Model Approach for Risk-Based Monitoring

Module 3: RiskAssessment

Trainer Guide
# Model Approach for Risk-Based Monitoring

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### Module 3: Risk Assessment

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These materials are intended to facilitate and reduce the burden on clinical trial sponsors and others in training personnel with regarding to risk-based monitoring methodologies. Each clinical trial sponsor or other company engaging in such training activities bears full responsibility for its own training and accompanying materials to ensure both the accuracy of the training and materials and compliance with all applicable local, state, and national laws and regulations. This training is not intended to replace any in-depth training that clinical trial sponsors or others may wish or need to provide to their personnel or investigator sites to educate them on required or desirable clinical trial monitoring methodologies.

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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 you 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.
Module 3: Risk Assessment

Goal
The goal of this module is to review how to identify and quantify risk as well as address one of the key measurement tools, the RACT, in detail.

Time
90 minutes

Overview
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.

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)
- 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
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Module 3: Introduction

For those of you who have participated in the previous course modules, we have introduced a number of the concepts and ideas leading to Risk Assessment; this module will focus on the details surrounding the “how to” of actually performing a risk evaluation for a clinical trial.
Module 3: Introduction

Slide 3

Course Overview - Five Modules

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

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 3: 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.
Module 3: Introduction

Module 3 Objectives

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

1. Discuss methods for identifying risk for planning purposes
2. Identify Critical Data/Processes for Risk-Based Monitoring (RBM) application
3. Use the Risk Assessment Categorization Tool (RACT) to perform risk assessment

Direct participants to the Participant Workbook

Module 3 Objectives

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

Review the objectives listed on this slide.
IMPORTANT NOTE

The image is meant to provide a “sign post” for learners to orient them to how this module’s content relates to the overall RBM methodology process. Introduction of each numbered step can be provided as necessary for specific groups of learners.
Module 3: Introduction

RBM High Level Process

The image on the screen shows an overview of TransCelerate’s methodology. The methodology proceeds in a stepwise fashion; at each step, sponsors should document the decisions made, rationales, and appropriate plans.

This module focuses on Steps 1 and 2 in the process flow –

- **Step one:** the completion of risk assessments and identification of Critical Variables. The RACT (Risk Assessment Categorization Tool) is a tool which can be used for risk assessment. You will have an opportunity to work directly with the RACT and practice identifying Critical Data and Processes in this module.
- **Step two** involves defining Critical Variables which includes Critical Data and Processes, first at the program level, and then in further detailed evaluation at the protocol or trial level.
- **The third step** is related to the development of the Integrated Quality and Risk Management Plan, also called the IQRMP. 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 final or fourth step** involves the execution of the pre-determined monitoring activities.
Module 3: Objective 1

IDENTIFYING RISK FOR PLANNING PURPOSES

Objective 1: Identifying Risk for Planning Purposes

In this section we will be defining risk and the general steps in the cycle of risk assessment. The output of all risk assessment activities leads into the overall plan for monitoring the study.
Identifying Risk for Planning Purposes

Slide 7

Background

- Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm
- For risks there are three major questions:
  1. What might go wrong?
  2. What is the likelihood it will go wrong?
  3. What are the consequences?

What is Risk?

What is a risk? Risk is defined in the Quality Risk Management (Q9) topic from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as “the combination of the probability of harm occurring and the severity of that harm”. We can think of a project or protocol risk as something that can go differently than planned and thus, jeopardizes the sponsor’s ability to achieve a goal or objective.

There are three key questions that can be used when working with risks:
  1. What might go wrong?
  2. What is the likelihood it will go wrong?
  3. What are the consequences?

The answers to these questions help us identify risks and ensure we plan for those that are most likely to occur and have the greatest impact.
Identifying Risk for Planning Purposes

Risk and the RBM Methodology

- Early identification of risks is the best way to manage the situation if a risk “materializes”
- Identifying and evaluating risks = Risk Assessment

Let’s start by giving you a chance to challenge yourself and see what you already know about risk assessment

Risk and the RBM Methodology

An understanding of risks and their management is fundamental to the RBM methodology. So, the early identification of risks is a core principle of the RBM process and allows us to plan for managing risks that arise during the study. The process of risk assessment includes identifying potential risks, evaluating their likelihood and impact on the program and/or clinical trial, and either preventing or managing the risks.

IMPORTANT NOTE

Challenge Yourself question is on the next slide
Identifying Risk for Planning Purposes

Slide 9

Challenge Yourself

Which of the following best describes the recommended timing for performing risk assessment? (select one)

A. After monitoring activities have identified a risk
B. Before any planned data analysis
C. Before protocol finalization and in an ongoing manner
D. After protocol finalization but before first subject screened

Let’s see what you already know about risk assessment...

Challenge Yourself – Multiple Choice

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

IMPORTANT NOTE

The answer key is on the next slide and may be hidden if you choose not to use it
Identifying Risk for Planning Purposes

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. 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 open it 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.

Challenge Yourself – Answer and Debrief

ANSWER: C
The assessment of risk should be performed early in the project (i.e., before the protocol and CRFs are finalized) and in an ongoing manner as changes occur in the project or as new risks are identified.
Direct participants to the Participant Workbook

Make the following key points:

- Risk mitigation plans may start to be drafted but their finalization is completed after protocol approval.

- If a new risk is identified after the study conduct phase starts and monitoring activities are in place, the plans are reviewed and where necessary, new risk mitigation plans are determined and applied.

IMPORTANT NOTE

Details of this process flow may differ depending upon individual company procedures.
Identifying Risk for Planning Purposes

The Risk Assessment Process

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

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

- Arrow 1: Once a protocol synopsis is drafted, the team identifies any protocol-level Critical Data/Processes and performs the study-level risk assessment using the RACT.
- Arrow 2: When the protocol is approved, then the risk mitigation plans are finalized. The various components of the Integrated Quality Risk Management Plan (IQRMP) are created, such as the Monitoring Plan, Data Plan, Safety Plan, Risk Indicators, Thresholds, and action/response plans.
- Arrow 3: Finally the study conduct phase starts as subjects are enrolled and the planned monitoring activities take place. Throughout study conduct, actions are taken for pre-identified risks when Thresholds are reached.
Identifying Risk for Planning Purposes

Risk Assessment Cycle

1. Risks are identified

2. Risks are evaluated and ranked

3. Risks are prevented or planned for

Direct participants to the Participant Workbook

Make the following key points:

- It is important to recognize that there is some level of risk inherent to all activities
- In our efforts to focus on the risks that matter most, we need to understand that risks vary in their significance
- If a risk can be prevented, that is preferable
Identifying Risk for Planning Purposes

Risk Assessment Cycle

Before proceeding, let’s think about the idea of risk in clinical research and ensure everyone understands why this is such a crucial point in RBM.

