# Ask the Expert

by MyRBQM® Academy

**October 28, 2021**

**Jo Burmester**
Clinical Research Specialist
MyRBQM® Academy

**Dr. Johann Proeve,**
Chief Scientific Officer
Cyntegrity

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# Are You Audit and Inspection Ready?

# Speaker

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## Jo Burmester

CLINICAL RESEARCH SPECIALIST

Jo is a pharmacology graduate and began her career in clinical research in 1987. She worked as a CRA and senior CRA for 5 years before moving into a full time clinical research training role in 1992. She currently designs and delivers clinical research for a wide variety of audiences.

Her career has included experience in the pharmaceutical industry and the CRO world and she has worked internationally, covering ICH, EU and FDA requirements.

She is the author of a book on Continuing Professional Development and regularly chairs and presents at international clinical research conferences.

# Speaker

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## Dr. Johann Proeve

CHIEF SCIENTIFIC OFFICER

Johann Proeve has more than 35 years of experience as a bio-pharmaceutical industry expert mostly in the former international role of Head of Global Data Management at Bayer AG.

Awarded one of the 2018 MCC Champions by the Metrics Champion Consortium, Johann is widely regarded as the go-to source for Clinical Data Management and RBQM. In this regard, Johann has been invited to speak to clinical organizations worldwide, including regulatory bodies, sponsors, and CROs, at conferences like DIA, SCDM, PCT, PharmaForum, and SCOPE.

Johann holds a PhD in Zoology/Animal Biology, and he currently lectures at the University of Essen Duisburg (Master of Science (MSc) in Pharmaceutical Medicine).

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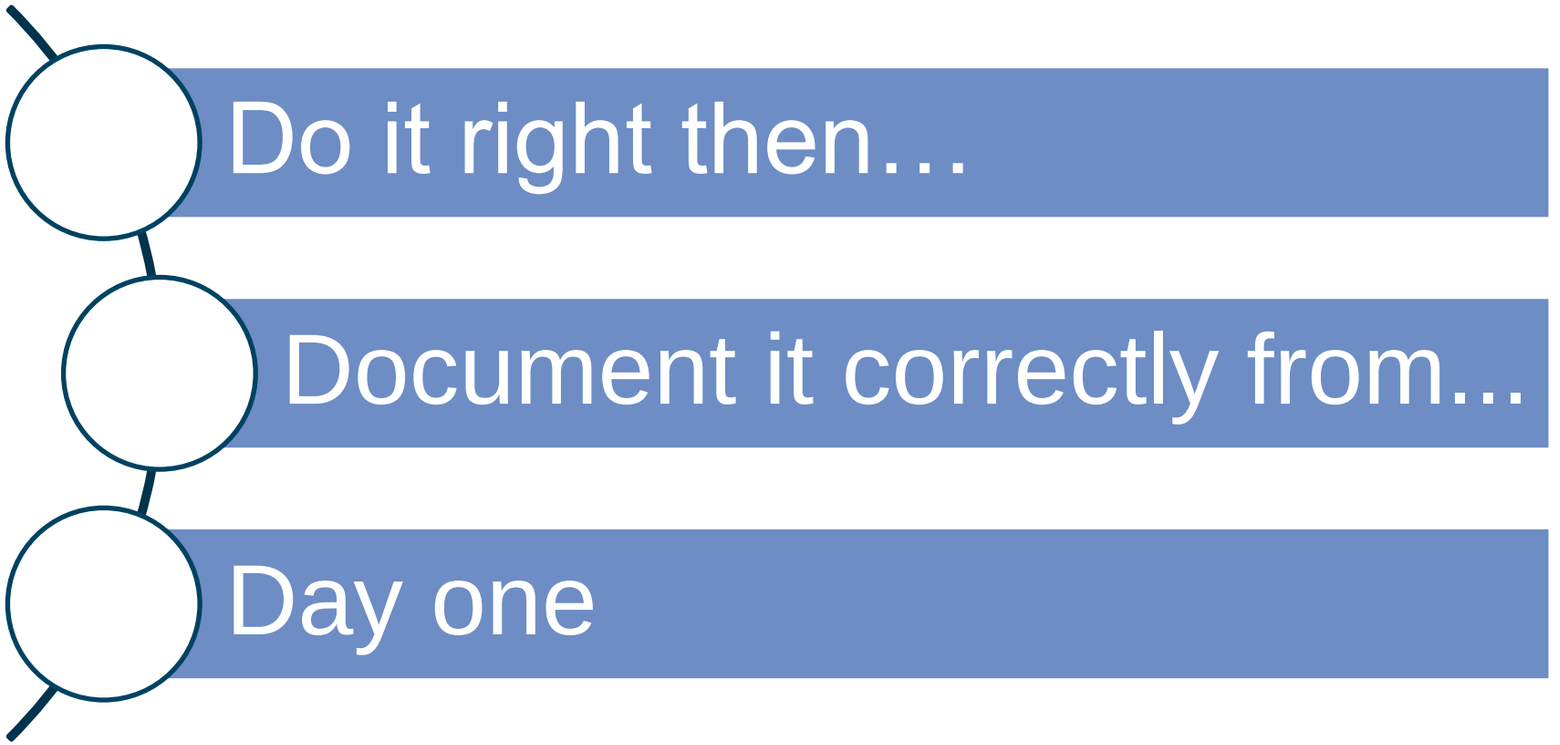
# Nobody is Perfect

## ARE YOU AUDIT AND INSPECTION READY?

# The Best Audit/Inspection Preparation



# The Auditor's Mantra

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***"If it's not documented it didn't happen"***

# …My Amended Version

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***"If it's not documented it wasn't done right"***


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# How a Risk-based Approach Can Help

## ARE YOU AUDIT AND INSPECTION READY?

# How Risk-Based Quality Management (RBQM) Can Help

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# Some Real Life Examples

ARE YOU AUDIT AND INSPECTION READY?

# EXAMPLE 1 | TMF Inspection Finding

**MHRA Critical Finding (part of finding report):**

- There were a number of essential documents for a trial retained by vendors which were not defined in the TMF plan or TMF index.
- There was a lack of effective oversight QC of an eTMF by the sponsor.
- Several issues were identified with the eTMF including examples of missing, misfiled, misnamed and duplicated documents.

# EXAMPLE 1 | TMF Oversight

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**ANTICIPATE**

What are risks with CRO management of TMF?

