TransCelerate Risk-Based Monitoring Technology Considerations Part 2

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Contents

1 Purpose

Technology Considerations to Enable the Risk-Based Monitoring Methodology[1], published in the journal of Therapeutic Innovation & Regulatory Science in 2014, provided a preliminary description of the capabilities necessary for an integrated Risk-Based Monitoring (RBM) technology solution. This white paper presents functionality details for an integrated Risk-Based Monitoring technology solution and expands upon the initial framework previously presented. The intended audiences are sponsors and their representatives as they select and implement a system to perform RBM, and technology vendors as they develop solutions that support risk based approaches to monitoring.

Nothing in this paper should be construed to suggest that sponsors cannot or should not use systems not meeting the proposed criteria. Every sponsor is differently situated, implements RBM differently, and has different systems with which an RBM system must interface. The differences between sponsors means that there is no one-size-fits-all approach to design.

Accordingly, this paper is not prescriptive – it merely aims to lay out criteria that may aid in implementation of RBM.

2 Introduction

Organizations need to have a firm understanding of the RBM methodology[2] and how it is being implemented in their clinical trials operations prior to introducing a technical solution. Those TransCelerate member companies which have implemented RBM in the last year reinforce this assertion and illustrate a broad range of current technical solutions; some companies have introduced advanced technologies whereas others have used more basic software solutions leveraging their existing systems. Despite differences in technology capabilities, improvements in clinical trial risk management are already being identified. Member companies have found that successful implementation of RBM is predicated on the effective combination of people, process and technology: the people must be trained and supported, the business processes must be aligned with organizational goals, and technology must enable efficient delivery of the right information to the right person.

The considerations described in this paper represent alternatives recommended by the TransCelerate member companies participating in the RBM technology solution workstream. Member companies participated in discussions to envision what ideal technology solutions might contain; the resulting recommendations for future state functionalities are contained in the appendix. Additionally, member companies provided anonymized criteria for their individual RBM system projects, and those results are included in the appendix as well. These activities identified several common RBM functionalities, especially with regard to risk and issue management, data integration, adaptive monitoring processes, and risk assessment, reporting and analysis.

Since RBM technology is relatively new and rapidly evolving, successful technology solutions should enable RBM implementation with the capability to adapt to future needs. As a result, it is important to consider not only what their products offer today but also to include the investments the vendors are making in their products for the future. To gather this information from the vendors we conducted a vendor survey of current and future RBM functionality. As with all TransCelerate surveys, participation was voluntary. The survey was open to all vendors that support clinical trials, and several methods of communicating the survey were used (e.g., emailed invitations to known contacts, sent Linked In invitations, tweeted invitations on the TransCelerate Biopharma twitter page, etc.) to ensure a broad participation from a variety of vendors. The survey questions focused on current functionality as well as

publicly available functionality each vendor envisions for their system in the next 2-5 years. The survey was available for vendors to complete between late July and late August 2015. The results of the survey have been incorporated into the manuscript and the list of criteria in the appendix, and the list of vendor survey questions is also included in the appendix.

3 Definitions, Acronyms and Abbreviations

This section defines all terms and acronyms used in this document.

Term	Definition
CRO	Contract Research Organization
CTMS	Clinical Trial Management System
eDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcomes
eTMF	Electronic Trial Master File
IRT	Interactive Response Technology
RACT	Risk Assessment Categorization Tool
RBM	Risk-Based Monitoring
SaaS	Software as a Service
RI	Risk Indicator
SDR	Source Data Review
SDV	Source Data Verification

4 Reading this paper

Risk-based monitoring (RBM) is an adaptive approach to clinical trial monitoring that directs monitoring focus and activities to evolving areas of greatest need which have the most potential to impact patient safety and data quality. It relies on technical capabilities which include management of clinical trial risk through: risk and issue management; data integration; adaptive monitoring process; and risk assessment, reporting and analysis (Figure 1). A optimal RBM system would be strong in each of these areas. However, it is unlikely that a single technology will thoroughly address all of these complex areas; therefore, multiple technologies may be required for a holistic system solution. As a result, an RBM system must be able to integrate with independent systems that complement it to ensure all of the requisite features and functions are available. For example, an RBM system may not provide issue

management, which is provided separately by a Clinical Trial Management System (CTMS), so the RBM system should be able to integrate with the CTMS to provide a comprehensive solution.