The steps of risk assessment and management are shown here in a cycle diagram because there is the potential for new risks to be identified in a clinical development program at any time. Therefore, whenever a new risk is identified, the remaining steps should also be completed –

- assessing the risk (ranking it),
- eliminating its occurrence, or if that’s not possible, managing the risk to minimize its impact. In some cases, the study team will decide to accept a given risk as is.

First of all, it is important to recognize that there is some level of risk inherent to all activities.

- For example, there is risk for error whenever untrained site personnel dispense Investigational Product.
- There is also risk, however, even with a trained site if there is a complicated randomization procedure. One of these risks is a study level, Risk-Based on the procedure, and the other risk is a site level risk, based on the inexperience of a site.

Secondly, in our efforts to focus on the risks that matter most, we need to understand that risks vary in their significance.

- It is not necessary or prudent to take actions to prevent or address every risk in a clinical trial. We should, however, take actions to prevent or manage those risks that are both likely to occur and would have relatively significant consequences.
- For our previous example, the complicated randomization procedure is more significant because it applies to every site on the study and therefore has a higher likelihood.

Finally, if the risk can be prevented, that is preferable. However, we must accept that it is not possible to eliminate every risk in clinical studies. We can, however, anticipate many risks and be proactive in our planning to quickly identify them and take actions to lessen their impact.

Let’s learn a bit more detail about the steps in this cycle by starting with identifying risks.
Identifying Risk for Planning Purposes

Slide 13

Step One: Identifying Risks

Risks may exist at three different levels:

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

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

Identifying Risks

**Program-level**: these risks apply to all trials conducted for the Investigational Product (IP). May involve asking if there are specific safety issues for the IP, identifying new/unique tools or procedures associated with the program, etc.

**Trial-level**: these risks are specific to each study and may involve considerations of the specific subject population, comparator products, complexity of the trial, etc.

**Site-level**: these risks are specific to the population of sites being used for a particular study or may reflect individual site characteristics that raise risk.
Identifying Risk for Planning Purposes

Challenge Yourself – Key Questions to determine risks

**IMPORTANT NOTE**
The following slides contain examples of questions to be asked/used in evaluating each level. They can be hidden or displayed depending upon learners’ needs or personal preference.

Module 4 is titled *Risk Management* and will include more detail on these 3 levels of risk.

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**Facilitating the Activity**

This activity should take approximately 10 minutes.

**Direct participants to the Participant Workbook**

The participant’s workbook provides a page for the learners to write down their answers and the classroom thoughts for this activity.

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

Ask each participant to write one key question for each of the different levels as shown on the slide. Take volunteers from the audience to share their questions and flipchart the answers to compile a list of questions for each of the different levels before going into the debrief of answers shown on the following slides.

**Webinar Workshop Participants (online)**

Ask participants to use the chat box to share one key question for each of the different levels shown on the slide. Open the audio line to allow the audience members to volunteer sharing their questions while whiteboarding the answers to create a list of questions for each of the different levels before going into the debrief shown on the following slides.
Identifying Risk for Planning Purposes

Slide 14

Identifying Risks: Program-Level

- Are there new/unique tools or procedures associated with the program?
- Are there specific safety requirements or adverse events of special interest?
- Are there any issues that are unique for the product such as storage requirements that are potentially difficult?
- Are there risks inherent to the indication and/or therapeutic area?
- Are there risks from a regulatory perspective?

Debrief

Compare these questions to the generated list from the classroom and determine any that were not identified by the class.

IMPORTANT NOTE

This slide can be hidden or displayed to further provide examples of questions to be asked/used in evaluating each level.
Identifying Risk for Planning Purposes

Slide 15

Identifying Risks: Trial-Level

- Are there new/unique tools and procedures being used on this trial (especially any that may differ from standard of care)?
- Are there unique safety considerations as a result of comparator drugs or the indication?
- Are there competitive studies that need to be considered?
- Does the complexity of the study increase risks?
- Are some inclusion/exclusion criteria open to interpretation?

Debrief

Compare these questions to the generated list from the classroom and determine any that were not identified by the class.

IMPORTANT NOTE

This slide can be hidden or displayed to further provide examples of questions to be asked/used in evaluating each level.
Identifying Risk for Planning Purposes

Slide 16

Identifying Risks: Site-Level

- Do the sites participating in the study represent a risk in any way?
  - Limited experience in clinical research
  - Limited infrastructure
  - Limited access to subject population
- Are any participating sites also working on competitive studies?
- Could personnel or equipment changes at sites present a risk to the study or product development?

Debrief

Compare these questions to the generated list from the classroom and determine any that were not identified by the class.

IMPORTANT NOTE

This slide can be hidden or displayed to further provide examples of questions to be asked/used in evaluating each level.
Identifying Risk for Planning Purposes

Risk Assessment Cycle

1. Risks are identified
2. Risks are evaluated and ranked
3. Risks are prevented or planned for

Risk Assessment Cycle – Evaluation & Ranking

After the program, trial, and site-level risk have been identified, they need to be evaluated and ranked for their likelihood and significance. Let’s look then at step 2 of the cycle.
Identifying Risk for Planning Purposes

Slide 18

Step Two: Evaluating Risks

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

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Direct participants to the Participant Workbook

Evaluating Risks

The evaluation of risks often starts with considering the significance or “rank” of the risk. Determining the “rank” of one risk is often relative to other identified study risks.

Categories of monitoring activity risk might, for example, be ranked as high in red, medium in yellow, or low in green, based on discussions using agreed upon risk categorizations (i.e., completing the RACT or a similar tool).
Identifying Risk for Planning Purposes

Evaluating Risks

Evaluating risks also involves considering both the impact - the consequences of a risk on our development program, subject safety, data integrity, etc. and the likelihood – the probability of the risk occurring.

Sometimes a chart similar to the one shown here is used to “rank” potential risks according to both their likelihood and their impact.

