Model Approach for Risk-Based Monitoring

Module 2: Methodology and Team Members

Trainer Guide
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MODULES / LESSONS

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Getting Started

About This Guide

What’s the purpose of this guide?
This trainer guide provides a master reference document to help the trainer prepare for and deliver the *Model Approach for Risk-Based Monitoring* training program.

What you will find in this guide?
This trainer guide is a comprehensive package that contains
- checklists of necessary materials and equipment
- presentation scripts and key points to cover, and
- instructions for managing exercises, case studies, and other instructional activities regardless of delivery method (in-person classroom, webinar or a blended classroom environment).

How is this guide organized?
Refer to the introductory materials: About this Guide within the Leader Guide for Module 1 for further details on how this guide is organized, graphical cues and overall program information.
Methodology and Team Members

Goal
The purpose and goal of this module is to further explore the TransCelerate Methodology, introduce the RBM toolkit, discuss RBM team responsibilities within a company, and describe the on-site, off-site, and central monitoring activities in study oversight.

Time
90 minutes

Overview
This module is a combination of presentation of material and facilitated “challenge” exercises for the participants.

Some slides within this module are hidden content for trainer determination of whether or not they are necessary to show during the course.

Materials Needed
- Participant Workbook (one per participant)
- Flipcharts & Markers (one per every 2 tables – for face-to-face sessions)
- Prepared Flipchart to match slide 5 for activity
- Multi-Colored Index Cards labeled as follows (one per person for face-to-face sessions):
  - Red – one side marked with a large F and one with an A
  - Green – one side marked with a large T and one with a B
  - Yellow – marked with a large C
  - Orange – Marked with a large D
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Module 2: Introduction

Module 2

RISK-BASED MONITORING: METHODOLOGY AND TEAM MEMBERS

Welcome to Module 2

Welcome to Module 2. In this module, we will be providing an overview of the TransCelerate Methodology process and toolkit, comparing off-site, on-site, and central monitoring, and finally, considering the functional areas or roles supporting RBM. Throughout, we will be discussing RBM as a multi-layered team approach rather than solely as a Monitor or Clinical Research Associate's requirement for reviewing data.
Module 2: Introduction

Course Overview - Five Modules

1. Introduction to Risk-Based Monitoring (RBM)
2. Methodology and Team Members
3. Risk Assessment
4. Risk Management
5. Transitions
Module 2: Introduction

Course Program Overview

The course information will be broken down into five distinct modules. While information may overlap, the intent is to individually explore the concepts, tools and implementation of evaluating risk and implementing management and monitoring techniques. Each module will consist of three to four key objectives, broken into lessons.

The modules are as follows:

*Module 1- Introduction to Risk-Based Monitoring (RBM).*

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

*Module 2- Methodology and Team Members.*

The focus of module 2 will be to further explore the TransCelerate Methodology, introduce the RBM toolkit, discuss RBM team responsibilities within a company, and describe the on-site, off-site, and central monitoring activities in study oversight.

*Module 3- Risk Assessment.*

In module 3 we will be focusing on how to identify and quantify risk and will address one of the key measurement tools, the RACT, in detail.

*Module 4- Risk Management.*

Module 4 will further address risk management and how to define critical Risk Indicators and Thresholds in decision-making. We will also talk about risk mitigation plans, activities, and risk response.

*Module 5- Transitions.*

The focus of the final module is on the application and considerations of RBM plan implementation. In this section we will address a practical approach to implementation and management, as well as how to transition projects, protocols and sites into the RBM model.

**IMPORTANT NOTE**

Not all participants will be required to take all five modules of this program. Remind the participants that they will be participating in the modules as appropriate to them.
Module 2: Introduction

Module 2 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

Module Objectives

Review the module objectives as noted on the slide.

While these objectives are less focused on application of knowledge, they form the foundation for later modules in which the learner will practice using components of the RBM toolkit and completing steps in the RBM methodology process.

Direct participants to the Participant Workbook
Module 2: Introduction

Introduction

The RBM Methodology developed by TransCelerate Biopharma Inc. was set forth in a position paper published in May 2013 and is the foundation of this course.

What do you already know about the TransCelerate RBM methodology?

NOTE: The challenge question is on the next slide.
Module 2: Introduction

Slide 6

Challenge Yourself

Quality Risk Management is the foundation to ensure subject safety and data quality

1. 2. 3. 4. 5.

What are the quality risk management concepts?

*Hint: These 5 concepts were introduced in Module 1.*

Challenge Yourself Activity

Ask learners to recall the information as presented in Module 1 regarding quality risk management concepts. Use the facilitation guidance below to conduct the activity.

NOTE: Allow approximately 10 minutes for this activity.

**IMPORTANT NOTE**

The answers for each of the challenge yourself activities are listed on the slide following the question. These may be hidden if you choose not to use the slide to reveal the answers.

Facilitating the Activity
Module 2: Introduction

Classroom Workshop Participants (face-to-face)

Provide each table team with a prepared flip-chart with the stair steps and numbers. Ask the team to recall (to the best of their ability without referring to module one materials), what the five concepts covered in Module one were and write the answers in the corresponding stair steps on the flip chart.