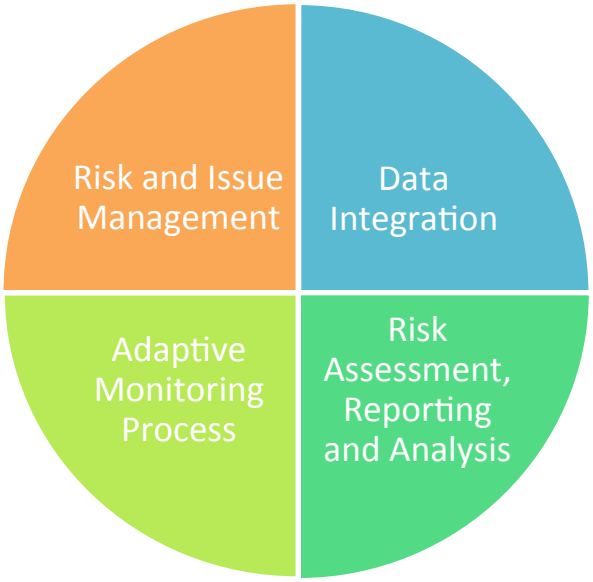

Figure 1 - Key Aspects of a System-Supported RBM Solution

This manuscript provides a broad view of considerations which support business needs across the four key aspects of an RBM solution illustrated in Figure 1, and provides a means for evaluating potential system-supported RBM solutions. As noted above, adaptation may be necessary to account for the existing system landscape of each company as well as the integrations necessary to enable a comprehensive RBM system solution.

The appendix of this paper describes considerations in the four key aspects of RBM illustrated above as well as considerations for functional elements needed to support the entire system (e.g., audit trail features).

The business roles that will use RBM system functionality will vary among sponsors and specific technical privileges and functional capabilities of different users will vary by company and system. Consequently, the roles have been defined in general terms in this paper so as to guide the reader but not prescribe a specific function for use by a given role.

- The role “User” is intended to represent any member of the RBM team working in the system to perform duties directly related to RBM tasks within their company (e.g., reviewing Risk Indicators (RIs) for a study and taking appropriate action).
- The role “Administrator” is intended to represent any person using the system to perform system administration (e.g., initial configuration of the system) as well as those using the system to support RBM indirectly (e.g., managing a library of RIs).

Finally, to aid readability, the paper is organized into sections to describe features in each of the four key aspects illustrated in Figure 1. Further considerations for many of the features are listed in the appendix.

5 Data Integration

Data Modeling

Data is at the heart of RBM. To facilitate RBM and generate necessary RIs, data from multiple sources will need to be integrated into a common platform. In order to enable the data integration and transformation, as well as to provide the ability to include data from Contract Research Organizations (CROs) and other data providers, the system should allow for a flexible data model. The ability to support a flexible data model is vital as companies evolve their RBM strategies and make ongoing adjustments to their business operations. In support of the flexible data model, the system should employ a source agnostic data model that can be mapped to a source system data model. In addition, the data modeling should enable data consumption by mapping the data into a format that enables efficient generation and management of RIs. Given the complexity of the data landscape, the system should have capabilities that help manage the related metadata for easy traceability from source to destination.

Data Sourcing

The system should have extensive data sourcing capabilities, with a scalable infrastructure that supports multiple integration formats. The system should have the ability to integrate with internal systems within the corporate firewall, and this becomes more important if the system is offered as a software as a service (SaaS) solution. If outsourcing to functional service providers and CROs, the system should also have the ability to source data from third party data sources that are outside the corporate firewall. The system should have features to enable defining and monitoring data validation to ensure data consistency and data integrity. The system should have functionality to perform structural validation across data sources; this is critical for file based data sourcing, but can also help identify changes to source system feeds. The system should have features that enable administrative alerts and notifications that are configurable based on use cases. The system should have a high performance infrastructure. Finally, the system should enable data operations (e.g., “Create Algorithms”, “Manipulate Data”) against heterogeneous data (i.e., data from all/any source systems).

Integration with Third Party Systems

The data required to execute RBM will commonly be found within a variety of source systems. These include both transactional source systems and data warehouses. The system should be able to integrate data from each of these types of sources, using a standards based approach whenever possible.

Typical System Integrations:

Typical source system integrations that the RBM system should support include:

- Quality Management Systems
- Electronic Data Capture (eDC) Systems
- Interactive Response Technologies (IRT)
- Central Laboratory Systems
- Clinical Trial Management Systems
- Issue Management Systems
- Electronic Trial Master File (eTMF)
- Electronic Patient Reported Outcomes (ePRO)
- eConsent and other eSource technologies

- Drug Safety Systems

Integration and Harmonization Considerations

Key identifiers required for integration of disparate sources will not always align. The system should have mechanisms for mapping and aligning key data as part of its integration components.

