Risk based monitoring using integrated clinical development platform

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Abstract

Post FDA's final guidance on Risk Based Monitoring, Industry is transitioning from routine visits to clinical sites and 100% Source Data Verification to risk-based approaches to monitoring, focusing more on critical data elements by practicing Centralized Monitoring; relying more on technological advancements thus reducing trial cost and time significantly.

MaxisIT® brings innovative solution to this challenge with its cloud based integrated solution, enabling standardization and storage of data , allowing integration with different EDC,CTMS, Safety, PV, Health Care, and document management systems. Source data verification and application of quality checks pre and post centralized storage, makes our solution unique. Our tool allows multi-level analytics to assess risks at every stage of drug development by strategically adjusting to oversight based on signaling. User friendly dashboard gives ease of use for non-technical groups, minimizing drastically requirement for customized programming support services, and ongoing Centralized Monitoring, to focus on risk based monitoring approach.

Executive Summary

Regulatory agencies need to ensure, Sponsor oversee their clinical trials by proper monitoring to protect the safety of the research subjects and ensure trial data integrity. Rising cost of the drug development and need to focus more on critical data elements has changed the paradigm of traditional monitoring approach to risk- based monitoring to improve the safety and data quality concerns. Risk based approach has tremendous ability to strategically adapt to onsite-monitoring and keep evolving to the changing risk level.

Traditional Monitoring rely more on 100% source data verification by visiting study sites, checking through all critical and non critical data which makes the clinical trial process more cumbersome and costly, delaying the process of drug development ultimately.

Centralized monitoring usage routine review of the submitted data and statistical and other analysis remotely through routine review of submitted data to identify and follow-up on missing data trends, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site which otherwise not easily detected by onsite monitoring, such as unusual distribution of data within and among study sites, high screen failure or withdrawal rates, high frequency of eligibility violations, delays in reporting data etc.; predicting and focusing more on critical data elements.

Ever since the Regulatory guidelines has come over to adopt the risk based monitoring, Sponsors are looking forward to bring their monitoring approach in the same line and to achieve the goal by partnering with the integrated solution providers to get actionable real time analysis improve on overall quality and compliance.

MaxisIT with its cloud based integrated solution brings an opportunity to sponsor to improve oversight of clinical investigations by enabling standardization and storage of data, allowing integration with different EDC,CTMS, Safety, PV, Health Care, and document management systems. Predictive analytics with dashboard for metrics, key performance indicators, key risk

indicators, configurable thresholds, triggers, alerts, escalations and workflows to drive proactive risk mitigation and actionable outcomes are the major features associated with our solution, enabling sponsors to take timely decisions and reassess the monitoring strategy throughout the monitoring cycle.

In this paper we will discuss about MaxisIT®'s solutions to sponsors looking forward to adopting Risk Based Monitoring, thereby complying with the regulatory agencies and ensuring enhanced patient safety and data quality, effective protocol design, reduced costs, and the ability to strategically adjust oversight in keeping with changes in risk level.

Introduction

Increasing clinical development costs for drugs has been a concern for industry over the years[1] and multidirectional efforts have been made to lower these costs through more efficient study-management. Since monitoring accounts for a substantial proportion of the total study costs, major focus is towards lowering the monitoring costs through the analysis of risks involved during a clinical drug development lifecycle. Savings of over 20% have been claimed through the use of modified site management; centralized and planned source document verification with only essential onsite source data verification emerging out of inconsistencies assessed through centralized risk based monitoring[2].

Monitoring is an essential element of clinical trials, ensuring quality and integrity of a clinical investigation. Monitoring uncovers potential problems such as data entry errors or missing data, assures that study documentation exists, assesses the familiarity of the site's staff with the protocol and required procedures, and provides a sense of the overall quality of a site[1]. Post FDA's final guidance and EMA reflections on Risk Based Monitoring, Industry is transitioning from routine visits to clinical sites and 100% Source Data Verification to risk-based approaches to monitoring, focusing more on critical data elements by practicing Centralized Monitoring; relying more on technological advancements thus reducing trial cost and time significantly.