Risks ranked in the upper right area of the table would be the ones we should prioritize for prevention or proactive management.
Module 3: Risk Assessment

Identifying Risk for Planning Purposes

Slide 20

Risk Assessment Cycle

1. Risks are identified

2. Risks are evaluated and ranked

3. Risks are prevented or planned for

Risk Assessment Cycle – Prevention or Planning

The final step in this cycle involves either eliminating significant risks or designing a plan to mitigate their impact and occurrence.
Identifying Risk for Planning Purposes

Slide 21

Step Three: Preventing or Planning For Risks *

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

* Topic of Module 4

Preventing or Planning for Risks

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

However, we must accept that it is not possible to eliminate every risk in our studies. We can, however, plan our risk management activities to detect, measure, and act upon our anticipated risks in a timely manner to lessen their impact.

Monitoring strategies can also be adapted to ensure oversight of what is not prevented via protocol or CRF design. These aspects of risk management are the topic of Module 4 of this course and will be reviewed in more detail there.
Module 3: Objective 2

IDENTIFYING CRITICAL DATA/PROCESSES FOR RBM APPLICATION

Objective 2: Identifying Critical Data / Processes

Monitoring activities and resources are focused on Critical Data and Processes in the application of the RBM methodology. This section will cover Critical Data/Processes and their relationship to risk assessment.
Identifying Critical Data/Processes

Slide 23

**Critical Data and Processes - Definitions**

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

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

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Direct participants to the Participant Workbook

**IMPORTANT NOTE**

Try and solicit as many real world examples as possible. If you have specific company examples from case studies or pilot programs, please share these as an example or to solicit further input from the audience.

**Challenge Yourself Activity**

Inform participants that the slide indicates high level information about Critical Data and Critical Process Definitions.

Using the facilitation guidance below, facilitate a discussion with the participants on examples of Critical Data and Critical Processes in the Studies they have worked on.
Identifying Critical Data/Processes

Facilitating the Activity

This activity should take approximately 10 min.

Classroom Workshop Participants (face-to-face)

Ask table teams to discuss their experiences and flipchart at least 3 examples of each (Critical Data and Critical Processes).

Webinar Workshop Participants (online)

Open a new whiteboard with a segregated line down the middle. Label the top of one side with Critical Data and the other Critical Processes. Ask each participant to add at least three examples to each side.

Discussion Debrief: Critical Data and Processes

Using the examples provided by the learners in the classroom, ensure that the following key elements were covered within the discussion.

Critical Data includes data that

- support primary and key secondary objectives
- is critical to subject safety (e.g. serious adverse events, events leading to discontinuation of treatment).
- will be used to make decisions about the product’s safety and efficacy profile.

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.

Critical Processes include processes that

- underpin data quality such as blinding, referring events for adjudication, and controlling inter-rater variability.
- 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.
- For example, in a psoriasis study, a Critical Process may be the 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.
Identifying Critical Data / Processes

In the RBM methodology, the cross-functional team starts by identifying program-level Critical Data and Processes. So, the team would generate an initial list of data to be treated as Critical Data across all protocols in the development program for the product. Some examples of program level Critical Data might include the following:

- Adverse Events of Special Interest based upon the class of drug or the product’s safety profile
- Eligibility criteria to prevent the inclusion of subjects for whom administration of the product would be unsafe, such as concomitant medications or laboratory values related to kidney function

Similarly, program level Critical Processes would be identified and would apply to all protocols conducted for the product. These might include a required process for preparation or reconstitution of the investigational product.

Moving next from the program-level to the protocol-level risk, the initial list of Critical Data and Processes is expanded as risks are assessed in greater detail during protocol development. Based on the particular protocol’s efficacy and/or safety objectives, Critical Data and/or Processes would be identified that relate only to the individual study and not necessarily to the entire program.
Identifying Critical Data/Processes

Critical Data/Processes – Possible Questions

- What are the data and/or processes which are critical to program and/or protocol success?
- What Critical Data must be collected in order to satisfy the development and/or protocol objectives?
- What are the Critical Processes that must be done correctly to ensure subject safety, data quality, and/or GCP and regulatory compliance?
- Are there any Critical Processes in the program and/or protocol which are especially vulnerable to error?

Possible Questions – Critical Data / Processes

Certain questions that may be helpful in the process of identifying Critical Data and Processes include [read slide].

IMPORTANT NOTE

This list is not intended to be all-inclusive but to provide some possibilities.
Identifying Critical Data/Processes

Group Challenge – Critical Data/Processes (1)

Study Design:
- Phase 2, randomized, double-blind study
- Twice daily subcutaneous doses of X118 in subjects with impaired renal function (defined as estimated creatinine clearance of <80 mL/min)
- Placebo controlled
- Duration: 3 days

Underline any terms above that reflect potential Critical Data and/or Critical Processes

Group Challenge Activity
Let’s work through an example together to understand how to identify Critical Data and Processes.

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

Facilitating the Activity
Allow 5 minutes for this activity
Identifying Critical Data/Processes

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

Ask a participant to read the study design description aloud. Once read, facilitate a group discussion and consensus on what the correct terms that should be underlined per the question on the slide. Use the tools within PowerPoint to underline the terms on the slide.

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Group Challenge – Critical Data/Processes (1)

Answer Key

Study Design:

- Phase 2, randomized, double-blind study
- Twice daily subcutaneous doses of X118 in subjects with impaired renal function (defined as estimated creatinine clearance of <80 mL/min)
- Placebo controlled
- Duration: 3 days

Group Challenge – Debrief

Answer is shown on the slide.

- The randomization process and maintenance of the blind should probably be considered Critical Processes for this study.
- Additionally, it will be important for the twice daily subcutaneous dosing regimen to be followed correctly so this is also a potential Critical Process.
- Critical Data would likely include the estimated creatinine clearance values as this defines the subject population – this is a critical eligibility criterion.
Identifying Critical Data/Processes

Slide 28

Group Challenge – Critical Data/Processes (2)

Primary Objective:
• To evaluate the safety and tolerability of X118 given twice daily as a subcutaneous dose in subjects with renal impairment.

Secondary Objective:
• To obtain information about the pharmacokinetics and pharmacodynamics of subcutaneously administered X118 in subjects with renal impairment.

List the Critical Data and/or Critical Processes derived from these objectives

Group Challenge Activity
Continuing with this same protocol, let’s look now at the primary and secondary objectives and identify any Critical Data and/or Processes we can find within this information.

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

Facilitating the Activity
Allow 5 minutes for this activity

Classroom OR Webinar Workshop Participants (face-to-face OR online)
Ask a participant to read the study design description aloud. Once read, facilitate a group discussion and consensus on what the correct list of Critical Data / Processes should be from these objectives. For Classroom training – write these on a flipchart; for Webinar training – write them on a whiteboard.
Identifying Critical Data/Processes

Group Challenge – Critical Data/Processes (2)

Answer Key

Primary Objective:

- To evaluate the safety and tolerability of X118 given twice daily as a subcutaneous dose in subjects with renal impairment.

