Model Approach for Risk-Based Monitoring

Module 1: Introduction

Trainer Guide
# Model Approach for Risk-Based Monitoring

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Legal Disclaimer

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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?
This section, “Getting Started,” contains all of the preparation information for the *Model Approach for Risk-Based Monitoring* training program, such as learning objectives, pre-work, required materials, and room set-up.

Following this section is the “Training At A Glance” table. This table can serve as your overview reference, showing the module names, timings, and process descriptions for the entire program.

Each module begins with a one-page summary showing the Goal, Time, Overview, and Materials for the module. Use these summary pages to get an overview of the module that follows.
About This Guide

How is the text laid out in this guide?

Every action in the program is described in this guide by a text block like this one, with a margin icon, a title line, and the actual text. The icons are designed to help catch your eye and draw quick attention to “what to do and how to do it.”

For example, the icon to the left indicates that you, the trainer, say something next. The title line gives a brief description of what to do, and is followed by the actual script, instruction set, key points, etc. that are needed to complete the action.

A complete list of the margin icons used in this guide is provided on the following page.

IMPORTANT NOTE

You may also occasionally find important notes such as this one in the text of this guide. These shaded boxes provide particularly important information in an attention-getting format.
About This Guide, continued

Graphic Cues

Module Blocks

<table>
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<th>Goal</th>
<th>Time</th>
<th>Overview</th>
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Lesson Blocks

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IMPORTANT NOTE

Most cues here are used within the trainer guide. All are listed so that you can choose which cues to utilize as a member company and delete the ones appropriate for your organization.
The Program in Perspective

Learning Objectives
This course has been designed to provide 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.

Program Timing
The entire program is designed to be delivered in modular increments, five modules in total. Not all participants will take all five modules. If all five modules were presented the total program would be 7 hours.

• Module 1: 90 minutes (1.5 hours)
• Module 2: 90 minutes (1.5 hours)
• Module 3: 90 minutes (1.5 hours)
• Module 4: 90 minutes (1.5 hours)
• Module 5: 60 minutes (1 hour)

Number of Participants
The optimal number of participants (regardless of classroom type: in person, through a webinar or blended) is 25 – 35 individuals.

NOTE: Each member company can modify this to fit their specific needs based upon total number of participants and typical class sizes.
Program Preparation

Pre-Work

All participants will be provided with a pre-work packet and email. Of these materials, the following reading is expected for all participants:

- 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

Additionally, participants are instructed to conduct meetings with management pre and post completion of this program. The instructions provided are within the Appendix of this guide.

NOTE: The provided pre- and post-work within the Appendix of this guide are templates provided by the Risk-Based Monitoring team, as a trainer, you should check within your organization for any customizations of these templates.

Room Set-Up

Classroom Delivery

- Half-moon round tables with 5 people per table facing the front of the room.
- One flip chart and markers set for each 2 tables.
- Materials and participant workbooks placed at each participants seat.

Webinar Delivery

- Online meeting room with chat, status (or minimally hand rising) capabilities and white boarding.
- Visual and Audio capabilities for presenter and participants.
Program Preparation

Required Materials

- Participant Workbook (one per participant)
- Post-it notes available on each table (for face-to-face sessions)
- Flipcharts & Markers (one per every 2 tables – for face-to-face sessions)
- Prepared Flipchart to match Module 2: 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 – one side marked with a large C and one with MEDIUM
  - Orange – one side marked with a large D and one with HIGH
  - Blue – one side marked with a large LOW
- Regular index cards with scenario assignments (per table for face-to-face sessions) for activity in Module 4.
  - Three index cards with the Critical Data / Processes from Activity 1 in Module 4.
  - 5 index cards each with Scenario 1, Scenario 2, Scenario 3 written on them

Trainer Preparation

As the trainer, you should:

- Complete the pre-read materials to ensure knowledge and familiarity with the materials
- Review all slides, the participant and trainer guide (including activity facilitation notes) prior to the session.
- Be aware that in the case of a blended classroom (Live in the room participants and online webinar participants), you will need to provide both facilitation instructions.
- Send the participant workbook to each participant prior to the course date for sessions that have online (webinar) format.

If you are facilitating a session that includes an international audience, consider sending the slide deck with speaker notes (but NOT the answer key slides) to the participants prior to the session. All speaker notes are embedded within the slide deck and not all information is shown within the slides. This will assist with global audience learners.
# Training at a Glance

<table>
<thead>
<tr>
<th>Time</th>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 minutes</td>
<td>Module 1: Introduction</td>
<td>This module is a combination of presentation of material and facilitated “challenge” exercises for the participants. This modules uses pre-quiz questions to assess participants' base understanding of concepts as well as intermittent and summary knowledge checks. Some slides are hidden (not automatically shown in presentation view). The trainer determines whether it is necessary to unhide/show these slides to participants.</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Module 2 – Methodology and Team Members</td>
<td>This module is a combination of presentation of material and facilitated “challenge” exercises for the participants.</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Module 3 – Risk Assessment</td>
<td>This module is a combination of presentation of material and facilitated “challenge” exercises for the participants. This module uses questions, discussions and case scenario exercises to assess and facilitate participants’ learning.</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Module 4 – Risk Management</td>
<td>This module is a combination of presentation of material and facilitated “challenge” exercises for the participants. This module uses questions, discussions and case scenario exercises to assess and facilitate participant learning.</td>
</tr>
<tr>
<td>60 minutes</td>
<td>Module 5 - Transitions</td>
<td>This module is a combination of presentation of material and facilitated “challenge” exercises for the participants.</td>
</tr>
</tbody>
</table>
Transition to **Module 1**

**IMPORTANT NOTE**

Not all participants will attend all modules within this program. HOWEVER, all participants will complete this first module.
Introduction to Risk-Based Monitoring

Goal
This module introduces the concept of RBM, how it varies from traditional monitoring approaches and why we are focusing on implementing this methodology. It also introduces definitions and assumptions underlying the TransCelerate Position Paper: Risk-Based Monitoring Methodology that was published May, 2013.