Missing documents, extra documents, misfiling, misnaming and **misnumbering …**

**MEASURE**

What KRIs and QTLs do we need in place?
Completeness; Timeliness; Retrieval
What are the thresholds? E.g. 90% completeness during trial conduct
What QC do we put in place? Review of metrics; **TMF Spot checks; Audit**

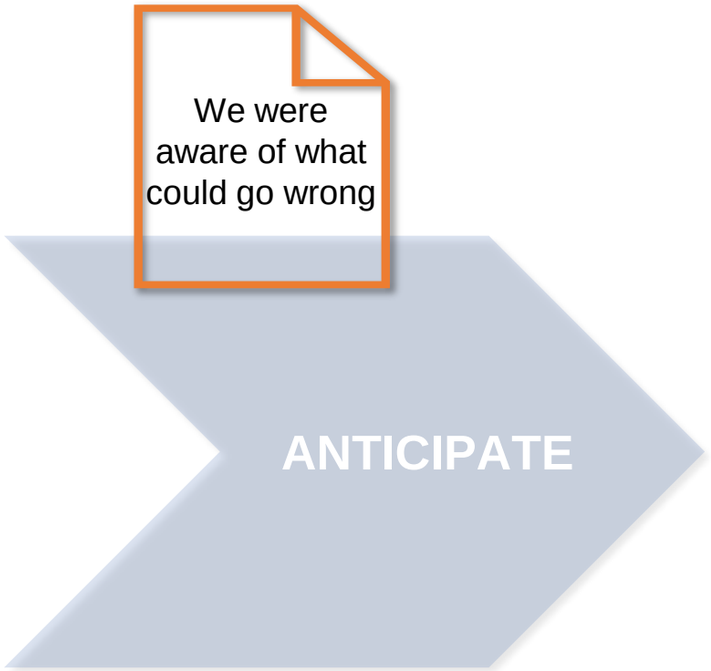
**TRACK**

Who measures? Who reports? Who reviews and when?
What is the escalation process?

**ADDRESS**

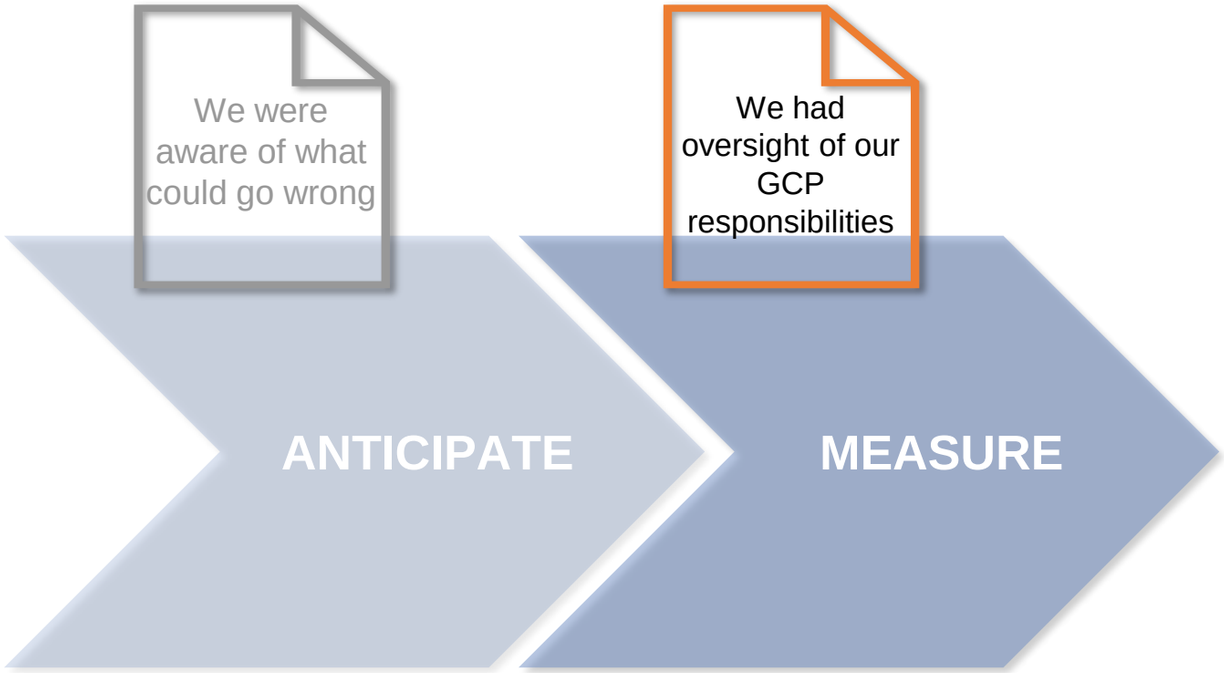
What mitigations are planned?
Resource; Additional QC; Filing Process and Training
How do we implement? How do we assess success?

# How Risk-Based Quality Management (RBQM) Can Help




- Risk Assessment
- What could go wrong?
- **QTLs** and **KRIs**

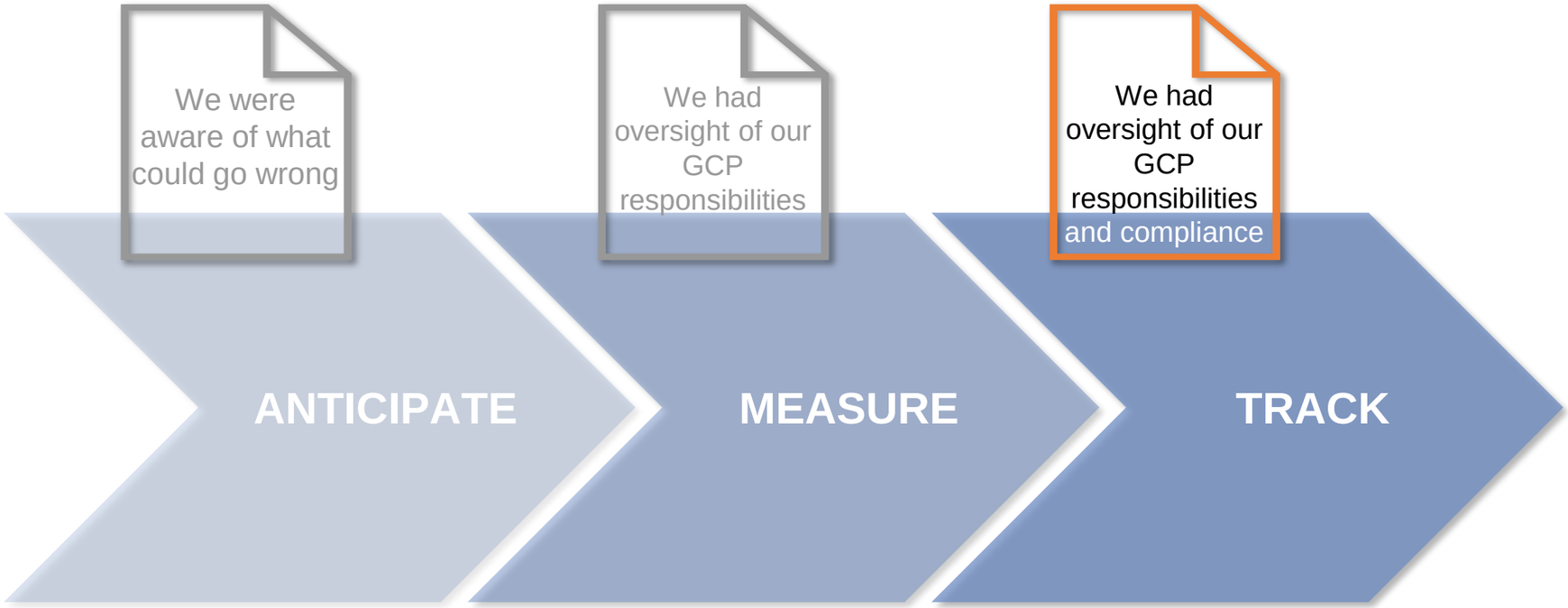
# How Risk-Based Quality Management (RBQM) Can Help




