Model Approach for Risk-Based Monitoring

TransCelerate
BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

September 2013
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Introduction to the Course

Welcome to the TransCelerate Risk-Based Monitoring Course! This course has been designed to provide you with the knowledge, tools, and skills to successfully apply the principles of the TransCelerate Risk-Based Monitoring (RBM) methodology across the program, study, and site levels. This interactive training consists of self-study materials, instructional content, and application activities that can be used in any form of instructional setting (i.e. virtual or classroom). You may or may not participate in all modules of the course, depending upon your role and/or organizational needs. We encourage you to actively participate, ask questions, and share your experiences as we learn about this exciting initiative.

Course Overview

Self-study:

- TransCelerate’s “Position Paper: Risk-Based Monitoring Methodology”
- FDA’s “Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring”
- Draft EMA Reflection paper on risk based quality management
- CTTI paper (optional)

The papers for self study have been provided already as pre-course work.
Course outline for instructor led modules:

<table>
<thead>
<tr>
<th>RBM Training Module</th>
<th>Learning Objectives</th>
</tr>
</thead>
</table>
| 1. Introduction to Risk Based Monitoring (RBM) | 1. Describe the RBM Model as compared to traditional monitoring methods  
2. Explain the rationale for RBM  
3. Describe TransCelerate’s key assumptions and concepts |
| 2. Methodology and Team Members       | 1. Describe the TransCelerate RBM Methodology, including the RBM Toolkit  
2. Summarize responsibilities of functional team members involved with RBM  
3. Describe on-site, off-site, and central monitoring activities used in study oversight |
| 3. Risk Assessment                    | 1. Discuss methods for establishing and identifying risk for planning purposes  
2. Identify critical data for RBM application  
3. Use the RACT to perform risk assessment |
| 4. Risk Management                    | 1. Define and utilize Risk Indicators and Thresholds in decision-making  
2. Discuss implementation of risk mitigation plans  
3. Describe how to conduct monitoring activities in the RBM model  
4. Describe appropriate responses to potential issues and risks throughout the study |
| 5. Transitions-Application and Considerations of RBM Plan Implementation | 1. Inform sites about the RBM model  
2. Describe metrics used to measure the impact of the proposed methodology  
3. Apply effective transition techniques for studies and sites  
4. Discuss challenges with implementation within different cultures and systems |

This participant guide contains selective main topics from the individual modules and some activities as knowledge check. Completed slide sets might be provided by the trainer.

Activities are marked with following icon:
Module 1
Introduction to Risk-Based Monitoring (RBM)

This module will give an introduction to the concept of RBM, how it varies from traditional monitoring approaches and why TransCelerate is focusing on implementing this methodology. It will also introduce to definitions and assumptions underlying the TransCelerate Position Paper: Risk-Based Monitoring Methodology that was published May, 2013.

Objectives

At the conclusion of this module, learners will be able to:
1. Describe the RBM Model as compared to traditional monitoring methods
2. Explain the rationale for RBM
3. Describe TransCelerate's key assumptions and concepts
Objective 1  
Describe the RBM Model as compared to traditional monitoring methods

Traditional Approach: On-Site Monitoring

In person evaluation carried out by sponsor/CRO personnel at the investigative site location

The visits are generally conducted based on a set visit window schedule such as every four to six weeks and all data is source verified 100% regardless of the type of study, safety risks, phase of the study, stage of the study, or experience of the individuals conducting the study.

Visit objectives:

- Identify missing data in source records and data entry errors in case report forms
- Assess compliance with protocol and investigational product accountability
- Evaluate Investigator supervision
- Review essential documents

How does RBM differ from “Traditional” monitoring?

- RBM customizes approach and/or schedule as needed based on trial related risk assessment to identify potential issues.
- Leverages technology to allow sponsors/CROs to supervise study conduct without having to be at the site location.
- Shares monitoring responsibilities across many functional areas
- Relies more heavily on central and off-site monitoring
What means Central and Off-Site Monitoring?

Central monitoring involves a review of centralized data not just reviewing data from a central location. Off-site monitoring (sometimes called remote monitoring) is an evaluation carried out by sponsor personnel or representatives at a location other than the investigative site.

What needs to be done?
- Check that data is consistent and complete
- Identify un-usual distribution of data
- Identify higher risk sites to target additional monitoring
- Ensure routine review of data in real time

How to do it?
- Through analytics and visualization of data across the study, across regions, across a site and across a patient.

Who will do it?
It may be carried out by the same individual that would conduct on site monitoring such as a Clinical Research Associate or Clinical Monitor, or by other functional roles such as a data manager or statistician.

Conclusion:
A significant amount can be done proactively in addressing issues before ever going on site and identifying study risk factors and potential indications of risk.