Factors like central data collection systems, and real time data standardization and analytics are important to get a sense of the big picture in order to effectively perform risk-based monitoring. EDC and CTMS have made central data collection possible with higher level of data accuracy than that with traditional data collection methods. Modern analytics tools and technologies are driving the emergence of centralized monitoring because they provide powerful insights into data. Considering the large scales of current clinical trials, accuracy and effectiveness is problematic with on-site monitoring. Large problems go unnoticed when data results are only skimmed through on-site monitoring practices.

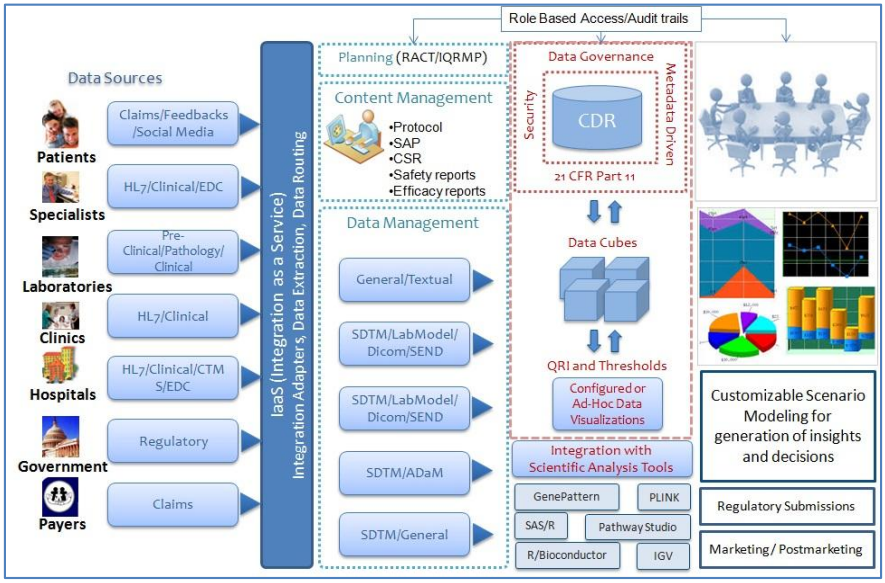
RBM Guidelines Perspective

The EMA emphasizes on the identification of potential risks and prioritization should commence at a very early stage in the preparation of a trial, as part of the basic design process. The concerns with trial and protocol design, design of data collection tools/instruments, the design of the monitoring and data management strategies and plans, including the relative role of

centralized versus on-site activities and the data quality tolerances, and the design of record keeping for the study should be addressed within the framework of these dimensions, implementing a quality by design approach. Risk assessment and mitigation plans should be appropriately disseminated within the organization, regularly reviewed and updated when new information becomes available[3].

FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The monitoring plan should identify the various methods intended to be used and the rationale for their use. Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. Sponsors should prospectively identify critical data and processes, perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes. The guidance highlights the importance of documenting the monitoring plan after assessing the project risks and needs. It also recommends that sponsors analyze ongoing data to continuously assess and adjust the monitoring strategy. [4]

Both regulatory encourage sponsors to adopt strategies that reflect a risk-based monitoring approach using a combination of monitoring strategies and activities. The approach should emphasize focus on centralized monitoring, by identifying critical elements and a plan to address data integrity risks[3, 4, 5].



Several initiatives are underway to promote RBM paradigms and different methodologies are been suggested to achieve maximum out of RBM approach. TransCelerate developed a methodology for RBM that can be widely applied to the conduction of various clinical trials. This methodology helps to improve monitoring efficiency by changing the focus to Central or Off-site Monitoring activities that are intended to identify potential issues sooner than a monitoring strategy that relies primarily on site monitoring visits.