For some sources, like eDC and ePRO, the schema of the data will vary from study to study based on specific protocol needs. The system should have the ability to harmonize the data to a common target. This harmonization could include aligning various form designs and code lists.

In addition to transactional source systems, many organizations also have data warehouses in which the data required by the RBM system is already integrated. The RBM system and corresponding processes should allow for direct integration with these types of warehouses and should not rely on direct source integrations.

Outbound Integrations

As mentioned earlier, an RBM system may not provide all of the features needed in one comprehensive solution; consequently, the system will also need to be a provider of data to other consuming systems. The system should allow for the extraction of key data through a web application programming interface or other export mechanism. For example, to facilitate storage of all issues in an independent issue management system, the RBM system would need to provide issue data to the issue management system. Another example of a possible outbound integration would be the need for the RBM system to establish a sampling approach for Source Data Verification (SDV) and Source Data Review (SDR) that has a starting baseline level and can be adjusted in the eDC system based on evolving risks and/or issues at a site.

Integration Mechanics

Given the wide variety of source systems, the RBM system needs to be flexible in its interfaces. The system should have the ability to support both file and service based integration. While a service based approach is more common, and therefore preferable, the reality of legacy systems requires that file based integration be supported.

For sources like eDC and CTMS, where there are limited product alternatives, the RBM system may look to develop custom adapters targeted at these specific systems. This will aid the speed of implementation and minimize integration costs but should not be dependent on these systems as the only means of consuming these types of data.

Data Lineage

The system should be maintained with a full data lineage that traces each data point from its origin through data integration to its use in the user interface and RIs. The lineage should show each major point of persistence and any transformation, derivation, aggregation or harmonization that occurs to the data. The lineage should be technically sound enough to aid the technical development and support of the solution but should also be simple enough to allow end users to follow the data back to the source when responding to a signal (e.g. RI exceeding a threshold).

Data Aggregation

The system should have the ability to aggregate data across various dimensions. The dimensions used in aggregations should be flexible to accommodate specific needs of different risk factors but, at a minimum, should include program, study, region, country, site and time.

6 Risk Assessment, Reporting and Analysis

Risk Assessment Categorization Tool (RACT)

The RBM system should enable risk identification and assessment process, preferably using a tool such as the RACT[3]. The RACT should be validated and version controlled. The expectation is that the RACT will be entered into the system following discussions by a cross-functional team.

The system should support the RACT at the program and study levels and it should be possible to import program level RACT information to study level RACTs within the program (Figure 2). The responses entered into the RACT questions will drive risk scores for each category. The overall risk score is calculated based on the category risk scores and the respective weight of each category. The "Overall Risk Level" (i.e., High, Medium or Low) is then determined based on the overall risk score and drives the level of SDV and SDR for the study. The category risk scores along with the overall risk score should be used to recommend RIs. The RACT should be editable or versionable if needed (e.g. based on an interim analysis, protocol amendment). Since it is expected that TransCelerate will continue to evolve the RACT, and also that individual sponsors may choose to customize the RACT and/or develop a RACT alternative, the RBM system should allow the sponsor to modify and version the RACT template as necessary.