Time
90 minutes

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

This modules uses pre-quiz questions to assess participants' base understanding of concepts as well as intermittent and summary knowledge checks

Some slides are hidden (not automatically shown in presentation view). The trainer determines whether it is necessary to unhide/show these slides to participants.

Materials Needed
- Participant Workbook (one per participant)
- Post-it notes available on each table (for face-to-face sessions)
- Flipcharts & Markers (one per every 2 tables – for face-to-face sessions)
- 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
Module 1: Introduction

Welcome to the training on the TransCelerate approach to Risk-Based Monitoring.
This course will take you through five modules of information to introduce you to the concepts behind risk-based monitoring, the TransCelerate Approach, some hands on exercises and some information to provide to sites as well on tips for transitioning projects and studies into the new model.
Module 1: 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 we are 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 1: Introduction

**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. ALL participants will be attending this module.
Module 1: Introduction

Slide 4

Module 1

INTRODUCTION TO RISK-BASED MONITORING (RBM)

Our first module is an introduction to Risk-Based Monitoring, which we will refer to as RBM.
Module 1: Introduction

Module 1 Objectives

At the conclusion of this module, learners will be able to:

1. Describe the Risk-Based Monitoring (RBM) Model as compared to traditional monitoring methods
2. Explain the rationale for Risk-Based Monitoring (RBM)
3. Describe TransCelerate’s key assumptions and concepts

Review of Module 1 Objectives

At the conclusion of this module, you should be able to describe the RBM Model as compared to traditional monitoring methods, explain the rationale for RBM, and describe TransCelerate's key assumptions and concepts.

This course was designed to be very interactive and as we move through the materials we will ask you to challenge yourself and to share your knowledge. Many of you already probably know quite a bit about RBM and some of the questions we will be asking are designed to help you determine if there are areas in which you still have questions.

Direct participants to the Participant Workbook

These objectives are outlined within your participant workbook.

Activities are associated with each objective to assist in facilitating your learning throughout the workbook.
Module 1: Introduction

Slide 6

**Challenge Yourself – Question 1**

**True or False:**

RBM is a fixed approach to clinical trial monitoring that assumes all trials and all data points represent the same level of risk to product development.

---

**Challenge yourself – Question 1 Transition**

As noted, we will be asking a lot of questions and pushing you to challenge yourself and test your knowledge. Let’s go ahead and begin with a true/false question.

---

**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.
Module 1: Introduction

**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.

---

**Challenge Yourself – Question 1 Debrief**

**ANSWER:** False

RBM is not fixed; it is 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.

Each clinical trial requires its own customized monitoring approach to ensure that risks are minimized and sponsor responsibilities are satisfied. It is based on awareness that different trials, different data points/processes, and different sites represent differing risks to the product’s development.
Module 1: Introduction

Challenge Yourself- Question 2

True or False:
According to the TransCelerate Position Paper, current monitoring practices in the industry generally focus on source document verification (SDV) which is defined (in the paper) as the **process by which data within the CRF or other data collection systems are compared to the original source of information to confirm that the data were transcribed accurately.**

**IMPORTANT NOTE**

The question is meant to allow the audience to gauge their understanding of the TransCelerate paper (if they did the pre-course work and read it) and to generate some interest in the material to be further clarified later.

All companies will have different definitions or understanding of SDV, this question is focused on the TransCelerate approach as it will be defined later in the presentation.

Let’s try another one. Use the same process to indicate your answer.
Module 1: Introduction

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

Challenge Yourself – Question 2 Debrief

ANSWER: True

SDV can be thought of as a “transcription check” to ensure that data in source documents are accurately transcribed into the CRFs.

One aspect of the TransCelerate risk-based monitoring methodology is a reduced reliance on SDV as a means of assuring patient safety and data quality.

The TransCelerate Position Paper further defines another concept called Source Data Review, or SDR, which we will discuss in detail later.
Module 1: Introduction

Slide 10

**Challenge Yourself - Question 3**

True or False

The FDA’s Final Guidance on A Risk-Based Approach to Monitoring states that current monitoring practices vary widely, are reactive, premised on retrospective detection of errors, and include periodic, frequent visits with 100% source data verification.

Slide 11

**Challenge Yourself – Question 3**

Let’s try another one. Again, use the same process to indicate your answer.

You may choose to show the slide with the correct answer highlighted.
Module 1: Introduction

Challenge Yourself – Question 3 Debrief
ANSWER: True

FDA Final Guidance on RBM identified the following as characteristics of the clinical trial monitoring:

- Wide range of monitoring practices
- Periodic, frequent visits with 100% source data verification
- Reactive and premised on retrospective detection of errors
- Oversight efforts are not aligned with risks
- May not optimally address significant risks to trial integrity, particularly systemic error
- Resource intensive
RBM Model Compared to Traditional Methods

Objective 1

**RBM MODEL AS COMPARED TO TRADITIONAL MONITORING METHODS**

Risk-Based Monitoring, or RBM, is not a new concept and there has been a significant amount of discussion around the topic for the past several years.

Many sponsors and CROs have adapted to a type of RBM based on recent regulatory guidance documents circulated in the US and in Europe.

In this module we will compare the RBM model to traditional monitoring methods in order to better understand the intent of RBM.

Direct participants to the Participant Workbook

Please follow allow in your participant workbook for specific key points as we review the material.
RBM Model Compared to Traditional Methods

Slide 13

Types of Monitoring

- Term “Monitoring” is used in different ways in the clinical trial context
  - Site Monitoring
  - Safety Monitoring
  - Quality Control monitoring by Sponsor and CRO internal processes and systems

For the purposes of RBM discussion, the focus is on updating and revising “traditional” site monitoring approaches

Defining Monitoring Terms

The term “monitoring” is used very loosely in the industry and has come to refer to a number of different activities conducted by sponsor and CRO personnel in clinical trials.

We have seen it in the context of an individual that goes to the site to review data, or when data is checked by data management.

Medical monitors and/or pharmacovigilance groups review safety data and this may be referred to as monitoring.

And finally, there may be Quality Control monitoring by Sponsor and CRO internal processes and systems.