Challenge the table teams to see who can complete the chart first without using their books.

NOTE: You can keep score throughout the day on a separate flipchart or give small candy prizes to teams for each activity.

Webinar Workshop Participants (online)

Utilize the annotation functionality within your webinar provider and ask users to write their responses on the slide within the meeting room.

Encourage some competition seeing how fast each of the five can be completed and using the initials within the annotation feature, you can determine who completed the most answers. If able, offer a small incentive for the most responsive participant throughout the session.

Challenge Yourself - Answer Key

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

1. Build QbD into trials
2. Perform early and ongoing risk assessment
3. Focus on Critical Processes and Data
4. Use of Risk Indicators, Thresholds & Action Plans
5. Adjustment of monitoring activities
Module 2: Introduction

Debrief Challenge Yourself Activity

While presenting the answer key slide, review the content from module one.

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

1. building QbD into trials,
2. performing early and ongoing risk assessment,
3. a focus on Critical Processes and Critical Data,
4. The use of Risk Indicators and Thresholds, and
5. adjustment of monitoring activities based on the issues and risks identified throughout the study.
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Module 2: Objective 1

TRANSCELERATE RBM METHODOLOGY AND TOOLKIT

The RBM Methodology and Toolkit through TransCelerate

Our first objective is to describe the TransCelerate RBM Methodology and the Toolkit provided in the position paper.

We will be approaching this at a general level and introducing the key processes and tools to allow us to later apply the methodology through simulations and activities.
RBM Methodology & Toolkit

Slide 9

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

Make the following key points:

Key ideas in the TransCelerate RBM methodology include

- applying an efficient monitoring approach to rapidly detect and correct issues while the study is ongoing,

- focusing on errors that represent risks to subject safety, critical data, data integrity, and/or regulatory compliance, and

- recognizing that Investigators are responsible for their site’s data quality and are expected to partner with the Sponsor to address, resolve, and prevent issues

Direct participants to the Participant Workbook
RBM Methodology & Toolkit

Slide 10

Risk-Based Monitoring (RBM) Methodology - High Level Process Map and Associated Tools

1. Risk Assessments
   - Complete Risk Assessment Categorization Template (RACT)
   - Define at the Program Level
   - Reassess at the Protocol Level

2. Critical Variables
   - Includes Critical Data and Processes

3. Risk Plan
   - Develop Integrated Quality and Risk Management Plan (IQRMP)
   - Define Central, Off-site, and On-site Monitoring Activities and other risk mitigation activities in Functional Plans (e.g., Monitoring Plan, Data Plan)

4. Monitoring Execution
   - Execute Monitoring Activities

IMPORTANT NOTE

The image is meant to provide an overview of the key elements in the TransCelerate RBM. Introduction of each numbered step can be general as the next several slides provide more detail.

Page 21-22

Direct participants to the Participant Workbook
RBM Methodology & Toolkit

Process & Associated Tool

This is an overview of TransCelerate’s methodology and the fundamental connection between Quality by Design and RBM. The methodology proceeds in a stepwise fashion; at each step, sponsors should document the decisions made, rationales, and appropriate plans.

1. As you can see, RBM Methodology begins with the completion of risk assessments (labeled with the number one).
2. 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.
3. The third step is related to the development of the Integrated Quality and Risk Management Plan, also called the IQRMP. In the RBM methodology, 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) 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.
4. The final or fourth step involves the execution of the predetermined 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.

Let’s now look at steps 1 and 2 in more detail.

Some possible tools have been developed by TransCelerate and are outlined as well within the process flow.

- The RACT (Risk Assessment Categorization Tool) is a tool which can be used for risk assessment. This tool will be reviewed later in more detail; in module 3, learners will have a chance to work with the RACT.
- A companion guide has been developed by TransCelerate to provide guidance on Risk Indicators and Thresholds.
Make the following key points:

- The program and protocol level assessments are not strictly sequential, but should be performed as a constant cross-functional and collaborative effort. Critical Data and Processes for each specific protocol or trial are identified and expanded as the assessment moves from a program level to a protocol level.

- When defining Critical Data, cross-functional collaboration is necessary to ensure appropriate identification and monitoring of the data and to avoid duplication of efforts across functions. Emphasis should be placed on the quality of data required to meet the trial objectives and to obtain reliable results.
RBM Methodology & Toolkit

Steps 1 & 2: RBM Methodology

Let’s focus now on the first two steps from the TransCelerate methodology –
Risk Assessment and identification of Critical Data and Processes.

1. The first step requires a cross-functional risk assessment at the program level.
   • Program-level risks are not specific to a particular protocol, but rather are common across all studies in the program such as safety considerations. Generally, any identified safety issues would be consistent across all studies within a development program. The program-level risk assessment includes identification of the initial list of data which are to be treated as Critical Data across all protocols in the program.
2. After risk assessment at the program level, a protocol-level risk assessment will be applied.
3. The input from the risk assessments will lead to the output of identified Critical Data points and Processes.