Notes:

Notes:
What is Risk-Based Monitoring (RBM)

An adaptive approach to clinical trial monitoring that **directs monitoring focus** and activities to the evolving areas of greatest need which have the most potential to impact patient safety and data quality.

RBM provides sponsors with an ability to evaluate and plan for risks before a study starts and continuously adapt monitoring activities to areas that have the most potential to impact patient safety and data quality.

Fill steps for RBM into the frames in the correct order:

- Develop Monitoring plan
- Assess risk level
- Identify Critical Variables
Objective 2
Rationale for RBM

RBM Industry Movement

<table>
<thead>
<tr>
<th>CTTI</th>
<th>FDA Guidance</th>
<th>EMA Reflections Paper</th>
</tr>
</thead>
</table>
| Quality by Design  
  - Change approach  
  - No single approach is appropriate  
  - Tailor monitoring approach  
  - Protocol quality impacts monitoring quality | Quality Clinical Trial Data  
  - Assess Risk  
  - Combination of monitoring activities  
  - Tailor Monitoring Plan | Risk Based Quality Management  
  - Plan  
  - Adapt  
  - Build on experience and advances |

These three documents provide a framework for some of the concepts that are driving the industry to change away from the idea of “one size fits all”.

Why Should the Traditional Monitoring Approach be changed?

From the sponsor perspective, there may be multiple and varied reasons for changing the approach to monitoring. The rationale for change may vary depending upon everything from the size of the sponsor to the type of study being conducted.

The endorsement of a change in monitoring by key regulatory authorities serves as a rationale for looking at monitoring in a different way. These regulatory authorities are communicating that monitoring can and should be designed and customized to meet the specific needs of the program and study.
Various Reasons for Change

Complete the following graphic with additional reasons for change as given in the course presentation.

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Objective 3
Transcelerate’s key assumptions and concepts

TransCelerate BioPharma Inc. Introduction

TransCelerate BioPharma Inc. is an independent non-profit organization focused on accelerating the development of new medicines.

Mission:
  • Tasked with identifying and solving common drug development challenges to improve the quality of clinical studies and bringing new medicines to patients faster
  • Formed as an independent non-profit organization focused on accelerating the development of new medicines
  • Incorporated and launched in 2012

Solving industry-wide challenges collaboratively

Notes:
Partnering with Existing Collaborations

Risk-Based Monitoring is an industry wide initiative and not just a sponsor or CRO driven initiative. Potential stakeholders include regulatory bodies, industry initiatives, patient advocacy, and research and CRO community organizations.

Notes:

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TransCelerate BioPharma Inc. developed a methodology that shifts monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk-driven monitoring.

The TransCelerate RBM team started from an understanding that by building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely.

Industry stakeholders have recognized that although current on-site monitoring practices do provide a level of control, advances in risk-based approaches and technology provide an opportunity for a more holistic and proactive approach. This philosophical shift in monitoring processes employs Centralized and Off-site mechanisms to monitor important study parameters holistically and uses adaptive On-site Monitoring to further support site processes, subject safety, and data quality.
TransCelerate Monitoring Methodology:
Assumptions

There are 9 assumptions underlying the TransCelerate monitoring methodology

Fill in the gaps in the following text for the 9 assumptions

1. ___________ and ___________ monitoring are the foundation
2. ___________ activities are responsive to issues/risks
3. Tailor ___________ to available _______________
4. ___________________________ and query resolution are critical
5. Functional ___________ and documents should respond to changes/risks
6. RBM expectations can be formalized in ________________
7. Methodology applies to ____________ types and phases of __________
8. __________________________ plans should be tailored for efficiency
9. Risk ________________ should take place prior to protocol/CRF finalization

Notes:
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TransCelerate Approach

Building Quality by Design (QbD) is the first step in the TransCelerate approach. TransCelerate developed a model approach for RBM that can be adopted for any type, phase, and stage of trial.

TransCelerate’s RBM methodology uses quality risk management as a foundation in ensuring subject safety and data quality through the implementation of the following:

- **Build QbD into trials**
- **Early and ongoing risk assessment**
- **Focus on Critical Processes and Data**
- **Use of Risk Indicators, Thresholds & Action Plans**
- **Adjustment of monitoring activities**

The TransCelerate RBM methodology improves 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.
Module 1 Summary

- RBM is intended to improve upon the “traditional” monitoring model
- Rationale for RBM is driven by industry, risk, and technology changes
- TransCelerate’s key assumptions and concepts include a proactive quality by design approach to assess, mitigate, and manage risks

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Module 2
Risk-Based Monitoring: Methodology and Team Members

Within this module the TransCelerate Methodology will be explored in more detail.