Make the following key point:

- For the purposes of our RBM discussion, the focus is on updating and revising “traditional” site monitoring approaches.
RBM Model Compared to Traditional Methods

Slide 24

Discussion Point

What does “traditional” monitoring mean to you?

Discussion on “Traditional Monitoring”

Ask the learners what “Traditional” Monitoring means to them?

NOTE: Allow approximately 5 – 10 minutes for learners to generate responses.

IMPORTANT NOTE

The intent of the question is to ensure the audience comes to a general consensus on what traditional monitoring means as everyone may have a slightly different interpretation and this should lead to some discussion.

Further information regarding the answer to this activity is available on the next slides.
Facilitating the Discussion

If necessary during the discussion, you can provide some examples as well, such as monitoring on-site, monitoring on a fixed schedule, source verifying all data on-site.

Specific guidance based upon your classroom, is provided below:

Classroom Workshop Participants (face-to-face)

Have participants work in small groups at their tables and write create a list on the flip chart closest to their table.

Walk around while the group is discussing and documenting ideas and jot down any new or different ideas than what is provided on the following slide.

Webinar Workshop (all participants are online)

Utilize the whiteboard functionality within your webinar provider. Open a new whiteboard and type at the top: “Traditional Monitoring”. Allow all participants annotation rights to add their thoughts to the whiteboard.

Debrief the Discussion

Review the answers generated by the participants.

Inform participants that for the purpose of this training program, the next slide will further define on-site monitoring.

NOTE: Generally, this should be considered general traditional monitoring practice in the industry (although some companies may have taken a different approach, monitoring on-site every 4-6 weeks and performing 100% source document verification on-site has been typical).
RBM Model Compared to Traditional Methods

Traditional Approach: On-Site Monitoring

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

- 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
RBM Model Compared to Traditional Methods

Traditional Approach: On-Site Monitoring Definition

We generally think of traditional site monitoring as an approach consisting of monitoring all data, in person, on-site.

Traditional on-site monitoring can be defined as an in-person evaluation carried out by sponsor or CRO representatives at the location where the study is being conducted. The visits are generally conducted based on a fixed-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.

On-site monitoring is conducted to:
- Identify missing data in source records and data entry errors in case report forms,
- Assess compliance with protocol and investigational product accountability, and
- Evaluate investigator supervision.

Remember that we were monitoring before there was technology, so there was little choice in the approach we could take to review the data other than reviewing it on-site.

RBM Model Compared to Traditional Methods

Slide 16

How Does RBM Differ from “Traditional” Monitoring?

- Customizes approach and/or schedule as needed
- Identifies potential issues proactively
- Leverages technology
- Shares monitoring responsibilities across many functional areas
- Relies more heavily on central and off-site monitoring

Page 8

Direct participants to the Participant Workbook
RBM Model Compared to Traditional Methods

RBM vs. Traditional Monitoring

So, if RBM is an approach that updates our concept of monitoring from the “traditional” approach, how are they different?

- While traditional monitoring is conducted in a “one size fits all” schedule and approach (every site is visited every 4-6 weeks), RBM customizes the monitoring approach to each individual trial based on risk assessment to identify potential issues.
- RBM makes use of all available technology to allow sponsors/CROs to supervise study conduct without having to be at the site location.
- RBM involves many different functions and roles of the sponsor/CRO, not just Clinical Research Associates or Monitors. It includes recognition that monitoring is a cross-functional responsibility.
- As opposed to depending primarily on activities conducted at the site (on-site monitoring), RBM relies more heavily on central and off-site monitoring activities.

Let’s look next at what is meant by central or off-site monitoring.
Central and Off-Site Monitoring

Remote evaluation carried out by sponsor/CRO personnel at a location other than the investigative site to:

- Check that data is consistent and complete
- Identify unusual distribution of data
- Identify higher risk sites to target additional monitoring
- Ensure routine review of data in real time

Direct participants to the Participant Workbook

This information and a place for notes can be found in your workbook.
Central and Off-Site Monitoring

As technology has evolved we have been enabled to conduct less on-site monitoring and focus more on centralized and off-site monitoring techniques.

- 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.

Both of these techniques may be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time. In other words, we can do a significant amount to be proactive in addressing issues before ever going on-site and identifying study risk factors and potential indications of risk.

Ensuring that data is consistent and complete and identification of unusual distributions of data can be realized through analytics and visualization of data across the study, across regions, across a site and across a patient. Also, in order to be able to ensure that data is consistent and completed, there will need to be emphasis on the ability to integrate data from disparate sources.

Central monitoring 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.

According to data from the Clinical Trials Transformation Initiative, even though many sponsors have access to centralized data, 33% or fewer sponsors use centralized data monitoring to guide, target, or replace site visits.

So this leads us to considering further changes to our monitoring approach to make better use of technology and our resources.
**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.

- Assess risk level
- Identify Critical Variables
- Develop Monitoring plan

---

**Direct participants to the Participant Workbook**

This information can be found in your workbook along with a challenge activity and a place for additional notes.
Risk-Based Monitoring (RBM)

In addition to being able to review data from a remote location, we are further adapting our processes to work smarter and focus on what really matters instead of trying to look at everything.

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.

An RBM approach may utilize a variety of monitoring types, such as on-site and central monitoring, to fit the needs of the program and individual studies, and even to manage each site.

The process includes three key ideas.

- First, the sponsor assesses the risks at the program, protocol, and site levels.
- Then the sponsor determines the Critical Variables (Critical Data and Processes) for the trial. Once the Critical Variables are identified, it is important to know what to look for as an indication of the risk turning into an actual issue, these are called Risk Indicators and Thresholds to determine what type of action needs to be taken.
- The last step is to clearly define the monitoring approach within an Integrated Quality Risk Management Plan or IQRMP which includes various functional plans (e.g. the Monitoring Plan, Data Management Plan).

We will discuss all of these steps in detail as we progress through the program.

Make the following key point:

- Risk must be assessed, Critical Variables identified, and a plan documented for addressing risks that may include a change in the monitoring approach.
Challenge Yourself Activity

We are now ready to see what you think! Based on your experiences in the industry and the definition we just discussed for RBM, can you identify at least four differences between traditional monitoring and RBM?