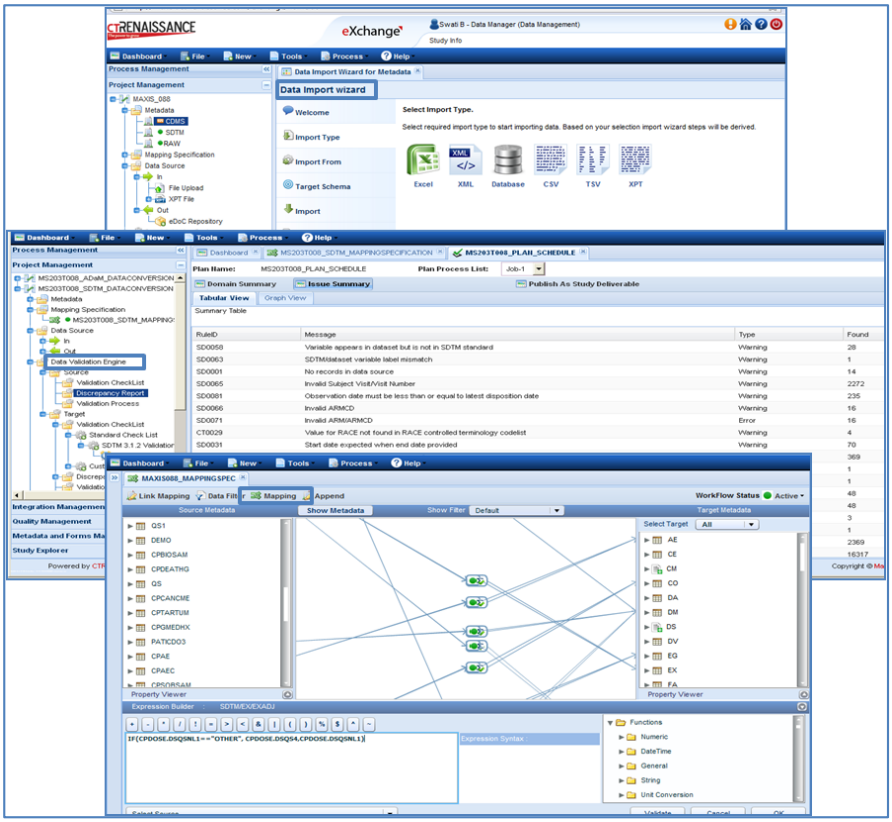
MaxisIT® has been constantly in pursuit of providing best innovative solutions to divergent requirements of pharmaceutical industry. With unique integrated clinical development platform

and analytical capabilities, our solutions have provided sponsors great ease of work enabling them analyze disparate data sources and derive critical decision scenario on the fly.

Centralized monitoring requires integration, aggregation and review of disparate data and analyze remotely to identify and follow-up on missing data trends, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site which otherwise not easily detected by onsite monitoring, such as unusual distribution of data within and among study sites, high screen failure or withdrawal rates, high frequency of eligibility violations, delays in reporting data etc.; predicting and focusing more on critical data elements like adverse event and serious adverse events and so on. MaxisIT®'s Holistic and Flexible solution architecture offers complete solution for RBM approach in a real sense.

Data Integration

As technology is playing vital role in data collection during clinical trial conduction, multiple data sources like EDC, CTMS, PV, IVRS need to be handled by sponsor. Before applying analytics on the data it is of utmost importance to place all data at single place. MaxisIT®'s unique data integration capability enables tool to communicate with disparate data sources. As integration is metadata driven it is highly configurable to sponsor specific metadata as well as standard metadata.