Objectives

Upon completion of this module, learners will be able to…

1. Describe the TransCelerate Risk-Based Monitoring (RBM) Methodology, including the RBM Toolkit
2. Summarize responsibilities of functional team members involved with RBM
3. Describe on-site, off-site, and central monitoring activities used in study oversight
Objective 1
TransCelerate RBM Methodology and Toolkit

RBM Methodology – Key Ideas

- Focus on Central and/or Off-site monitoring activities
  - Identify and resolve issues more quickly
- Focus on errors that matter
  - Related to subject safety, data integrity, and/or regulatory compliance
- Recognize Investigators’ responsibility for data quality
  - Partners with the Sponsor to address, resolve, and prevent issues
The image shows an overview of TransCelerate’s methodology and the fundamental connection between Quality by Design and RBM. It is a stepwise approach, at each step; sponsors should document the decisions made, rationales, and appropriate plans.

RBM Methodology begins with the completion of risk assessments (labeled with the number one). The RACT (Risk Assessment Categorization Tool) is a tool which can be used for risk assessment. This will be discussed more detailed in module 3.

Step two involves defining Critical Variables which includes Critical Data and Processes, first at the program level, and then in further detailed evaluation at the protocol or trial level.

The third step is related to the development of the Integrated Quality and Risk Management Plan, also called the IQRMP. This is an overarching plan that connects all of the various quality and risk management strategies. The IQRMP may include the
Medical Monitoring Plan, Data Plan, Training Plan, Monitoring Plan, Safety Plan, and Statistical Analysis Plan, just to name a few.

The Monitoring Plan (MP) as part of the IQRMP will describe central monitoring, off-site and on-site monitoring activities. The development of the monitoring plan includes the identification of Risk Indicators and Thresholds. One of the key central monitoring activities is the implementation of those Risk Indicators and Thresholds. A companion guide has been developed by Transcelerate to provide guidance on Risk Indicators and Thresholds.

The final or fourth step involves the execution of the pre-determined monitoring activities. The entire process is dependent on QbD starting with the protocol and case report form development as an important foundation with an impact on quality and efficient monitoring.

Notes:

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Defining Critical Data and Processes

This refers to graphic on page 21 step 2

<table>
<thead>
<tr>
<th>Critical Data</th>
<th>Critical Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Support primary and key secondary objectives</td>
<td>• Underpin data quality</td>
</tr>
<tr>
<td>• Critical to subject safety</td>
<td>• Underpin subject safety</td>
</tr>
<tr>
<td>• Support decision-making about efficacy of the IP</td>
<td>• Support ethical and GCP compliance</td>
</tr>
</tbody>
</table>

Once defined, Critical Data and Processes should be monitored accordingly as documented in the Monitoring Plan, including details of changes in the monitoring based on identified Thresholds.

Monitoring Plan

This refers to graphic on page 21 step 3

This includes the development of the plans for monitoring which describes central monitoring, off-site and on-site monitoring activities. The plan includes the identification of Risk Indicators and Thresholds. One of the key central monitoring activities is the implementation of those Risk Indicators and Thresholds. A companion guide has been developed by Transcelerate to provide guidance on Risk Indicators and Thresholds.
RBM – Toolkit

RACT - Risk Assessment and Categorization Tool

1. Determine risks which could affect patient safety, data integrity, and/or regulatory compliance
2. Identify how and by which function(s) risk will be managed
3. Categorize risks which will be managed by and affect the Monitoring Plan
4. Determine Overall Risk Level (high, medium, or low) for monitoring activities
5. Apply the Overall Risk Level to determine the baseline monitoring approach

This ensures monitoring strategies are tailored to risks that are focused on Critical Data and Processes.

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IQRMP – Integrated Quality and Risk Management Plan

1. Document protocol-level risks and mitigations from the RACT in the various components
2. Document Risk Indicators and associated Thresholds and actions
3. Align associated quality management plans

Core of Quality Risk Management

The functional plans are all aligned around the risk assessment, Critical data, and Risk Indicators and their Thresholds.
The procedures and activities described within the IQRMP should not duplicate instructions contained in Standard Operating Procedures. The IQRMP should describe the trial-specific actions/processes that will be implemented to address identified risks and focus on Critical Data/Processes.
The IQRMP is not intended to duplicate the content of existing functional plans; these are linked or referenced within the IQRMP and accountability for each plan remains with the relevant function.

The overall accountability for the development and maintenance of the IQRMP should be assigned to a centralized function such as project or program management to ensure that the key elements are aligned across all functional areas.