Secondary Objective:

- To obtain information about the pharmacokinetics (PK) and pharmacodynamics (PD) of subcutaneously administered X118 in subjects with renal impairment.

Critical Data/Processes include: Adverse events (AEs), AE collection and reporting, PK and PD data, PK and PD analysis, PK and PD specimen collection and processing, subcutaneous administration of X118

Group Challenge – Debrief

Answer is shown on the slide.

- The objective related to evaluating safety and tolerability provides insight that adverse events (AEs) are Critical Data. Therefore, the collection and reporting of AEs should be considered Critical Processes.
- The objective related to PK and PD information should trigger the identification of PK and PD data as Critical Data for the protocol. So, the analysis of samples and the PK/PD specimen collection and processing are all Critical Processes.
- Finally, the timing of X118 administration and the proper administration are Critical Processes because errors here can impact the PK and PD data and analysis. For example, if X118 is administered intra-muscularly instead of subcutaneously, this could definitely impact the PK and PD data.

We’ll now give you an opportunity to apply these concepts to the identification of Critical Data and Processes in Activity #1.
Identifying Critical Data/Processes

Slide 3

Activity #1 – Identifying Critical Data/Processes

Locate Activity #1 in your participant workbook and complete the exercise as directed by the instructor.

Challenge Yourself Activity

Direct learners to open the instructions and sample protocol synopsis in their participant workbook.

IMPORTANT NOTE

This activity will be completed through review of a sample protocol synopsis. Instructions for the activity are provided separately in the participant workbook.

Recognizing that some organizations may prefer to use an internal protocol synopsis to make the activity more applicable to the specific work environment, you may replace the activity with a specific one for your organization as applicable.
Identifying Critical Data/Processes

Facilitating the Activity

Allow 20 minutes for this activity

Capture your notes here.

Review activity instructions (as provided in the facilitation notes by workshop type below as well as the participant guide for additional instructions). Capture any specific notes regarding the activity below.
Identifying Critical Data/Processes

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

Allow learners to work in their table teams. After reviewing the protocol synopsis, instruct them to complete, as a team, the worksheet for critical data and critical processes. Once complete, have each team flipchart their team’s results. After all teams complete, each team can then report their findings in a 2 minute presentation back to the full group.

*Webinar Workshop Participants (online)*

Ask learners to work independently. After reviewing the protocol synopsis, instruct them to complete, independently, the worksheet for critical data and critical processes. Once complete, open a new whiteboard on the webinar room with one side labeled Critical Data and one labeled Critical Processes. Ask the learners to begin writing their answers up on the board, not duplicating answers that their colleagues have written.

**Challenge Debrief**

Using the flipchart or white boarded answers, facilitate a discussion to ensure that the participants have included all elements from the answer key.

**IMPORTANT NOTE**

Answer key for activity is available in APPENDIX A of this trainer guide.
Application of the RACT

Module 3: Objective 3

APPLICATION OF THE RACT TO PERFORM RISK ASSESSMENT

Introduction to Objective 3

Now that we have a sound understanding of the identification of Critical Data/Processes, let’s move into the next step of risk assessment.

It is helpful to establish categories of risk and/or questions to guide team members in evaluating risk. This ensures both a thorough process and consistency in gauging risks of our projects. The RACT provided in the RBM Toolkit is an example of this kind of tool.

Let’s review how to use the RACT from the RBM toolkit to perform a risk assessment for a clinical trial.
Application of the RACT

Slide 32

Risk Assessment Categorization Tool (RACT)

First a little bit about the RACT....

- What is it?
  - Part of RBM Toolkit
  - Excel document
  - Protocol-specific
  - Version controlled
- Purpose: facilitate risk assessment and risk mitigation

Page 41

Direct participants to the Participant Workbook

What is the RACT?
The acronym stands for Risk Assessment Categorization Tool. It was developed by TransCelerate and is provided as part of the RBM Toolkit in the position paper.

- This is an excel-based document (spreadsheet) with a second tab (sheet) that provides instructions on expanding and collapsing the content in the main worksheet.
- The document is intended to be protocol-specific. It is recommended for the RACT to be version controlled as this is an “auditable” document.

What is the purpose of the RACT? To facilitate risk assessment and risk mitigation

IMPORTANT NOTE
Remember to communicate your version control guidelines.
### Application of the RACT

#### Slide 33

**RACT – What Does It Look Like?**

<table>
<thead>
<tr>
<th>Category Number</th>
<th>Category</th>
<th>Objective</th>
<th>Function Plan(s) Impacted</th>
<th>Monitoring Risk Level (high, medium, low)</th>
<th>Questions for Discussion</th>
<th>Examples/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Safety</td>
<td>Determine any known risk for patient safety</td>
<td>Monitoring Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Study Phase</td>
<td>Factor the risks inherent in the study phase into</td>
<td>Monitoring Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Complexity</td>
<td>Determine how the complexity of the study impacts risk</td>
<td>Monitoring Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Technology</td>
<td>What level of technology competence is required for a successful study?</td>
<td>Monitoring Plan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What does the RACT look like?**

Here is an illustration of what the RACT actually looks like – you can see the column headings as well as a partial list of the potential categories for risk assessment (Category Numbers 1-4).

All 4 of these Risk Categories shown would likely impact the assignment of Monitoring Activities so the Monitoring Plan is noted in the column labeled “Function Plan(s) Impacted”.

We’ll look more closely at the details of the RACT a bit later. But first, let’s make sure we understand the purpose of the RACT.
Application of the RACT

How to Complete the RACT

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

How to complete the RACT?

The purpose of the Risk Assessment and Categorization Tool (RACT) is:

- Each category is reviewed (including discussing questions and examples for consideration provided) to determining the risks which could affect subject safety, data integrity or regulatory compliance.
- A risk level (high, medium, or low) is then determined for each category.
- The team next decides which function(s) will manage the risk.
- Using the agreed-upon risk levels for each applicable category, an Overall Risk Level for the protocol will be determined.
- This Overall Risk Level (high, medium, or low) is used to determine the baseline monitoring approach and activities to be used for the protocol
Application of the RACT

Slide 35

**RACT - Discussion Point**

- When?
- Who?

**Discussion**

Facilitate a discussion among participants to answer the questions of:

- When is the RACT completed?
- Who is involved in completing the RACT?

