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Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations

Marriott Marquis ● Washington, DC
July 17, 2019

Welcome and Overview

Opening Comments from FDA

Session 1: Regulatory Foundation for Risk-Based Monitoring

Improving Implementation of Risk-Based Monitoring Approaches in Clinical Trials

Session 1: Regulatory Foundation For Risk-Based Monitoring

David Burrow, Pharm.D., J.D.
Director, Office of Scientific Investigations
U.S. Food and Drug Administration

July 17, 2019

A Common Foundation

- Shared interest in development of safe and effective products, and confidence in the clinical trial process

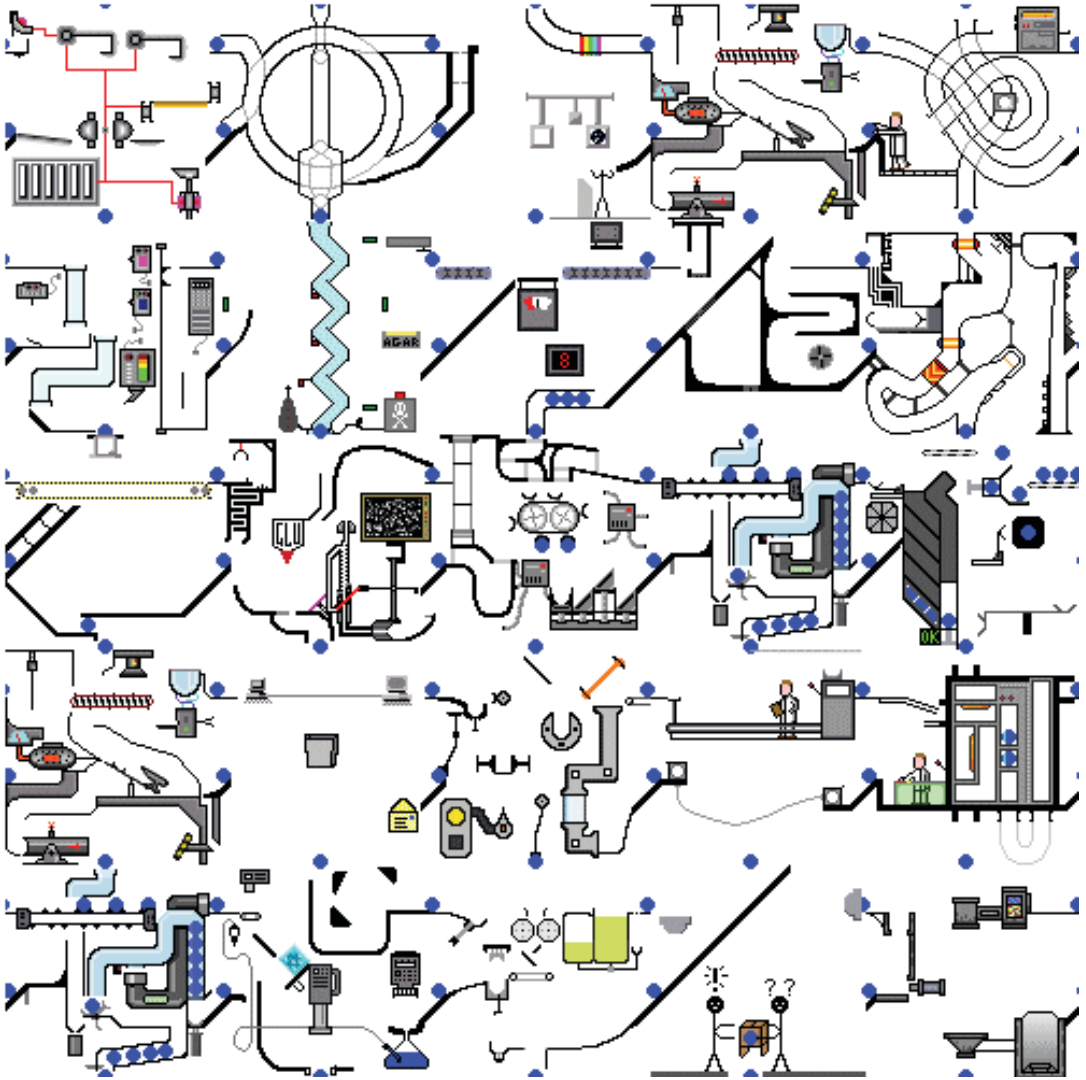
- Focus for today: Risk-Based Monitoring and Risk-Based Quality Management

- Three Common Elements:
  - Risk assessment (pre-study, and ongoing)
  - Well-designed and articulated protocol and investigational plan
  - Risk-Based monitoring plan

Risk-Based Monitoring

- Why
  - Quality, reliability, interpretability → approvability
  - Shared interest: The absence of errors that matter
  - Regulatory requirement to ensure proper monitoring
- What
  - Varied monitoring activities
    - On-Site
    - Centralized
    - Remote
- How
  - Risk Assessment → Protocol Development → Risk-Based Monitoring
  - Use of monitoring activities in a risk-based manner
  - According to a pre-specified plan, based on appropriate assessments, with mitigation, escalation and remediation strategies

Monitoring a Complex System



Public Resources

- FDA Guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, 2013
- ICH: E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1), 2018
- FDA Draft Guidance: A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers, 2019
- ICH: E8 (R1) [Step 2] General Considerations for Clinical Studies, 2019
- Plus, additional EMA resources…

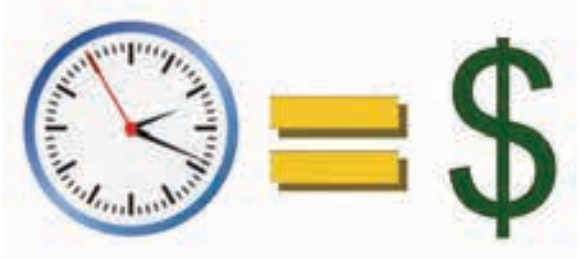
- 100+ outreach events
- 10+ face-to-face meetings RE: RBM systems, strategies, technologies

Why Does Quality Matter?

When trial participants are protected and data are:

- ✓Reliable
- ✓Interpretable
- ✓Traceable

FDA may take action on the application prior to the user fee deadline.



What is a Clinical Inspection Summary?

- A Clinical Inspection Summary (CIS) is OSI's primary communication to the Office of New Drugs (OND) regarding OSI's assessment and recommendations following requested PDUFA/BsUFA site inspections.

- The CIS reviews the following:
  - Data quality, reliability and/or acceptability of study data
  - Adequacy of study conduct by the inspected entities
  - Subject safety and welfare protections
  - Record keeping and documentation

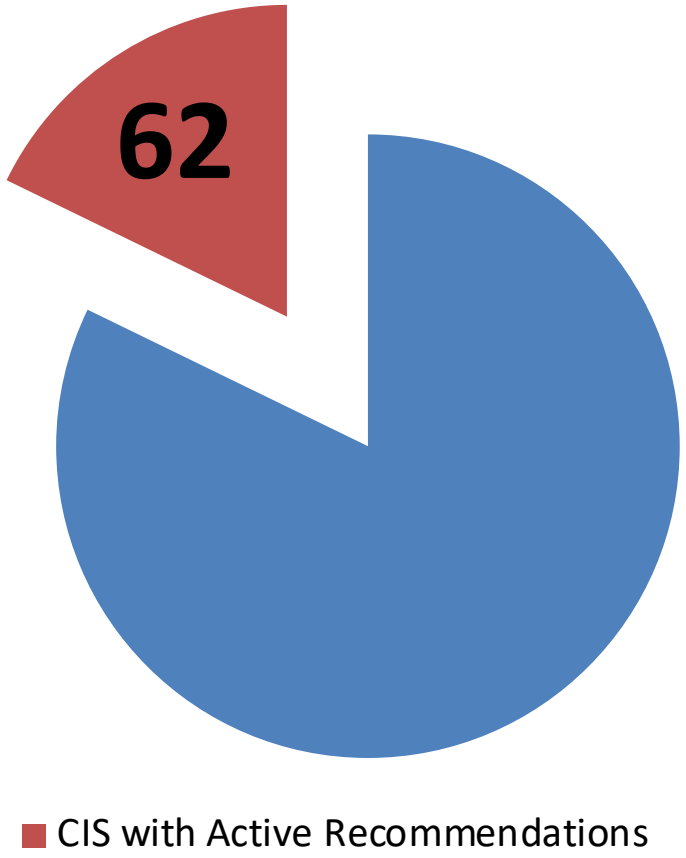
CIS Recommendations to OND

- Passive – data appear reliable in support of the application

- Active – a recommendation for action based on inspection findings. May include one or more of the following:

  - ❑ Recommend a sensitivity analysis (data reliability concerns)
  - ❑ Recommend excluding data generated from all or individual inspected sites
  - ❑ Recommend need for additional inspections to verify outstanding issues
  - ❑ Descriptions of violations (isolated vs pattern) impact on interpretability
  - ❑ Subject safety and/or efficacy concerns

OSI Active Recommendations to OND (FY15-17)



62 of 334 CIS with OSI Active Recommendation to OND

= 19%

Inspection Classifications

FY15-17

NAI	VAI	OAI
176	113	15

A CIS with an active recommendation does not correlate with OAI inspection classifications – **tremendous value found with NAI and VAI inspections!**

Points to Consider

- Regulatory compliance does not equate to overall clinical trial quality
  - 19% of CISs with active recommendations driven primarily by NAI and VAI inspection findings compiled across multiple site inspections

- When good quality risk management and quality by design processes inform the development of RBM, effective implementation of RBM can maximize study quality by focusing monitoring activities on processes and procedures critical for the protection of trial participants and maintaining data integrity

- Consistent use of common terminology is critical

- Valid, reliable, and interpretable data are in the shared interest of both the applicant and the Agency

Session 1: Regulatory Foundation for Risk-Based Monitoring

Risk-Based Monitoring – Shaping a New Paradigm

Session 1: Regulatory Foundation for Risk-Based Monitoring Approaches – Duke Margolis Center for Health Policy, Washington, DC

Presented by Camelia Mihaescu on 17 July 2019
Committees and Inspections Department

Table of Contents

Overview of EU regulatory resource documents on risk-based approaches to clinical trials

December 2012: OECD Recommendation on the Governance of Clinical Trials

November 2013: EU GCP IWG Reflection paper on risk based quality management in clinical trials

April 2014: Regulation (EU) No. 536/2014

April 2017: Risk proportionate approaches in clinical trials- EU recommendations

June 2017: ICH E6 (R2) becomes effective in EU

Setting the scene

Quality in clinical trials

Quality:

- fitness for purpose, i.e. ability to generate reliable information to answer key questions and support decision making while protecting study subjects.