Notes:

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## Risk Indicator - Terminology Review

<table>
<thead>
<tr>
<th>TransCelerate Definition from position paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Data and other study variables to be assessed (in many cases by comparing across program / protocol / country / site)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Working Definition for the course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables which are considered to have underlying influence on the quality of a study and are assessed by comparison across a program, study, country, and/or site</td>
</tr>
</tbody>
</table>

## Threshold - Terminology Review

<table>
<thead>
<tr>
<th>TransCelerate Definition from position paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>The level, point, or value associated with a Risk Indicator that will trigger an action</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Working Definition for the course</th>
</tr>
</thead>
<tbody>
<tr>
<td>A pre-determined study specific number, value, % or range associated with a Risk Indicator that indicates the need for a follow-up action</td>
</tr>
</tbody>
</table>
Objective 2
Responsibilities of functional team members

The TransCelerate RBM methodology outlines various activities to be completed and documents to be finalized in establishing an RBM approach to monitoring clinical trials. Different organizational structures, differing departments and/or job roles will be involved in these various processes. But, important to understand within your organization which functional areas will have responsibility for and/or be involved in the core RBM methodology activities outlined here.

Here are some examples: Data managers, Clinical Research Associates or field based monitors, Monitoring Managers, In-house Clinical Research Associates or monitors, Medical Monitors, Project Managers, Clinical Scientists, Quality Assurance, Statisticians, Regulatory associates, Investigators, and Study Coordinators.

Who Does What?

– Identify Critical Data/Processes

– Risk Assessment (which may include participation in RACT discussions)

– Author the IQRMP

– Author the Monitoring Plan

– Identify Risk Indicators and Thresholds

– Execute monitoring activities
Objective 3
Central, Off-Site, and on-site monitoring activities

Central Monitoring Activities

Comparisons of Risk Indicator data and information (across studies, between investigative sites, etc.) may include:

- Protocol deviation rates
- Data entry and query resolution metrics
- Adverse event trends or outliers
- Subject discontinuation trends
- Unusual data trends or patterns
- Error rates in Critical Data/Processes

Central monitoring focuses on Risk Indicators and can best be thought of as review of centralized data rather than a centralized review of individual site data.

Notes:
Off-Site Monitoring Activities

Examples may include:
- Confirm timeliness and quality of data entry
- Review query resolution
- Review CRF to check protocol compliance
- Confirm site’s completion of previously identified actions
- Review essential documents
- Assess site’s recruitment and enrollment
- Monitor investigational product
- Monitor for changes in site staff
- Monitor delegation of responsibilities
- Conduct training

Key message: everything that CAN be done remotely SHOULD be done remotely since it can be done in a timelier manner and issues can be identified sooner.

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On-Site Monitoring Activities

Examples may include:
- Source Data Review (SDR)
- Source Data Verification (SDV)
- Informed Consent Review
- Investigational Product Accountability
- Essential Documents Review (if appropriate)
- Face-to-face training and discussions with site staff

Notes:

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Source Data Verification (SDV)

- Transcription Check
- Two-way check (Source to CRF and CRF to Source)
- Done on Critical Data only
- Amount varies by risk

Source Data Review (SDR)

- Reviewing source documents for important areas where there is no associated CRF data field
- Monitoring the site’s Critical Processes
- Not a two-way review of Source to CRF
- Amount of review varies by risk

Why Distinguish SDV and SDR?
SDV is the process by which data within the 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.

In contrast, issues with compliance (i.e. protocol violations) are one of the reasons for study data being excluded from the final efficacy analysis. These types of errors are more readily identified through SDR.

SDV and/or SDR can be temporarily increased or decreased depending on the type of issues and risks noted at the site, country/region, or study level

Examples discussed during the course:
Module 2 Summary

- The TransCelerate RBM Methodology includes defined steps and tools to ensure quality and consistency
- The RBM steps are most efficiently completed through a cross-functional assessment and collaboration
- Study oversight is accomplished through an appropriate mix of central, off-site, and on-site monitoring activities
Module 3
Risk Assessment

This module we will give a more hands-on approach to the application of concepts, tools, and materials described in the TransCelerate Risk-Based Monitoring (RBM) methodology.

Objectives:

Upon completion of this module, learners will be able to…
1. Discuss methods for identifying risk for planning purposes
2. Identify Critical Data/Processes for Risk-Based Monitoring (RBM) application
3. Use the Risk Assessment Categorization Tool (RACT) to perform risk assessment
Objective 1
Identifying risk for planning purposes

Risk Assessment Process

This diagram illustrates the timing of the protocol synopsis, protocol approval, and first subject first visit and how these fit in with the risk assessments, identification of Risk Indicators, and development of risk mitigation plans.

Note: Details of this process flow may differ depending upon individual company procedures.

The first step is identification of Critical Data/Processes and risk assessment at the program level. These steps are completed using the RACT (see module 2).

Describe the activities and responsibilities below as given in the course presentation.

Arrow 1:
Arrow 2:

Arrow 3:
Risk Assessment Cycle

Why is it displayed a cycle?

There is the potential for new risks to be identified in a clinical development program at any time.

Therefore, whenever a new risk is identified, the remaining steps should also be completed - assessing the risk (ranking it), eliminating its occurrence, or if that’s not possible, managing the risk to minimize its impact. In some cases, the study team will decide to accept a given risk as is.
Step One: Identifying Risks

Risks may exist at three different levels:

- Program-level
- Trial-level
- Site-level

Can you identify at least one key question that should be considered to determine risk at each of the levels?