- Risk Assessment
- What could go wrong?
- **QTLs** and **KRIs**

- QTLs and KRIs
- **Parameters**
- **Metrics**

# How Risk-Based Quality Management (RBQM) Can Help




- Risk Assessment
- What could go wrong?
- **QTLs** and **KRIs**

- QTLs and KRIs
- **Parameters**
- **Metrics**

- Tracking
- Review
- **Alerts**

# How Risk-Based Quality Management (RBQM) Can Help

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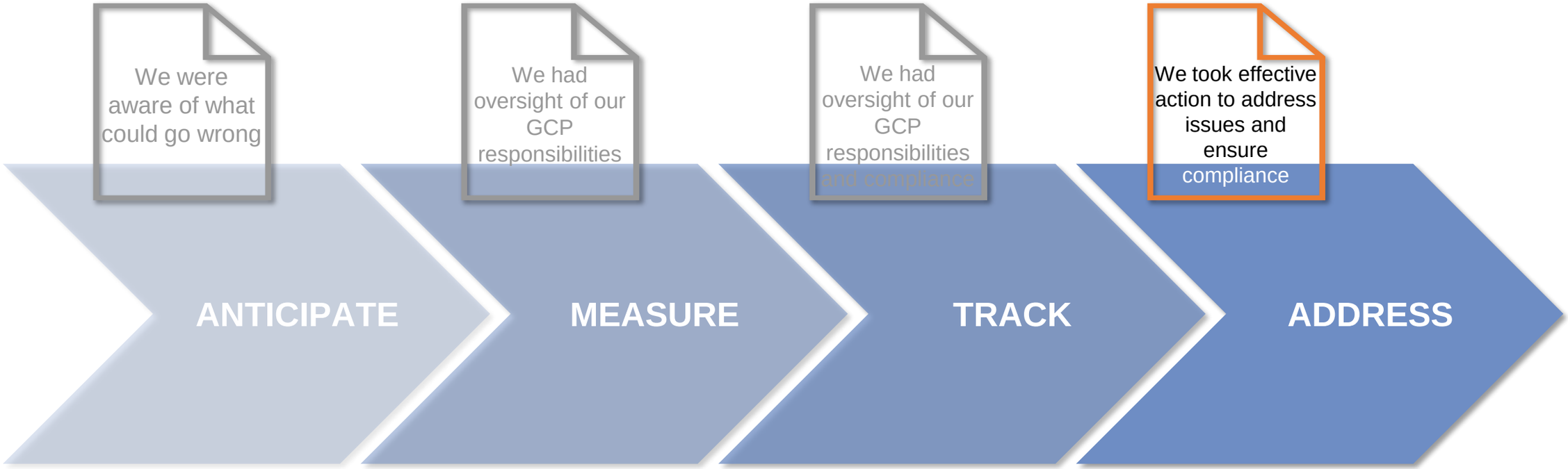



- Risk Assessment
- What could go wrong?
- **QTLs** and **KRIs**

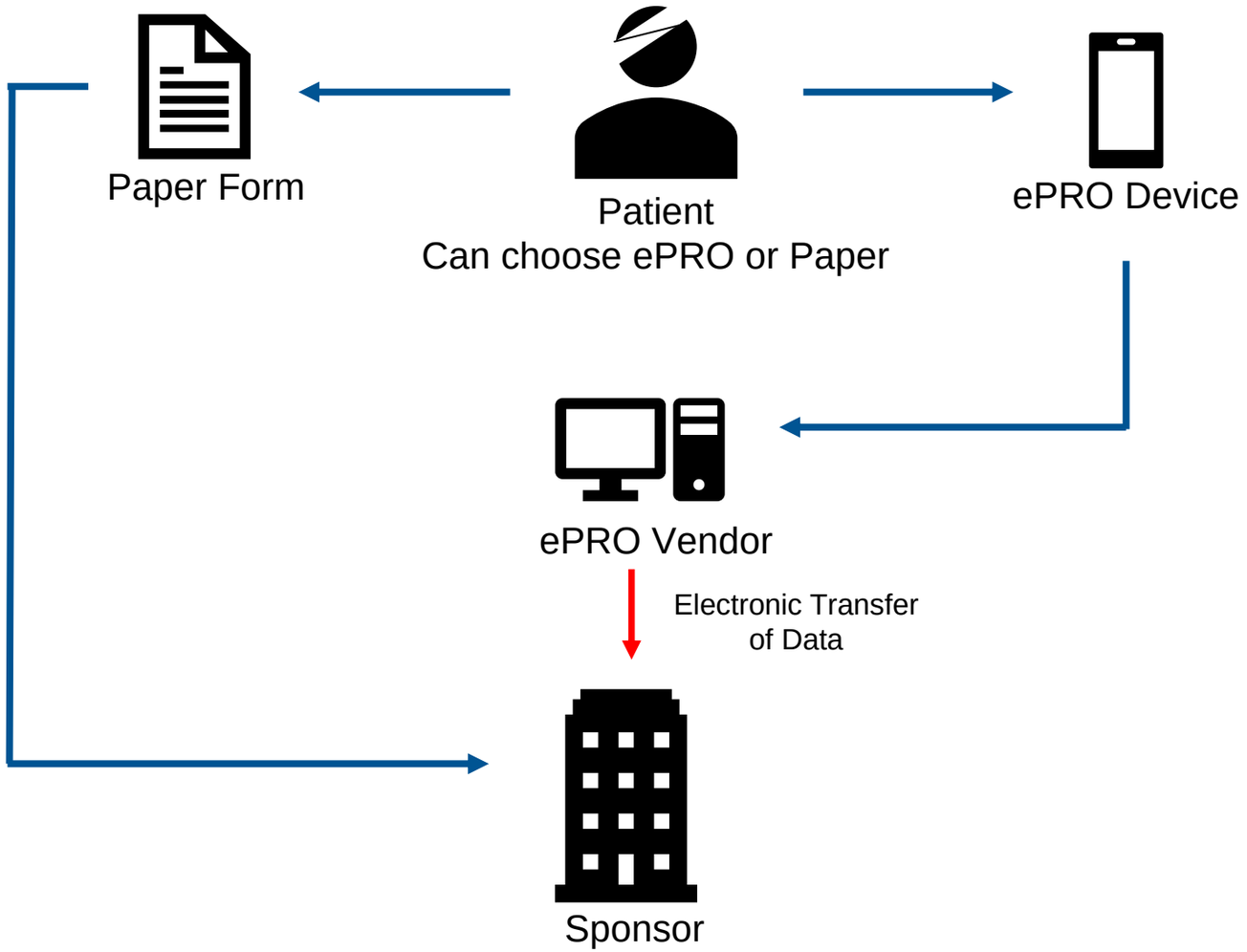
- QTLs and KRIs
- **Parameters**
- **Metrics**