NOTE: Both risk assessment and Critical Data identification will be further discussed and applied in an exercise in the module entitled Risk Assessment.
Make the following key points:

- In identifying critical data, team members should think about specific end point data that will be used to satisfy the study’s primary objectives for efficacy and/or safety.
RBM Methodology & Toolkit

Critical Data & Processes - Defined

**Critical Data**
Critical Data includes data that support primary and key secondary objectives and data that is critical to subject safety such as serious adverse events and other events leading to discontinuation of treatment. Critical Data includes data that will be used to make decisions about the product’s safety and efficacy profile.

**Critical Processes**
Critical Processes include processes that underpin data quality such as blinding, referring events for adjudication, and controlling inter-rater variability. Critical Processes also underpin subject safety and ethical/GCP compliance such as seeking appropriate medical consultation or scheduling extra visits or procedures in the event of significant clinical or laboratory findings.

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.

The level of monitoring will be identified and defined as to what points will need to be monitored on-site and off-site and whether data will be reviewed for protocol compliance, a process defined by TransCelerate as Source Data Review, SDR, or checked for transcription accuracy defined as Source Data Verification (SDV).

**For Example**

Given a psoriasis study:

**Critical Process** (answers below are options, not all possible answers): measures taken to ensure consistency in clinical evaluations such as requiring site evaluators to meet certain qualification requirements.

**Critical Processes** can include how exams are conducted, how lab specimens are processed and handled if they must be stored at exact temperatures, reconstitution or preparation of Investigational Product (IP), etc.

NOTE: Share or replace this example with as many real world case examples as possible specific to your experiences or solicit from peers or company.
Risk Plan: Step 3

We’ve just looked at steps 1 and 2 in more detail. Now let’s look at step 3.

NOTE: The image is meant to provide a “signpost” to indicate to learners where we are in the process.
The Integrated Quality and Risk Management Plan connects various quality and risk management strategies.

Direct participants to the Participant Workbook

The IQRMP

The third step is related to the development of the Integrated Quality and Risk Management Plan, also called the IQRMP.

In the RBM methodology, 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.

A companion guide has been developed by TransCelerate to provide guidance on Risk Indicators and Thresholds.
Methodology Breakdown – Step 3 (Monitoring Plan)

Direct participants to the Participant Workbook

Monitoring Plan

The third step also 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.

Resources

A companion guide has been developed by TransCelerate to provide guidance on Risk Indicators and Thresholds.
Monitored Execution

Finally, let’s take a look at step 4 – monitoring execution.

**NOTE:** The image is meant to provide a “signpost” to indicate to learners where we are in the process.
Breakdown of Monitoring Execution

Finally, the fourth step is “Monitoring Execution”.

This process includes the identification of performance gaps and application of monitoring activities based on the predetermined Risk Indicators, Thresholds and action plans.

Make the following key points:

- As a reminder, monitoring execution includes tasks performed by monitors as well as other functional team members.
Challenge Yourself

True or False:
Critical Data and Processes should be identified by a cross-functional team only at the program level.

Challenge Yourself – True / False

Let’s take a minute and see how much of this information we understand.

Facilitating the Activity

Classroom Workshop Participants (face-to-face)

Ask participants to use the colored index cards on their tables and hold up the one they think is correct: RED with an F is false and GREEN with a T is true.

This will allow you as the presenter to see quickly how many individuals in the room are aligned with this challenge and know the information.
RBM Methodology & Toolkit

Webinar Workshop Participants (online)

Ask participants to use raise their hand in the participant panel to show if they think the answer is False and do nothing if it is true.

This will allow you as the trainer to see quickly how many individuals answer for each.

You can also use additional capabilities within your webinar provider such as status icons, checkmark or x icons or the chat features.

IMPORTANT NOTE

The answers for each of the challenge yourself questions are listed on the slide following the question. These may be hidden if you choose not to use the slide to reveal the answers.

You may choose to show the slide with the correct answer highlighted.

Challenge Yourself – True/False Debrief

ANSWER: False
A cross functional team is responsible for the identification of risk and Critical Data and Processes at both the program and protocol levels.
Discussion Activity
Facilitate participant large group discussion to identify any types of tools that are currently being used in the organization. Encourage participants to think more deeply if necessary by asking these questions:
- Are there any tools used to document decisions made in the planning of clinical trials?
- Are there any tools used for risk management processes?
- Are there any tools used to identify investigative sites to be audited?
- Are there any tools used to track issues (like deviations) at sites, or trends in deviations across the study or program?
- Are there any tools used to make decisions about when a manager needs to co-monitor at a site or otherwise, get more involved?

Facilitating the Activity
While participants are providing answers, record their input on a flip chart and/or within a whiteboard (for webinars or blended classrooms).

NOTE: Allow approximately 10 minutes for this activity.
RBM Methodology & Toolkit

RBM Process & Associated Tools

You've just identified some of the tools currently being used in your organization for quality and risk management. As your teams transition to the RBM methodology, as when learning any new process, it is helpful to have tools available to support new concepts and activities.

The TransCelerate RBM methodology provides three such tools which we will now discuss –
1. the RACT (which again stands for Risk Assessment Categorization Tool), the
2. IQRMP (Integrated Quality Risk Management Plan), and the

Let’s start by looking at the RACT. In looking at the methodology process flow once again, the RACT is applicable to Step One – Risk Assessment.