**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 OR online)**

Facilitate a group discussion calling upon volunteers in the audience or via round robin if no participants are volunteering.
Application of the RACT

Slide 36

**RACT - Discussion Point**

**When?**
During study planning, before functional risk mitigation plans (Monitoring Plan, Data Plan, Safety Plan, etc.) are finalized

**Who?**
A cross-functional group involving various roles and team members (e.g., Data Managers, Monitors, Clinical Scientists)

**IMPORTANT NOTE**
Update the slide prior to the training session in order to properly communicate your company’s process/role & responsibilities.
Application of the RACT

Discussion Debrief

When is the RACT completed?
During study planning and before functional risk mitigation plans are finalized (such as the Monitoring Plan, Data Plan, Safety Plan, and/or other plans contained within the IQRMP).

Who is involved in completing the RACT?
This should be a cross-functional group involving various roles and team members. Some participants may include Data managers, Monitoring Managers, Medical Monitors, Project Managers, Clinical Scientists, Quality Assurance, Statisticians, Regulatory associates, and Safety/Pharmacovigilance representatives. The exact participants may vary depending upon company-specific infrastructure and processes.
Application of the RACT

Slide 37

**RACT: Preparation**

- Gather information
  - Program level
    - Product
    - Regulatory
  - Protocol level
    - Protocol (synopsis at minimum)
    - Site/facility requirements
- Gather the team

---

**IMPORTANT NOTE**

Update the slide prior to the training session in order to properly communicate your company’s process/role & responsibilities.
Application of the RACT

Make the following key points:

- It is important to have cross functional representation and knowledge in order to successfully perform the risk assessment and complete the RACT. For example, the medical monitor would usually be able to provide information to the team regarding the standard of care both in the US and globally.

- Team members should come prepared to the meeting(s) having reviewed all preliminary information.

RACT Preparation

In preparation for completing the RACT, two key steps should be performed: gathering information and gathering the team.

Information should be gathered at both the program and protocol levels. This information should include all Critical Data/Processes identified to date.

- Program level information would include product knowledge such as the Investigators’ Brochure or similar document as well as information related to the regulatory status or strategy of the program.

- Protocol level information would include the protocol synopsis at a minimum. A complete draft protocol, if available, would be preferable as it contains more detailed information that can inform the RACT discussion. Also, available information related to the protocol requirements for site experience, investigator specialties, facilities and equipment should also be obtained.

Then, the cross-functional team members should be identified and schedules coordinated to arrange the RACT meeting(s).
Application of the RACT

Using the RACT

Discussion

Functional Plan

Risk Level

Direct participants to the Participant Workbook
Application of the RACT

Using the RACT

As the team moves into using and completing the RACT, there are 3 activities that will be completed for each risk category. This diagram shows the 3 activities as a cycle because the team will repeat the steps as they move through each applicable category on the RACT.

- Each potential risk category should be fully discussed using a list of potential questions or examples that should be considered when determining the risks.
- After team discussion, each risk category should be ranked as high, medium or low.
- The team will then document the functional plans impacted by the risk and which will be used to manage the risk.

Let’s work through the steps by applying each to a sample protocol and evaluating the Complexity risk category. At each step, we will also allow you to see the individual sections of the RACT.

First, let’s look at the background for the protocol we’ll be assessing for risk.
Application of the RACT

**RACT Example - Preparation**

- Study comparing IP vs. placebo in subjects with Type 2 diabetes
- Primary endpoint: improvement in Hemoglobin A1c (HbA\(_{1c}\)) – collected every 6 weeks
- Secondary endpoints: improvement in fasting glucose, 2 hr oral glucose tolerance test (OGTT), and body weight – collected every 6 weeks
- Central lab analyzes HbA\(_{1c}\), fasting glucose, and OGTT; site collects body weight
- The IP as no known significant safety issues

**Ask a participant to read the synopsis on slide.**

Let participants know that this information is provided as part of the preparation for completing the RACT.
Ok, now that we’ve completed our preparation step by reviewing the background information, let’s move into the discussion step of the cycle.
Application of the RACT

Slide 41

**RACT Step One: Discussion**

- Objective provides focus
- Questions for discussion
- Examples/considerations

**IMPORTANT NOTE**

Be prepared to properly communicate your company’s process/role & responsibilities (e.g. which role(s) will arbitrate disagreement of risk, who will assess risk level).
Application of the RACT

RACT Step One Discussion

Within the Objective section of the RACT, there are specific instructions to help focus the use of the tool for each risk category.

- For example, in the Safety Category, the Objective is to “Determine any known risk for patient safety.”

Each risk category within the RACT can be expanded to display columns that provide “Questions for Discussion” and “Examples/Considerations”.

These are intended to provide sample questions for the team to evaluate and answer in order to better understand the risk(s) within each category. Examples of possible risks are also provided to facilitate the team’s discussion as each category is evaluated.

In working through our example, let’s focus on the Complexity risk category – what does it look like when expanded in the RACT?
### Application of the RACT

**Slide 42**

**RACT: Complexity Risk Category**

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

**Page 43**

Direct participants to the Participant Workbook
Application of the RACT

Complexity Risk Category

This slide shows the content from the RACT when the Complexity risk category is expanded.

You can see how for this category, there are questions to facilitate discussion and then considerations provided for how/why the answers to the questions could represent protocol risk.

I will allow you a moment to read through on your own; take specific note of the first question regarding complex or uncommon procedures beyond the usual standard of care.
Application of the RACT

**Slide 43**

**RACT Example – Discussion of Complexity Risk Category**

Question: Does the protocol require any complex or uncommon procedures beyond the usual standard of care?

Considerations: Consider the number of visits, the duration of the study, diagnostic testing that is not common for this patient population.

*What contributes to complexity of the protocol?*

*Are there any procedures required beyond usual standard of care (SOC)?*

**Page 43**

**Direct participants to the Participant Workbook**
Application of the RACT

Group discussion of Complexity Risk Category

Let’s look at the specific application of the RACT risk category for Complexity:
Question: Does the protocol require any complex or uncommon procedures beyond the usual standard of care?
Considerations: Consider the number of visits, the duration of the study, diagnostic testing that is not common for this patient population.
Within this one RACT question for discussion are two sub-questions.

Sub-question 1: What contributes to protocol complexity?
Sub-question 2: Are there any procedures required beyond usual standard of care (SOC)?

In order to clearly answer this question, our team will need to understand the standard of care for this indication, type 2 diabetes, more clearly. This is one reason why cross-functional representation and discussion for risk assessment is so important.