- Tracking
- Review
- **Alerts**

- Escalation
- **Mitigation**
- Review of effectiveness

# EXAMPLE 2 | ePRO Data Integrity

**ePRO Data Flow:**



# EXAMPLE 2 | ePRO

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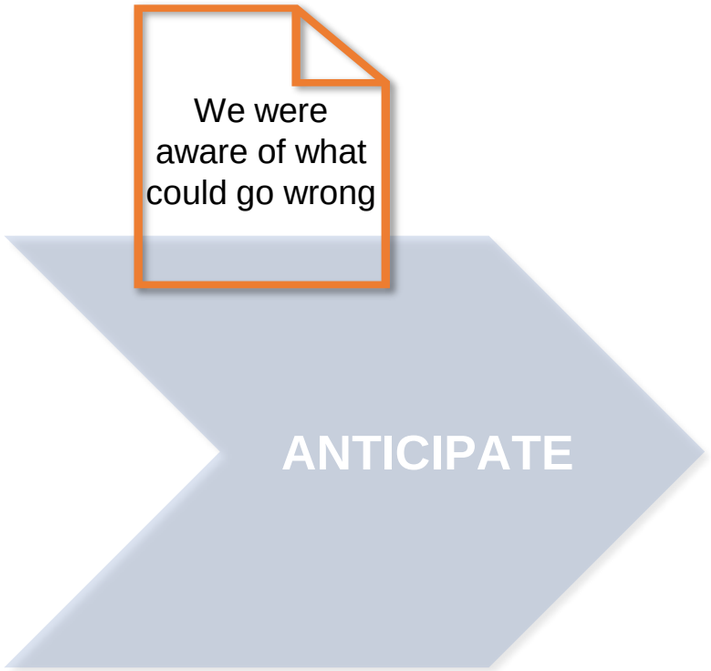
| | |
|---|---|
| **ANTICIPATE** | What are risks with this set up?<br>Patient Confidentiality – patient writes name on form. |
| **MEASURE** | How do we monitor this?<br>Log of redactions needed? Threshold – e.g. more than 1% of forms? |
| **TRACK** | How often do we review?<br>How does the log feed into the alert process? |
| **ADDRESS** | What mitigations are planned? Form design; investigator support for patients; additional instructions; change the process<br>How do we assess success? Continue to log redactions. |

# And More Examples

ARE YOU AUDIT AND INSPECTION READY?

# How Risk-Based Quality Management (RBQM) Can Help




- Risk Assessment
- What could go wrong?
- **QTLs** and **KRIs**

A protocol with **two questionnaires (QoL) that are very similar** will likely lead to different results without adding value.

**How can RBQM help?**

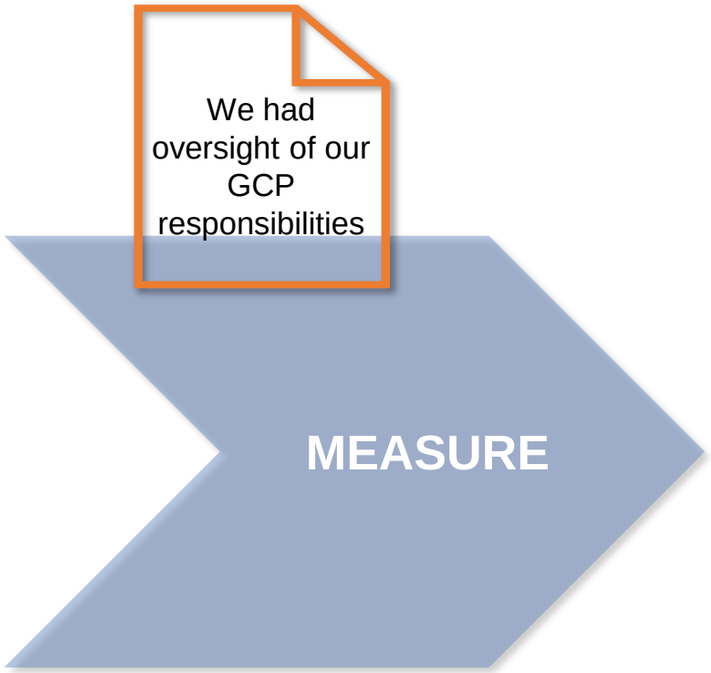
→ During protocol review, consider removing one of the questionnaires.

A protocol with **stratification into 8 sub-groups** will likely result in mis-randomization and stratification.

**How can RBQM help?**

→ Either modify the number of strata in the study or implement a KRI that identifies abnormalities in the strata allocation and/or randomization.

# How Risk-Based Quality Management (RBQM) Can Help




- QTLs and KRIs
- **Parameters**
- **Metrics**

A protocol with **five pages of in- and exclusion criteria** that cannot be simplified will likely result in many protocol deviations and thus jeopardize the study outcome.

