RISK-BASED MONITORING UPDATE
- VOLUME IV

1. Introduction
TransCelerate’s Risk-Based Monitoring (RBM) initiative continues to produce tangible outputs during the first half of 2015. The purpose of RBM Update Volume IV is to share progress and information with regard to the following topics:

» Frequently Asked Questions
» RACT Best Practices
» Quantitative Performance Metrics
» External Engagement Updates
» Upcoming Deliverables in 2015
2. Frequently Asked Questions

The most frequent questions received about RBM are regarding the Source Data Verification (SDV) and Source Data Review (SDR) ranges.

» The Position Paper provides guidance on application of SDV and SDR. The questions most often received from external sources pertain to the rationale behind the ranges for SDV and SDR highlighted in Table 2 of the position paper, which illustrates how risk categorization impacts on various monitoring activities. The final ranges contained in the position paper were illustrative and derived from discussion and feedback from regulators and not intended to be prescriptive. The intent was to allow the risk assessment of a particular trial to guide the level of sampling that would be done for several onsite activities. The expectation was that SDR would have more value and therefore would have higher sampling rates. The article, “Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, Therapeutic and Innovation and Regulatory Sciences TIRS, 2014, Vol 48(6), 671-680” supported the notion that sites transcribe data from source very well (96.3% of data unchanged) and that only 11% of Major or Critical findings through audit are detectable using SDV. Companies need to individually decide how best to apply SDV and SDR ranges based on what is appropriate for them.

» The types of questions or comments we often receive from external sources around SDR include having difficulty with defining the difference between SDV and SDR; distinguishing how they would assess source documentation, perhaps the same source documentation, for both verification purposes and review purposes; decision making related to when to increase SDV or SDR based on issues with either transcription errors or quality/process issues with the source data; and, a lack of documentation guidance primarily related to SDR to ensure compliance with what was laid out in a monitoring plan.

The RBM team is considering publishing best practices around these topics by the end of 2015. Regarding documentation of what the monitor may have checked, there seems to be three approaches to date within RBM studies; (1) use EDC systems, where enabled, to document subject visits that were assessed by SDR, (2) monitoring visit reports and (3) home grown reporting systems. In most cases these are workarounds that are in place until reporting systems provide better options. The debate now is what level of documentation is needed in order to ensure that site documentation was assessed for missing data, compliance with the Investigational plan, and the general quality of source documentation was acceptable.

Business use cases are being developed that will support development of documentation tools for SDR. We expect this to be available in the fall 2015 timeframe. A focus group has been established for the purpose of recommending best practices around the application of SDR.

» There have been comments and questions relating to the need to be compliant with TransCelerate RBM methods, in particular the SDV and SDR recommendations. TransCelerate has published a position paper on RBM and several other papers that were intended to facilitate implementation at companies who have made the choice to implement RBM. TransCelerate’s RBM methods are guidelines that can be used by sponsors and CROs.
3. RACT Best Practices

Feedback through quarterly surveys of member companies about the risk assessment process highlights the following best practices:

» Facilitation of the risk assessment process is important
  - *The individual who facilitates should ideally have inspection experience*
  - *Expect a learning curve for the facilitator to become familiar with conducting the process, modifying the internal tool, etc.*
  - *Consider developing a group of risk assessment Subject Matter Experts (SMEs) (number dependent on new studies in development)*
  - *Pre-populating the RACT tool expedites discussion and decreases the burden on the study team*

» Program level risk assessments are foundational to the life of a program, but can be challenging until moving into full program development. It is important that program level risks are applied to the study level risk assessments for consistency

» Risks assessed early during the course of a program may change; ensure mechanisms are in place to update program and protocol level assessment and documentation of risks for consistency

» Study level risk assessments should begin during the protocol development process

» Develop and maintain libraries of risks, critical data, critical processes, and mitigations to ensure consistency

» Embedding risk assessment into required processes ensures that the assessment will be conducted and assures that downstream activities, e.g. monitoring plan development, include the necessary focus on what is important. Without the necessary directives, the process sometimes becomes a debate as to whether it will be done

» Ensure there is documentation of the actual risk, not just the questions which drive the identification of risks

» Score non-applicable risk questions as 0 or NA for clarity, important not to delete items

» Document key discussions in the rationale column for risk items (provides documentation during inspections on decisions made)
Next Steps:

Feedback, through a survey of participating Member Companies, has indicated that several companies are modifying the tool in a number of ways in order to best fit the needs of their company. This may be simply to reword a question or to adjust the scoring from a 3 to a 5 point scale. The team, which manages the RBM toolkit, is of the opinion that the emphasis of their work should be on the following:

» Emphasizing the risk assessment process
» Highlighting the importance of identifying and assessing risks as foundational for RBM methods
» Better defining the program level risk assessment and differentiating it from the protocol risk assessment
» Highlighting possible modifications to the RACT tool that companies can consider
» Providing additional guidance on how to help teams assess/determine detectability, impact and probability

The team hopes to communicate this additional information in the second half of 2015.

Reminder:
Informational materials on the RACT and a sample completed RACT are available on the TransCelerate website.
4. Quantitative Performance Metrics

TransCelerate utilizes a core group of 8 metrics focused on 3 areas: quality, efficiency, and cycle time. The intent of the quantitative metrics is to determine the following:

- Determine the impact and effectiveness of the proposed RBM methodology on managing quality and risks associated with the conduct of clinical trials
- Determine if the RBM methodology works from the standpoint of operational impact on an organization, clinical sites and investigators

Metrics, represented in Table 1, are collected through a blinded third party on a quarterly basis. Metrics for this update were reported by 7 companies across 40 RBM studies that represent studies where sufficient data is available to report. As of April 2015, 10 companies have voluntarily implemented RBM methods in 83 studies in order to evaluate the methodology.