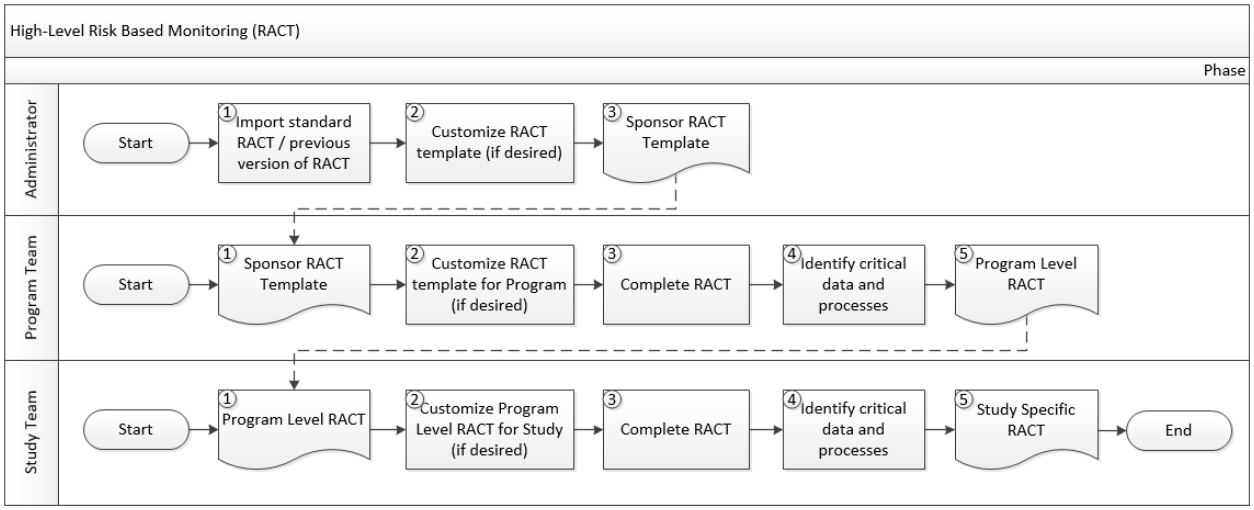

Figure 2 - Process to Create and Update the RACT for Programs and Studies

Select Risk Indicators/Define New RIs/Edit RIs

A library of Risk Indicators has been created by TransCelerate. The system should enable the sponsor to create a set of Risk Indicators. Each RI is intended to provide information on a particular risk or area of a site's performance that might predict whether there are issues that require attention. There are RIs that may be broadly applicable across programs or protocols and some that might be study specific. RIs may have one or more thresholds and these thresholds may vary even for the same RI based on the nature of

the risk within a study. The typical display often follows a traffic light analogy which may be used to indicate severity (i.e., High, Medium and Low). The system should evaluate raw or calculated data from systems containing clinical and operational data to apply the thresholds related to each RI. When a threshold is reached an alert may be triggered and an action suggested (Figure 3). Not all RIs result in actions; some RIs may simply be informative and have no associated action or alert (Figure 3).

Risk / Issue	Alert	RI	Threshold	Actions	Alert
Something may happen or has happened	No	a	> 0	Take action 1	No
			>= 5 and <= 10	Take action 2	No
				Take action 3	No
			>10	Take action 4	Yes
Something else may happen or has happened	No	b	> 'Study Median'	Take action 5	No
Something else may happen or has happened	No	c	Yes / No	No action	NA
Manual issue reported by study team member	Yes	NA	Not Applicable	Take action 6	NA
Another manual issue reported by study team member	Yes	NA	Not Applicable	Take action 7	NA

Figure 3 - Relationship of reporting/analysis components

An algorithm should be applied to the RIs and their related thresholds to calculate the overall level of risk (i.e., risk score or risk profile) at the program, study, region, country and site levels. The system should allow an administrator to create underlying algorithms to evaluate RIs and edit the algorithms by required level (i.e., at program, study, region, country and site levels). The system should allow the user to adjust the weights of the algorithms relative to the overall summary.

Initially, RIs should be created by an administrator and added to a library of RIs. RIs can then be selected for a program. Program level RIs can be applied to studies in the program (Figure 4). The administrator should be able to reuse, add or edit RIs and related thresholds and actions from a library for use on multiple studies and at multiple levels (program or study etc.) as appropriate.

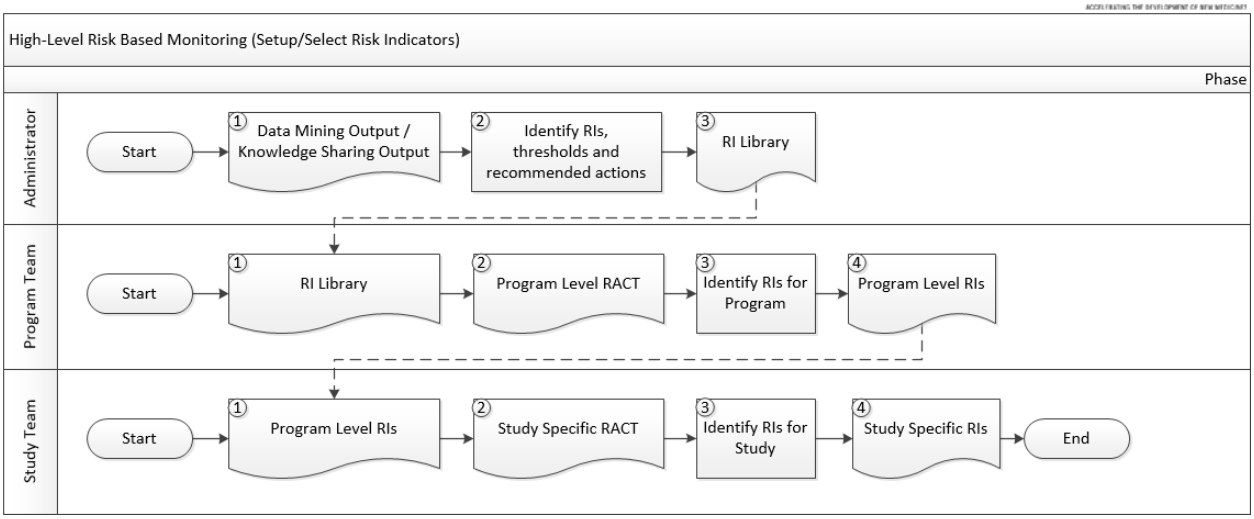

Figure 4 - Process to Build RI Library and Program and Study Specific RIs

Testing Algorithms

In order to create or edit RIs, the system should allow the user to test the algorithms using appropriate data (e.g., test data from a program, study, region, country or site) prior to making the algorithm available for production use (Figure 5). This feature can also allow the user to do informal testing or to dry run new algorithms.