Make the following key points:

- The tools will be briefly introduced at this time but learners may have the opportunity later in the course to work with some of the tools, if applicable to their functional role.
Don’t worry if you can’t read all of the text clearly. We just want you to be able to see what the RACT looks like.

The RACT is used as a tool to organize the discussions within the cross-functional team in evaluating the risks of the program and protocol. It includes questions and considerations that can also be used for guidance on this process.
The purpose of the Risk Assessment and Categorization Tool (RACT) is to facilitate risk assessment and risk mitigation by the following:

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.

The RACT

The purpose of the Risk Assessment and Categorization Tool (RACT) is to facilitate risk assessment and risk mitigation by the following:

- Determining the risks which could affect patient safety, data integrity or regulatory compliance and by identifying how and by which functions the risk will be managed
- Categories of monitoring activity risk will be ranked as high, medium or low, based on discussions with appropriate functions.
- Using the agreed-upon risk categorizations and application to Monitoring Plan activities, an Overall Risk Level for monitoring activities will be determined. This Overall Risk Level of high, medium, or low will determine the baseline level of Monitoring Activities.
- Monitoring strategies are then tailored to risks that are focused on Critical Data and Processes.

Specific Instructions on completing the RACT will be discussed in another module.
The next tool provided by TransCelerate is related to the Integrated Quality Risk Management Plan or IQRMP. In looking at the methodology process flow, the IQRMP is applicable to Step Three.
### Toolkit Component #2: IQRMP

<table>
<thead>
<tr>
<th>Key Elements of the IQRMP</th>
<th>Description</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Section</td>
<td>Documents agreement and sign off by all relevant functions.</td>
<td></td>
</tr>
<tr>
<td>Revision History</td>
<td>Provides version control and tracking.</td>
<td></td>
</tr>
<tr>
<td>Critical Data</td>
<td>Defines and documents the Critical Data for the study. Critical Data is data that is critical to the reliability of the study findings, specifically those data that support primary and key secondary endpoints. Other Critical Data includes data critical to subject safety, such as serious adverse events and events leading to discontinuation of treatment.</td>
<td></td>
</tr>
<tr>
<td>Medical Monitoring Plan</td>
<td>Describes clinical review/medical monitoring data review and cleaning activities.</td>
<td></td>
</tr>
<tr>
<td>Safety Plan</td>
<td>Describes how pharmacovigilance/safety will manage safety risks related to a product.</td>
<td></td>
</tr>
<tr>
<td>Data Plan</td>
<td>Describes the procedures for data collection/review/cleaning.</td>
<td></td>
</tr>
<tr>
<td>Statistical Analytic Plan</td>
<td>Describes the procedures for executing the statistical analysis of the primary and secondary variables and other Critical Data.</td>
<td></td>
</tr>
<tr>
<td>Monitoring Plan</td>
<td>Describes the remote/OFF-site and ON-site Monitoring Activities based on the identified risks. Includes Risk Indicators (triggers) that will help to drive decisions on the type of monitoring to be conducted.</td>
<td></td>
</tr>
</tbody>
</table>

Integrates various functional plans and activities to focus efforts on the specific needs of the trial.
IQRMP Toolkit Component

Again, don’t worry if you can’t read all of the text clearly – this slide shows a section of the RBM Toolkit that lists the standard elements of the IQRMP.

It should be clear from its name, that the IQRMP integrates various functional plans and activities to focus efforts on the trial-specific needs and risks.
RBM Methodology & Toolkit

RBM Toolkit: IQRMP

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
RBM Methodology & Toolkit

The RBM Toolkit: IQRMP

The IQRMP provides a tailored and integrated plan for a specific clinical trial that will:

1. Define the actions that each function will take to proactively identify, assess, and manage risk throughout the life of a clinical trial Protocol-level risks and mitigation plans are documented in the various components of the IQRMP.
   - The individual plans which may be contained in the IQRMP, such as a Monitoring Plan, should be developed based on a risk assessment that takes into consideration the impact and likelihood of error, activities which can prevent or minimize impact of the risks, and the extent to which the error would be detectable.

2. Define the Critical Data/Processes identified by cross-functional representatives
   - Risk Indicators for each should be assigned with Thresholds which, once reached, are designed to trigger an action such as increased data scrutiny or site follow-up, such as a telephone call or visit to the site.

3. Align associated quality management plans including the Monitoring Plan across identified risks and defined Critical Data and Processes to ensure cross-functional teams focus on the risks that are most important to subject safety, data quality and regulatory compliance

Examples of Plans which may be included as part of the IQRMP are the Medical Monitoring, Safety, Data, Statistical Analysis, Monitoring, Training, and Quality Plans.

IMPORTANT NOTE

Emphasize that the identification of Risk Indicators and associated Thresholds will be discussed in a future module for those learners who may perform these tasks. Opportunity to practice these activities will be provided at that time.
Discussion Point

What quality and/or risk management plans are used in our organization that could be combined under the IQRMP or a similar overarching plan?

Discussion Activity

In order to better discuss IQRMP, let’s talk about what quality and/or risk management plans are being used in your organizations.

Facilitating the Activity

Facilitate the generation of a participant generated list of various plans that may be used by different functional areas that could be connected to or combined under the IQRMP.