IMPORTANT NOTE
Type 2 Diabetes standard of care information is provided on the next slide.
The answer key is on the following slides and may be hidden if you choose not to use it.

Facilitating the Activity
This activity should be a group walkthrough (for both time and knowledge purposes).

Classroom OR Webinar Workshop Participants (face-to-face OR online)
Walk participants through questions and allow for volunteers (through live hand rising or virtual webinar hand rising) to add to the discussion through the following slides.
Application of the RACT

**Slide 44**

**RACT Example – Background on Diabetes Standard of Care**

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

- Perform the HbA$_{1C}$ test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control)
- Perform the HbA$_{1C}$ test quarterly in patients whose therapy has changed or who are not meeting glycemic goals

**Based on this information, are there any procedures required beyond usual SOC?**

**Diabetes SOC information – Application to Example**

Let’s apply this information to our previous sub-question

#2: Are there any procedures required beyond usual SOC?

- Yes, the ADA recommends HbA1c testing only every 3 months or twice a year.
- Our study requires this testing every 6 weeks.
- This increased complexity could represent a risk because site personnel will not be accustomed to performing the test so frequently and may miss required testing.
- Also, this level of testing increases the burden on study subjects and could create a risk of subject withdrawal or missed study visits and data.
Application of the RACT

Slide 45

**RACT Example – Complexity Discussion**

**Answer Key**

**What contributes to complexity of the protocol?**
- Multiple procedures performed every 6 weeks increasing subject burden = risk for subject withdrawal
- Subject fasting labs required for every study visit = risk that subjects won’t fast and endpoint data affected

**Are there any procedures required beyond usual SOC?**
- Yes, HbA1C test performed more often than SOC
  - Increased complexity = risk of site personnel missing required testing
  - Increased subject burden = risk for subject withdrawal of missed study visits and data

**Complexity Discussion – Answer Debrief**

**Answer Key:**

Sub-question 1: What contributes to protocol complexity? Possible answers:
- Multiple procedures are performed every 6 weeks so this may be burdensome to subjects
- Subjects will need to be fasting for every study visit (fasting plasma glucose and OGTT) – subjects may not be able to do so and failure in this Critical Process can impact endpoint data quality

Sub-question 2: Are there any procedures required beyond SOC?
- Yes, HbA1C test performed more often than SOC.
- Increased complexity = risk of site personnel missing required testing
- Increased subject burden = risk for subject withdrawal of missed study visits and data
Application of the RACT

Direct participants to the Participant Workbook

Using the RACT – Risk Level

The second step in our cycle is to assign a risk level for the category we are evaluating based on the discussion of risks. Let’s see how this assignment of risk level is accomplished.
Step 2 – Risk Level

In step two, the team will assign a High, Medium or Low ranking to each risk category.

The RACT is programmed to include a drop-down box for this field as you can see in this screenshot of the RACT.

Remember that this ranking should be assigned based on the combination of the likelihood of the risks within each category and their impact.
Application of the RACT

Slide 48

**RACT Example: Risk Level**

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

- High
- Medium
- Low

**Challenge Yourself Activity – Risk Level**

Ask participants to review the information and answers from the Complexity question we discussed earlier (they can review in their Participant Guide workbook).

**IMPORTANT NOTE**

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

**Facilitating the Activity**
Application of the RACT

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: ORANGE (HIGH), YELLOW (MEDIUM), BLUE (LOW)

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.

Webinar Workshop Participants (online)

If possible, utilize your polling options within your webinar provider. Create a poll and open it 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.

Challenge Yourself – Risk Level Debrief

Answer Key: Medium

First, let’s consider the likelihood of these risks occurring. There is probably at least a moderate likelihood that all of the possible risks could occur, at least at some sites and especially early in the study conduct phase.

Secondly, we should consider the impact or consequences of the risks should they occur. Since several factors relate to missed endpoint data (Critical Data) or errors in the procedures collecting that data (Critical Processes), the impact should be considered relatively high.

So, at minimum, a medium risk level would generally be applied to this category based on these factors.
Finally, the third step in using the RACT is to determine how the risk in each category impacts functional plans.
Direct participants to the Participant Workbook

RACT – Impact to Functional Plans

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

In this screenshot of the RACT, you can see that the first seven risk categories in the RACT have been pre-identified by TransCelerate as those commonly impacting the Monitoring Plan. Team members should determine the impacted Functional Plan(s) for the remaining 8 categories.

By identifying the Functional Plan(s) impacted, the team establishes clarity around which functional area is responsible for developing the plan to mitigate or manage that risk category.
Application of the RACT

Slide 42

RACT Categories and Monitoring Impact

- Study Medication IP Logistics
- Geography
- Budget
- Operational Complexity
- Organizational Experience
- Blinding
- Supply Chain Logistics
- Safety
- Study Phase
- Complexity
- Technology
- Patient Population
- Data Collection and CRF Source
- Endpoints

Monitoring Plan

Page 47

Direct participants to the Participant Workbook
Application of the RACT

RACT Categories and Monitoring Impact

Here you can see the categories of potential risk as listed on the RACT.

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

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

Focusing our risk evaluation on those factors which most significantly impact Critical Data and Processes ensures our monitoring approach is truly “risk-based.”
Module 3: Risk Assessment

Application of the RACT

Slide 53

RACT Example: Impact to Functional Plans

Identify the Functional Plan(s) impacted for each risk identified for the Type 2 diabetes study

<table>
<thead>
<tr>
<th>Risk</th>
<th>Functional Plan(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subject withdrawal due to study complexity</td>
<td>1. ??</td>
</tr>
<tr>
<td>2. Missed study visits and data due to study complexity</td>
<td>2. ??</td>
</tr>
<tr>
<td>3. Endpoint data doesn’t reflect subject fasting</td>
<td>3. ??</td>
</tr>
<tr>
<td>4. Site personnel miss required endpoint testing</td>
<td>4. ??</td>
</tr>
</tbody>
</table>

IMPORTANT NOTE

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

Challenge Yourself Activity

Let’s return one last time to the Type 2 diabetes study we’ve been using as our RACT example. Let’s identify the functional plan(s) that may be impacted for each risk we identified – as displayed on the left part of the slide.

Facilitating the Activity
Application of the RACT

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.