Program level:

______________________________________________________________

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______________________________________________________________

Trial level

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______________________________________________________________

Site level

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Step Two: Evaluating Risks

- Risk ranking is often relative
  - For example, a risk with a high impact but low likelihood may or may not be prioritized above a risk with a moderate impact and higher likelihood
  - Risk Level may be defined as high, medium, or low

Step Three: Preventing or Planning For Risks

- Elimination of risks is preferable
  - Not always possible
  - Protocol and/or Case Report Form (CRF) design
- Plan for risks that are not preventable
  - Risk management
  - Detection, measurement, and action

Conclusion:
It is always preferable to prevent risks from occurring if at all possible. Once a significant risk is identified, team members should decide if the risk can be eliminated by modifying the protocol or case report form(s).

Notes:
Objective 2
Identifying critical data/Processes for RBM application

Critical data and processes have been explained already in module 2.

What are some examples of Critical Data and Critical Processes in the studies you’ve worked on?

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Course Activity
You can find in the attachments a protocol synopsis and an exercise document. Work on activity #1 as given in the document.

TransCelerate_RBM Activity Protocols Mod 3 Activity Instructions
Objective 3
Application of the RACT to perform risk assessment

Risk Assessment Categorization Tool (RACT)

Check with module 2

What is the RACT?

- Part of RBM Toolkit
- Excel document
- Protocol-specific
- Version controlled

What is the purpose of the RACT?

- Facilitate risk assessment and risk mitigation

How to complete the RACT?

- Review a category by discussing all of the questions and reviewing the examples and consideration
- Determine a risk level for that category (level (high, medium, or low)
- Determine by category the function(s) responsible for mitigating or monitoring the risk
- Determine an Overall Risk Level for the protocol
- Determine baseline monitoring activities based on the Overall Risk Level for the protocol

How to prepare the RACT?

- **Gather information**
  - Program level
    - Product
    - Regulatory
  - Protocol level
    - Protocol (synopsis at minimum)
    - Site/facility requirements
- **Gather the team**
  - Cross-functional team members
Example – Preparation

- Study comparing IP vs. placebo in subjects with Type 2 diabetes
- Primary endpoint: improvement in Hemoglobin A1c (HbA₁C) – collected every 6 weeks
- Secondary endpoints: improvement in fasting glucose, 2 hr oral glucose tolerance test (OGTT), and body weight – collected every 6 weeks
- Central lab analyzes HbA₁C, fasting glucose, and OGTT; site collects body weight
- The IP has no known significant safety issues

The preparation of RACT can also be seen as a cycle:

RACT Step One: Discussion

- Objective provides focus
  There are specific instructions to help focus the use of the tool for each risk category.

- Questions for discussion and Examples / considerations
  Each risk category within the RACT can be expanded to display columns that provide “Questions for Discussion” and “Examples/Considerations”. These are intended to provide sample questions for the team to evaluate and answer in order to better understand the risk(s) within each category.
### Objective ‘Complexity risk category’

<table>
<thead>
<tr>
<th>Questions for Discussion</th>
<th>Examples /Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the protocol require any complex or uncommon procedures beyond the usual standard of care?</td>
<td>Consider the number of visits, the duration of the study, diagnostic testing that is not common for this patient population.</td>
</tr>
<tr>
<td>Will the study collect PK?</td>
<td>If yes, consider number of time points.</td>
</tr>
<tr>
<td>Will the complexity affect patient burden?</td>
<td>Consider the possibility of noncompliance or withdrawal of consent</td>
</tr>
</tbody>
</table>

Let’s check the first question:
‘Does the protocol require any complex or uncommon procedures beyond the usual standard of care?’

Within this one RACT question for discussion are two sub-questions.

Sub-question 1: What contributes to protocol complexity?

Possible answers as result of the discussion within the course:

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Sub-question 2: Are there any procedures required beyond usual standard of care (SOC)?

To answer this question the team will need to understand the standard of care for this indication, type 2 diabetes.

American Diabetes Association (ADA) 2013 guidelines for assessment of glycemic control in patients with Type 2 diabetes:

- Perform the HbA$_1c$ test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control)
- Perform the HbA$_1c$ test quarterly in patients whose therapy has changed or who are not meeting glycemic goals

Possible answers as result of the discussion within the course:
RACT Step Two: Risk Level

- RACT is programmed with drop-down box
- High, Medium, or Low risk

There are two questions the team should discuss:

1. What is the likelihood of the risks occurring?
2. What is the impact or consequences of the risks should they occur.

Based on previous discussion within this example of the Type 2 diabetes study, what risk level should be assigned to the Complexity category?