Emphasize the purpose of the IQRMP (or other analogous plan) is to reduce duplication of effort and keep everyone focused on Critical Data/Processes and risk mitigation.

NOTE: Allow approximately 10 minutes for this activity.

IMPORTANT NOTE

The answer, or a visual diagram from the position paper, is provided on the next slide that can be used as an answer key. These may be hidden if you choose not to use the slide to reveal the answers.
RBM Methodology & Toolkit

Classroom Workshop Participants (face-to-face)

Have participants work within their table teams and flipchart their responses.

Webinar Workshop Participants (online)

Utilize the annotation functionality within your webinar provider and start a new whiteboard within your session titled with this question. Ask users write their responses on the board within the meeting room. (Note: if you are in a blended room, this whiteboard becomes the flipchart for the virtual participant team) Allow all participants annotation rights to add their thoughts.
Slide 28

IQRMP: Core of Quality Risk Management

Page 25-26
Direct participants to the Participant Workbook
Debrief Discussion & IQRMP

Here the IQRMP is graphically depicted.

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.

Make the following key points:

- Notice that the functional plans are all aligned around the risk assessment, Critical data, and Risk Indicators and their Thresholds
Risk Indicators – within the Process

The third tool provided by TransCelerate is a Companion Guide to be used when working with Risk Indicators. In the high-level process flow, you can see that this tool also fits into step three.

First, let’s be sure that we all understand the definition of two important terms - Risk Indicator and a Threshold.
Risk Indicator Terminology

Take a minute to review the definition of a Risk Indicator (from the TransCelerate position paper) as well as more of a “working definition” for the term.

Risk Indicators can be thought of as variables defined through risk assessments that need to be tracked to indicate whether there is a danger of an actual risk occurring. Risk Indicators are variables assessed by comparison across a program, study, country, and/or site. All Risk Indicators are considered to have underlying influence on the quality of a study.
Threshold Terminology

Thresholds are defined as on this slide – again, you see the TransCelerate position paper definition and a “working definition.”

Thresholds are set in order to clearly understand when the data/information from the Risk Indicators is inconsistent with the data we expect.

From a quality perspective, whenever a Threshold is reached, action is needed to evaluate or follow-up on the Risk Indicator.
Companion Guide to Risk Indicators

Her we have one final screenshot of a section from the Companion Guide to Risk Indicators.

This section specifically relates to the Risk Indicator of Adverse Event collection/reporting.

Three separate Thresholds for tracking that Risk Indicator are illustrated here along with an action plan or plans for each. This companion guide can be used to facilitate consistency among team members in applying Risk Indicators and Thresholds for decision-making and responding to risks.
RBM Toolkit: Companion Guide to Risk Indicators

Describes how Thresholds are determined and used
- Assigning Thresholds for a specific Risk Indicator
- Using dashboards or other visual systems
- Responding to Thresholds

Specific examples of Risk Indicators, Thresholds, and action plans are provided in the tool.
RBM Methodology & Toolkit

Companion Guide to Risk Indicators

The purpose of the Companion Guide is to provide instructions and help ensure that there is a consistent approach to the application of Risk Indicators and associated Thresholds.

The Companion Guide consists of five key areas:

1. Determination of Thresholds for a specific Risk Indicator
2. Attention to Risk Indicators
3. Responses to Thresholds
4. Availability of Data
5. Acceptable Error Rates

Thresholds are defined as the level, point, or value associated with a Risk Indicator that will trigger an action.

TransCelerate created a collection of Risk Indicators that are intended to be monitored Centrally or Off-site on an ongoing basis. In the absence of technology that enables continual monitoring of Risk Indicators, monitoring the Risk Indicators at specific intervals or time points is recommended to ensure key risks are managed throughout the study.

Monitoring Risk Indicators Centrally or Off-site allows for more rapid detection of possible issues and conduct of targeted actions to either further investigate or mitigate an issue. Those investigations can determine whether a problem is real and requires actions to be taken or if the problem just requires continued monitoring.

Thresholds can aid in decision-making and can positively impact subject safety, data quality and GCP compliance. This guide describes how Thresholds are determined and how they are viewed, including specific examples.

IMPORTANT NOTE

Intent here is just to provide an introduction to the companion guide at this time. In a future module, where Risk indicators and Thresholds are implemented through activities, details from the companion guide will be reviewed.
Challenge Yourself

Which of the following tools is intended to align various quality management plans to ensure cross-functional teams focus on the greatest risks to patient safety, data integrity, and GCP compliance? (select one)

A. Companion Guide to Risk Indicators
B. Monitoring Plan (MP)
C. Integrated Quality Risk Management Plan (IQRMP)
D. Clinical trial protocol

Challenge Yourself Activity

Let’s try this question.

Provide instructions per the Facilitation guidance following.

IMPORTANT NOTE

The correct answer appears on the following slide. This can be hidden or shown as desired in the session.

Facilitating the Activity
RBM Methodology & Toolkit

**Classroom Workshop Participants (face-to-face)**

Ask participants to use the colored / labeled index cards at their table and hold up their answer choice(s). This will allow you to see quickly what the majority of the room responds with.