RACT Example: Impact to Functional Plans Answer Key

Identify the Functional Plan(s) impacted for each risk identified for the Type 2 diabetes study

<table>
<thead>
<tr>
<th>Risk</th>
<th>Functional Plan(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject withdrawal due to study complexity</td>
<td>1. Monitoring Plan, possibly Data Plan</td>
</tr>
<tr>
<td>Missed study visits and data due to study complexity</td>
<td>2. Monitoring Plan</td>
</tr>
<tr>
<td>Endpoint data doesn’t reflect subject fasting</td>
<td>3. Monitoring Plan, possibly Safety Plan</td>
</tr>
<tr>
<td>Site personnel miss required endpoint testing</td>
<td>4. Monitoring Plan</td>
</tr>
</tbody>
</table>
Application of the RACT

Challenge Yourself – Impact to Functional Plans Debrief

Answer Key:
The TransCelerate methodology identified the Monitoring Plan as being impacted by the Complexity risk category. Therefore, the Monitoring Plan should be listed as one functional plan impacted by all of these risks. For example, a mitigation strategy might be included in the Monitoring Plan to specify that central monitoring will take place to identify any missing endpoint data at the first one or two visits following subject enrollment. This would allow the team to identify a potential issue with risks #2 and #4 in a timely manner and take actions to investigate or address these risks.

The Data Plan might also be impacted for risk #1 and a plan could be designed to track subject withdrawal rates through central monitoring. Finally, risk #3 could impact the Safety Plan because lab values for subjects who are not fasting might be abnormally high and potentially signal a safety issue. The Safety Plan could include activities to evaluate high lab values to determine if subjects were not in a fasting state. Any identified occurrences could be communicated to the study team for follow-up and mitigation.

We’ll now give you an opportunity to practice the completion of the RACT for the simulated protocol synopsis through Activity #2.

IMPORTANT NOTE
This is not an exhaustive list.
Consider if other Functional Plans (e.g. Statistical Analysis Plan) are impacted and update the slide prior to the training session in order to properly communicate your company’s approach.
Application of the RACT

Activity #2 – Completing the RACT

Locate Activity #2 in your participant workbook and complete the exercise as directed by the instructor.

IMPORTANT NOTE

This activity will be completed through review of a sample protocol synopsis. Instructions for the activity are provided separately in the participant workbook.

Recognizing that some organizations may prefer to use an internal protocol synopsis to make the activity more applicable to the specific work environment, you may replace the activity with a specific one for your organization as applicable.

Challenge Yourself Activity

Direct learners to open the instructions and sample protocol synopsis in their participant workbook.
Application of the RACT

Facilitating the Activity
Allow 10 minutes for this activity

Capture your notes here.
Review activity instructions (as provided in the facilitation notes by workshop type below as well as the participant guide for additional instructions). Capture any specific notes regarding the activity below.
Application of the RACT

Classroom Workshop Participants (face-to-face)

Allow learners to work in their table teams. After reviewing the protocol synopsis, instruct them to complete, as a team, the worksheet for critical data and critical processes. Once complete, have each team flipchart their team’s results. After all teams complete, each team can then report their findings in a 2 minute presentation back to the full group.

Webinar Workshop Participants (online)

Ask learners to work independently. After reviewing the protocol synopsis, instruct them to complete, independently, the worksheet for critical data and critical processes. Once complete, open a new whiteboard on the webinar room with one side labeled Critical Data and one labeled Critical Processes. Ask the learners to begin writing their answers up on the board, not duplicating answers that their colleagues have written.

Challenge Debrief

Using the flipchart or white boarded answers, facilitate a discussion to ensure that the participants have included all elements from the answer key.

IMPORTANT NOTE

Answer key for activity is available in APPENDIX A of this trainer guide.
Now we're reaching the planning stage of risk assessment. Each risk category on the RACT is ranked individually as we've seen in step 3 of the RACT process/cycle.

The TransCelerate RBM methodology helps us to determine an Overall Risk Level for monitoring of each trial.

As we've previously seen, the first 7 risk categories on the RACT are commonly associated with and impact the Monitoring Plan. Therefore, the individual risk levels for these categories are evaluated as a whole in order to assign an Overall Risk Level to the protocol.

Based on the defined Overall Risk Level (high/medium/low), a standard monitoring approach is defined in the MP. Monitoring activities are aligned with the Overall Risk Level assigned at the protocol level; as Overall Risk Level decreases, the level of monitoring should decrease, except as needed to address issues.
Overall Risk Level Examples

The table on the screen shows several examples of how the RACT category risk levels can be evaluated to determine the Overall Risk Level of a trial. This example appears on page 16 of the Position Paper and is shown here for illustrative purposes only.

An algorithm for defining the Overall Risk Level is not available but each company should be prepared to explain their rationale for determining the final Overall Risk Level for the trial.

The “%” notation in the left hand column indicates that study teams may find it valuable to assign a “weight” to certain categories according to their risk impact if it is felt that some high risk categories are more significant than others.

Once determined, the Overall Risk Level can be used to design the baseline monitoring approach which details how, when, where, and to what extent Critical Data will be monitored during the trial.

<table>
<thead>
<tr>
<th>Category</th>
<th>Study A Phase III, endpoint/mortality study</th>
<th>Study B Phase IV study with some remote data entry by subjects</th>
<th>Study C Phase II study in a well known population and well categorized disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety (xx%)</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Study Phase (xx%)</td>
<td>Med</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Complexity (xx%)</td>
<td>Med</td>
<td>Low</td>
<td>Med</td>
</tr>
<tr>
<td>Technology (xx%)</td>
<td>Low</td>
<td>Med</td>
<td>Low</td>
</tr>
<tr>
<td>Patient Population (xx%)</td>
<td>High</td>
<td>Low</td>
<td>Med</td>
</tr>
<tr>
<td>Data Collection (xx%)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Endpoints (xx%)</td>
<td>High</td>
<td>Low</td>
<td>Med</td>
</tr>
<tr>
<td>Overall Risk Assessment Category</td>
<td>High</td>
<td>Low</td>
<td>Med</td>
</tr>
</tbody>
</table>
Application of the RACT

Overall Risk Level and Baseline Monitoring Approach

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

IMPORTANT NOTE

Review the monitoring activities and point out how the sampling percentage changes based on whether the Overall Risk Level for the study is high, medium, or low.
Application of the RACT

Overall Risk Level & Baseline Monitoring Approach

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

In the RBM methodology, it is acceptable to assign differing Overall Risk Levels for various stages of the study.

- For example, the Overall Risk Level may be high during active enrollment or the period in which subjects are receiving IP but then be set as low during the subject follow-up phase. The type, amount, and location of monitoring activities may also vary accordingly. Module 4 will discuss this concept in more detail.