Critical to quality factors:

- aspects of study design or conduct critical to:
  - protection of study subjects
  - generating reliable data
  - decisions made based on the study results

source: ICH E8(R1) draft Guideline

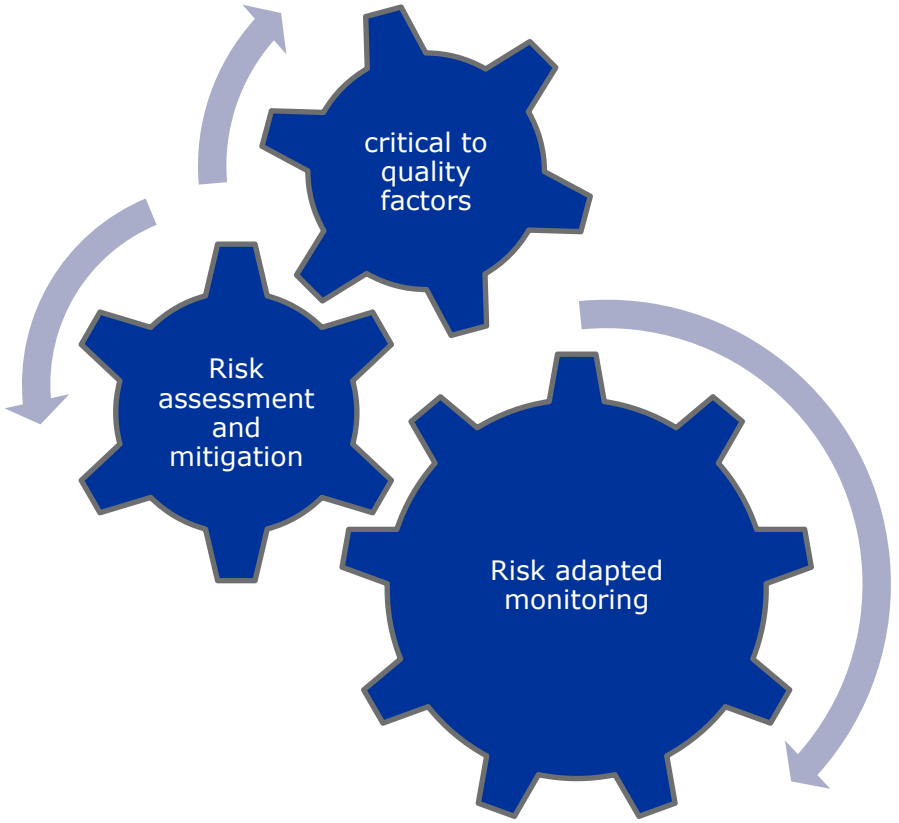
Quality in clinical trials - Contd.

Quality by Design (QbD):

- Quality is designed into the study protocol and processes;
- Focus on *critical to quality factors* to ensure protection of study subjects and data reliability;
- Proper management of the risks to the critical to quality factors (e.g. by implementing a risk based quality management system)

Risk based quality management

- Ensures quality is consistently maintained in a clinical trial
- Risk assessment and mitigation allows for the identification of higher risk areas that can be mitigated and lower risk areas that can be adapted and simplified
- **Risk adapted monitoring should be embedded in a risk-based quality management approach**



Monitoring: why?

Monitoring is a key element of drug development, aimed at safeguarding:

- Subjects' safety
- Data quality
- Protocol compliance

by focusing sponsor's oversight on the most important aspects of study conduct.

Monitoring tools

- On site monitoring relying heavily on SDV is not the only mean to ensure subject safety and data quality

- Monitoring strategies may involve **central tools** to identify the need for targeted monitoring visits based on assessment (statistical or other) of centrally accrued data and information;
- Type and combination of monitoring activities should be **trial specific**:
  - On-site monitoring
  - Remote monitoring
  - Centralised monitoring

Monitoring tools - Contd.

- Purpose of **centralised monitoring**:

- Identification of missing or inconsistent data, data outliers, unexpected lack of variability and protocol deviations;
- Analysis of data trends (e.g.range, consistency, variability of data) within and across sites;
- Identification of systematic errors or data integrity issues;
- Analysis of site characteristics and performance metrics;
- Selection of sites and/or processes for targeted on-site monitoring.

Monitoring tools - Contd.

- Monitoring activities should be **documented**;

- Monitoring plan should be **reviewed and updated**, based on the update of the risk assessment and mitigation plan.

Points to consider in relation to GCP inspections

- Is monitoring planned and implemented **in parallel** with the protocol and CRF design, contractual agreements, training activities etc. ?

- Does the risk-based approach take into account **trial specific risks** or is it using generic parameters only to define scope/content/frequency of visits/SDV sample size?

- Is **remote monitoring** used for SDV of subject-related data ?

Points to consider in relation to GCP inspections Contd.

- Is the **documentation of monitoring results** (on-site as well as centralised) sufficiently detailed to allow verification of compliance with the monitoring plan?

- Is a **periodic risk review** and **monitoring strategy review** performed?

- Is risk-based monitoring focusing on critical to quality factors and on aspects of the trial that are **not routine clinical practice** and that require additional training?

Take home messages

Quality should rely on **good trial design and conduct** and not on overreliance on retrospective document checking, monitoring, auditing or inspection.

Risk adaption allows for **a shift in focus** from the correctness of individual data points to trial results reliability.

Take home messages – Contd.

Implementation of a **study specific quality management strategy** and a **multi-disciplinary approach to study design** are key features of good quality clinical trials.

Risk based monitoring is a great tool … if used correctly

Thank you very much for your attention!

Further information

Contact:
Camelia.mihaescu@ema.europa.eu

Session 2: Experiences with Implementation of Risk-Based Monitoring Approaches

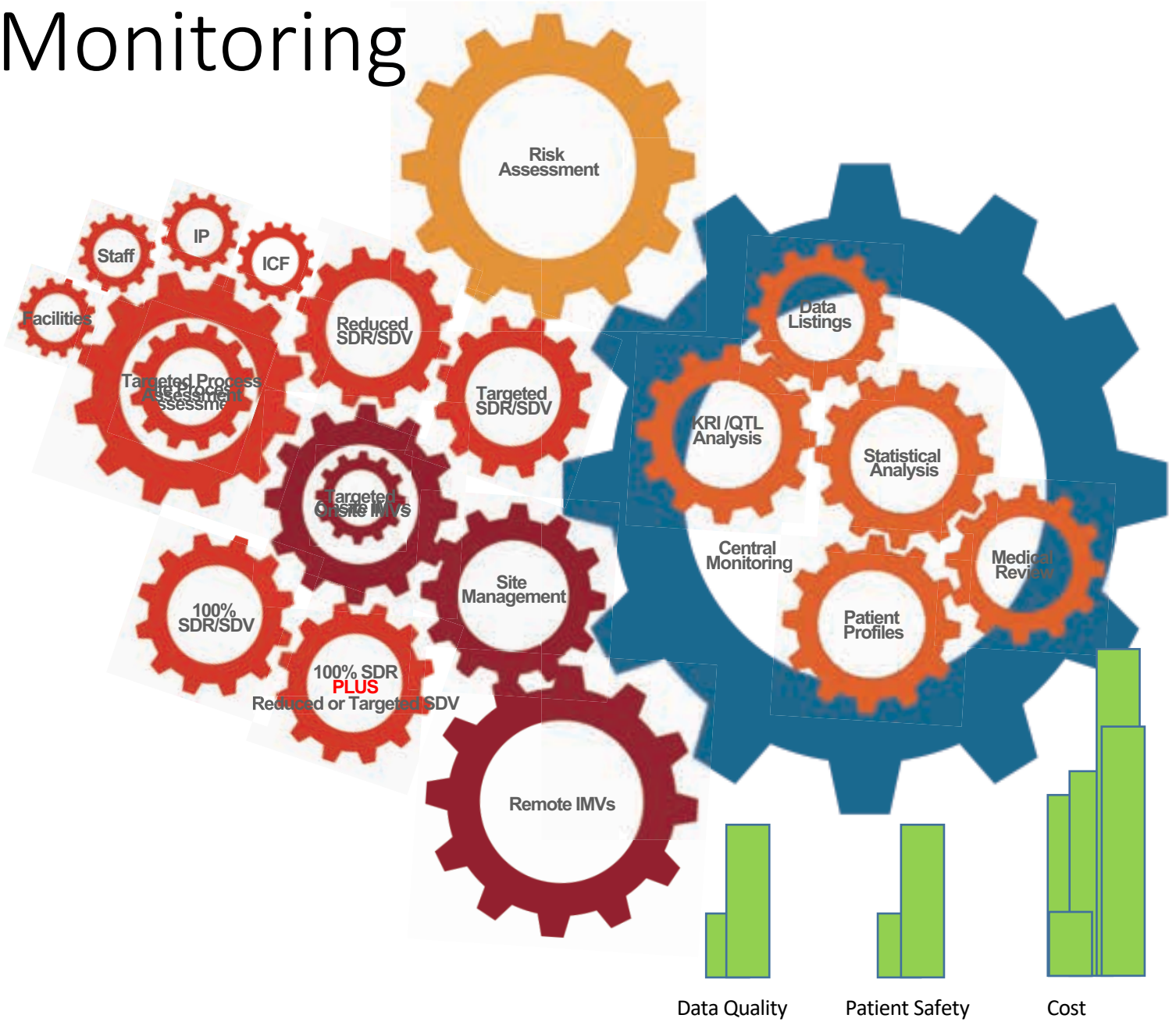
The Risk-Based Monitoring Challenge

Solution MUST result in:

- Better quality data
- Better patient safety
- Cost efficiencies

Complicating factors:

- Order of operations
- Roles
- Process integration
- Technology
- Change management
- Fear



Risk Based Monitoring – Global Collaboration in Ph III/IV Studies

Ty Rorick
Interim Head of Research Operations
Duke Clinical Research Institute
Durham, NC

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Defining Quality- Guiding Principles

1) Have we enrolled the **right participants** according to the protocol with adequate consent?	**The Right Patient**
2) Did participants receive the **assigned treatment** and did they stay on the treatment?	**The Right Treatment**
3) Was there complete ascertainment of primary and secondary **efficacy data**?	**The Right Data**
4) Was there complete ascertainment of primary and secondary **safety data**?	**The Right Data**
5) Were there any **major** GCP-related issues?	**Do the Right Thing**

—RM Califf 1997

Global RBM Plan Development

- Sponsor Expectations
  - Intensity of Activity during Enrollment vs Follow-Up
  - Changes in Enrollment or Follow-up Patterns
  - Agree on Minimum Expectations (visits at least annually for example)
  - Review of Consent/Regulatory Documents
- Global CRO Process & Systems
  - Blending Sponsor and Academic Ideas with Global Process/SOPs
  - Fit-for-Purpose, Configurable System that allows flexibility
- Developing a Global Operational Plan
  - Agreement on Key Risk Indicators
  - SDV Requirements (eligibility, event ascertainment, etc.)
  - Consistent Global Monitoring Plan