- A = Red (write an A on the back of the red index card with an F on it)
- B = Green (write a B on the back of the green index card with a T on it)
- C = Yellow with a C written on it
- D = Orange with a D written on it

**Webinar Workshop Participants (online)**

If possible, utilize your polling options within your webinar provider. Create a poll and pull it up within the meeting room, ask participants to vote on their answer.

You can also use additional capabilities within your webinar provider such as status icons, or the chat features.

You may choose to show the slide with the correct answer highlighted

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**Debrief: Challenge Yourself Activity**

**ANSWER: C**

One of the purposes of the IQRMP is to maintain alignment of all quality management plans to ensure cross-functional teams focus on Risk Indicators, Critical Data/Processes, errors related to subject safety, data integrity, and regulatory compliance, etc.
Transition

We will now briefly discuss responsibilities of functional team members who are involved with RBM.

TransCelerate describes RBM approaches that are carried out by various roles including Statisticians, Data Managers, and Monitors.

When other functions, not traditionally labeled as Monitors, are performing RBM activities, these functions should describe their risk mitigation strategy and any activities in a documented plan. The important thing to remember is that RBM is not just a data monitoring or clinical monitoring activity.
Functional Team Members

Teamwork

Every aspect of RBM is based on approaching all aspects of study design and implementation proactively.

Team members cannot operate in a silo and must each collaborate on the various functional plans that comprise the IQRMP and define the monitoring approach.

A true collaborative team effort is required in a successful RBM program - input from all departments and the output will affect everyone involved in the execution of study activities.
Functional Team Members

Slide 38

Discussion Point: Who Does What?

- Who within our organization performs these tasks?
  - 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

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Direct participants to the Participant Workbook

Discussion Activity: Who does What?

The TransCelerate RBM methodology outlines various activities to be completed and documents to be finalized in establishing an RBM approach to monitoring clinical trials.

Of course, in different organizational structures, differing departments and/or job roles will be involved in these various processes. It is, however, 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. Let’s try this question.

Provide instructions per the Facilitation guidance following.
Functional Team Members

Facilitating the Activity

Allow approximately 10 min for this activity

Classroom Workshop Participants (face-to-face)

In your table team, discuss who, within your organization, does each of the identified tasks and activities.

Webinar Workshop Participants (online)

Pick two of the identified activities and chat in who at your organization does each of the tasks / activities.

Who does what? Debrief

Debrief as a large group and ensure that you identify a couple of roles for each activity / task.

Examples of some of the individual roles that will actively participate in and or be affected by RBM include 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.
Discussion Activity: Who does What?, continued

Continue building from the prior discussion (using the same format and instructions) asking participants to identify the steps in the methodology process where/when the various roles and functional areas will be involved.

Allow approximately 5 minutes for this activity.

Make the following key points:

- It is important to clarify role relationships and who is managing what aspects of monitoring to ensure limited overlap of activities.
Monitoring Activities

Slide 40

Module 2: Objective 3

CENTRAL, OFF-SITE, AND ON-SITE MONITORING ACTIVITIES

Introduction

Our final objective in this section is to describe on-site, off-site, and central monitoring activities used in study oversight.

The appropriate use of each of these monitoring approaches is fundamental to the TransCelerate RBM methodology.

Before detailing each of these, let’s review some of the key assumptions underlying the application of the RBM methodology as detailed in the position paper.
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

Direct participants to the Participant Workbook
Monitoring Activities

Central Monitoring Activities

Central monitoring activities may be performed by Clinical Research Associates/Monitors or by other roles within clinical operations.

Additionally, central monitoring may be performed by other functions within the sponsor or CRO, for example, Statisticians, Data Managers, Medical Monitors, Pharmacovigilance/safety, etc.

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.

This list is not all inclusive; there may be other reports, metrics, and/or trends identified by cross-functional teams depending upon identified Critical Data and/or Processes. The results of these central reviews may lead to interventions for one site or all sites, depending on the identified issues.

For example

A high query rate for a given variable across multiple sites should lead to investigation to determine if validation or edit checks are firing correctly. If yes, an appropriate response would be to provide additional site training on how to complete the field correctly.
Monitoring Activities

Slide 42

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

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Direct participants to the Participant Workbook
Monitoring Activities

Off-Site Monitoring Activities

*These are just examples and this is not an all-inclusive list.*

Activities performed during Off-site Monitoring may be identified depending on the risk assessment for the study.

Information obtained from other monitoring activities (on-site and/or Central) should be utilized to ensure that off-site reviews and follow-up are focused on identified risks and issues.

Make the following key points:

- 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.
Monitoring Activities

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

Direct participants to the Participant Workbook
Monitoring Activities

On-Site Monitoring Activities

These are just examples and this is not an all-inclusive list.

Activities performed during on-site monitoring may consist of a mix of the ones listed on the slide depending on the risk assessment for the study. Some activities may be required at every visit, and others may be required more infrequently.

Information obtained from Off-site Monitoring review and Central monitoring should be utilized to ensure that necessary on-site follow-up is focused on identified risks and issues.

- **SDR and SDV** – these represent two distinct on-site monitoring activities in the TransCelerate RBM model and will be described in more detail on the next two slides.