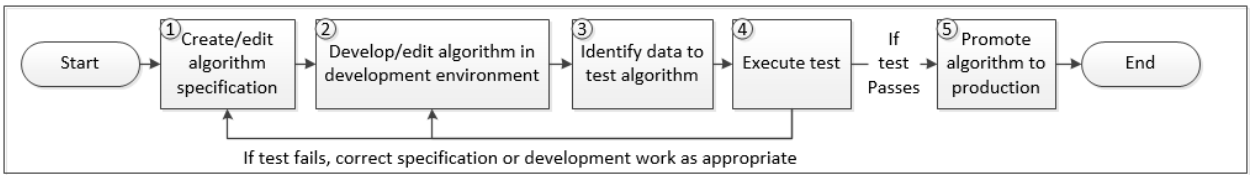

Figure 5 - Process to test algorithms

Set/Define Actions

The “Overall Risk Level” in the RACT and the RIs should be linked to a set of actions (e.g., establish SDV and SDR levels) which should be incorporated into the site monitoring plan. The system should propose actions, or provide a selection of possible actions, so that actions appropriate to the circumstance may be assigned. The actions should initially be drawn from a library to minimize the variation in the way that similar actions are described (e.g., “Contact site” vs. “Call site” vs. “Phone site”), although it should be possible to add study specific actions.

The system should allow for several actions to be completed before a risk is resolved. In addition, it should be possible to structure actions so that the result of one action may drive a subsequent action, following escalation pathways based on business process designs (i.e., documented escalation paths in an Integrated Quality and Risk Management Plan). For example, if a call to the site does not resolve a particular issue then the action may be escalated to a site visit.

Once action has been taken and RIs have returned to acceptable values, ongoing escalated activities such as an increase in SDV/SDR may be reduced (e.g., to a lower level or the original level).

Create and Set Alerts

Actions should be triggered based on the thresholds that are met as described above. Users should be able to proactively use the RBM system to review the thresholds and the resulting actions that they should take. For example, they should login to the RBM system and see their necessary actions on a dashboard in order to plan for study monitoring activities. However, the system should also actively alert users when specific actions have been triggered. Actions vary in urgency; that is, some actions may need to be (or can be) taken quickly (e.g., call the site). Other actions, while important, cannot be (or need not be) done immediately (e.g., visit the site). Therefore, users should be able to determine which actions require alerts, adjust the frequency of alerts and choose to receive alerts every time new actions are triggered or in batches (e.g., once per day, once per week). There are a number of factors to consider when setting alerts, such as "Overall Risk Level" and RI weight as well as personal preference and an individual's work style. Therefore, users should be able to subscribe to alerts (i.e., set the alerts to their personal preference and work style).

Data Discovery and Knowledge Acquisition

To establish robust RIs, it is necessary to mine data, develop deeper knowledge of the data and build and test hypothesis. This can be done directly in external statistical systems, but perhaps with some difficulty. Ideally, the system should allow the user (who may not be a SAS programmer) to manipulate and visualize data to uncover useful patterns, trends, outliers or other knowledge that may lead to new RIs, may help identify appropriate thresholds for RIs or may lead to useful visualizations.

Fraud Detection

The system should be able to incorporate advanced statistical analyses, predictive analytics and pattern finding for identifying serious compliance issues that might include fraud. The system should be able to use these methods to automatically flag any suspected cases of fraud and direct the case to specified users for review. The system should support data quality detection as outlined in two data integrity manuscripts to be published shortly[6,7].

Predictive Analytics

Analytics are typically used on business data to describe, predict and/or improve business performance. The predictive analytics area covers areas of statistical techniques in data modelling/mining and machine learning, where statistical models (algorithms) are used to make predictions on future events/outcomes.

The predictive models are derived from historical data. Once in place, the success rate of the predictive model can be monitored and adapted if a better predictive model is identified. The system should either provide predictive analytics capabilities or interfaces to systems that can undertake this.