**How can RBQM help?**

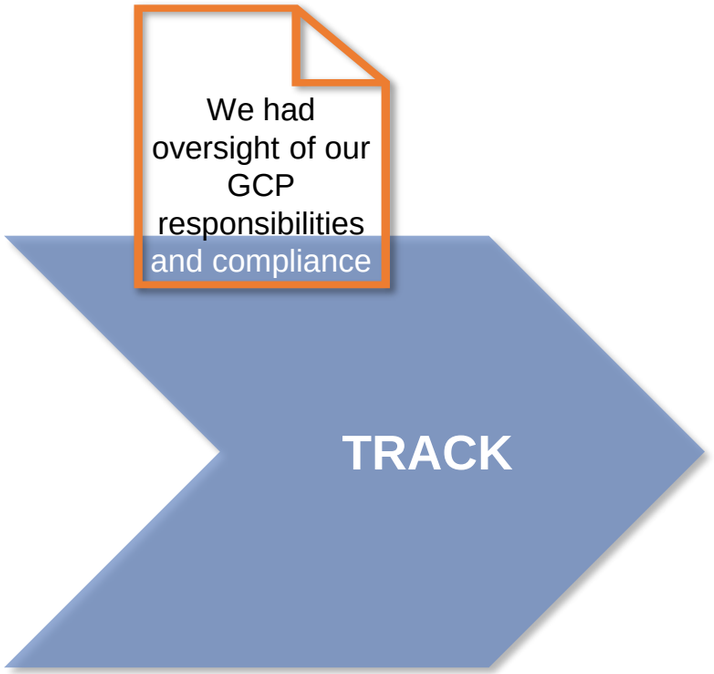
→ Implement a KRI for the measurement of protocol deviations related to in- and exclusion criteria and alert the sponsor company in case a certain acceptable threshold is being exceeded.

A study with several sites with **countries across the globe** and **different medical standards** also requires recording of adverse events. This will likely result in a different reporting pattern of AEs and SAEs.

**How can RBQM help?**

→ Implement a KRI for the detection of under-reporting or over-reporting of SAEs and AEs.

# How Risk-Based Quality Management (RBQM) Can Help




- Tracking
- Review
- **Alerts**

An outcome protocol in a cardiovascular disease requires the documentation of the patients developing a stroke, MI, or any other cardio-vascular disease in this 5-year treatment trial. The **number of drop outs is critical for the acceptance** of the study outcome by the FDA etc.

**How can RBQM help?**

→ Implement a KRI for the measurement of drop outs and track in particular those that are due to ‘lost to follow up’ or ‘informed consent withdrawn.

A site in a study is **constantly changing the start date** of an adverse event and other fields on the eCRF.

**How can RBQM help?**

→ Run analyses across the study DB and check for fields that have been modified/corrected more than once either indicating that the site is trying to ‘streamline the data,’ making up the data or not knowing how to enter data into the EDC system in the first place.

# How Risk-Based Quality Management (RBQM) Can Help


- Escalation
- **Mitigation**
- Review of effectiveness

**Several issues have been identified** at a site related to delays in data entry, response time to queries, missing visits and outcome data, and adherence to the in- and exclusion criteria.

**How can RBQM help?**

→ RBQM should create a list of tickets addressing all of the above breaches of the maximum tolerated delays etc. The ticket list will have to be responded to prior to the database lock, ensuring that there are no loose ends, since that is what inspectors will very likely look at.

# Establish Full Traceability

## ARE YOU AUDIT AND INSPECTION READY?

# Data Entry Delay

## ANTICIPATE & MEASURE | *Risk Statement & Risk Assessment*

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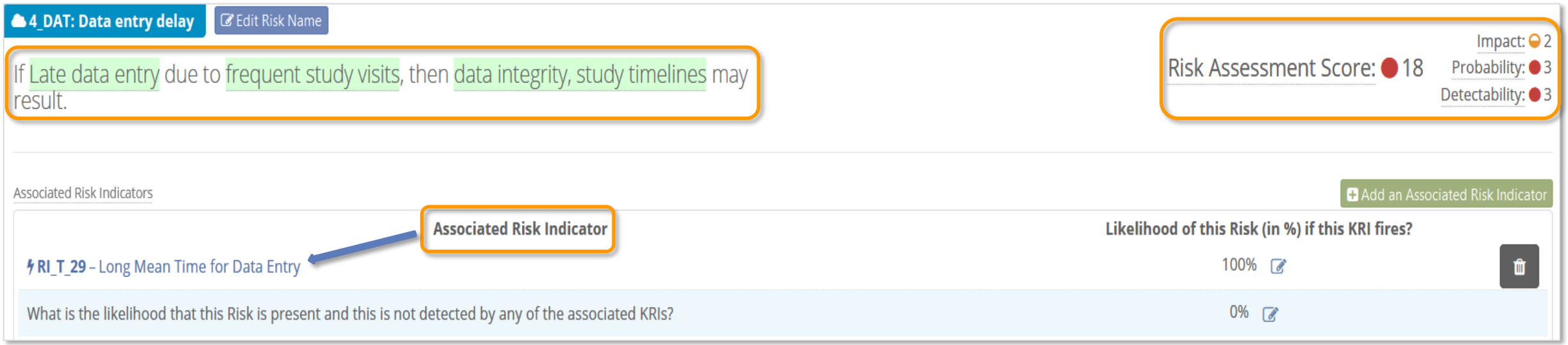