NOTE: Allow participants approximately 5 minutes to complete this activity before debriefing

IMPORTANT NOTE

The answer key is on the next slide and may be hidden if you choose not to use it

Facilitating the Activity
**Classroom Workshop Participants (face-to-face)**

Have participants work within their table teams and flipchart their responses to the questions on the slide.

**Webinar Workshop Participants (online)**

Utilize the annotation functionality within your webinar provider and ask users to begin writing their responses on the slide within the meeting room. Allow all participants annotation rights to add their thoughts.

---

**Slide 20**

**Answer Key - Traditional Monitoring vs. RBM**

<table>
<thead>
<tr>
<th>Traditional Monitoring</th>
<th>RBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixed approach</td>
<td>1. Adaptive approach</td>
</tr>
<tr>
<td>2. Reactive</td>
<td>2. Proactive</td>
</tr>
<tr>
<td>3. On-site Monitoring</td>
<td>3. On-site, Off-site, and</td>
</tr>
<tr>
<td></td>
<td>Central Monitoring</td>
</tr>
<tr>
<td></td>
<td>Activities</td>
</tr>
<tr>
<td>4. Paper based</td>
<td>4. Technology based</td>
</tr>
</tbody>
</table>

---

**Debrief: Challenge Yourself Activity**

Debrief activity by reviewing the correct answers and determining how many participants understand the materials. Answer any questions.
Challenge Yourself Activity

Let’s try this question.

Provide instructions per the Facilitation guidance following.

Facilitating the Activity

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.

Ensure that you allow multiple correct answers when creating the poll.

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.

Debrief: Challenge Yourself Activity

ANSWER: All statements are true definitions, potential uses, and/or appropriate applications of centralized monitoring.
Objective 2

RATIONALE FOR RBM

Now that we understand how RBM differs from traditional monitoring, what is driving the adoption and move towards risk-based monitoring in the clinical trials industry?
Rationale for RBM

Regulatory Agencies - Leading the Movement

- 1998 FDA Guidance provides standards for minimal on-site monitoring
- 2009 CTRI focuses on clinical trial monitoring efficiency and effectiveness
- 2013 FDA Final Guidance on RBM (issued August 2013)

- 1996 ICH E6 provides flexibility in how trials are monitored
- 2007 Janet Woodcock, FDA, introduces risk-based approach concepts in clinical research
- 2009-10 FDA sponsor warning letters citing “inadequate monitoring”
- 2013 FDA supports TransCelerate with review of pilot RBM plans

Formation of TransCelerate
Rationale for RBM

Why RBM?

As you can see based on the timeline on the screen, there have been a number of actions taken that are directed towards modifying our monitoring approach.

The 1988 FDA Guidance on Monitoring of Clinical Investigations stressed personal contact between the monitor and investigator. This was withdrawn by FDA in 2010 as evidence grew for the need of a shift in our approach to monitoring.

The 1996 ICH E6 (GCP Guideline) provided flexibility in how trials monitored; centralized monitoring alone appropriate only in exceptional circumstances.

In 1998 there was an FDA Guidance issued in which the agency suggested more flexibility in what’s considered acceptable monitoring and provided data standards for studies with minimal on-site monitoring.

In 2007 at the IFPAT meetings (GMP Manufacturers), Janet Woodcock, Chief Medical Officer of CDER/FDA talked about the intersection of Process Analytical Control (PAT) in GMP and Quality by Design (QbD) in clinical development. Additionally, Helen Winkle (Director, Office of Pharmaceutical Science, CDER/FDA) gave a presentation on QbD in September 2007.

In 2009 CTTI was formed with the mission to identify practices that through broad adoption will increase quality and efficiency of clinical trials. 120 members from FDA, academia, industry, government, and patients/investigators participating. One of the earliest projects was to identify current monitoring practices and apply Quality by Design (QbD) principles to clinical trials.

Between 2009 and 2010 we saw more FDA Warning Letters to Sponsors with findings of failure to adequately monitor clinical investigators. This finding includes improper selection of investigators who subsequently fail to meet GCP requirements, failure of monitors to find protocol compliance issues, and/or failure of sponsors to promptly take actions to correct deficiencies when identified through monitoring.

In 2011 two draft documents were issued from the FDA and the EMA, and can be considered a clear indication that the industry is being encouraged to modify its practices.

In 2013, the FDA finalized its guidance document.
## Rationale for RBM

### RBM Industry Movement

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

---

### Direct participants to the Participant Workbook

This information along with additional room for notes is in your workbook.
Rationale for RBM

Movement in the industry

Some of the documents mentioned on the timeline include the Clinical Trials Transformation Initiative, the FDA Guidance for Industry, A Risk-Based Approach to Monitoring, and the EMA Reflection Paper on Risk-Based Quality Management in Clinical Trials.

The CTTI project focused on gathering data, confirming the current industry approaches to monitoring, and verifying that the primary focus should shift from post-hoc inspection to incorporation of quality into the scientific and operational design of a trial. CTTI stated there is not one single approach that is appropriate or necessary in all circumstances, and that the monitoring approach for a given clinical trial should be tailored to the needs of the trial and may combine several methods of monitoring. Furthermore, the CTTI participants agreed that the quality of the protocol is likely an important determinant of the quality of monitoring.

The FDA Guidance was intended to assist sponsors in developing risk-based monitoring strategies and plans tailored to the specific human subject protection and data integrity risks of the trial. It included a focus on critical study parameters, encouraged the use of a combination of monitoring activities and promoted greater reliance on centralized monitoring practices, where appropriate.

The EMA Reflections Paper focused on Risk-Based Quality Management through assessment of the use of risk identification and control. The key points were to develop a plan at the start of a program, adapt protocol by protocol, build on experience gained with each study and build on technical, regulatory, and other advances.

Make the following key point:

These three documents provide a framework for some of the concepts that are driving the industry to change.