Reporting and Dashboards

The system should provide robust reporting and dashboard capabilities across different stages of the RBM process. Reports and dashboards should allow the user to visualize data. This includes but is not limited to identifying trends in subject data, reporting on site risks, issues and actions taken and overall data quality and site performance. The system should allow reporting on multiple levels as designated by the sponsor (e.g., program, study, region, country, site). The data sources and levels of reporting should

be configurable and the frequency of data updates should be based on the currency of the data source and specific study needs.

The system should provide visualizations and reports needed to identify trends, patterns and outliers to gauge performance across multiple levels (i.e., program, study, region, country, site). In addition to analyzing current data, the reports and visualizations should include any predictive analytics that may mitigate risk in the future.

The tool should provide the capability to create role-based dashboards that are user friendly and intuitive. These dashboards should display targeted data and information most needed for a defined role. The dashboard visualization should allow users to drill down to more specific information as needed.

The system should also provide performance metrics on risk scores at a variety of levels (e.g., study or site level risk) as well as show how risk scores changed during the conduct of the study. This includes metrics related to issue status and aging of issues (i.e. how long it took to resolve a particular issue).

The system should be able to produce a risk performance report for any prior point in time. For example, sponsors should be able to produce a risk performance report for a particular site based on the previous six months' activities.

Ideally the system should also provide overall performance metrics on whether RBM methodology is achieving the sponsor goals. For example, are significant issues being resolved in a timely manner, are risks being proactively addressed?

In order to efficiently review data, the system should allow the user to perform standard operations such as sorting, filtering and searching. The system should enable the user to access and review underlying data used to develop aggregate measures (e.g., drill down). In addition, the system should surface an alternative, such as Structured Query Language, to enable more complex queries to be executed.

7 Adaptive Monitoring Process

A premise of RBM is that monitoring activities should be adapted to direct the monitoring focus to the areas of greatest need; RBM technology and systems should be designed to support this directed, data-driven, risk based approach to monitoring. The system should provide data from multiple sources (i.e., issue management system, risk scores, CTMS, eDC, etc.) during the trial so the user can access information when there is a need to adjust the related monitoring activities.

Adjustments to the central monitoring plan and tasks for a study may be necessary for multiple reasons, (e.g., protocol amendments, new RIs are identified); and the RBM system should enable changes to the central monitoring capabilities 'on-demand'[5]. Additionally, it may be necessary to adjust the frequency for specific analytics to be reviewed more or less often so that some are included as part of a monthly dashboard review while others can be reviewed on a more frequent schedule.

On-Site Monitoring processes including the frequency of site visits or level of SDV/SDR may change over the course of the study based on the identified risks. So over the course of the study the on-site monitoring activities may increase or decrease based on changes in risk and/or identification or resolution of issues and the system should enable this adaptive monitoring design which is at the foundation of RBM.

Source Data Verification and Source Data Review Definitions

In RBM, SDV is 'transcription checking', the process by which data within the CRF or other data collection systems are compared to the original source data to confirm that the data were transcribed accurately. SDR is defined as the review of source documentation to assess the quality of the source, review protocol compliance, ascertain investigator involvement and appropriate delegation, and assess compliance to other areas (e.g., SOPs, ICH GCPs[8]). SDR is not a comparison of source data against CRF data.

Create Source Data Verification / Source Data Review Plan

As described above, the RACT determines an overall risk level, and the overall risk level, the category risk levels and/or individual mitigation recommendations should be used to create a baseline plan for SDV and SDR. Baseline plans are driven by the risk assessment including the detectability of the risks as well as the critical data and processes. Adjustments in the plan are driven by issues at the site as well as the assessment of RIs. Companies manage the governance differently, but the relationship between the RACT, RIs and the SDV/SDR plan should be appropriate for study specific needs.

The system should allow for a sampling approach to be taken for both SDV/SDR. Optimally the system should establish the SDV/SDR plan in the RBM or eDC system once the RACT is finalized. The system should provide the administrator or user with the ability to adjust SDV/SDR rates either at the study or site level as the risk levels change over the course of the study and at individual sites. The system should display or link to the appropriate system to display what critical data or subjects require SDV/SDR, record documentation of SDV/SDR activities and track progress of completed verified/reviewed data over the course of the study. The site monitor should also be able to document any issues identified while performing SDV/SDR in the issue management system which, in turn, may result in adjustment of the SDV/SDR approach.

Estimate Workload

The calculated risk level for the study and the resulting activities required in the SDV/SDR plan should provide the basis for estimating the site monitoring resources needed for a given study. That is, the system should help inform the monitoring workload for a study. For example, the greater need for SDV/SDR generally necessitate greater resources and more frequent on-site monitoring trips. The resource algorithms should take into account the work to be done on-site only as the remote and central monitoring teams are likely to be comprised of a fixed number of resources.