Risk level: ____________________________

Rationale:
Likelihood: ____________________________  Impact: ____________________________
RACT Step Three: Impact to Functional Plans

The cross-functional team members will identify the Functional Plan(s) that are impacted by the risk in each category.

The first seven risk categories in the RACT have been pre-identified by TransCelerate as those commonly impacting the Monitoring Plan.

Team members should determine the impacted Functional Plan(s) for the remaining 8 categories.

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RACT Categories and Monitoring Impact

These are the categories of potential risk as listed on the RACT.

Those with the blue background could potentially impact the monitoring plan but other functional plans (i.e., data management, safety, communication, outsourcing/vendor oversight, etc) should be considered for risk management.

Those categories with the yellow/orange background will impact the monitoring plan most significantly. These are the categories that will be considered in determining the Overall Risk Level (as related to monitoring activities) for the study.

**Conclusion:**

Focusing our risk evaluation on those factors which most significantly impact Critical Data and Processes ensures our monitoring approach is truly “risk-based.”

**Course Activity**

You can find in the exercise document. Work on activity #2 as given in the document
Overall Risk Level and Baseline Monitoring Approach

<table>
<thead>
<tr>
<th>Monitoring Activity</th>
<th>High Risk</th>
<th>Medium Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation and Review of Data (Central/Off-Site)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SDV of Critical Data for 1st Randomized Subject</td>
<td>&gt;75 - 100%</td>
<td>&gt;50 - 75%</td>
<td>0 - 50%</td>
</tr>
<tr>
<td>SDV of Critical Data for Subsequent Randomized Subjects</td>
<td>&gt;15 - 25%</td>
<td>&gt;5 - 15%</td>
<td>0 - 5%</td>
</tr>
<tr>
<td>SDR of Critical Data for 1st Randomized Subject</td>
<td>&gt;75 - 100%</td>
<td>&gt;25 - 75%</td>
<td>0 - 25%</td>
</tr>
<tr>
<td>SDR of Critical Data for Subsequent Randomized Subjects</td>
<td>&gt;25 - 40%</td>
<td>&gt;10 - 25%</td>
<td>0 - 10%</td>
</tr>
<tr>
<td>Informed Consent Review</td>
<td>&gt;75 - 100%</td>
<td>&gt;50 - 75%</td>
<td>20 - 50%</td>
</tr>
</tbody>
</table>

This is a sample application from the TransCelerate position paper where the baseline approach to monitoring for various activities has been assigned based on the Overall Risk Level of the study (high, medium, or low).

In the RBM methodology, it is acceptable to assign differing Overall Risk Levels for various stages of the study. For example, the Overall Risk Level may be high during active enrollment or the period in which subjects are receiving IP but then be set as low during the subject follow-up phase. The type, amount, and location of monitoring activities may also vary accordingly. Module 4 will discuss this concept in more detail.

Note: This chart reflects the baseline approach to monitoring; results from monitoring (Central, Off-site, or On-site) may guide specific interventions and require a change in the risk level and/or approach.

Course Activity
Your course trainer did provide you with a protocol synopsis and an exercise document. Work on activity #3 as given in the document
Module 3 Summary

- Early and proactive identification and assessment of risks is a core activity of the RBM methodology
- Risk assessment should focus on the Critical Data and Processes which have been identified at the program and protocol levels
- The RACT is a valuable tool to facilitate a systematic risk assessment process
Module 4
Risk Management

This module will focus on the use of Risk Indicators and Thresholds in designing risk mitigation plans and assuring issues are identified and resolved in a timely manner.

Objectives:

Upon completion of this module, learners will be able to…

1. Define and utilize Risk Indicators and Thresholds in decision-making
2. Discuss implementation of risk mitigation plans
3. Describe how to conduct monitoring activities in the RBM model
4. Describe appropriate responses to potential issues and risks throughout the study
Risk-Based Monitoring (RBM) Methodology - High Level Process and Associated Tools

This high level process has been introduced in module 2.

The discussion of Risk Indicators and Thresholds takes us into Step 3 of the process. Risk mitigation planning occurs in Step 3 and is implemented in step 4.
Objective 1
Risk Indicators and Thresholds in decision-making

Risk Management Components of the RBM Methodology – Risk Indicators

‘Roadmap’

1. Now that we know what our risks are, what helps us to detect that risk?
   Risk indicators are established to allow us to detect potential problems or risks in the study.
2. At what point in the study will we know there is a potential problem requiring action?
   Establishing Thresholds for our Risk Indicators helps us to establish expectations and sets a trigger point for action.
3. How will we respond when a Threshold is reached and/or a potential problem is found?
   Actions are designed to appropriately respond to data and information that indicates a possible problem.
Step 1: Risk Indicator - Terminology Review

Risk indicators have been introduced in module 2. Below you can find again the definitions.

