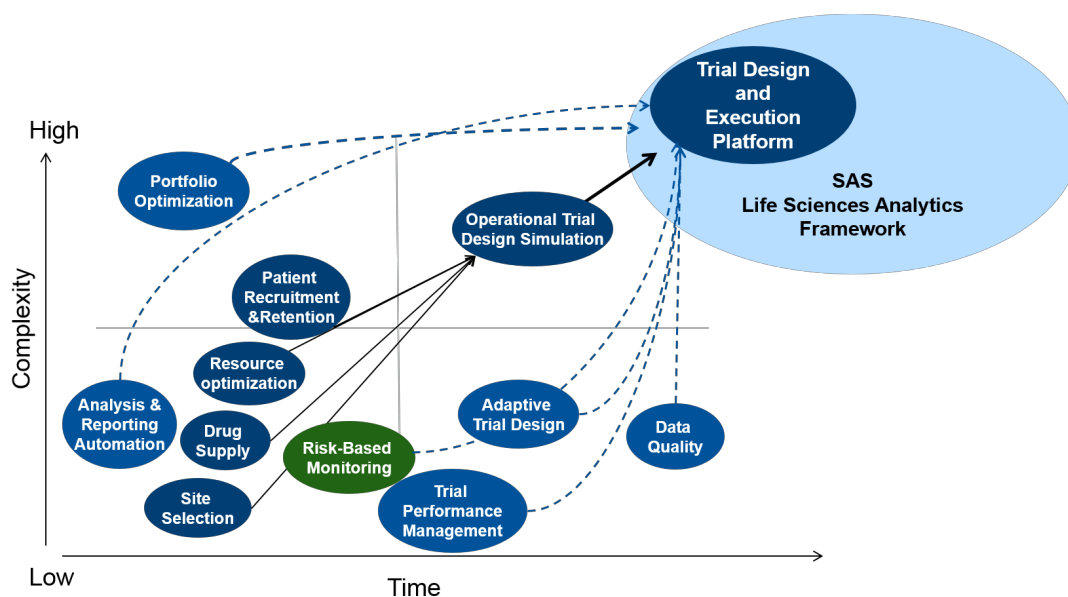


Figure 7 – Leveraging RBM Data Store for Broader Clinical Operations Analysis

Information management and analytical processes are critical technology elements for detecting risk in clinical trials. In today's world, the dissemination of that information to responsible parties can happen near real-time, with accessibility to knowledge literally at one's fingertips. Extending analytics across clinical trial operations can potentially lead to faster recognition of patient safety issues, more targeted recruiting and enrollment, better protocol compliance, lower costs, and overall improved clinical trial performance. Ideally, the adoption of risk-based monitoring and other innovative uses of technology will continue to drive efficiencies and help to bring new therapies to market for the betterment of global health.

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RECOMMENDED READING

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