The system should:

- Provide output to indicate the estimated amount of work (effort and duration) needed to perform on-site monitoring
- Provide output to estimate the frequency of visits needed to perform on-site monitoring (both SDV and SDR)
- Allow the user to define per protocol: amount of data that can be reviewed/checked per monitoring visit (i.e., 8 hours)

8 Risk and Issue Management

Risk and issue management includes the functionality in the system to facilitate efficient triaging, tracking, assignment, follow up and closeout of risks (events that may occur/impact the trial) and issues (events that have occurred/are affecting the trial). One of the primary goals of the system in support of the RBM methodology is to identify risks so they can be managed before they become issues.

Risks and issues should arise throughout the course of a program or study and should come from many sources. The system should evaluate RIs to determine if thresholds or other visualization criteria (e.g., control chart parameters, outliers) have been triggered. Criteria that have been triggered should be clearly indicated so that review and/or action can be taken. Risks and issues can also arise as a result of the various data review activities performed, statistical analysis, central monitoring review, site visits, etc.

Risks and issues should be managed holistically in a single system (either the RBM system or an external system) to operate efficiently. Maintaining risks and issues in multiple systems would lead to duplication, challenges in escalating issues (e.g., across functions using different systems) and difficulty accounting for issues overall. A single system should also facilitate risk and issue documentation and reporting.

Knowledge Management

As risks and issues are identified and actions are taken to resolve them, it is important to retain the information in such a way that it can be used for learning, future system enhancements and re-application. The RIs that led to a risk or issue should be identified and the action taken to resolve them should be stored by the system for reuse. It is expected that users will learn more about the data available and its relationship to site quality as they use the system and as the practice of RBM evolves; RIs should be linked to risks and issues and actions but the experience should lead to better or advanced ways of identifying them in the future. The knowledge should be reusable so that as new studies are initiated in the system, the user can leverage information learned on prior studies to develop new RIs, thresholds, actions or escalation paths.

9 Overall Considerations

Auditability

The system should maintain an audit trail of all transactions as desired by sponsors and mandated by regulators by user, date and time. The audit trail should be accessible in either the user interface and/or through reporting. The audit trail should not be available for deletion. The sponsor should be able to retrieve historical data so that a record could be retrieved that shows the state of the data at any given point in time.

Security Management

The system should be tested and certified against all vulnerability assessments. The system should be secure and should prevent unauthorized access. In addition, the system should have the ability to detect, record and report attempts at unauthorized access. If hosted, the vendor should describe how they ensure physical security of computing hardware (servers, storage, networking equipment) used to store data.

User Role Management

The user interface should be able to manage access and security at multiple levels throughout the structure to enable secure, role-based access to data. The sponsor should control which roles have access to which levels of data (e.g., program, study, site) as well as which elements of the software (e.g., RACT, Issue Management, Reporting) each role can enter or read/browse. A sponsor should determine which roles have access to assigned site(s) and whether a given role should be able to update or only be

able to read documents (e.g. the RACT). This control should also extend to any external users (CROs) the sponsor allows access and should include control of blinding/unblinding access to data.

Sign-on and authentication should either be tied to the sponsors or, in the future, the system may incorporate single sign-on capabilities should that functionality become prevalent in the industry. The sponsor should have ultimate control on how access is assigned (e.g., manually creating role, automatically through another internal system like CTMS).

10 What's Next for RBM?

Risk-based monitoring is rapidly evolving in the clinical trial landscape, and changes are driven by lessons learned from the methodology as well as arising capabilities in supporting technology. For example, the increasing use of eSource may impact the volume and timeliness of the e data and this may influencee additional advancements in RBM technologies.

Companies continue to measure the value and success of the RBM methodology, and the RBM technology solutions will need to demonstrate added value. For example – the success of RBM technology solutions could be measured in reduced costs, better relationships with sites, increased data quality, reduction in compliance risk or increased fraud detection.

As the implementation of RBM approaches expands, we will have the ability to measure performance and compliance across the industry and to make adjustments to the methodology and technology as appropriate.

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12 Appendix

Functionality Library

The enclosed is a list of suggestions for potential RBM system functionality. Sponsors and/or vendors can pick from the list that would be most meaningful to their RBM implementation.

Worksheet in TransCelerate RBM T

RBM Vendor Survey Questions

We conducted a vendor survey of current and future RBM functionality and this information is incorporated in the paper. The survey was open to all vendors that support clinical trials and several methods of communicating the survey to the vendors were used to ensure a broad participation from a variety of vendors (emailed invitations to known contacts, Linked In invitations, invitations on the TransCelerate Biopharma twitter page, etc.) The questions are listed below as reference (the survey specified only to include publically available information, not to include trade secrets). The survey was open and available to vendors to complete between late July and late August 2015.