We will not be spending a great deal of time discussing these documents, but it is important to understand that there is a regulatory drive to adapt the industry’s practices according to risk and move away from the idea of “one size fits all.”
Rationale for RBM

Discussion Point

Take a couple of minutes and see if you can name at least three reasons why the industry’s traditional monitoring approach may need to be changed.

Reasons for Change Discussion

Provide instructions for discussion activity as applicable to your workshop audience (see guidance).

Facilitation of Reasons for Change Discussion

Possible answers/solutions are on the next slide. Allow participants to generate / provide some of their own ideas before displaying the slides.

NOTE: Allow approximately 15 minutes for this activity.

Classroom Workshop Participants (face-to-face)

Ask each person to write their three reasons on a sticky note and share with their table group. Each group will then share with the full class.

Webinar Workshop Participants (online)

Ask each person to type their three reasons in the chat box so that the full class can see.
Rationale for RBM

You may choose to show the slide with these answers.

Direct participants to the Participant Workbook

Use this page in your workbook to record some of the reasons we have for changing (as well as any you have selected from the activity that are not in the chart).

Debrief the Reasons for Change Discussion

Review the reasons that were identified from the group discussions (either through sharing by groups or reading common themes from the chat box), then share the various reasons shown on the Answer Key Slide:

<table>
<thead>
<tr>
<th>Complex Protocols</th>
<th>Benefit Ratio</th>
<th>Limited Resources</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Technology</td>
<td>Regulatory Shift</td>
<td>Adapt to Needs</td>
<td></td>
</tr>
</tbody>
</table>

From a sponsor’s 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.

Some challenges facing the industry, such as protocol complexity, focus on cost-benefit ratio, and limited resources, just to name a few, are also serving to help drive a shift in our monitoring philosophy.

Finally, changing the monitoring approach potentially provides benefits such as improved risk mitigation, adapting monitoring to the needs of the trial or site, and more effective use of current state technology.
“Application of risk based quality management approaches to clinical trials can facilitate better and more informed decision making and make the most use of the available resources.”

EMEA Draft Reflection Paper on Risk-Based Quality Management in Clinical Trials, August 2011
Rationale for RBM

Make the following key point:

This quote from the EMA paper stresses that applying Risk-Based quality concepts to clinical trials can help us maximize the use of resources and result in better, more informed decisions and conduct of our trials.
Rationale for RBM

Slide 69

Challenge Yourself

The rationale for focusing on RBM includes all of the following EXCEPT: (select one)

A. To increase efficiency  
B. To refocus monitoring efforts on protocol compliance  
C. To reduce the monitoring workforce  
D. To update industry practices to make use of advanced technology

Challenge Yourself Activity

Take a look at this question in regards to the factors contributing to a focus on RBM.

IMPORTANT NOTE

The answer key is on the next slide and may be hidden if you choose not to use it

Facilitating the Activity
Rationale for RBM

Classroom Workshop Participants (face-to-face)

Ask participants to use the colored / labeled index cards at their table and hold up their answer choice. 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 answers

Debrief Challenge Yourself Activity

ANSWER: C is not part of the rationale or focus for RBM. Roles and responsibilities may change but this is not why RBM is being implemented.
Objective 3

TRANSCELERATE’S KEY ASSUMPTIONS AND CONCEPTS

At this point in the program, you may be wondering –

- What exactly is TransCelerate?
- Why did TransCelerate develop a RBM methodology?
- What are the core concepts of that methodology?

Direct participants to the Participant Workbook
TransCelerate's Key Assumptions & Concepts

TransCelerate in the News

You may have already heard quite a bit about the TransCelerate initiative in the news. We will be spending the rest of the presentation expanding upon one of their key initiatives, developing a model approach for RBM.

IMPORTANT NOTE

The TransCelerate detail slides (32, 33, 34 and 35) may be hidden depending on your audience and their background. Slides have been left in the presentation in the event you would like to use them.

Additionally, slide 37 on the true value of SDV can be hidden for the same reasons based upon audience and background.
TransCelerate's Key Assumptions & Concepts

TransCelerate BioPharma Inc. Introduction

- 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

Introduction to TransCelerate

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

TransCelerate was founded with a mission to identify and solve common drug development challenges with the end goals of improving the quality of clinical studies and bringing new medicines to patients faster.

TransCelerate was launched on September 19, 2012. At that time, the organization chose to focus on five initiatives related to clinical trials – designed to increase efficiency, reduce costs and enhance patient safety.
TransCelerate's Key Assumptions & Concepts

Who makes up TransCelerate?

As you can see a number of industry leaders are members of TransCelerate and have contributed to identifying and capturing efficiencies relating to clinical trial execution. This is an unprecedented industry collaborative effort that is fully supported and encouraged by health authorities. For example, FDA and EMA representatives reviewed the RBM position paper and provided feedback prior to its publication and release.
TransCelerate's Key Assumptions & Concepts

Partnering with Existing Collaborations

External Engagement with the Larger Ecosystem
Outside organizations, including regulatory, public, government and industry-based entities, are being engaged.

- Industry Initiatives
- Patient Advocacy
- TransCelerate BioPharma Inc.
- Regulatory Bodies
- Research and CRO Community

Direct participants to the Participant Workbook
This graphic is available in your workbook with additional space for notes.

Make the following key points:

- As you can see, Risk-Based Monitoring is an industry wide initiative and not just a sponsor or CRO-driven initiative. Stakeholders include regulatory bodies, industry initiatives, patient advocacy, and research and CRO community organizations.
TransCelerate's Key Assumptions & Concepts

The Position Paper

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. Additionally, by working with industry stakeholders, TransCelerate determined 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. Through modernization, including use of technology enablers, efficiencies can be gained without impacting subject safety by implementing quality risk management approaches to clinical trial oversight.
TransCelerate's Key Assumptions & Concepts

Monitoring: What is the True Value of SDV?

TransCelerate Retrospective Analysis

- The average percentage of SDV queries generated was 7.8% of the total number of queries generated.
- The average percentage of SDV queries that were generated in Critical Data was 2.4%.
- The rate of SDV-only discrepancies in Critical Data suggests that SDV has a negligible effect on data quality.