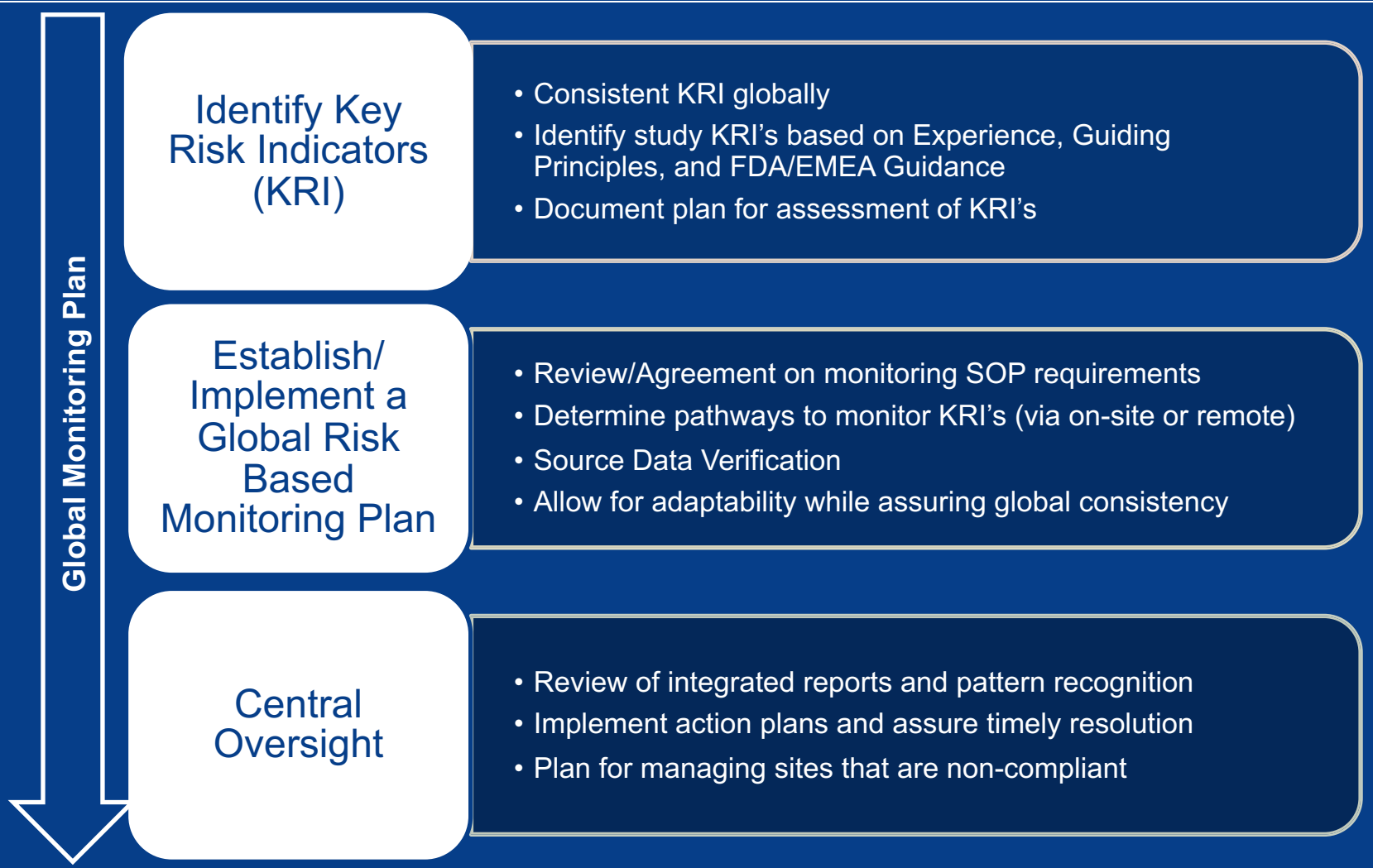
Key RBM Differentiators for a Global Program

- Streamlined/Efficient Processes
  - Focus on Guiding Principles/ Guidance (Do Not Overly Complicate)
  - System Integration
- Ability for Immediate Intervention
  - Easy to use system access (reporting, etc.)
  - Ensuring the trial team has integrated tools at their fingertips
  - Programmed alerts to team (LTFU, WD Consent, Drug Discon, incorrect drug assignment, etc.)
- Additional On-Site Visits are typically not the answer
  - Action is typically rapid communication
  - Ability to quickly identify rapid/high recruiters
    - Additional on-site visits may be required at these sites

Typical Global RBM Principles

- Single Global Plan
- Based on the 5 Guiding Principles and FDA/EMEA Guidance
  - Ask for FDA Input/Review of Plan
- Blend of the following:
  - Remote: data currency, report review, and rapid site follow-up
  - On-Site: consent review, SDV, drug accountability
- Provides Road Map for CRAs both Remote & On-Site
- Focused and Clear
- Allow for Adaptability
- Ensures Global Quality and Consistency

Global Monitoring



Key Risk Indicator (KRI) Examples

- Access to Records (PI, Coordinator, CRA, etc.)
- Type of Site (freestanding clinic, research only, affiliated health system, etc.)
- Identification of Patients (referrals, etc.)
- Site Team (back-up coordinators, Sub-Investigators, etc.)
- Turnover of Site Team/CRAs
- Enrollment Patterns (rapid, high, low)
- Data Currency & Cleanliness
- Safety/Event Reporting

Key Messages

- Align Expectations Early
- Create a Single Global Plan
- Focus on the Guiding Principles
- Be Consistent & Allow for Adaptability and Flexibility
- Understand the Likely Areas of Vulnerability
- Engage the Sites in Planning RBM
- Submit Monitoring Plan in Advance for Feedback
- Keep it Simple

Session 2: Experiences with Implementation of Risk-Based Monitoring (RBM) Approaches: An Industry Perspective

Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations Public Workshop
July 17, 2019

PhRMA
RESEARCH • PROGRESS • HOPE

Barriers to RBM Implementation

- Inconsistent Acceptance of RBM Approaches by Regulatory Authorities may Negatively Impact Global Product Development Programs
  - Regional differences based on monitoring practices, GCP inspection experience and/or culture, etc.
- Industry Concerns Regarding RBM Implementation of Clinical Investigations, include:
  - The quality of data
  - Unknown audit findings by Inspectors and impact on registration
  - Differences in Clinical Research Organizations (CRO) RBM methodology and impact for Sponsor oversight
  - Accidental unblinding of sponsor
- Lack of clarity on how to implement RBM with differing study types.
  - Complex Trial Designs
  - Trials with a small sample size (e.g., oncology, biologics, early phase, umbrella & basket studies).
- Uncertainty on FDA expectations around Quality Tolerance Limits (QTLs)
- Data privacy regulations and evolving use of electronic medical records (EMR) for remote source document review

RBM Implementation Considerations for Industry

- Risk management and tailored monitoring strategy of RBM can have positive impact on all study types, even if study too small/short/simple to leverage advanced data analytics
- Change management is critical throughout all levels of Sponsor organizations and site staff
- Cross-functional collaboration is critical at study RBM start and ongoing throughout study to remain adaptive
- RBM cannot be a one size fits all approach.
- Sponsors should leverage prior experience in managing RBM risks to streamline approach, however study-specific considerations are essential.
  - Identified risks may be weighted by impact, probability, and detectability to inform the RBM plan
- Data availability is critical to maximize power of central monitoring
- Roles dedicated to RBM are important to implementation success (i.e., Risk Managers, Central Monitors)

How FDA Can Help Industry Overcome Barriers

- Update Bioresearch Monitoring Program (BIMO) Inspection Guidance
- Train field Inspectors in RBM expectations, including QTLs, tolerance and acceptability of low risk findings
- Provide use case examples highlighting appropriate and inappropriate implementation approaches for RBM and lessons learned from Inspections
- Provide a communication mechanism for Sponsors to obtain FDA feedback on study de-risking questions and monitoring approaches, including early feedback/input from FDA inspectors.
- Support ICH work to harmonize RBM approaches across global regulatory agencies

How FDA Can Help Industry Overcome Barriers

- PhRMA believes further guidance is needed from FDA on:
  - QTL definitions, expectations, and best practices for how to include these in CSR/BLA
  - How/if to implement RBM on small studies
  - Source Data Verification (SDV)
  - Source Data Review (SDR)
  - If RBM is appropriate for certain study types (e.g., complex study designs, including oncology, umbrella, basket designs, early phase)
- PhRMA recommends that RBM implementation should include FDA accepting that:
  - RBM approaches may need to be adaptive, as sponsors may need to change an RBM approach as needed across and during studies
  - The RBM approach should be holistic and cross-functional
  - RBM approaches may vary by sponsors
- Facilitate creation of open channels of communication for sharing information on RBM successes and challenges across industry
- Provide reference data sets with which Sponsors/CROs can measure their data analytics tools for consistency with FDA expectations

Risk Based Monitoring
The Site Perspective

Michele Cameron, RN, BSN, MBA
Director of Clinical Research
Clearwater Cardiovascular Consultants
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Society for Clinical Research Sites, Inc. is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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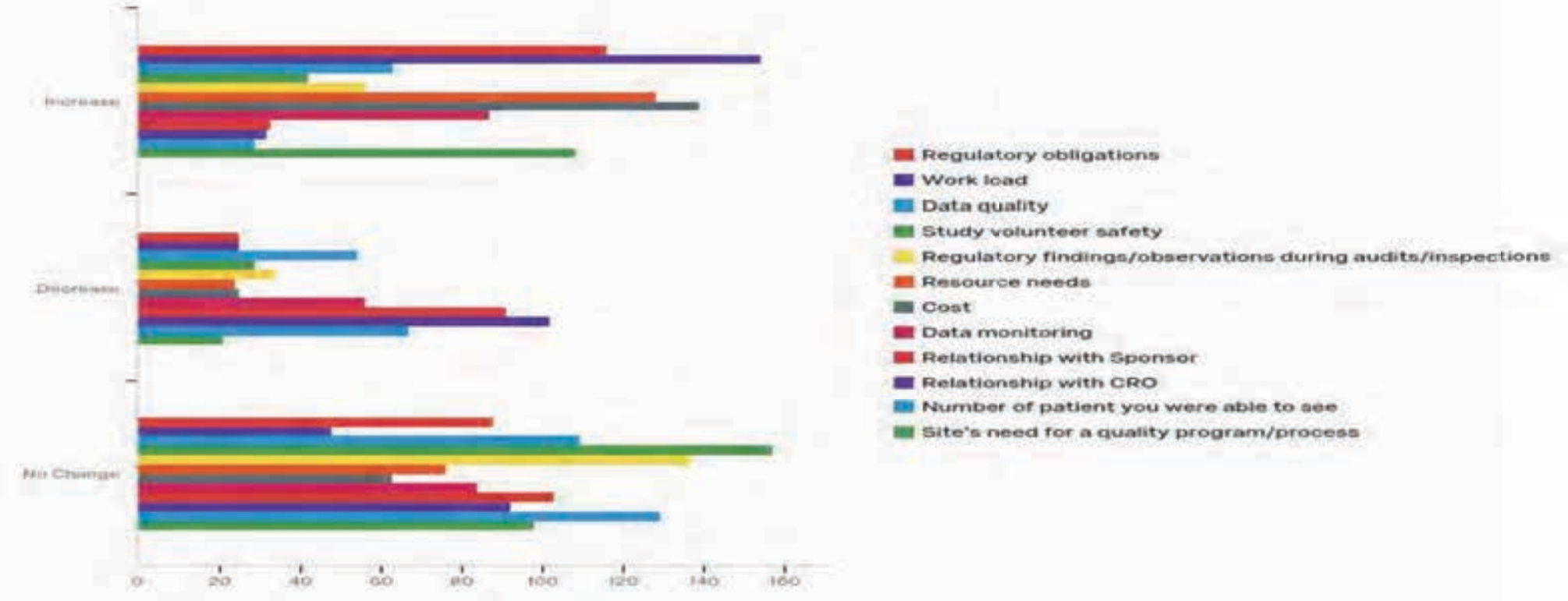
Risk Based Monitoring - The Site Perspective

Q11 - What was your 2016 experience with Risk-Based Monitored studies compared to traditional monitored studies?

#	Answer	%	Count
1	Better	10.68%	33
4	Same	35.60%	110
5	Worse	32.69%	101
6	No Experience	21.04%	65
	Total	100%	309

Risk Based Monitoring - The Site Perspective

Q12 - How has Risk-Based Monitoring impacted your site?



Risk Based Monitoring - The Site Perspective

Site Interpretation of RBM

Risk Based Monitoring vs. Remote Monitoring

Monitors & CRA's not able to provide clarification

Operational Changes are Required

- Passing the Work on to the Sites
- Add Quality Assurance Personnel to Do the Work of the Monitor
- Required to submit redacted documents

Risk Based Monitoring - The Site Perspective

Sites are on the front-line of data collection. Many times they must take qualitative data and fit it into quantitative boxes created for them so that the information can be analyzed and questions can be answered. This requires a collaborative effort.