Summaries of collected metrics provide an indication in any given quarter where a particular metric may have worsened, remained neutral, or exceeded expectations. Companies use their own control values and report the results based on their individual requirements of what constitutes better or worse. The majority of the outcomes of the quarterly assessments remain improved or neutral; however, there were a few quarters within RBM studies where a particular metric was assessed as worsening when compared to established baselines within that company. A couple of the metrics are described in more detail below in order to provide representative samples to illustrate what we are seeing with the quantitative metrics. The RBM TransCelerate team continues to closely observe these metrics as they may have an impact on either the RBM methodology or learnings on implementation of the methodology.
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Metric Definition</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Quality</td>
<td>Ave. # major/critical audit findings per audited site</td>
<td>Improved focus on what matters should benefit results of QA process</td>
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<tr>
<td>Quality</td>
<td>% per site of unreported, confirmed SAEs compared to total SAEs</td>
<td>Enhanced focus on safety event reporting</td>
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<tr>
<td>Quality</td>
<td># of Significant Protocol Deviations per site</td>
<td>Indicates impact on safety and/or protocol compliance</td>
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<tr>
<td>Efficiency</td>
<td>Average Monitoring (all types) cost per site</td>
<td>Broader monitoring types may affect cost within new structure</td>
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<tr>
<td>Efficiency</td>
<td>Average interval between on-site monitoring visits per site</td>
<td>Indicator of whether more work is being done remotely</td>
</tr>
<tr>
<td>Cycle Time</td>
<td>Median number of days from patient visit to eCRF data entry</td>
<td>Impacts on ability to centrally monitor</td>
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<tr>
<td>Cycle Time</td>
<td>Median number of days from query open to close</td>
<td>Surrogate for unintended consequences of reduced site visits</td>
</tr>
<tr>
<td>Cycle Time</td>
<td>Median number of days from issue open to close</td>
<td>Surrogate for earlier identification and resolution of issues</td>
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To better highlight the findings two of the metrics are presented in more detail below:

1. Average number of major/critical audit findings per audited site
   » Results have been very positive. Reducing the number of findings related to quality assurance activities is the expected outcome. Details can be seen in Figure 1.

2. Median number of days from patient visit to eCRF data entry
   » Results have been mixed. The expected outcome is reduction in the time it takes for sites to enter information. The timeliness of data entry is a key enabler of central monitoring activities. Details can be seen in Figure 2
5. External Engagement

Research sites, Regulatory Authorities and Contract Research Organizations (CRO) are three areas of external focus for the TransCelerate RBM team in 2015. In addition, there are several Industry conferences (Table 2) where you may expect to see a TransCelerate perspective on RBM. The goals for interactions with the stakeholder groups are to build awareness of the TransCelerate methodology for RBM, to share best practices and lessons learned, to share information on new work of the team and to collect feedback that can be used to improve the methodology. Messaging on RBM also often needs to address the practices that are not conducive to improving the way Industry implements RBM, such as the example provided by an EMA speaker at DIA, identifying the use of a camera phone by one individual for remote monitoring.

The CRO industry, has coordinated the development of a CRO forum in which several of the workstreams of TransCelerate participate. The CRO forum is coordinated by the Association of Clinical Research Organizations (ACRO) and is open to all CROs including non-ACRO members (press release). This forum allows for an information exchange on the RBM methodology. In regards to sites, companies that have implemented RBM can choose to utilize a survey developed by the RBM workstream as a tool to collect feedback directly from sites on how that particular company’s RBM methodology has fared at the site-level. The RBM workstream also continues to share information with Regulators around the world in regards to what is being learned through the application of RBM.

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
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<tbody>
<tr>
<td>DIA China (TransCelerate’s Quality Management System and Risk Based Monitoring initiatives)</td>
<td>27 May 2015</td>
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<td>DIA Annual Meeting US</td>
<td>14-18 June 2015</td>
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<tr>
<td>SCRS Global Site Summit</td>
<td>8-11 Oct 2015</td>
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<td>SCRS EU Summit</td>
<td>1-2 Nov-2015</td>
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<td>CBI Annual Risk Based Monitoring in Clinical Trials</td>
<td>5-6 Nov 2015</td>
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<td>Partnerships in Clinical Trials - EU</td>
<td>19-20 Nov 2015</td>
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6. Deliverables in 2015

Data Integrity and GCP Misconduct Team
Framework Paper – expected to focus on providing a framework for the detection of serious data integrity and GCP misconduct issues. Primary methods include survey of companies plus literature search. Expected to be submitted for publication in September 2015.

Algorithm project – expected to provide an assessment of statistical monitoring assessments ability to identify falsified data within datasets that have been produced to be representative of both large and small studies. Expected to be submitted for publication in the fall of 2015.

Central Monitoring Team
Central Monitoring Part II paper – expectation is that this paper will refine information based on lessons learned over the past year in regards to Centralized Monitoring models. Expected to be submitted for publication in September 2015. As part of this work effort a library of risk indicators will also be published.

Technology Team
The work of the team is focused on developing business use cases that will allow for continued innovation in the technology that supports RBM methods. This paper expands on the work published in, “Technology Considerations To Enable The Risk Based Monitoring Methodology, Therapeutics and Innovation Sciences, 2014 Vol 48(5), 536-545”. This document is expected to be posted to the TransCelerate website by November 2015.