TransCelerate methodology proposes shifting the on-site monitoring focus away from 100% source data verification (SDV) to a risk-driven level of SDV and source data review (SDR).

The True Value of SDV?

To better understand the impact of existing SDV approaches on overall data quality, TransCelerate member companies evaluated data discrepancies for completed studies to determine the rate of queries identified via SDV as compared to all queries for a study. Those queries were then further assessed to determine what percentages of SDV-generated queries were found in Critical Data.

The rate of SDV-only discrepancies in Critical Data (2.4%) suggests that SDV has a negligible effect on data quality. These data help support the TransCelerate methodology which recommends shifting the on-site monitoring focus from 100% source data verification (SDV) to a risk-driven level of SDV and source data review (SDR).

NOTE: Remember, this slide can be hidden dependent upon the knowledge and background of your participants.
TransCelerate's Key Assumptions & Concepts

Specific Information on the Queries / Study

Nine sample studies from 6 member companies were analyzed. Despite variability in the way companies manage their data review activities, all companies were similar in the low rate of SDV-generated queries. The average percentage of SDV queries generated was 7.8% of the total number of queries generated. The average percentage of SDV queries that were generated in Critical Data as represented as a part of the total number of queries was 2.4%.
TransCelerate's Key Assumptions & Concepts

TransCelerate Monitoring Methodology: Assumptions

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 changes/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/CRF finalization

Direct participants to the Participant Workbook

Follow along and complete the activity in your workbook as we discuss each of these.
TransCelerate’s Key Assumptions & Concepts

TransCelerate Monitoring Methodology Assumptions

There are 9 assumptions underlying the TransCelerate monitoring methodology promoted in the May 2013 position paper.

1. Central and off-site monitoring form the foundation of monitoring, complemented by targeted, risk-based on-site monitoring activities.

2. Monitoring activities should be responsive to issues/risks identified and increased in a targeted, temporary manner. The goal should always be to return to the baseline level of monitoring. Root cause analysis is critical to prevent identified issues from recurring.

3. Monitoring methodology and activities must be tailored to the technology available for the program, study, and/or site.

4. Since central/off-site monitoring is the foundation of sponsor oversight, timely data entry and query resolutions are critical. Sponsors should establish expectations in site contracts.

5. The IQRMP is a living document and should be revised/amended throughout the study as needed in response to changes in the study, identified risks, etc.

6. It is acceptable to define risk-based monitoring standards in associated SOPs rather than within each study-specific IQRMP.

7. The defined methodology is applicable to all phases of studies, types of studies, and stages of clinical trials.

8. Communication plans should be tailored or customized in whatever way is necessary to maximize effectiveness.

9. Risk assessment should be completed prior to protocol and CRF finalization as a means to address and minimize risks before the trial starts. Then, monitoring strategies can be used to oversee and manage risks that cannot be prevented via protocol/CRF design strategies.
TransCelerate's Key Assumptions & Concepts

Quality by Design (QbD) Concepts

Program and Protocol Development

- Build Quality into the scientific and operational design and conduct of clinical trials
  - Focus on what matters
  - Critical Data AND Critical Processes that impact on:
    - Patient safety or
    - Data Integrity
    - GCP / Regulatory Compliance

Study Execution

- Identify risks at the program, study, and site level in order to employ the appropriate level of monitoring
  - Map the risks to appropriate monitoring plans
  - Employ mechanisms to monitor important parameters (inclusive of Central monitoring activity)
  - Smarter use of Technologies that enable effective oversight
  - Targeted on-site interventions
TransCelerate's Key Assumptions & Concepts

Quality by Design Concepts

TransCelerate’s RBM methodology embraces the concept of building “Quality by Design” (QbD) into clinical trials starting with protocol development and extending across all aspects of a trial. A well-written protocol and CRF are important facets which may impact the success of the RBM methodology.

Quality refers to the ability to effectively and efficiently answer the intended question about benefits and risks while assuring subject safety. Decisions are supported by quality data which is not considered error-free data, but rather fit-for-purpose data that sufficiently supports conclusions equivalent to those derived from error-free data. QbD includes a focus on identifying key risks to subject safety, data quality, and GCP/regulatory compliance. QbD also involves the application of an efficient monitoring approach to rapidly detect and correct issues while the study is ongoing and developing a quality risk management plan that focuses on factors that are at high risk for generating errors.

It is also critical to apply monitoring strategies that are tailored to risks, permit timely oversight (through central/off-site monitoring and use of technology), and are focused on Critical Processes and Critical Data. On-site interventions should be targeted in nature.

Make the following key points:

In summary, QbD provides a basis for implementation of RBM and is a fundamental principal of the TransCelerate methodology and tool application as we will discuss in later modules.
TransCelerate's Key Assumptions & Concepts

Direct participants to the Participant Workbook

Make the following key points:

- TransCelerate developed a model approach for RBM that can be adopted for any type, phase, and stage of trial.
- 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.
- The TransCelerate RBM methodology is aligned with the QbD paradigm, and with the monitoring and study oversight expectations of health authorities. When RBM methods are used, applicable ethical standards, subject rights, laws and regulations are expected to be followed.
- TransCelerate’s methodology is being developed concurrent with the transition to risk-based inspection processes by health authorities.
TransCelerate’s Key Assumptions & Concepts

The TransCelerate Approach

As you can see Building QbD is the first step in the TransCelerate approach.

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) early and ongoing risk assessment, (3) a focus on Critical Processes and Critical Data, (4) use of Risk Indicators which are critical Data and other study variables to be assessed (in many cases by comparing across program / protocol / country / site) and Thresholds, defined as the level, point, or value associated with a Risk Indicator that will trigger an action. Details surrounding the Risk Indicators and Thresholds will be documented in the various study plans, which fall under the Integrated Quality and Risk Management Plan, or IQRMP, (which we will discuss in detail in a later module) and (5) adjustment of monitoring activities based on the issues and risks identified throughout the study.