Risk Based Monitoring - The Site Perspective

Challenge #1: Allow for Site Diversity

Practice-Based, Academic, Institutional, Independent

Single or Multi-Therapeutic

Staff Size & Role Differentiation

Structure & Operations

Experience

Risk Based Monitoring - The Site Perspective

Challenge #2: Provide Sites with Clear RBM Guidelines

Many Sites still do not understand the concept / value of RBM

Sites are the END-USERS but have little or no input in the RBM Plan

Sites require timely, detailed information for proper study planning

Risk Based Monitoring - The Site Perspective

Challenge #3: Make the End-User at the Site more Efficient

Provide Site with knowledgeable contacts that have direct access to superiors that can exact change quickly if necessary

Limit e-queries & consider triggers for collaborative phone calls

Less Frequent more substantial regular Phone Visits

Risk Based Monitoring - The Site Perspective

Summary of Site Specific Considerations for your RBM Plan

Communicate the Monitoring Plan

Allow for Adaptability

Collaborate with Sites during the RBM Plan process

Consider efficiencies for the Site End-User

Provide Sites with a well-informed contact that can exact change

Risk Based Monitoring
The Site Perspective

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Session 3: Analytical Tools and Methods to Support Risk-Based Monitoring

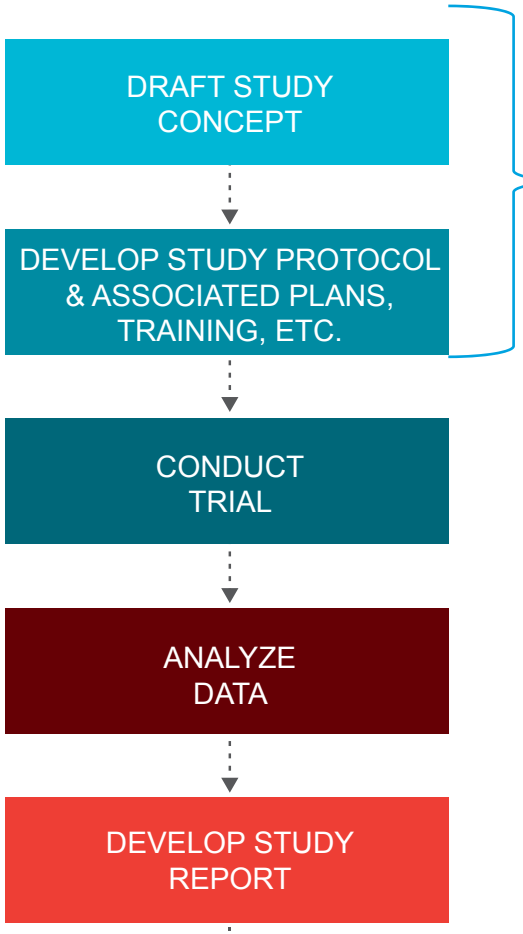
IMS Health & Quintiles are now IQVIA®

From Quality by Design to Risk-based Monitoring and Analytics

17 June 2019

Ann Meeker-O'Connell, VP Quality Assurance

Risk-based Monitoring: One Outcome of Applying Quality by Design

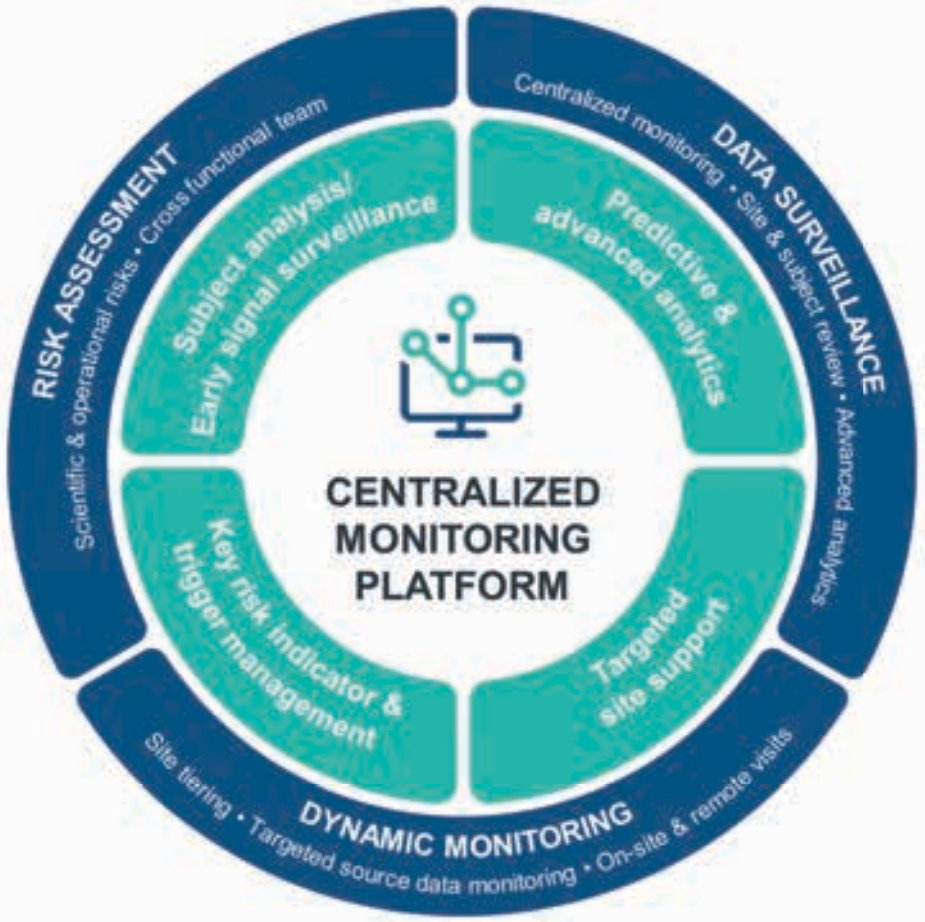


1. **Identify** Critical to Quality (CTQ) aspects of trial design and associated risks
   - *Inclusive of critical data and critical processes*
2. **Evaluate** risks and determine which require mitigation
3. **Tailor study design** to avoid errors that could impact evaluability or participant safety
   - Verify that trial is operationally feasible
4. **Highlight** important risks in CTQ aspects requiring additional mitigation

Outcomes of design-stage reviews translated into tailored oversight

- ❑ **Identify targeted strategies** to reduce important risks in CTQ areas
- ❑ **Tailor trial oversight plans** (including **monitoring plans**) to focus on early detection of important errors and associated actions to be taken
- ❑ **Define analytics** to facilitate risk monitoring

Risk Assessment Process Outcomes Link to Analytics



Outcome of Risk Assessment

1. Risk assessment and mitigation plan (RAMP*)
2. **Operational Risks: Key Risk Indicators identified**
3. **Scientific Risks: Critical / Key Data Variables documented**
4. Monitoring strategy finalized

Critical / Key Data Variables (Examples)
Primary and secondary efficacy endpoints
SAE recording and reporting
Informed Consent Process
Inclusion/ Exclusion Criteria variables
Events leading to discontinuation of treatment
Variables related to patient visit schedules/ treatment windows
Variables related to dosing/ IP management
Other study-specific variables dependent on study design

*Aligned to Transcelerate RACT (Risk Assessment and Categorization Tool

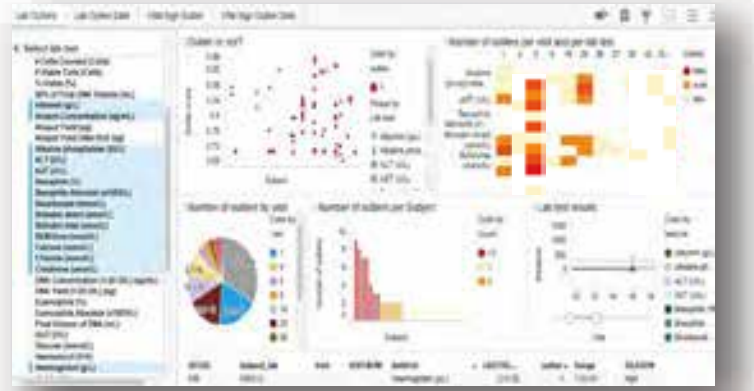
Implementing Centralized Monitoring Analytics

Advanced Analytics

Composite site ranking for holistic risk assessment at sites

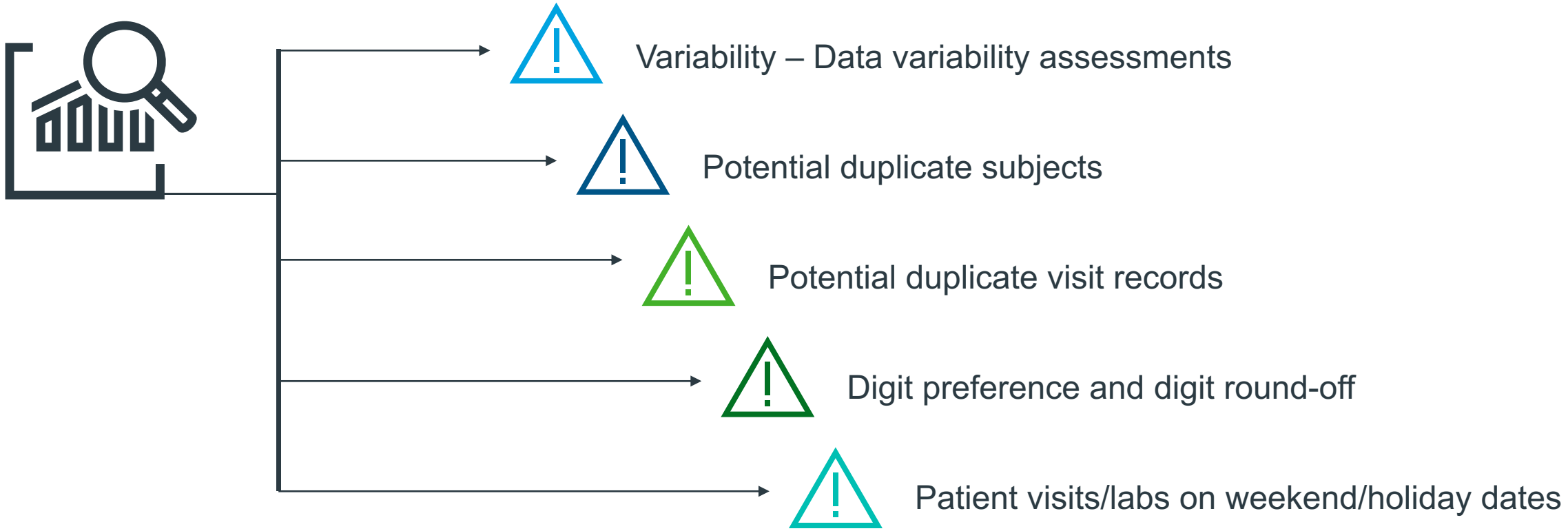
Machine Learning

Which subjects are at potential safety risk with high outliers in lab analytes



Potential Fraud Surveillance

Few key capabilities to monitor data integrity



Session 3: Analytical Tools and Methods to Support Risk-Based Monitoring

Analytical Tools and Methods to Support Risk-Based Monitoring

A CRO perspective

Anne S Lindblad, PhD
President and CEO

Risk Based Monitoring Activities

- Informed Consent
- Protocol Compliance
- Pharmacy
- Training/Personnel

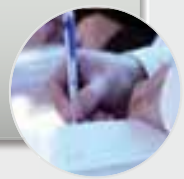
On-Site Monitoring

- Enrollment
- Dash boarding accumulating data
- Monitoring KRI
- Algorithms

Central Monitoring

- Source Data Verification
- Source Data Review
- AE and PD supportive material
- Essential Documents

Off-Site Monitoring



Create a Risk-Based Monitoring Plan

- Assemble multi-disciplinary team
- Assess risks associated with complexity of protocol execution
- Identify complexity and potential failure points in data collection
- Evaluate and select surveillance methods to catch anomalies early and often
- Detail risk mitigation strategies, action and escalation plans
- Evaluate plan effectiveness during execution

Automate Sampling Plan

- **Write specifications**
- **Translate to code**
- **Test**
- **Implement**
- **Track**
- **Adjust**