# Data Entry Delay

## **TRACK** | *Risk Development, dynamic over the time*

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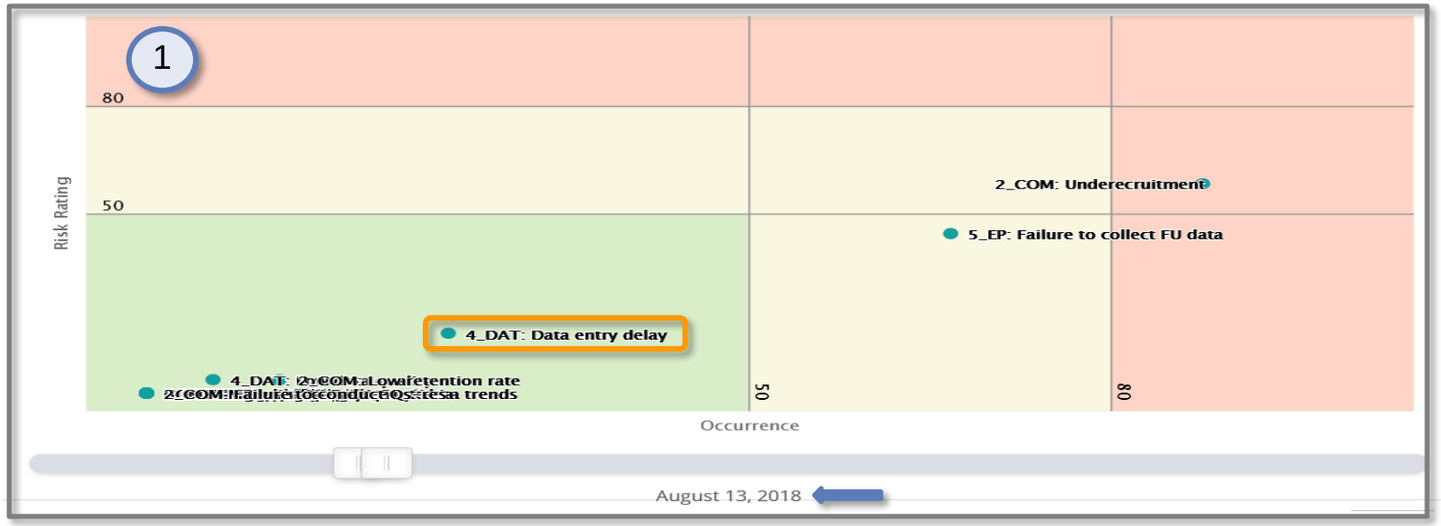


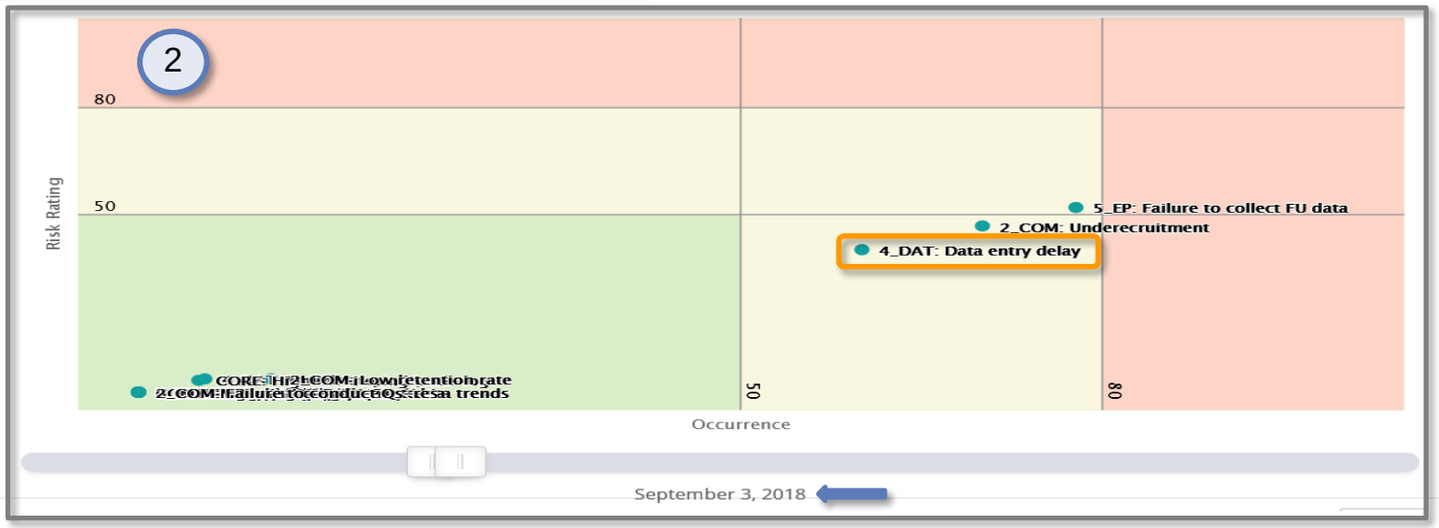

# Data Entry Delay

## **TRACK** | *Risk Development, dynamic over the time*

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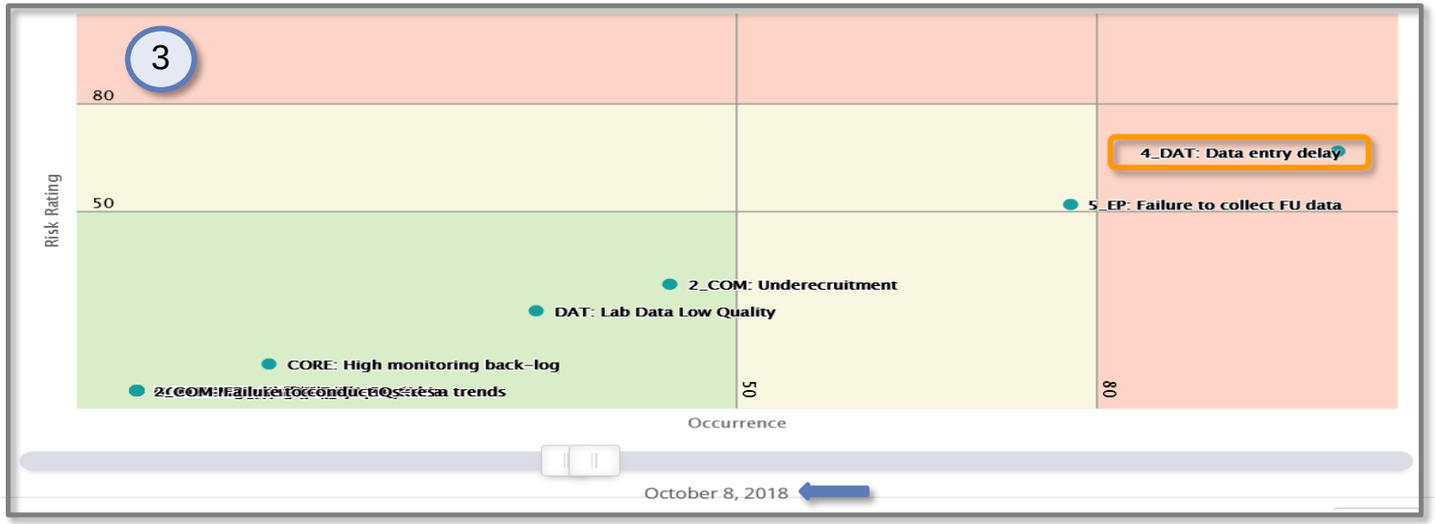