By monitoring available data Off-site or Centrally, On-site Monitoring can be targeted to activities which cannot be assessed remotely. Additionally, TransCelerate has adopted the term Source Data Review (SDR) which describes review of source data for protocol compliance, quality of documentation, as well as site processes in contrast to transcription checking, referred to as Source Data Verification (SDV).
TransCelerate's Key Assumptions & Concepts

Slide 41

TransCelerate Fundamentals: A Snapshot of Items We will Be Addressing

Risk Assessment (high, medium, low)

Risk indicators

q. 6.1 Riskstrategies

<table>
<thead>
<tr>
<th>Categories of Risk</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>- Serious adverse events (SAEs)</td>
</tr>
<tr>
<td>- Mortality</td>
<td>- Unintentional deaths (UDEs)</td>
</tr>
<tr>
<td>- Non-Safety</td>
<td>- Protocol deviations</td>
</tr>
</tbody>
</table>

Thresholds

<table>
<thead>
<tr>
<th>Risk indicator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>SAEs</td>
</tr>
<tr>
<td>- 1 SAE per site</td>
<td></td>
</tr>
<tr>
<td>- 5 SAEs per site</td>
<td></td>
</tr>
<tr>
<td>- 10 SAEs per site</td>
<td></td>
</tr>
</tbody>
</table>

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Rev. Date 11/8/2013
TransCelerate's Key Assumptions & Concepts

TransCelerate Fundamentals: Snapshot

In future modules, we will be further breaking out how RBM should be implemented, what tools can be used and how risk assessment should be completed.

We will define key Risk Indicators and address tasks to be performed on-site or centrally.

We will also focus extensively on quality plans and Risk Indicators for adjusting the type and amount of monitoring based on metrics.
Challenge Yourself - Confirming Definitions

Match the term with the most appropriate keywords:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Critical Data</td>
<td>A. Adaptive approach to clinical trial monitoring which focuses activities on evolving areas of greatest need, having the most potential impact on what matters most (e.g. subject safety and data quality, regulatory compliance).</td>
</tr>
<tr>
<td>2. Source Data Review</td>
<td>B. Data that are critical to the study findings, data that support primary and secondary endpoints and/or data related to subject safety.</td>
</tr>
<tr>
<td>3. Risk-Based Monitoring</td>
<td>C. Check of source documentation to assess quality of source, review of protocol compliance, ensure Critical Processes and source documentation are adequate, to ascertain Investigator involvement and appropriate delegation.</td>
</tr>
</tbody>
</table>

Challenge Yourself - Definitions

As we move through the remaining modules in our presentation we will be using a number of terms from the TransCelerate Position Paper. To make sure you are comfortable with the definitions, go ahead and match the term with the correct definition on this slide. If you are not sure of a definition, they can be found in the TransCelerate Position Paper on pages 13 and 14.

Provide instructions to participants from the Facilitations instructions section based upon your classroom type.

NOTE: Allow approximately 10 minutes for this activity.

IMPORTANT NOTE

The answer key is on the next slide and may be hidden if you choose not to use it.
TransCelerate's Key Assumptions & Concepts

Facilitating the Activity

Classroom Workshop Participants (face-to-face)

Ask participants to work within their groups at their tables and flipchart their group responses to how the terms match with the definitions shown on this slide.

If you are running short on time, use the Red, Green and Yellow index cards (A, B & C) and run through each term asking participants to hold up the card that they think is the definition best fitting for the term.

Webinar Workshop Participants (online)

Allow annotation rights to all participants on the webinar and ask them to draw lines from the term to the appropriate definition.

If you are in a blended classroom and need to use the time saving option, ask participants to send their selection (A, B or C) through chat.

You may choose to show the slide with the correct answers

Debrief Challenge Yourself - Definitions

Correct Answers:

- 1 is B
- 2 is C
- 3 is A
TransCelerate's Key Assumptions & Concepts

Challenge Yourself - Confirming Definitions (cont)

Match the term with the most appropriate keywords:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Quality by Design (QbD)</td>
<td>D. Processes that are critical for the reliability of the study findings, related to ensuring subject safety, and which satisfy compliance with ICH-GCP and regulations.</td>
</tr>
<tr>
<td>5. Risk Indicator</td>
<td>E. Systematically building quality into clinical trial design through ensuring that processes are focused on 'what is critical', and through mitigation of risks which impact subject safety and data quality.</td>
</tr>
<tr>
<td>6. Critical Processes</td>
<td>F. Level, point, or value associated with a Risk Indicator that will trigger an action.</td>
</tr>
<tr>
<td>7. Thresholds</td>
<td>G. Critical Data, study variables to be assessed.</td>
</tr>
</tbody>
</table>

Challenge Yourself - Definitions

Let’s check our understanding of a few more definitions. Again, if you are ever lost on a term or definition, these can all be found in the position paper.

Use the same instructions as the first definitions exercise.

NOTE: Allow approximately 10 minutes for this activity.

You may choose to show the slide with the correct answers.
TransCelerate's Key Assumptions & Concepts

Debrief Challenge Yourself - Definitions

Correct Answers:

• 4 is B
• 5 is D
• 6 is A
• 7 is C
Module 1: Summary

Module 1 Summary

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

Direct participants to the Participant Workbook

Module One Summary

In summary, the RBM Model varies from traditional monitoring methods through using a combination of On-site, Off-site, and Central Monitoring and risk assessment to identify critical study points and plan an individualized approach for monitoring based on the risks of the study.

The rationale for RBM is based on changes in the industry driven by protocols, technology, and resources

TransCelerate’s key assumptions and concepts include a focus on a proactive approach to monitoring through quality protocols and case report forms, and shifts monitoring processes from an excessive concentration on SDV to comprehensive risk-driven monitoring based on risk assessment, mitigation and management.
Module 1: Summary

Links

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

References

The links for the documents referenced in this portion of the presentation are included on this slide for your reference.
Module 1: Summary

Slide 48

Questions

Any questions?
Transition

Transition to Module 2 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.
APPENDIX A:  Pre-/Post- Communication

Welcome Risk-based Monitoring program Participant,

You are invited to participate in the Risk-based Monitoring (RBM) training in <location>. OR
Welcome to Risk-based Monitoring (RBM) training. Thank you for your registration.