Specifications for Implementation

Group	Description	Membership Criteria	Forms	Rule types
A	Enrollment	Enrollment is entered	ENR A, X	Form, Field
B	DS2	DS2 is entered	DS2	Form, Field
C	SDV	At least selected 20% of participants at each site * the first participant enrolled must be selected and * participants that meet any AE1 criteria below must be selected - AE1.A1CAUSE = '1' - (AE1.A1BDFCT or AE1.A1DISAB or AE1.A1DEATH or AE1.A1HOSP or AE1.A1LFTHRT or AE1.A1MDIMPR = '1') - AE1.A1SEVEVE = '3'	DEM, DS1, CM1, MH1, PE1, VS1, EX1	Participant, Field
D	LB1	LB1 form that meet below criterion - (LB1.L1ALBCS or LB1.L1ALTCS or LB1.L1ASTCS or LB1.L1BUNCS or LB1.L1CRECS or LB1.L1PROCS = '1')	LB1	Form, Field
E	AE1	AE1 form that meet any criteria below - (AE1.A1CAUSE = '1') - (AE1.A1BDFCT or AE1.A1DISAB or AE1.A1DEATH or AE1.A1HOSP or AE1.A1LFTHRT or AE1.A1MDIMPR = '1')	AE1	Form, Field

Track Outcomes

Generate Report | Download Report

Show 10 entries | Search:

Segment	Participant	Site	Form	Visit #	Key Fields	Status	Flagged Fields Evaluated	Total Fields Evaluated	Outstanding Discrepancies	Total Discrepancies	Initial Evaluation Date	Initial Evaluation By
B	061	UAC01	SAE Information Page 2	Non-Visit	B6	Pending	1/2 [50.0%]	1	0/1 [0.0%]	0/1 [0.0%]	03/11/2019	Amrut Patil
B	070	UAC01	Enrollment Review	Non-Visit		Pending	0/3 [0.0%]	0	NA	NA		
B	070	UAC01	SAE Information Page 2	Non-Visit	B1	Pending	2/2 [100.0%]	2	2/2 [100.0%]	2/2 [100.0%]	03/07/2019	Amrut Patil

Risk Based Monitoring Activities

- Informed Consent
- Protocol Compliance
- Pharmacy
- Training/Personnel

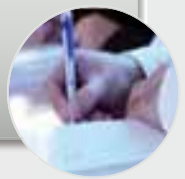
On-Site Monitoring

- Enrollment
- Dash boarding accumulating data
- Monitoring KRI
- Algorithms

Central Monitoring

- Source Data Verification
- Source Data Review
- AE and PD supportive material
- Essential Documents

Off-Site Monitoring



Statistical

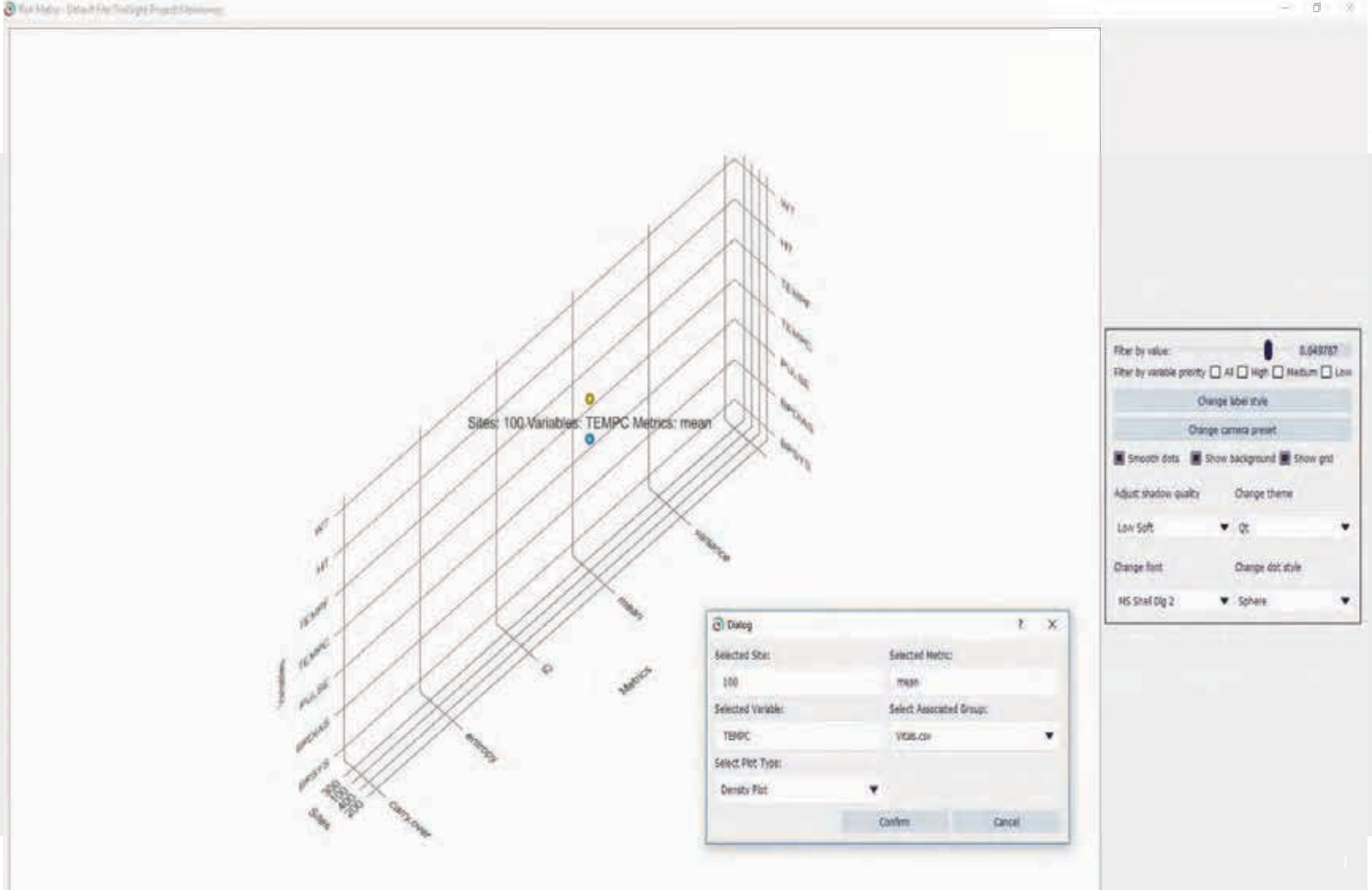
Central Statistical Monitoring

Includes:

- Modeling and pattern detection
- Visual analytics
- Quantification of signal vs noise
- Machine learning

What is needed?

- Seamless integration into RBM program
- Data system independence
- Easily accessible and visible to a multi-functional team
- Intuitive
- Flexible and adaptable as knowledge accumulates
- Efficient and transparent interpretation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Filter by variable priority: All High Medium Low
Change label style
Change camera preset
Smooth dots
Show background
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Change theme
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Confirm
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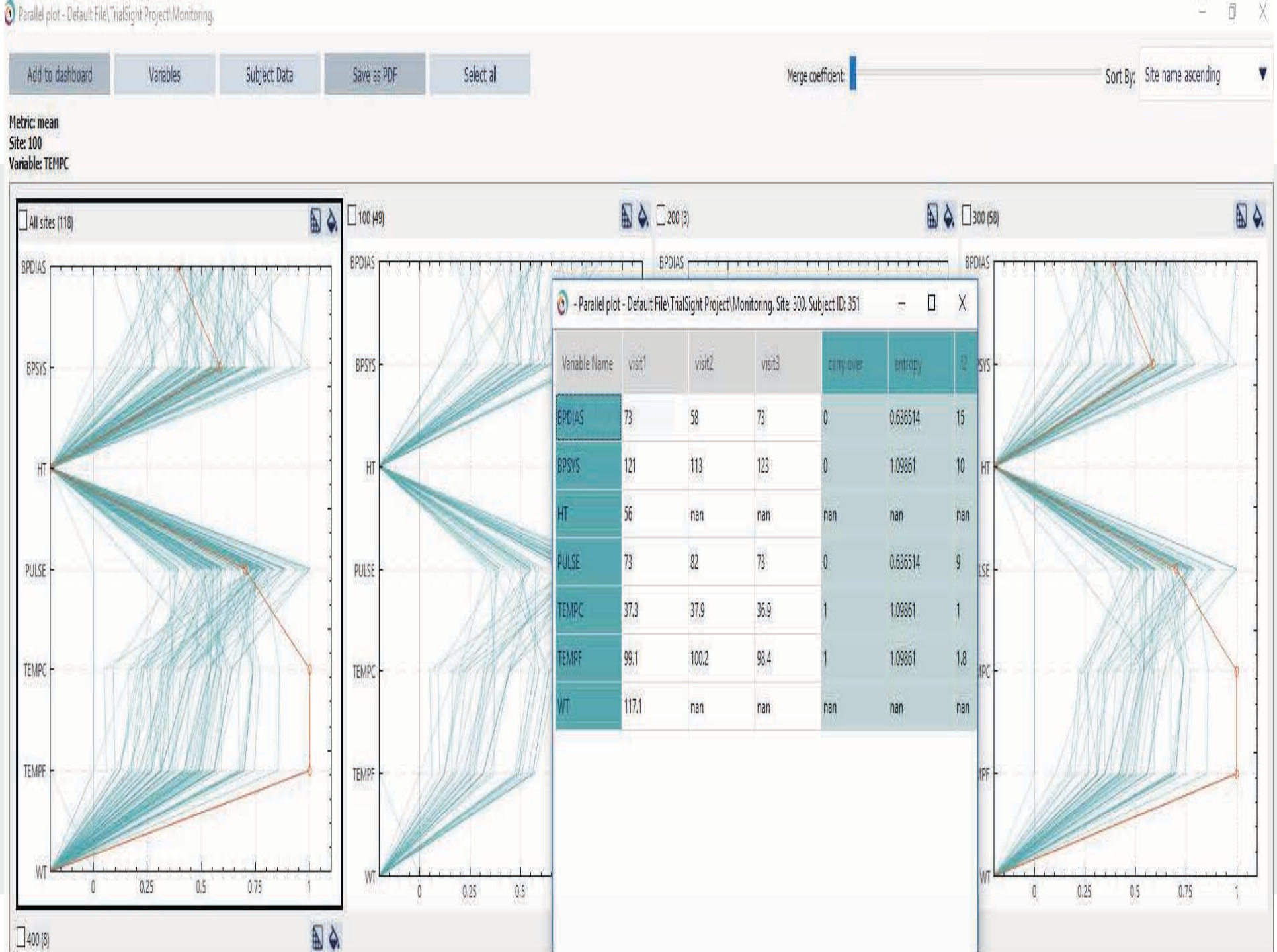
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Add to dashboard
Variables
Subject Data
Save as PDF
Select all
Merge coefficient:
Sort By:
Site name ascending
Metric: mean
Site: 100
Variable: TEMPC
All sites (118)
100 (49)
200 (3)
300 (58)
400 (8)
BPDIAS
BPSYS
HT
PULSE
TEMPC
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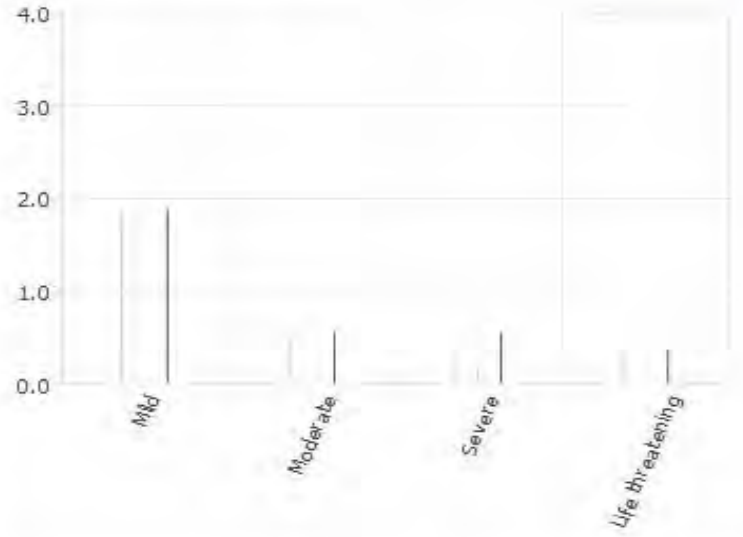
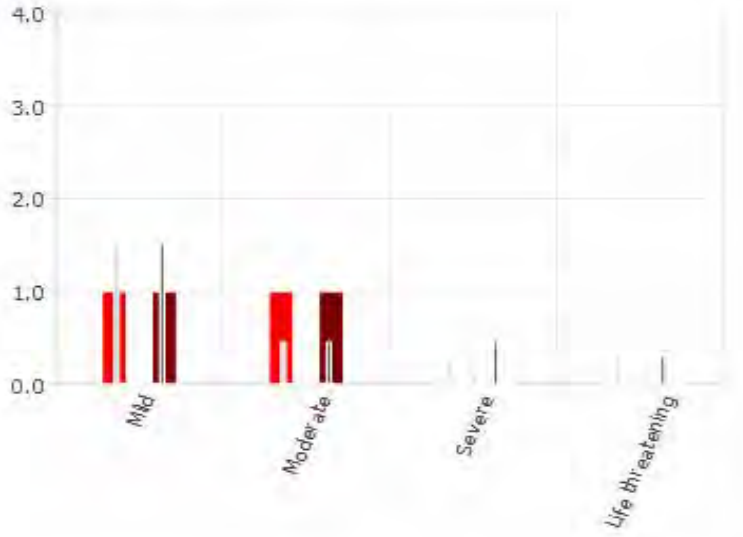
WT
0
0.25
0.5
0.75
1
- Parallel plot - Default File\TrialSight Project\Monitoring. Site: 300. Subject ID: 351
Variable Name
visit1
visit2
visit3
carry over
entropy
BPDIAS 73 58 73 0 0.636514 15
BPSYS 121 113 123 0 1.09861 10
HT 56 nan nan nan nan nan
PULSE 73 82 73 0 0.636514 9
TEMPC 37.3 37.9 36.9 1 1.09861 1
TEMPF 99.1 100.2 98.4 1 1.09861 1.8
WT 117.1 nan nan nan nan nan