- **Consent Forms** - Consent forms may not require 100% review but the size of sample should be based on risk and on the types of issues identified off-site or on-site. For example, if an unauthorized person has obtained consent, the consent review sample may be increased.

- **Investigational Product** – Accountability and reconciliation activities performed on-site include verifying protection of the blind, ensuring that correct subject assignments have been made against treatment assignments, ensuring product use dates are suitable and that IP logs are up-to-date. The RBM methodology does not recommend verification of pill counts for subject-level accountability.

- **Essential Documents** – On-site review should be based on issues and risks identified for the site. Unless part of issue and risk management, there should not be a requirement to perform a detailed on-site regulatory file review nor on-site reconciliation with the TMF. Review of Essential Documents can occur remotely. Periodically, the Monitor can conduct a cursory evaluation of the site file for general appearance while on-site to ensure there are no obvious issues.

- **Site Interactions**: Face-to-face training and discussions with site staff will occur as needed to support changes in staff, issue resolution, and Risk Indicators.
Monitoring Activities

Slide 44

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

Direct participants to the Participant Workbook
Monitoring Activities

SDV

Commonly known as ‘transcription checking’, SDV is the process by which data within the site’s original source documentation are compared to data within the CRF (or other data collection systems) (and *vice versa*).

SDV involves 1:1 verification. Its purpose is to confirm that the data were transcribed accurately (i.e. data from source matches data in the CRF or other system and *vice versa*).

SDV is performed on Critical Data only and decisions about the amount of SDV are based upon the risk assessment process and outcomes.
Monitoring Activities

Slide 45

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

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Direct participants to the Participant Workbook

SDR

SDR mainly involves reviewing **key** pieces of source documents **for areas where there is no associated CRF data field.**

SDR also provides a means of reviewing the processes by which the data were collected - including protocol compliance, PK collection, ICF process, investigator involvement and delegation, etc. This can provide additional assurance of data integrity.

SDR is sometimes performed by reviewing source documents and other records in their entirety – like reading a book that tells the story of the subject’s participation in the study.
Monitoring Activities

For Example

Let’s consider a few examples of SDR.

1. Let’s assume that the CRF only includes the lab test name and the result (e.g. blood glucose value of 105 mg/dl).
   - Whereas SDV is verifying that the blood glucose value shown on the local lab report is accurately entered into the CRF (i.e. value of 105 in the CRF matches the value in the source and vice versa),
   - SDR might involve reviewing the source to check that the patient was fasting for the glucose test (if fasting was required per protocol).

2. Let’s think about another example involving weight measurement.
   - Whereas SDV is verifying the source weight measurement is accurately entered into the CRF (i.e. CRF matches the source and vice versa),
   - SDR might involve checking how the weight was obtained (e.g. with shoes on or off, using the same scale across visits) to determine if the protocol requirements for obtaining the weight were followed.
Monitoring Activities

Why Distinguish SDV and SDR?

- Address different risks
- Answer different questions
- Use according to needs

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.

Direct participants to the Participant Workbook
Monitoring Activities

Why SDV and SDR?

TransCelerate draws a distinction between Source Data Verification (SDV) and Source Data Review (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**.

- Transcription errors identified by SDV are typically infrequent, insignificant, and do not lead to study data being unusable. This was supported by the retrospective analysis of monitoring and SDV conducted by TransCelerate.

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**.

The two activities address different risks in study conduct and can help sponsors get answers to different questions about site performance.

Therefore, different levels of SDV and SDR can be used according to the study-specific needs to address risks.
Challenge Yourself – 9 Assumptions

1. ______ and off-site monitoring are the foundation
2. Monitoring activities are ________ to issues/risks
3. Tailor ______ to available technology
4. ______ data entry and query resolution are critical
5. Functional oversight and documents should respond to ______
6. RBM expectations can be formalized in ______
7. Methodology applies to all types and ______ of trials
8. Communication plans should be tailored for ______
9. Risk assessments should take place prior to ______ and CRF finalization

SOPs, central, protocol, efficiency, timely, responsive, phases, risks, methodology

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IMPORTANT NOTE

A slide with the full answer key is provided next. Additionally a reference slide is available (slides 49, 50) with the full text from the position paper. You may choose to show or hide this text.
Monitoring Activities

Facilitating the Activity
Allow approximately 10 minutes for this activity

*Classroom OR Webinar Workshop Participants (face-to-face or online)*
Regardless of delivery type, facilitate this activity as a large group session, taking each statement and ask for a volunteer (or call on someone) to fill-in the blank.

Ensure that you are equally calling on those on the phone and in the room if in a blended classroom.