#	Question
	Business Value / Client Experience
1	Provide three specific examples on how your tool is/has provided business value for your existing clients.
2	Have your clients experienced a reduction in site monitoring with the help of your tool? If so, please quantify such improvement for each of the business drivers below: • Reduction in time at site • Reduction in number of on-site visits
3	Describe the impact on study operations of your clients resulting from use of your product. What have been the outcomes in terms of efficiency and productivity? What has been the feedback from the end users in terms of usability?
4	What is the maturity of your product – that is for how long has your product been used in a production setting? How many clients are using your product? In how many trials (completed and active) has your tool been used?
5	From your experience, what may be key challenges that the sponsor is likely to face as we move forward with this project? How do you suggest sponsors can adequately prepare for implementation?
6	Can your tool be hosted for sponsor use? If so, please describe this service offering. Include SaaS and cloud options as well as technology support and business services.
7	Describe the roadmap of your product(s) for the next 5 years.
	Risk Management
8	It is sometimes necessary to adjust the underlying calculations for risk assessment/indicators, for example when applying statistical adjustments for mega trials vs small trials. Does your product currently allow the customer to configure these calculations to best align with business goals? Do you have plans to enhance this in the future?

	• Drop down on configurability • Risk indicators • Tolerance limits • Risk weightings (grouping of certain risks) Aggregation of risks (study, region, site, program)
9	If configuration is not possible, please describe specifically how such calculation adjustments are made/maintained within your tool. If this adjustment is only being provided as a service offering from your company, please provide an overview of this service. Do you have plans to enhance this in the future?
10	Does your product currently provide for the recording/linking of ACTIONS taken as a result of the risk indicator/notification within a CTMS, CDMS or issue management system? Do you have plans to enhance this in the future?
11	For the purpose of auditing risk actions, does your product currently provide traceability of interventions (e.g. SDR/SDV) performed in relation to a risk indicator/notification? If so, please describe how. Do you have plans to enhance this in the future?
12	Does your product currently allow for the customer configuration of risk mitigation actions and/or workflow and/or escalation options? For example – can the action request on-site monitoring visit? Do you have plans to enhance this in the future?
13	If risk indicators can currently be applied (or not) at any level, does the risk score/calculations for the unapplied risk indicators impact the risk score? Do you have plans to enhance this in the future?
14	Does your system currently support links to documentation (e.g., site monitoring plans, data review plans)? Do you have plans to enhance this in the future?
Integration / Data Sourcing	
15	What methods does your tool currently support to integrate data from different sources? Include clinical and operational data. Do you have plans to enhance this in the future?
16	Please describe the process the sponsor would currently follow to add a new data source to support a risk indicator or site identification. For example, a new sponsor study being managed by a new CRO. Do you have plans to enhance this in the future?
17	Does your product currently come pre-populated with any industry benchmarking data? If so, please describe this data and the general processes that you use to manage these data. Do you have plans to enhance this in the future?
18	Does your tool currently integrate with COTS products in the following categories: • eTMF • Clinical Trial Management Systems • Clinical Data Management Systems (including eDC tools) • Issue Management

	• Reporting and Visualization Tools • Other Do you have plans to enhance this in the future?
19	How is your system currently optimized for countries with low bandwidth? Do you have plans to enhance this in the future?
	User Interface/Display
20	Does your product provide role based access management currently? For example – granting access to 3rd party collaborator and central versus site monitor. Do you have plans to enhance this in the future?
21	Is the user interface currently optimized for multiple browsers (e.g., IE, Chrome, Safari) and platforms (e.g., PCs, Macs, tablets)? Do you have plans to enhance this in the future?
22	Describe the current predictive analytics capability of your tool. Do you have plans to enhance this in the future?
23	Does your system currently support visualizations of trending (e.g., risk levels over time)? Do you have plans to enhance this in the future?
24	Does your tool currently have the ability to display historical data (e.g., snapshots of data from one year ago)? Do you have plans to enhance this in the future?
25	Describe or provide examples on how the tool currently displays the following: • Issue identification • Trends • Analysis at program, study, region or site levels • Knowledge Management Do you have plans to enhance this in the future?
26	How is the tool currently prepared to support Big Data? Do you have plans to enhance this in the future?
27	What extent is the data in your tool able to be integrated with other commercial visualization tools (e.g., Spotfire, JReview) currently? Do you have plans to enhance this in the future?