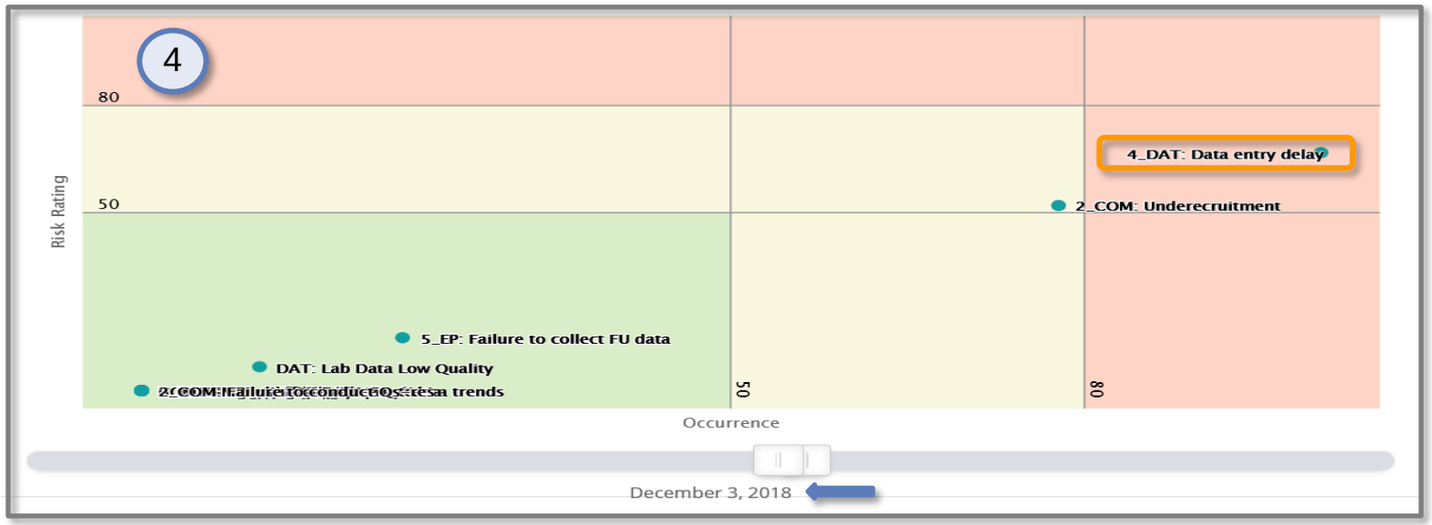

# Data Entry Delay

## ADDRESS | *Mitigation Actions*

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**Closed**

**MIT_35**

Owner
[redacted]

Risk
4_DAT: Data entry delay

Closed
Closed 4 years ago by [redacted]

Responsible
[redacted]

Review Settings
Once at Nov 29, 2017

Associated Risk Indicators
None selected

Mitigation Goal
Payment dependency on eCRF completion (in contracts)

Study Plans
**N/A**

Mitigation Actions
**N/A**

Functional Plans
*None yet*

**Closed**

**MIT_34**

Owner
[redacted]

Risk
4_DAT: Data entry delay

Closed
Closed a month ago by [redacted]

Responsible
[redacted]

Review Settings
Every 1 months

Associated Risk Indicators
None selected

Mitigation Goal
MP - remote control of eCRF completion, phone contacts to re-train and push
Consider enrollment stop when issues identified

Study Plans
**N/A**

Mitigation Actions
**N/A**

Functional Plans
*None yet*

# Data Entry Delay

## ADDRESS | *Mitigation Actions*

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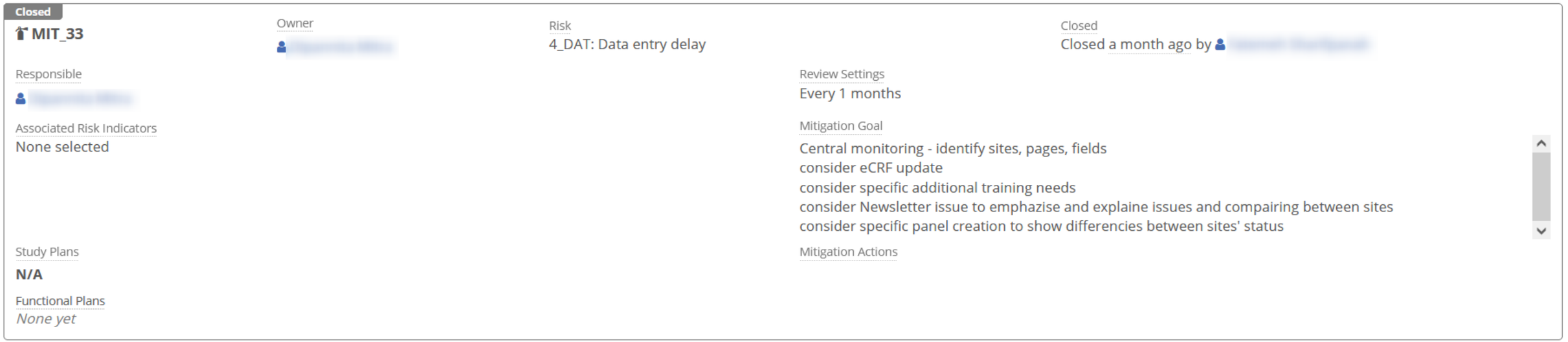