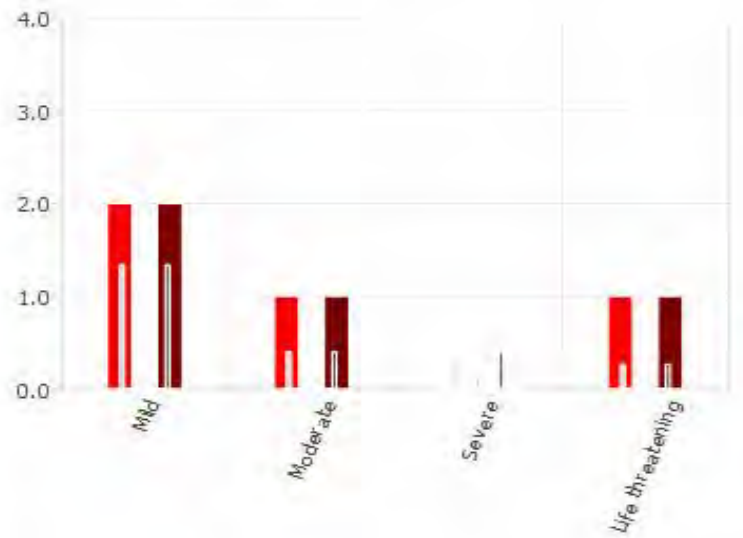
10 (15) Followup time = 2464 τ = 0.189117



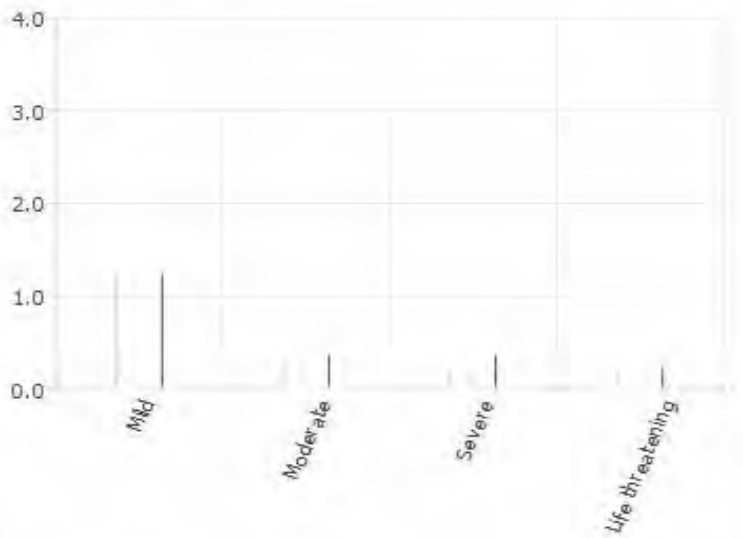
6 (12) Followup time = 1969 τ = 0.151124