Source Data Validation (SDV)

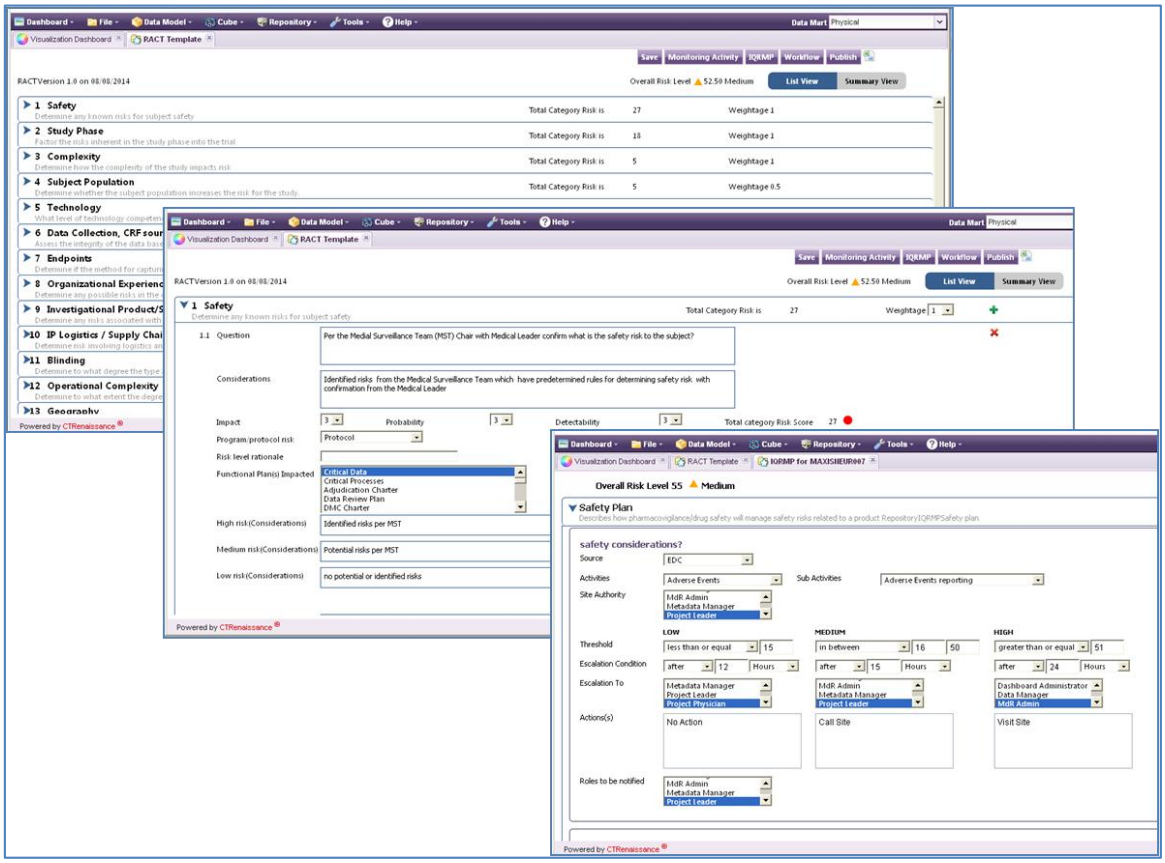
Risk based monitoring emphasizes on selective source data validation in place of onsite 100% source data validation. Our solution offers seamless, real time data validation to extract discrepancies like missing data, duplicate records, data outliers, and inconsistent data. SDV engine also enables users to identify data fraudulence. This level of data validation increases data integrity and quality.

Data Standardization

Data standardization is the first step to ensure that your data is able to be used for analysis and shared across the regulatory. This establishes trustworthy data for use by other applications. Ideally, such standardization should be performed during data entry. If it is not done a comprehensive back end process is necessary to eliminate any inconsistencies in the data. Our standardization capability provides most comprehensive data standardization and transformations across the standards. Being a Metadata driven process it is flexible and configurable across different data standards. Its drag and drop utility makes data standardization easiest ever.

Risk Assessment and Categorization Tool (RACT)

As per the guidance of EMA and FDA on adoption of RBM, early assessment of potential risks in the trial from all departments is recommended. Transcelerate has developed a Risk



assessment and Categorization Tool (RACT) compliant to regulatory guidance for risk assessment. Our solution follows this methodology and offers a RACT with required access controls and connectivity to different plans like safety plan, monitoring plan etc. It is validated with Transcelerate methodology for risk levels and algorithms for risk calculation. RACT allows users to assess critical data and critical processes during risk assessment and help setting the risk priorities before designing the protocol and monitoring and safety plans. This allows user to have author, reviewer workflow with functionalities like auto-population of categorical risk queries to relevant plans in Integrated Quality and Risk Management Plan (IQRMP). It also has version control and audit trails to track the changes and maintain updated versions.