<table>
<thead>
<tr>
<th>TransCelerate Definition from position paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Data and other study variables to be assessed (in many cases by comparing across program / protocol / country / site)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Working Definition for the course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables which are considered to have underlying influence on the quality of a study and are assessed by comparison across a program, study, country, and/or site</td>
</tr>
</tbody>
</table>
Risk Indicator Categories and Examples

The table shows 8 TransCelerate categories. Enter an example for each of a potential Risk Indicator based on the course presentation.

<table>
<thead>
<tr>
<th>Safety</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment/Discontinuation</td>
<td>Issue Management</td>
</tr>
<tr>
<td>Data Quality</td>
<td>On-Site Workload</td>
</tr>
<tr>
<td>Essential Documents</td>
<td>Staffing, Facilities, Supplies</td>
</tr>
</tbody>
</table>

Your course trainer did provide you with an activity document. Locate activity #1 and complete the exercise as directed by the instructor.
Step 2: Thresholds

Different levels of Thresholds may be set for a specific Risk Indicator. This practice can facilitate directing our response activities in accordance with the level of perceived risk.

An example shown here involves three different levels (high, medium, and low) and shows how they can be conceptualized.

- A Risk Indicator in the high range reflects a warning and would require more immediate attention than an item coded as Medium or Low.
- The medium range provides more of an awareness of a potential problem.

A Risk Indicator in the low range may be considered more acceptable in terms of risk and possibly require no action.

<table>
<thead>
<tr>
<th>Threshold Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Warning range</td>
</tr>
</tbody>
</table>
RBM Toolkit:
Companion Guide to Risk Indicators

The Companion Guide to Risk Indicators has been discussed already as part of the RBM Toolkit.

This guide can be used to facilitate consistency among team members in applying Risk Indicators and Thresholds for decision-making and responding to risks.

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Examples of Action(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- 5% more/less than the average reported AE rate (Green)</td>
<td>No action</td>
</tr>
<tr>
<td>+/- 5.1 to 15% more/less than the average reported AE rate (Yellow)</td>
<td>No action, Assess data remotely (e.g. determine if AE symptoms were listed as separate AEs versus entered as one diagnosis, consider if the site's subject population is associated with a higher than average number of AEs), Call the site, Visit the site</td>
</tr>
<tr>
<td>Greater than 15% of the average reported AE rate (Red)</td>
<td>Assess data remotely, Call the site, Visit the site</td>
</tr>
</tbody>
</table>

Your course trainer did provide you with an activity document. Locate activity #2 and complete the exercise as directed by the instructor.
Step 3 Actions: Responses to Thresholds

- Possibly no action needed beyond ongoing monitoring

- Continue central and/or off-site monitoring
  - Assess other data remotely
  - Contact site to get additional information

- Contact site to get additional information
  - Collect site documentation
  - Visit site to review documentation not available remotely

Notes:
Sample Decision Tree for Responding to Thresholds

In some situations, it may be useful for an action plan to make use of a decision tree. This would guide team members through the various steps of investigation when a particular Threshold is reached. A sample of this approach is provided here.

Your course trainer did provide you with an activity document. Locate activity #3 and complete the exercise as directed by the instructor.
Objective 2
Implementation of Risk Mitigation Plans

What is a Risk Mitigation Plan?

- Documented plan
- Assigns responsibility
- Actions taken to prevent or decrease the probability of a risk becoming an issue

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Objective 3
Monitoring activities in the RBM model

This is related to the High Level Process and Associated Tools step 4 ‘Monitoring Execution’

Key Ideas – Monitoring in the RBM Methodology

- Monitoring defined by risks
- Ongoing Central and/or Off-site monitoring activities
- Triggered On-site monitoring
- Monitoring is cross-functional
There are two terms related to monitoring are clarified in the TransCelerate position paper

Source Data Verification (SDV)

Source Data Review. (SDR)

Both have been already discussed in module 2 of this course. Look at these two terms and how they are defined and applied in the RBM methodology.

Which monitoring activity (SDV or SDR) would more readily identify each of the following? (choose only one – SDV or SDR)

A. Subject’s date of birth (DOB) in medical records doesn’t match DOB in case report form (CRF) ________________

B. An unqualified site employee is performing a critical study task ________________

C. Incorrect blood pressure value is recorded in CRF ________________

D. Abnormal lab results are not being assessed for clinical significance______________

E. Incorrect version of the informed consent document is being used ________________
Objective 4  
Responses to potential issues and risks throughout the study

This is related to the High Level Process and Associated Tools step 4 ‘Monitoring Execution’, see also objective 3.

Your course trainer did provide you with an activity document. Locate activity #4 and complete the exercise as directed by the instructor.