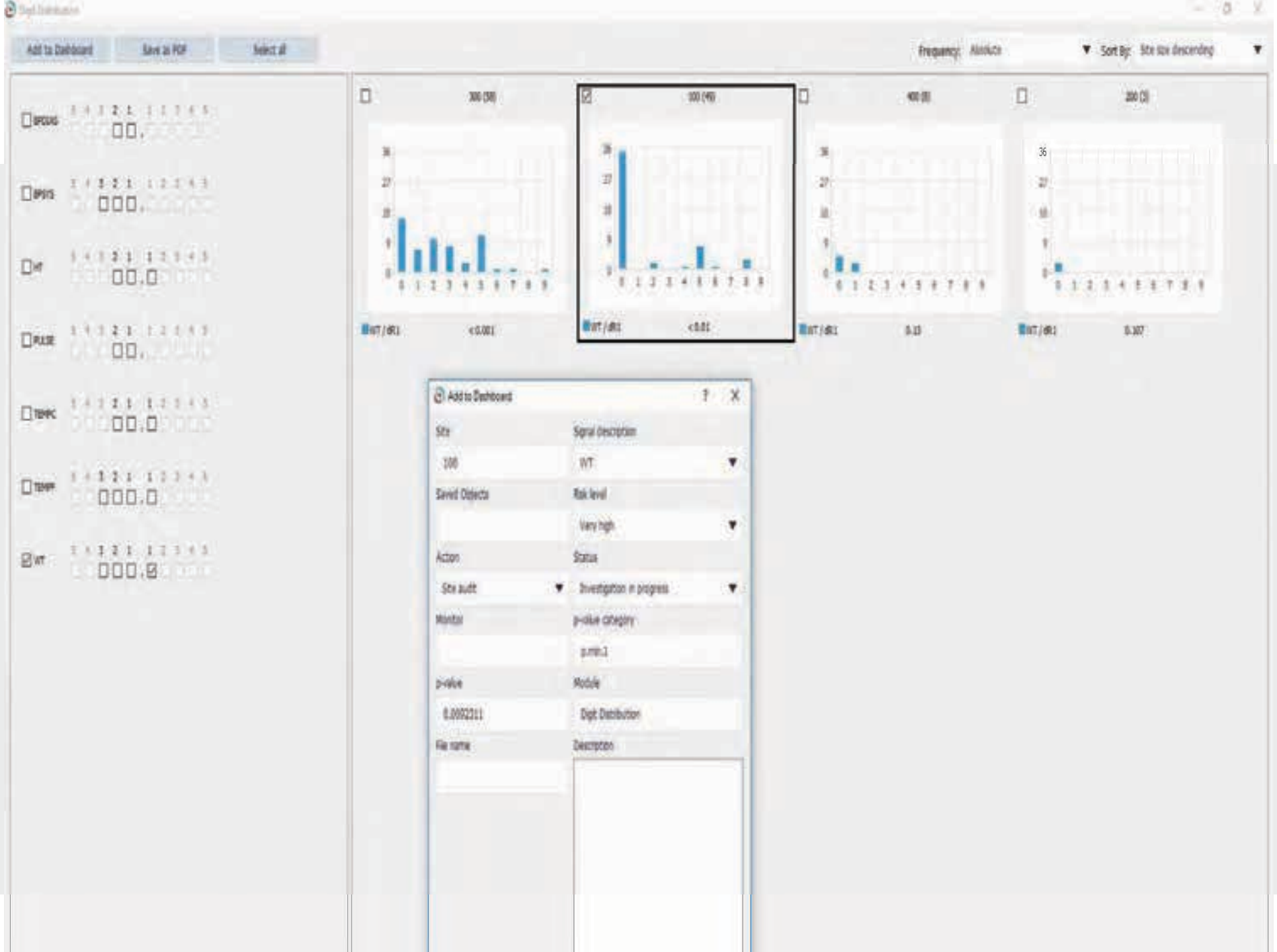


5 (11) Followup time = 1743 τ = 0.133778



9 (10) Followup time = 1627 τ = 0.124875

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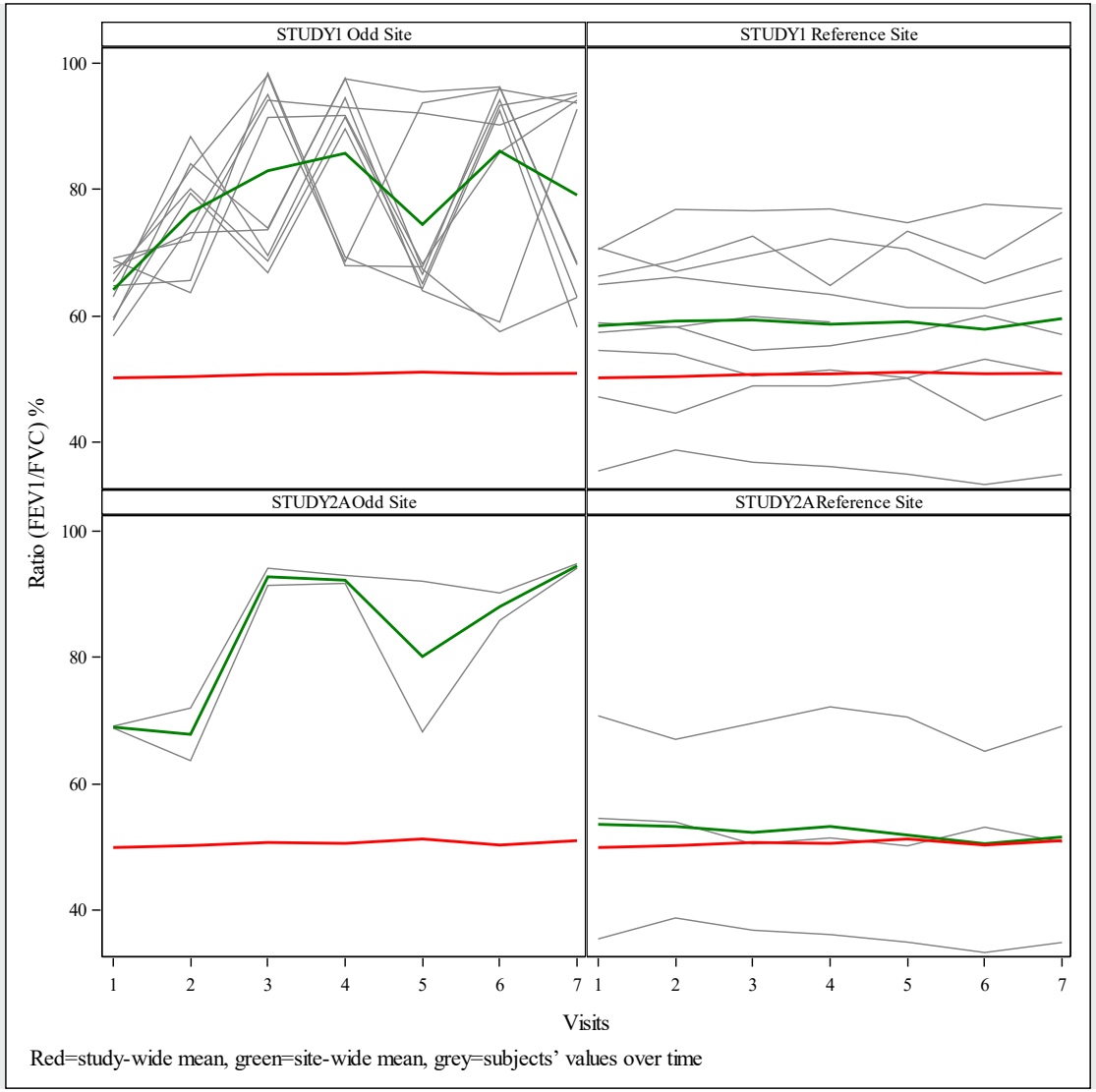
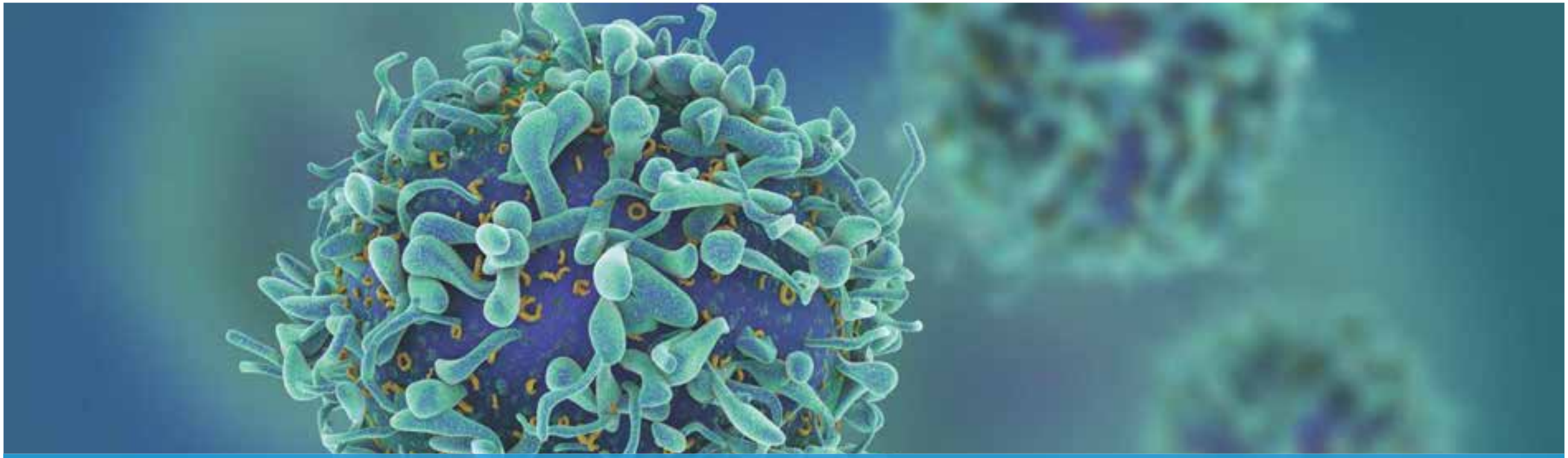
Module
Digit Distribution
File name
Description

Findings


STUDY1 Odd Site
STUDY1 Reference Site
STUDY2AOdd Site
STUDY2AReference Site
Ratio (FEV1/FVC) %
100
80
60
40
1
2
3
4
5
6
7
Visits
Red=study-wide mean, green=site-wide mean, grey=subjects' values over time

Thank You



Session 3: Analytical Tools and Methods to Support Risk-Based Monitoring

Stephanie Clark, Director
Risk Management-Central Monitoring
Janssen R&D, LLC | 17Jul2019

Duke Margolis Center for Health Policy:
"Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations"

janssen | Pharmaceutical Companies of Johnson & Johnson

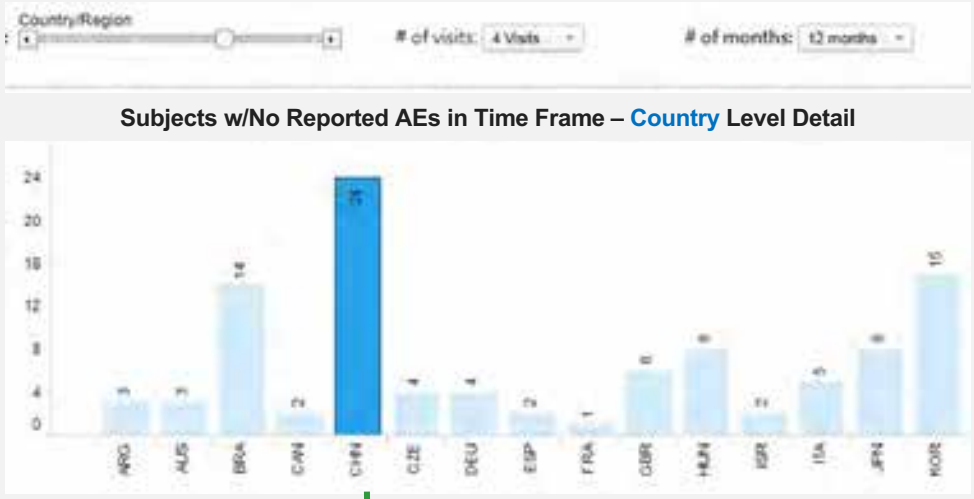
Analytic Approaches to Support Risk-Based Monitoring

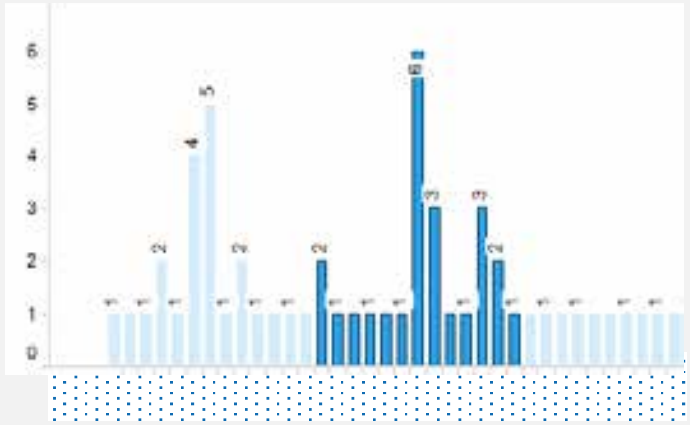
Standard Key Risk Indicators (KRIs)	Dashboard with *standard* operational and safety KRIs to indicate potential risks in countries/sites. Applicable across studies
Study-Specific Reports (SSRs)	Visualizations based on unique, *study-specific* Critical to Quality (CtQ) factors to identify potential risks in study/countries/sites
Central Statistical Surveillance (CSS)	Statistical analysis of entire trial data set to identify signs of intentional/unintentional noncompliance. Identifies sites that need further focused monitoring

Organizational Access to Data Visualizations

janssen | Johnson & Johnson

Standard Key Risk Indicator (KRI) – *example: No Reported AEs*





Safety Risks

AE under/over reporting
Time taken to enter AE
AE by period

Subjects w/ no reported AE
Subjects with open AEs
AE reporting relative to visit

Operational Risks

Timely Data Entry
Timely Query Resolution
Query Rates & Trending

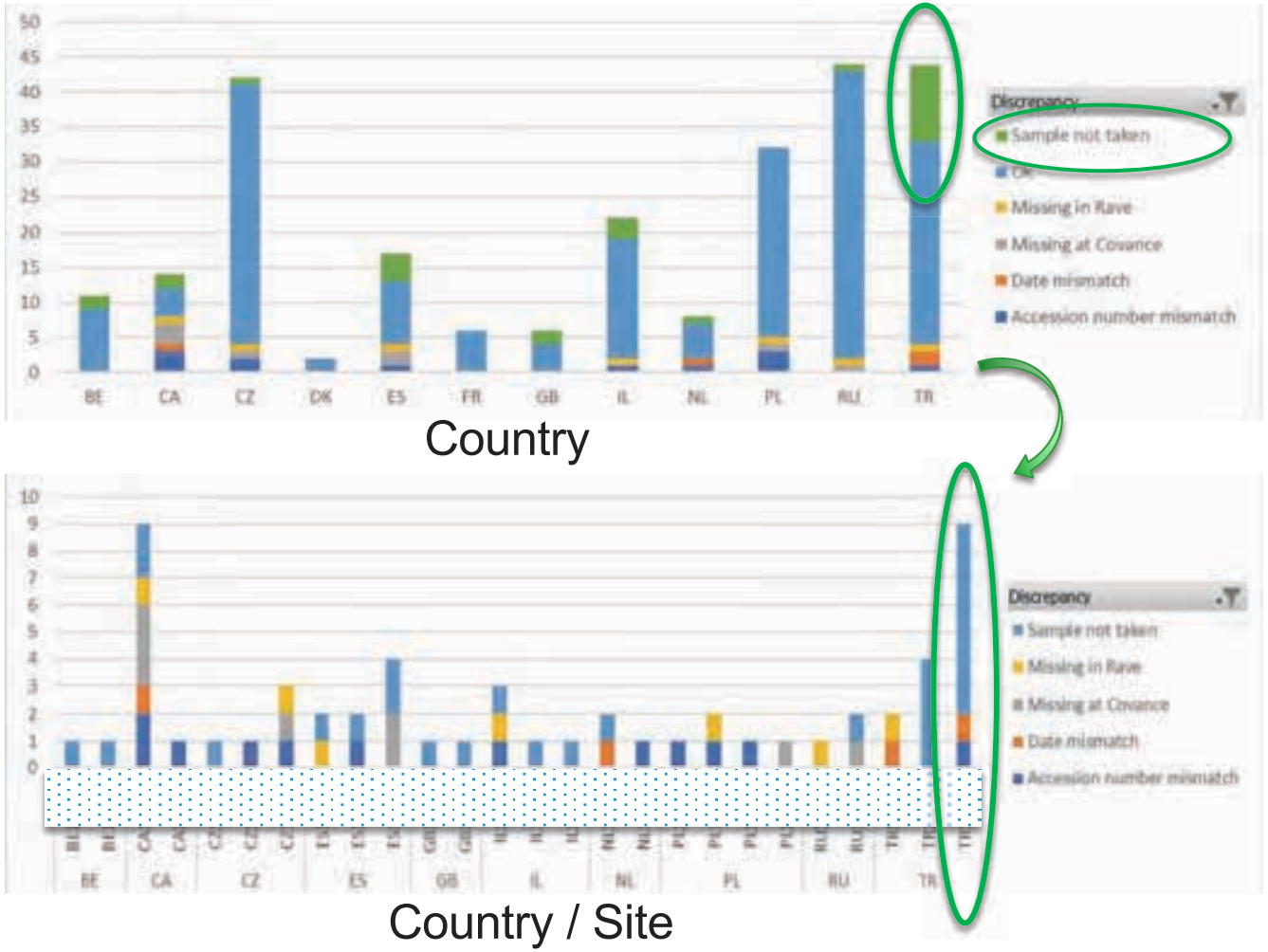
Major PD under/over reporting
Timely issue resolution
Site staff attendance & turnover

