

# Risk-Based Monitoring Update – Volume I

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## 1. Introduction

TransCelerate's Risk-Based Monitoring (RBM) project had a very productive year in 2013. Subsequent to publishing the [Position Paper on Risk-Based Monitoring Methodology](#) in May 2013, we have actively worked to network the concepts and embarked on piloting and/or assessing experience among companies that implemented the methodology.

The purpose of this RBM Update document is to share the following information in our continued efforts to move the RBM methodology from concept to practice:

- RBM methodology and revisions based on lessons learned from application of the tools
  - Lessons from the use of the Risk Assessment and Categorization Tool (RACT) to both identify and assess risks
  - Clarification of Source Data Verification (SDV) and Source Data Review (SDR)
- TransCelerate RBM Pilots including a status update and a summary of FDA feedback received following their review of a subset of Sponsor RBM planning and implementation packets
- Training materials developed for TransCelerate member companies including associated training guides
- External engagement and a preview of additional RBM publications from TransCelerate in 2014

## 2. Risk-Based Monitoring Methodology

The position paper which was published in May 2013 reflects the TransCelerate proposed RBM methodology. The first step in the methodology requires a cross-functional risk assessment of the program and protocol. The second step involves identification of critical data and processes, and the documentation of such, within an integrated quality risk management plan. The third step involves the assessment of potential Risk Indicators, which in alignment with critical data/processes, would direct the level of intervention when monitoring sites. The fourth step is the monitoring execution of the study which is not limited to just on site activities, but includes other centralized and/or offsite approaches.

### 2.1. Lessons from Risk Assessment and Application of the Use of the RACT

Three important lessons on process have been learned that should be reinforced regarding the assessment of risks using the RACT.

Risk identification and the assessment of likelihood and severity should be a **cross-functional activity**. Having the right people representing multiple facets of drug development is important in order to ensure a robust discussion around the identification and the management of risk.

It is also essential to have an individual who understands the overall process to **facilitate** appropriate risk discussions.

**Timing** of risk assessments is also important because early risk identification allows for programs and/or protocols to be developed which eliminate or reduce risks. Program level assessments allow for information to impact on the development and execution of all protocols, and protocol level assessments allow for study-specific mitigations and monitoring activities to be applied. Beyond directly impacting the writing of a protocol, the individuals involved with the RACT discussions also begin to identify other potential risk mitigations as well as monitoring tactics for identified risks.

The current published RACT was originally designed to facilitate risk assessment and risk mitigation by the following:

- Providing a consistent approach to determining risks
- Identifying how and by which function(s) the risks will be managed
- Identifying and documenting risk mitigations as appropriate
- Categorizing individual risks as high, medium, or low and delineating an overall risk level (high/medium/low)
- Guidance to determine the baseline level of monitoring activities including suggestions for SDV and SDR based on overall risk level

Considerable feedback has been received about the RACT from regulators and member companies. A focus group has been tasked with considering the following feedback and implementing changes to the tool:

- Guidance on how to align the output of the RACT with risk mitigations including monitoring tactics described in the Integrated Quality and Risk Management Plan (IQRMP)
- Guidance and examples for determining and ranking risk categories as high, medium or low to be adjusted by each company based on their risk tolerance
- Suggestion to provide a risk level per category and a written rationale for the determined risk level
- Modifications to some of the questions to add clarity
- Recommendation for identifying the decision structure for determining level of risk when a multi-disciplinary group cannot come to consensus
- Recommendation for documenting who was involved in the RACT discussions/decisions

## 2.2 Source Data Verification (SDV) and Source Data Review (SDR)

SDV and SDR, in particular Table 2 from the TransCelerate RBM Position Paper, have garnered a lot of interest and comments. Early in the development of the RBM methodology, there was inconsistency among TransCelerate members in the definition of SDV. Through the development of the methodology, TransCelerate members agreed on a common definition of SDV. SDV, commonly known as “transcription checking,” is the process by which data within the case report form (CRF) or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately (i.e., data from source matches data in the CRF or other system and vice versa).

Using guiding principles from European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), TransCelerate members recognized there was a need to better focus on-site efforts to issues related to site processes, protocol compliance and related documentation from a quality perspective. This shift in focus led to the creation of a second term, SDR, to highlight the need to focus on-site monitoring efforts on what is most important. SDR is defined as a review of source documentation to check quality of source, review protocol compliance, ensure critical processes and source documentation (e.g. accurate, legible, contemporaneous, original, attributable) are adequate, to ascertain Investigator involvement and appropriate delegation and assess compliance to other areas (e.g., SOPs, ICH GCPs). SDR is not a comparison of source data against CRF data.

As a quality control measure it was the opinion of the RBM working group that SDV as purely a transcription checking exercise was not as valuable. The data that was presented in the position paper from multiple sources illustrates SDV queries in critical data as being very low. Every sponsor has been choosing values in or outside of the ranges described in Table 2, and regardless of the amount of SDV, there is no expectation that sponsor and investigators are held less accountable for data quality.

To the end of providing more compelling evidence of the impact of SDV on data quality, the TransCelerate RBM project team has constructed a sub-team to focus on this particular aspect of monitoring. The primary objective is to assess the value of SDV as a quality control measure and to understand the optimal use of SDV in maintaining data integrity and subject safety. We intend to leverage a large data set and employ a retrospective standard analysis approach to further assess the value of SDV based on discrepancies generated and resulting changes to the data. The intent is to have a manuscript ready for publication by the end of May 2014.