Integrated Quality and Risk Management Plan (IQRMP)

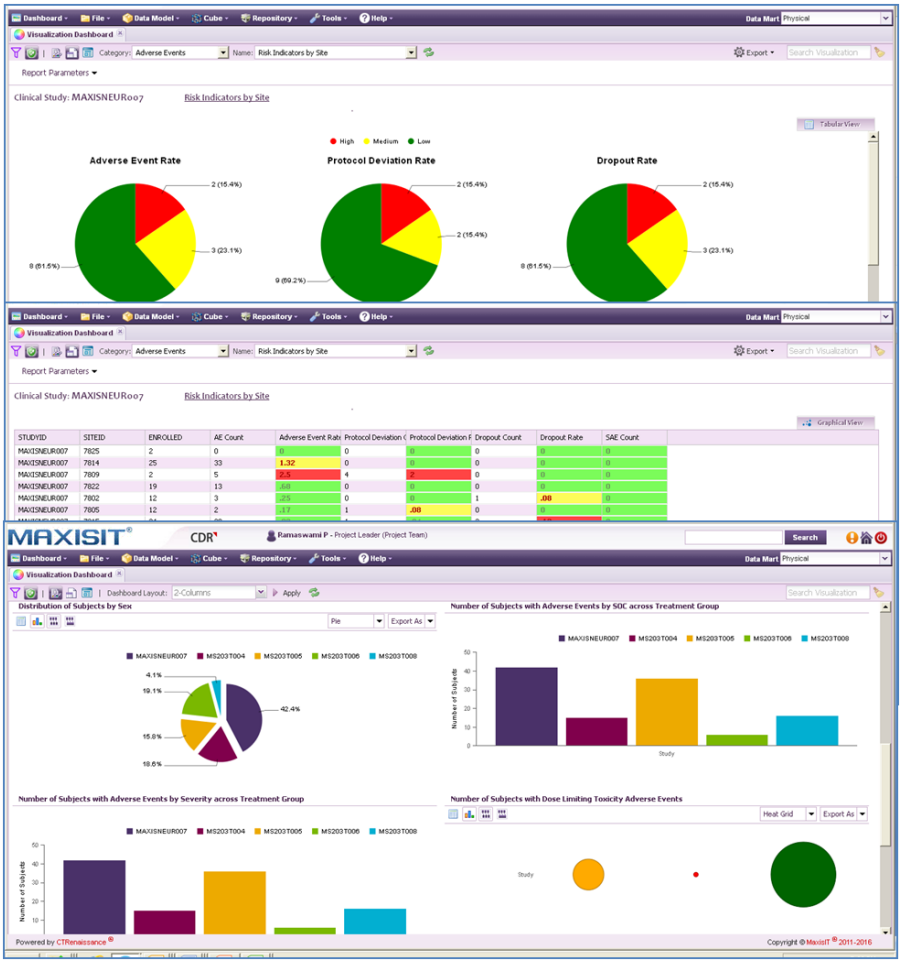
The IQRMP provides a tailored and integrated plan for a specific clinical trial. It defines the actions for risk management for the risks identified by cross-functional representatives (e.g. elements that impact primary efficacy endpoint and critical safety parameters), align associated quality management plans (including the Monitoring Plan) across identified risks and defined Critical Data and Processes.

Our solution allows user to easily navigate from RACT to IQRMP and setting quality risk indicators (QRI) and thresholds for risk triggers. System helps user to prepare IQRMP by auto populating IQRMP structure based on RACT queries. IQRMP allows user to set the quality risk indicators and reporting escalation thresholds and escalation levels in single interface.