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**Challenge Yourself – 9 Assumptions Answer Key**

1. Central and off-site monitoring are the foundation
2. Monitoring activities are responsive to issues/risks
3. Tailor methodology to available technology
4. Timely data entry and query resolution are critical
5. Functional oversight and documents should respond to risks
6. RBM expectations can be formalized in SOPs
7. Methodology applies to all types and phases of trials
8. Communication plans should be tailored for efficiency
9. Risk assessments should take place prior to protocol and CRF finalization

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**Challenge Yourself – 9 Assumptions Debrief**
See correct answers
Monitoring Activities

**Slide 49**

**Challenge Yourself- Full Assumption Statements**

1. Central and Off-site Monitoring Activities serve as the foundation of monitoring efforts and are complemented by targeted On-site Monitoring Activities based on a defined risk level, Critical Process and Data, ongoing assessment of Risk Indicators and instructions within the Monitoring Plan.
2. Regardless of the monitoring approach established in the MP, monitoring activities can be increased in response to issues and risks identified (whether identified by other functions e.g. Statisticians or during the Monitor’s Off-site or On-site Activities). Increases in monitoring activities should be done in a temporary, targeted manner with the goal of returning to the standard level of monitoring as described in the MP. To prevent the issue from recurring, it is important to identify and address the root cause of the issue.
3. The methodology is tailored to the available technology. For example, if electronic medical records are available for remote monitoring, the Monitor can perform certain activities (e.g. SDV, informed consent review) off-site (remotely).

**Slide 50**

**Challenge Yourself- Answer Key**

4. Central and Off-site Monitoring is dependent on the timely entry of data and query resolution. Sponsors should set expectations for data entry and query response timeliness in their contracts with sites.
5. Functional oversight and associated quality documents within the IQRMP may be amended at any point in the study in response to changing risks or identified issues (e.g. in response to a protocol amendment; instructions for monitoring a new safety signal).
6. Risk-based monitoring expectations can be documented as a standard process (e.g. SOP) rather than in a functional plan in the IQRMP, as appropriate.
7. The methodology may be applied to all phases (Phase 1 through Phase 4), types, and stages of trials.
8. Routes of communication should be tailored to what is most effective in ensuring successful conduct of the study.
9. Risk Assessments should be initiated prior to the finalization of protocols and CRFs to minimize risks in advance of starting the trial. Monitoring strategies are adapted to ensure oversight to what is not prevented via protocol or CRF design.

**IMPORTANT NOTE**

The prior two slides can be hidden or shown. They are specific text copies from the position paper regarding the assumptions and the content was addressed in Module 1.
Monitoring Activities

Challenge Yourself

True or False:
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 the use of on-site monitoring visits.

Challenge yourself – True or False Question

Let’s see how much we have remembered and retained.

NOTE: The answers for each of the challenge yourself questions are listed on the slide following the question. These may be hidden if you choose not to use the slide to reveal the answers.

Facilitating the Challenge Yourself Activity

Classroom Workshop Participants (face-to-face)

Ask participants to use the colored index cards on their tables and hold up the one they think is correct: RED with an F is false and GREEN with a T is true.

This will allow you as the presenter to see quickly how many individuals in the room are aligned with this challenge and know the information.
Monitoring Activities

**Webinar Workshop Participants (online)**

Ask participants to use raise their hand in the participant panel to show if they think the answer is False and do nothing if it is true.

This will allow you as the trainer to see quickly how many individuals answer for each.

You can also use additional capabilities within your webinar provider such as status icons, checkmark or x icons or the chat features.

**Slide 52**

You may choose to show the slide with the correct answer highlighted.

**Challenge Yourself – Question Debrief**

**ANSWER: True**

The methodology improves efficiency through the application of continuous monitoring activities to measure, evaluate, and assess the proactively identified risks for each study (and potentially each site). This shifts the focus to proactively mitigating risk and early detection of issues.
Monitoring Activities

Slide 53

**Discussion Point**

Name two possible activities performed
During Central Monitoring
During Off-site Monitoring
During On-site Monitoring

**Challenge yourself – Discussion**

Let’s see how much we have remembered and retained.

NOTE: Some potential answers for each of the challenge yourself questions are listed in the debrief section for your reference.

Allow approximately 10 minutes for this activity.

**Facilitating the Challenge Yourself Activity**

*Classroom OR Webinar Workshop Participants (face-to-face or online)*

Regardless of delivery type, facilitate this activity as a large group session, taking each statement and ask for a volunteer (or call on someone) start a list, flip charting OR white boarding in the webinar room.

Ensure that you are equally calling on those on the phone and in the room if in a blended classroom.
Monitoring Activities

Debrief: Discussion Point

Some potential answers for each of the listed monitoring types are:

Central:
- Comparisons of data and information across sites and/or studies
- Protocol deviation rates
- AE trends or outliers
- Subject discontinuation
- Metrics for data entry/query resolution
- Error rates for Critical Data/Processes

Off-site:
- eCRF completion and query management
- Essential documents review
- Completion of action items
- Cross reference meds and AEs (or other CRF comparisons)
- Assess recruitment/enrollment

On-Site:
- Source Documentation (SDV and SDR)
- Informed Consent Review
- Investigational Product Accountability
- Essential Documents Review (if appropriate)
- Face-to-face training and discussions with site staff
Module 2: Summary

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 2 Summary
Recap module 2 key points as listed

Direct participants to the Participant Workbook
Module 2: Summary

Questions

- Allow for questions?
Transition

Transition to Module 3 if all courses are provided at same time

IMPORTANT NOTE
Not all participants will attend all modules within this program.

If multiple modules are being conducted in one day, take a break for 15 – 30 minutes between modules.