The date for the training is <date>. The training starts promptly at <time> and ends at <time>. Your facilitators for the training are <name(s)>. The RBM program reflects the organization’s priorities and reinforces key messages of our goal to <insert>.

In order to experience the most value from the training program, you will be asked to complete several activities prior to the program, as well as post-course activities. Please complete the following pre-course activities before participating (shown in the recommended order of completion).

Pre-Course Activity Overview:

Pre-Read
In preparation for the course, it is mandatory for participants to read the articles referenced below. This reading will help provide you with a baseline level of knowledge about RBM and ensure that all participants enter the program with a common understanding of key RBM principles and terminology used in the course.

<table>
<thead>
<tr>
<th>Reading Required</th>
<th>Estimated Time Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>TransCelerate Risk-based Monitoring Position Paper</td>
<td>60 minutes</td>
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<tr>
<td><a href="#">PDF</a> TransCelerate Risk-based Monitoring Methodologo</td>
<td></td>
</tr>
<tr>
<td>FDA Final Guidance on Risk-based Monitoring and Draft EMA Reflection Paper on Risk-based Quality Management</td>
<td>90 minutes</td>
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<tr>
<td><a href="#">PDF</a> FDA Guidance for Industry - Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring</td>
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<tr>
<td><a href="#">PDF</a> MRC DH MHRA Joint Project Risk-adapted Quality Management</td>
<td></td>
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<tr>
<td>CTTI (optional)</td>
<td>30 minutes</td>
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</tbody>
</table>
APPENDIX A: Pre-/Post- Communication

<table>
<thead>
<tr>
<th>Risk-based Monitoring Training Outline</th>
<th>1 minute</th>
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</thead>
<tbody>
<tr>
<td>TransCelerate RBM Course Outline</td>
<td></td>
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</tbody>
</table>

**Manager Meeting**

It is important for you to meet with your manager to discuss expectations of your participation in this program. Having this conversation prior to the program will support the application of learning arising from participation in the program. Please read the pre-course articles prior to this meeting with your manager.

**Post-course Activity Overview:**

Following the training, you will have a follow-up meeting with your manager to discuss your experience during the program, RBM implementation plan, your strengths, development areas, and plan for development.

You will also be contacted by <Name> at 4 to 8 weeks post-program to assess <e.g. effectiveness of the program, progress with your action plan>.

Additional information about program logistics (meeting times, location, dinner, etc.) will be sent in a separate email. If you have any questions, please contact <insert name and contact information>.

We look forward to welcoming you at the session.

Kind Regards,

Name, Title
APPENDIX A: Pre-/Post- Communication

Dear Line Manager,

One or more of your direct reports will be participating in the <Risk-based Monitoring training program>. Please review the attached training outline. You have a crucial role in helping your direct reports, and thus the organization, adopt this new way of working. As such, we are providing you with brief activities and tools to help ensure your direct reports succeed in this transition. Please plan to meet with your direct reports before and after they attend the training session(s), using the following activities to guide the meetings. A recommended meeting guide is attached.

Activity: 15-Minute Pre-course Meeting

During this meeting, review and discuss the course outline and discuss expectations and benefits of the training program. Ensure your direct reports completed any prerequisites and read the articles which were assigned as pre-course work.

Activity: 45-Minute Post-course Meeting

Meet with your direct reports again within <e.g. 2 weeks> after completion of the program. Discuss their experience with the training program, the benefits of RBM, and the plan for implementation of RBM. Help your direct reports to assess their strengths, implementation challenges, areas for development as related to RBM, and associated development plans.

If you have any questions, please contact <insert name and contact information>.

Kind Regards,

Name, Title
APPENDIX A: Pre-/Post- Communication

<table>
<thead>
<tr>
<th>Pre-course Meeting Questions</th>
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</thead>
<tbody>
<tr>
<td>Have you had the opportunity to complete the pre-course reading? Do you have any questions about the articles?</td>
</tr>
<tr>
<td>In reviewing the course outline, what do you expect to learn in this course?</td>
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<tr>
<td>How do you think you may be impacted by this training?</td>
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</table>

<table>
<thead>
<tr>
<th>Post-course Meeting Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBM Training</td>
</tr>
<tr>
<td>• Tell me about your experience with the training program.</td>
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<tr>
<td>• What are some of the benefits of RBM?</td>
</tr>
<tr>
<td>• What did you learn?</td>
</tr>
<tr>
<td>• Were there any topics that you don’t understand or would like further clarification on?</td>
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<tr>
<td>Roles and Responsibilities</td>
</tr>
<tr>
<td>• How do you see your role in RBM?</td>
</tr>
<tr>
<td>• Do you see any challenges in implementing this new way of working?</td>
</tr>
<tr>
<td>• How could you overcome these?</td>
</tr>
<tr>
<td>• What do you see as your strengths in this new way of working?</td>
</tr>
<tr>
<td>• What do you see as your development areas related to RBM? How do you plan to develop in these areas?</td>
</tr>
<tr>
<td>Site Interactions and Relationships</td>
</tr>
<tr>
<td>• What are the benefits and opportunities for the sites?</td>
</tr>
<tr>
<td>• Can you think of any potential challenges your sites may pose when transitioning to this new way of working? How could you best respond?</td>
</tr>
<tr>
<td>• What will sites need to do differently? How will we help sites with this transition?</td>
</tr>
<tr>
<td>• What types of conversations are you expecting with your sites?</td>
</tr>
<tr>
<td>Internal Interactions and Relationships</td>
</tr>
<tr>
<td>• What are the benefits and opportunities for cross-functional collaboration?</td>
</tr>
<tr>
<td>• Can you think of any potential challenges &lt;e.g. certain roles or functions&gt; may pose when transitioning to this new way of working? How could you best respond?</td>
</tr>
<tr>
<td>• What will &lt;e.g. roles or functions&gt; need to do differently (e.g. in using the RACT or other tools)? How will we help with this transition?</td>
</tr>
<tr>
<td>• What types of internal conversations are you expecting?</td>
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