QRIs and threshold are key elements which enable ongoing risk assessment and mitigation during a study conduct. Specific QRI and thresholds can be applied to analytical reports. Whenever the thresholds are exceeded system alerts user about relevant risk and its action items.

Analytics and Reporting

Effective risk based monitoring can be achieved using different statistics on disparate data related to ongoing trials. Many analytical tools are focusing their efforts on developing RBM oriented analytical engines with user friendly dashboards. Statistics being a functional entity limited to specific user group, configuration of complex statistical reports is never been a welcome step for end user.

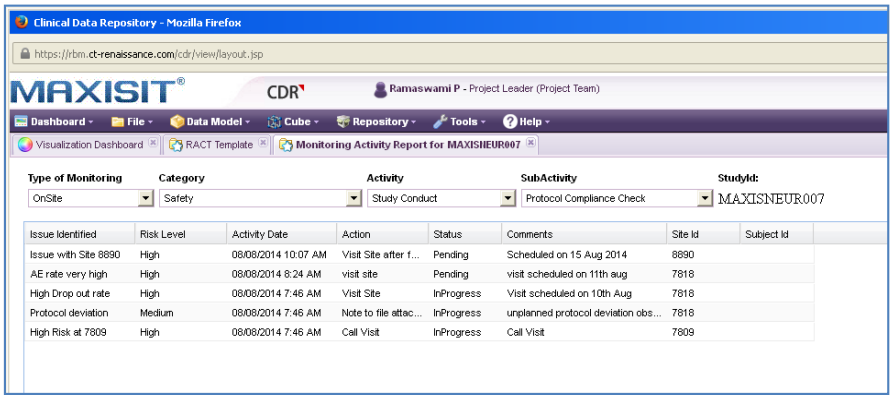


Data aggregation is imperative while handling disparate data for analytics. Our solutions provide metadata driven data aggregation which enables complex data analytics easier for user. It enables user to have cross functional report generation and better visibility through different data having linkage or dependencies.

MaxisIT®'s innovative analytics tool offers most user friendly operability and role based dashboard allowing users to have multiple reports like data driven visualizations, statistical reports and scenario modeling. Our analytics dashboard provides unique functionality of cross-functional drilldowns. Drilldown functionality allows user to navigate from one report to multiple another reports to understand depth of data and analyze root cause of issue. Similarly our unique entity of scenario modeling leverages understanding of complex cross-functional correlations and enables user to understand complex issue origins.

Monitoring Issue and Risk Management

Management of risks and issues emerged during central and onsite monitoring needs to be handled efficiently for faster resolution. Knowing the risks during monitoring execution and assessing the issues derived from central and onsite monitoring is centralized in our solution to allow user to have easier navigation through monitoring interfaces and better visibility of all issues, action and status with multiple levels of filters. User is able to generate monitoring reports based on the study, site, or other attributes by applying filters in our monitoring report generation interfaces. It also allows input of monitoring activities for onsite monitoring which updates central issue log. Our risk and issue log allows users to have an overview of complete status report and audit trails for all issues occurred during study.



All the reports generated are exportable in different formats like xls, pdf, png, jpg, html depending upon the report types.

Trial conduction also contains a large amount of content management in form of multiple documents and forms. Our content management platform gives users a simplified content development solution where content development is highly organized with author reviewer workflow and features like reusability, resulting in cost effective and quality content development.

Regulatory Compliance

MaxisIT®'s solution is highly compliant to different global regulatory standards like 21 CFR part 11 or CSV guidelines by EMA etc. Central and highly secured data storage adds to the completeness of the solution where complete organizational usability of solution is through its single sign on, role based user access facilities making it a highly reliable, scalable and complete solution for RBM.

Conclusion

MaxisIT® builds and delivers out of the box end to end solution for efficient risk based monitoring allowing business to stay agile and lean while making better and informed business

decisions that will allow them to achieve faster and quality clinical drug development compliant to regulatory and assured cost savings.

References

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