# Data Entry Delay

## ADDRESS | *Mitigation Actions*

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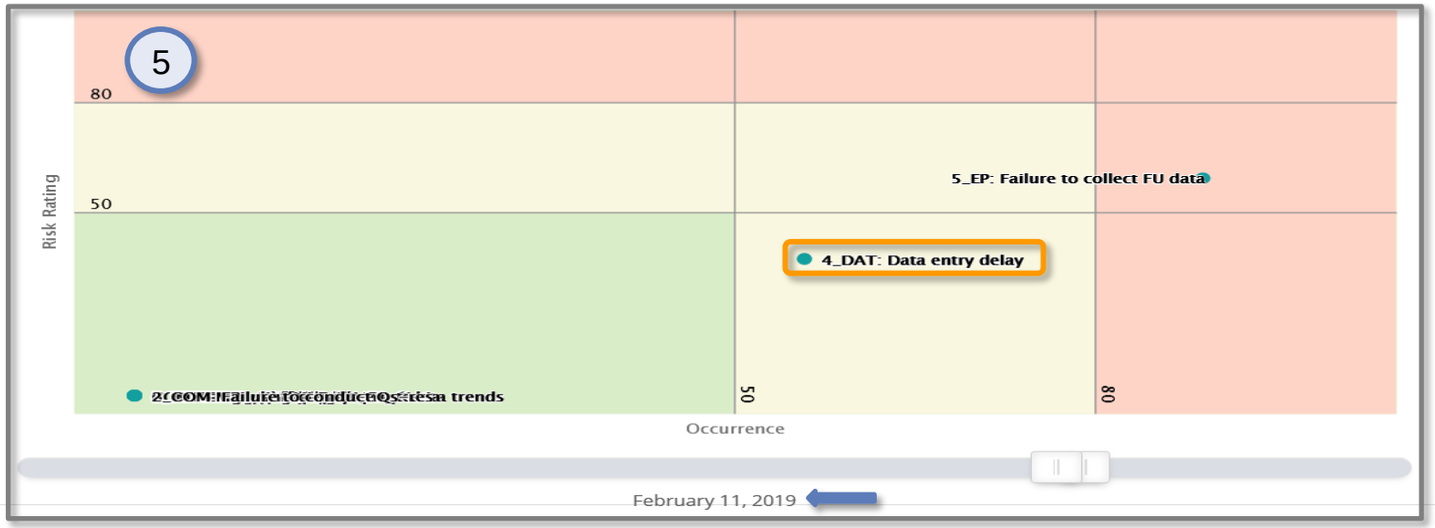
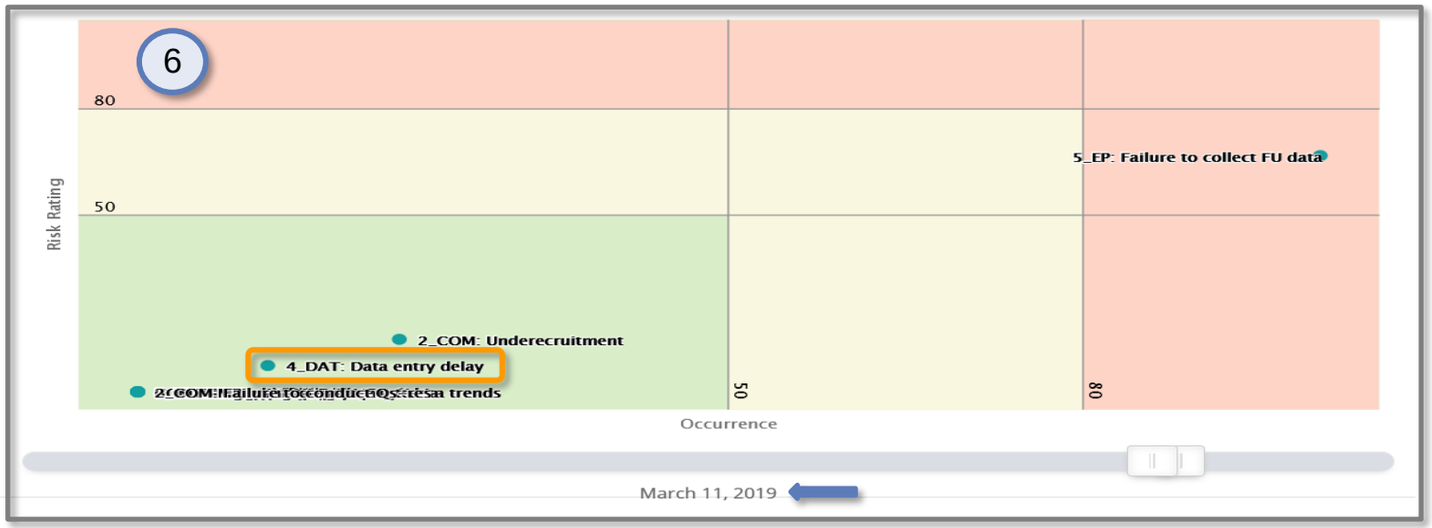


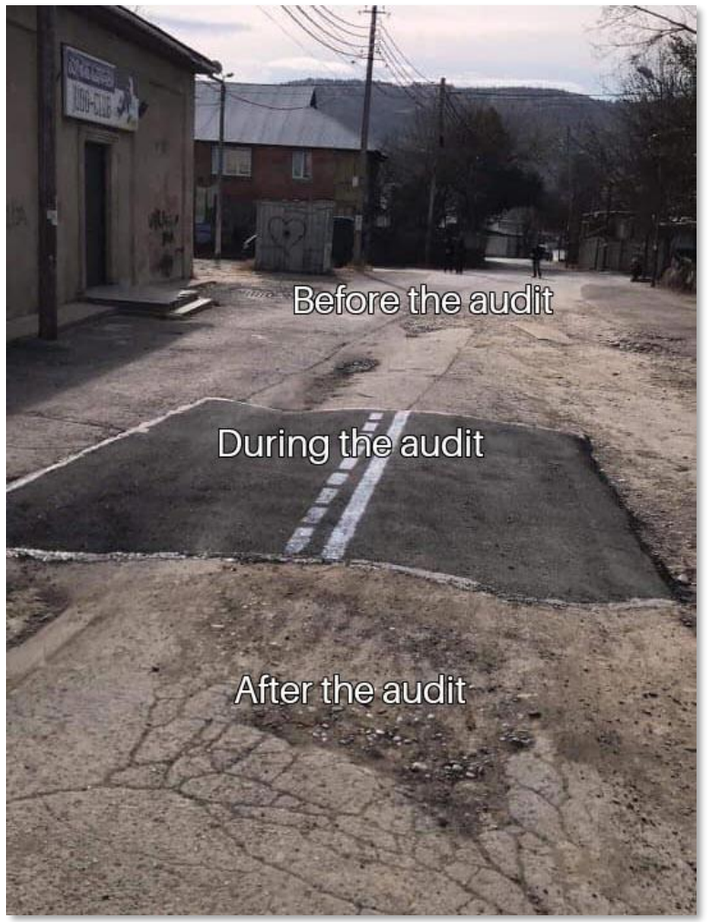
# Summary

## ARE YOU AUDIT AND INSPECTION READY?

# Summary

**Taking an ICH E6(R2) risk-based approach:**

- Nobody‘s Perfect
- Anticipate
- Measure
- Track
- Address
- Evidence is critical



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# Question & Answer

# Looking forward to seeing you again at MyRBQM® Academy!

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Cyntegrity
Trust in Data

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