Notes:

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Module 4 Summary

- Risk Indicators and Thresholds
- Risk mitigation plans
- Monitoring activities in the RBM model
- Responding to issues and risks
Module 5
Transitions – Application and Considerations of Risk-Based Monitoring (RBM) Methodology Plan
Implementation

Objectives:

Upon completion of this module, learners will be able to…

1. Inform investigative sites about the Risk-Based Monitoring (RBM) model
2. Describe metrics used to measure the impact of the proposed methodology
3. Apply effective transition techniques for studies and sites
4. Discuss challenges with implementation within different cultures and systems
Objective 1
Inform Investigative sites about the RBM model

Potential Discussion Points with Sites

RBM is defined as:

An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality.

The core principles of RBM include:

- Monitoring activities are designed to focus on the data that is critical to satisfy study objectives, protect the safety of subjects, and/or ensure regulatory compliance
- Shared responsibility for subject safety and data quality exists; investigators are responsible for their site’s data quality and are expected to partner with the Sponsor to address, resolve, and prevent issues
- Customize the monitoring approach to each trial based on risk assessment; includes greater reliance on central/off-site monitoring and expanding the concept of monitoring to a cross-functional responsibility
- Use of all available technology to allow sponsors to supervise study conduct without having to be at the site location; this allows for more rapid identification and resolution of potential issues
- Adapt the monitoring approach and activities as required in response to risks or issues that evolve during the trial; includes a more targeted approach for on-site monitoring visits (these are data driven not interval driven)
Potential Discussion Points with Sites (continued)

- Reduction in amount of source data verification
- More targeted source data verification
- Source data review performed to evaluate site processes
- Shift of priorities during on-site monitoring

Notes:
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Potential Discussion Points with Sites (continued)

- Investigators expected to take “ownership” of data
  - Timely data entry
  - Identify causes of problems when they occur
  - Take action to prevent recurrence of errors
- Opportunity for site quality assurance

Notes:

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Potential Discussion Points with Sites (continued)

- No fixed schedule of on-site monitoring
- Many different sponsor personnel may perform monitoring activities
- More central and off-site monitoring

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Potential Discussion Points with Sites (continued)

- Greater use of technology
- Timely data entry and query resolution
- Data reviewed off-site and sites contacted to resolve issues remotely
- Central monitoring to compare data and identify issues

Notes:

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Potential Discussion Points with Sites (continued)

– Teleconferences to discuss central/off-site monitoring findings
– Data, findings, or study events may “trigger” on-site monitoring
– Monitoring adjusts during study as risks change

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Objective 2
Metrics to measure impact of the RBM Methodology

Defining Metrics

What are Metrics?
Standards of measurement by which efficiency, performance, progress, or quality of a plan, process, or product can be assessed\(^1\)

\(^1\)Source: BusinessDictionary.com

In other words:
- Measurement
- Applied to quantifiable aspect of performance
- Used for decision-making

<table>
<thead>
<tr>
<th>Dimensions to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality</strong></td>
</tr>
<tr>
<td>Audit findings per site</td>
</tr>
</tbody>
</table>

Can you identify at least one more metric within each dimension to evaluate the effectiveness of the RBM methodology on clinical trial operations?
Objective 3
Effective transition techniques for studies and sites

Transition Scenarios for Ongoing Studies

- Sites
  - All Sites
  - Selection of Sites

- Stage
  - Prior to Study Start
  - Ongoing study
    - During enrollment
    - After enrollment is complete

Notes:

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Techniques for Transition – Summary

– Follow RBM methodology process
– Revise risk mitigation plans accordingly
– Consider technology, budget, and timeline factors
– Communicate (internally and externally)
– Identify and address training gaps
– Plan for lessons learned and metrics to evaluate

Notes:

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Objective 4
Challenges with RBM implementation

Challenges with Change

Whenever we encounter a change in the industry or with an internal process, there may be challenges and possibly resistance.

- Cultural – We’ve always done it this way
- Systems – The systems we have require that we do it this way

Notes:
Discussion Point

Can you name specific challenges that you would anticipate with your company and/or organization?

Here are some possible scenarios.

- SOPs may be complex or not easily changed
- Resourcing
- Change management
- Technology and systems
- Strategic partnerships

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Module 5 Summary

Successful transitioning to the RBM methodology requires

- Information to be provided to sites to help them understand and manage change
- Strategies to measure the impact of RBM
- Techniques to ensure efficiency
- Understanding and preparing for potential challenges

Notes:
Links:

Note: Links might be outdated soon if updated documents become available.

TransCelerate Home Page
http://www.transceleratebiopharmainc.org
FDA Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring [Final].
EMA Reflection Paper on Risk Based Quality Management in Clinical Trials (EMA/INS/GCP/394194/2011).
Clinical Trials Transformation Initiative. Effective and efficient monitoring as a component of quality.
https://www.ctti-clinicaltrials.org/project-topics/study-quality/effective-and-efficient-monitoring-as-a-component-of-quality