### **2.3 Member Pilots**

There are a number of pilots that are being conducted in multiple disease areas and in different phases of development. In some cases, pilots are focused on single elements of the methodology such as the risk assessment.

### 2.3.1 FDA Pilot Review

TransCelerate has arranged for submission, review and feedback on RBM/Monitoring plans for up to nine studies with the FDA. For the pilot study monitoring plans submitted to date, common areas of feedback include the following:

- Risk Assessment
  - Ensuring cross functional participation
  - Providing rationale for overall risk determination of study
  - In addition to areas sponsors had already focused on (e.g., subject eligibility, endpoint ascertainment, etc.), ensuring there is focus on
    - Discontinuation/Retention/Follow-up
    - Study drug compliance with dosing regimen
    - Adjudication process/identification of events
- Risk Mitigation
  - Threshold values triggering further action, actions that will be taken when threshold is exceeded, and, when possible, development of predefined contingency plan
  - Refinement and quantification of risk indicators and associated thresholds to ensure they are measurable and informative
  - Escalation of site/country/study/program issues as responsibility for central monitoring function
  - Defined Issue Communication Flow (e.g., timeliness, roles and responsibilities)
- Monitoring Plan
  - Clarity of monitoring responsibilities including required activities that must be done on-site, off-site (remote) and central.
- General Considerations
  - Consider how a shift to RBM may impact other program and study-related oversight processes (e.g., standard operating procedures related to vendor oversight, drug supply chain, etc.)
  - Site training regarding the application of RBM

### 2.3.2 Pilot Metrics

The intent of these pilots is to inform TransCelerate members on how well the methods and tools work. On a quarterly basis, qualitative and quantitative feedback is proactively collected from member companies and then assessed for impact. Quantitative metrics, focused on quality, efficiency and cycle time as defined in the table below are being collected. There should be sufficient data in the third quarter of 2014 to ensure these metrics are meaningful and worthy of sharing broadly.

| Indicator  | Metric   |
|------------|--|
| Quality    | Average number of major/critical audit findings per audited site   |
| Quality    | Percentage per site of unreported, confirmed SAEs as compared to total SAEs as discovered through any method |
| Quality    | Number of Significant Protocol Deviations per site   |
| Efficiency | Average Monitoring (all types) cost per site   |
| Efficiency | Average interval between on-site monitoring visits per site  |
| Cycle Time | Average number of days from data entry to initial monitoring (central, off-site or on-site)                  |
| Cycle Time | Median number of days from patient visit to eCRF data entry  |
| Cycle Time | Median number of days from query open to close   |

### 3. Risk-Based Monitoring Training Materials

In order to move from principle to practice, change management, including training, becomes a significant component to successful implementation. TransCelerate members recognize there are many stakeholders in the clinical development ecosystem, and therefore prepared training material to publically share for the benefit of all individuals and companies that may choose to implement RBM. The materials can be found at <http://www.transceleratebiopharmainc.com/rbm-resources/>.

The training material is comprised of five modules described below including train-the-trainer manuals, a participant workbook and recommended pre-course/post-coursework:

| Module   | Description  |
|--|--|
| <b><u>Module 1:</u></b><br><b><u>Introduction to Risk Based Monitoring (RBM)</u></b>       | This module describes the RBM model as compared to traditional monitoring methods. It then provides the rationale for RBM and describes TransCelerate's key assumptions and concepts.  |
| <b><u>Module 2:</u></b><br><b><u>Methodology and Team Members</u></b>                      | This module describes TransCelerate's RBM methodology including the RBM toolkit. It summarizes the responsibilities of functional team members involved with RBM. Finally, it describes on-site, off-site and central monitoring activities used in study oversight.   |
| <b><u>Module 3:</u></b><br><b><u>Risk Assessment</u></b>                                   | This module discusses methods for identifying risk for planning purposes. It provides guidance on how to identify critical data/processes for RBM. It also teaches the use of the RACT to perform risk assessments.  |
| <b><u>Module 4:</u></b><br><b><u>Risk Indicators and Thresholds in Decision Making</u></b> | This module introduces risk indicators and their definitions and provides insight to establishment of thresholds aligned to the risk indicators that would trigger an appropriate action. The module also provides guidance on how to implement risk mitigation plans, the appropriate monitoring activities in the RBM model, and responses to potential issues and risks throughout the study. |
| <b><u>Module 5:</u></b><br><b><u>Transitions</u></b>                                       | This module provides change management guidance for efficient and effective implementation of RBM. It includes approaches towards informing investigative sites about RBM, describes metrics used to measure the impact of the methodology, effective transition techniques for studies and sites, and discusses challenges with implementation within different cultures and systems.           |

## 4. External Engagement & What to Expect in 2014

In order to facilitate efficient and effective implementation of the TransCelerate RBM methodology, external engagement is critical. Members of our team have participated and presented at a variety of forums in 2013 and will continue to do so in 2014. Venues range from large industry meetings such as DIA to meetings with various Health Authorities, Research Organizations, and Public/Private Consortiums. In 2014, we look forward to sharing more information on how to tactically implement the methodology as well as learnings from TransCelerate member companies as we continue to pilot and/or implement.

In addition to presenting in various venues, the RBM team has a robust publication plan. For the 1<sup>st</sup> quarter of 2014:

- Revised RACT and updated guidance
- Metric collection from pilots underway

For the 2<sup>nd</sup> quarter of 2014:

- White Paper: Central Monitoring models being piloted by member companies
- Manuscript: Challenging the Value of SDV as a Quality Control Measure
- White Paper: Technology to Enable RBM
- Metric collection from pilots underway

In the second half of the year, expect to see further updates on pilot results.