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

Now, you will have an opportunity to assign the Overall Risk Level to the simulated protocol synopsis in Activity #3.
Application of the RACT

Slide 59

Activity #3 – Overall Risk Level

Locate Activity #3 in your participant workbook and complete the exercise as directed by the instructor.

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Direct participants to the Participant Workbook

IMPORTANT NOTE

This activity will be completed through review of a sample protocol synopsis. Instructions for the activity are provided separately in the participant workbook.

Recognizing that some organizations may prefer to use an internal protocol synopsis to make the activity more applicable to the specific work environment, you may replace the activity with a specific one for your organization as applicable.

Challenge Yourself Activity

Direct learners to open the instructions and sample protocol synopsis in their participant workbook.
Application of the RACT

Facilitating the Activity

Allow 10 minutes for this activity

Capture your notes here.

Review activity instructions (as provided in the facilitation notes by workshop type below as well as the participant guide for additional instructions). Capture any specific notes regarding the activity below.
Application of the RACT

Classroom Workshop Participants (face-to-face)

Allow learners to work in their table teams. After reviewing the protocol synopsis, instruct them to complete, as a team, the worksheet for critical data and critical processes. Once complete, have each team flipchart their team’s results. After all teams complete, each team can then report their findings in a 2 minute presentation back to the full group.

Webinar Workshop Participants (online)

Ask learners to work independently. After reviewing the protocol synopsis, instruct them to complete, independently, the worksheet for critical data and critical processes. Once complete, open a new whiteboard on the webinar room with one side labeled Critical Data and one labeled Critical Processes. Ask the learners to begin writing their answers up on the board, not duplicating answers that their colleagues have written.

Challenge Debrief

Using the flipchart or white boarded answers, facilitate a discussion to ensure that the participants have included all elements from the answer key.

IMPORTANT NOTE

Answer key for activity is available in APPENDIX A of this trainer guide.
Module 3: Summary

Module 3 Summary

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

Summary

In this module, we have discussed the importance of methods to proactively identify and assess risks in the RBM methodology.

Participants have learned about Critical Data and Processes and practice their identification as part of risk assessment.

Finally, we've reviewed the purpose and use of the RACT from the RBM Toolkit and seen how its use can facilitate a thorough and systematic risk assessment process.
Questions

Any questions?
Transition

Transition to Module 4 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: Answer Key to Activities

TransCelerate Risk-Based Monitoring (RBM) Training Initiative
Module 3 Hands-on Activities – Answer Key

These exercises provide an opportunity to practice applying the principles and activities of the RBM methodology to a simulated clinical trial protocol. Depending upon the training environment, this assignment may be completed in a group or individually.

Pre-Work:
Read the simulated protocol synopsis entitled “A Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Assess Safety and Efficacy of Doitall (loratadine 5 mg/pseudoephedrine sulfate 120 mg/ibuprofen 200 mg) compared to Claritin D™ (loratadine 5 mg/pseudoephedrine sulfate 120 mg) compared to Placebo in Relieving Allergic Rhinitis Symptoms in an Environmental Exposure Chamber Model”

DISCLAIMER: This synopsis does not contain all the detailed information which may be required by your organization’s Table of Contents or other controlled document process. The content is intended solely to satisfy the needs of learners in completing the exercise.
APPENDIX A: Answer Key to Activities

Activity #1 – Identifying Critical Data/Processes:
Identify the Critical Data and Critical Processes for this study.

<table>
<thead>
<tr>
<th>Critical Data/Processes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache VAS at Visit 3</td>
</tr>
<tr>
<td>MSC at Visit 3</td>
</tr>
<tr>
<td>EEC-QOL at Visit 3</td>
</tr>
<tr>
<td>Adverse event and SAE collection/documentation</td>
</tr>
<tr>
<td>Vital signs at Visit 3</td>
</tr>
<tr>
<td>Informed consent process</td>
</tr>
<tr>
<td>Correct application of subject eligibility criteria</td>
</tr>
<tr>
<td>EEC operations, functionality, and timing</td>
</tr>
<tr>
<td>Electronic programming of VAS and MSC for eligibility</td>
</tr>
<tr>
<td>Over encapsulation to preserve blinding</td>
</tr>
<tr>
<td>Enrollment, screen failure, and completion rates and timelines</td>
</tr>
</tbody>
</table>
APPENDIX A: Answer Key to Activities

Activity#2 – Completing the RACT:

1. Evaluate the protocol-specific risks and complete the first 7 categories of the Risk Assessment Categorization Tool (RACT).

   [Focus only on the first 7 categories as these can be readily evaluated from the information contained in the protocol synopsis. The remaining RACT categories require information for the sponsor/CRO organization, infrastructure, vendors, etc. and are, therefore, beyond the scope of this activity.]

2. Assign a monitoring risk level (high/medium/low) to each of the categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Level (High, Medium, or Low)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Low</td>
<td>IP is a combination of marketed products; little toxicity especially with single dose</td>
</tr>
<tr>
<td>Study Phase</td>
<td>Low</td>
<td>Although Phase 2, it is relatively large; no adaptive design and not pivotal</td>
</tr>
<tr>
<td>Complexity</td>
<td>High</td>
<td>EEC is a complex procedure; patient burden is high with long study days and restrictions on tobacco, alcohol, and caffeine</td>
</tr>
<tr>
<td>Technology</td>
<td>High</td>
<td>High dependence on electronics for critical data and eligibility</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Medium</td>
<td>Not vulnerable or critically ill but high number of detailed, strict eligibility criteria</td>
</tr>
<tr>
<td>Data Collection, CRF, and Source</td>
<td>High</td>
<td>Electronic and subject-reported; eligibility data transmitted overnight so no chance for real-time review to prevent incorrect randomization</td>
</tr>
<tr>
<td>Endpoints</td>
<td>High</td>
<td>Subjective data; potential to miss endpoint data due to missed collection during Visit 3 and/or subject withdrawals due to visit burden</td>
</tr>
</tbody>
</table>
Activity#3 – Determining the Overall Risk Level:
Determine the Overall Risk Level (high/medium/low) for this clinical trial, based on your individual category risk levels.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Level (High, Medium, or Low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Low</td>
</tr>
<tr>
<td>Study Phase</td>
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<tr>
<td>Data Collection, CRF, and Source</td>
<td>High</td>
</tr>
<tr>
<td>Endpoints</td>
<td>High</td>
</tr>
<tr>
<td><strong>Overall Risk Level</strong></td>
<td><strong>High</strong></td>
</tr>
</tbody>
</table>