Subjects w/No Reported AEs in Time Frame – Site Level Details

Cycles	Months	Rave URL	Therapeutic Area	Phase	Country/ Region	Site	Total Subjects	Subjects w/ no AE
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		13	2
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		4	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		6	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		4	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		3	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		9	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		15	6
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		5	3
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		10	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		11	1
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		12	3
4 Visits	12 months	JanssenRpt	Oncology	Phase II	CHN		6	2

Example shown: Phase 2 oncology study

Study-Specific Reports (SSRs)– *example:* Biomarker Samples



- Related to study endpoint
- Report created to identify and trend samples not taken per protocol/not received at central vendor
- Identified site in Turkey where biomarker samples were not taken for two consecutive months

✓ ACTIONS:

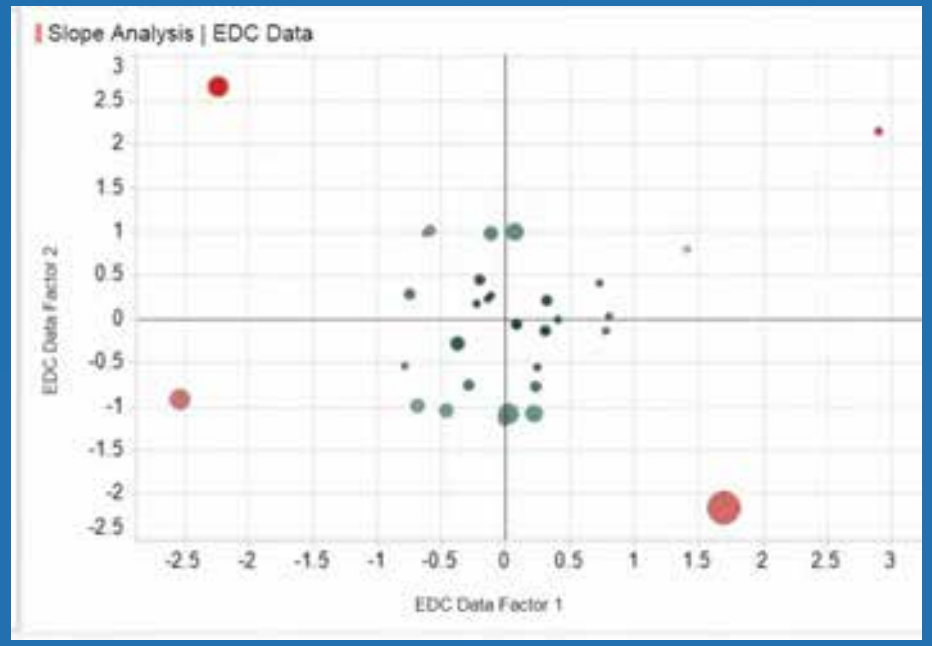
  - Raised as a signal in working group meeting
  - Site contacted and acknowledged confusion around protocol sampling process
  - Site retrained, no recurrence

✓ DOCUMENTATION: fully documented in issue tracking system

Example shown: Phase 3 oncology study

Central Statistical Surveillance (CSS)

Identification of sites that differ from the normal study data profile:

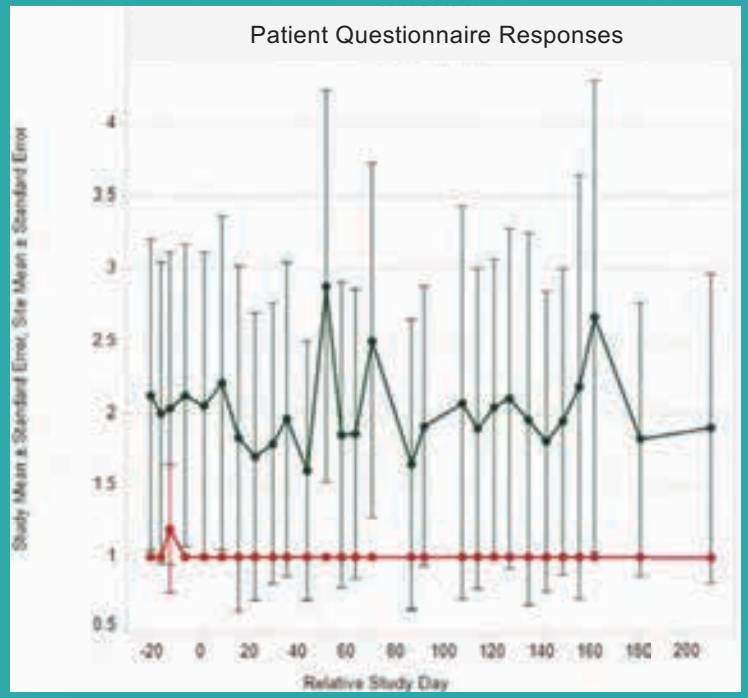


LEGEND:

- **Dot size**: number of subjects at site
- **Color**: darker red color indicates degree to which the site's data differs from all sites in the study

Example above shows analysis including all EDC, questionnaire, and lab data for all sites in the study

Results at site in question are more alike compared to the study norm:



LEGEND:

- **Green Line and Error Bars:** patient assessment results across all sites in study
- **Red Line and Error Bars:** site in question showing results differing from study norm and with almost no variation/error bars

Example shown: Phase 3 neuroscience study

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Other Technology and Tools that (Will) Support RBM

1. Predictive algorithms to trigger monitoring visits based on workload + key risk indicators (*i.e.* site performance)

2. Tools that maximize remote access to "real-time" actionable data:

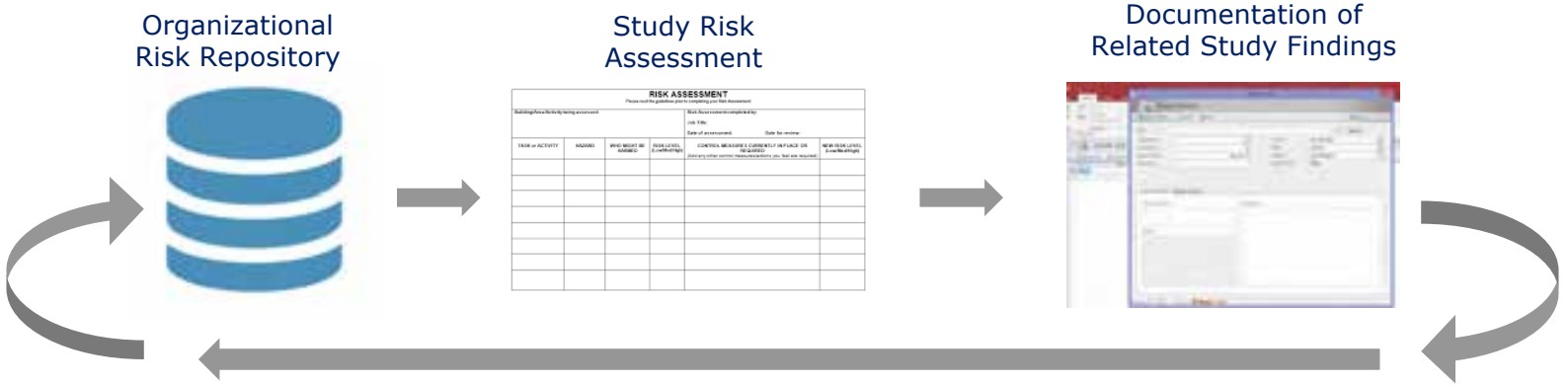
eICF - Electronic Informed Consent

ePRO/eCOA – Electronic Patient Reported Outcomes/Clinical Outcome Assessments

Data collection via wearables

Electronic Medical Records (EMR) with remote access for monitors

3. System for 'end-to-end RBM':



Strengths, Limitations, & Challenges of Analytics and Tools

Strengths

- Holistic view of study data to address significant outliers on early and ongoing basis, minimize missing data
- Ability to perform complex cross-checks difficult to do manually
- "Democratization" of data insights to empower all roles on study teams & site staff to improve data quality/subject safety
- Enable potential operational efficiencies, savings reinvested in further drug development

Limitations

- Ineffective without robust processes and skilled human resources to interpret & act on findings
- Dependent on strong protocol de-risking activities
- May require a minimum volume of data for analytics/statistics
- Can be limited by delays in access to data or related to need to build complex reports
- On-site visits may still be required for certain activities (drug accountability, pre-trial and closeout visits)

Challenges

- Insufficient use of analytics to drive monitoring strategies - SDV still seen as gold standard for data quality
- Need to move from deterministic monitoring visit schedules to predictive scheduling
- Advanced analytics present the risk of unintentional unblinding
- Analytical tools can be complex & expensive to develop or obtain via vendors, evolving at fast pace
- Ensuring proper Sponsor oversight of RBM studies outsourced to CROs with varying and evolving analytics to support their RBM models

Thank you

Stephanie Clark, Director

Risk Management-Central Monitoring

sclark23@its.jnj.com

SESSION 3: ANALYTICAL TOOLS AND METHODS TO SUPPORT RISK-BASED MONITORING

Jonathan Andrus, M.S., CQA, CCDM

Chief Business Officer

Clinical Ink

@datajonathan

Duke Margolis Center for Health Policy:
"Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations"

AREAS OF DISCUSSION

- Importance of data management in RBM
- Discussion on how members of the Society for Clinical Data Management have used tools to enable RBM (e.g. direct data capture, subject capture, targeted review, etc.)
- Emerging technology to effectively and efficiently streamline clinical trials

IMPORTANCE OF DM IN RBM

- Reports
- Study Setup/System Logic
- Integration of disparate data sources in order to enable a more comprehensive picture of patient and study risk
- Partnership with statistics, clinical and vendors in order to facilitate the best study set up and environment to enable reduction in redundant/unnecessary data review and more focused site visits

DATA MANAGEMENT RESPONSE

- How to embrace RBM and Innovative Data Review Approaches in a world with virtual studies, RWE, hybrid?
- Recently released:
  - **The Evolution of Clinical Data Management to Clinical Data Science: A Reflection Paper on the impact of the Clinical Research industry trends on Clinical Data Management**

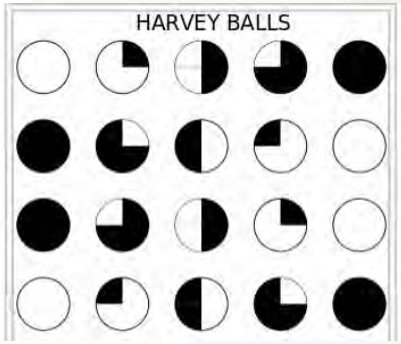
https://www.scdm.org/publications/white-papers/

INFORMAL SURVEY OF DM LEADERS

- Are your organizations using a risk-based approach to data and clinical review on a regular basis?
  - Top 3 Pharma:
    - **Just started down the path**. In a way, all of us have been doing RBM to some degree as our Data Review Plans (DRPs) were driven by the Statistical Analysis Plan (SAP) but we are diving into more analytics driven RB data review now.
  - Medium Sized Pharma
    - Yes. We have fully adopted RBM into our clinical and data review. We're just now rolling out TSDV as a component of it and *have finally begun to reduce our site monitoring visit frequency*, using the data to drive that.

INFORMAL SURVEY OF DM LEADERS

- Are your organizations using a risk-based approach to data and clinical review on a regular basis?
  - Small Specialty Focused CRO
    - We are using the **RACT** to identify areas of risk and identifying a method to determine if any of these identified risks approach a threshold that would indicate intervention. These are typically **site scorecards** showing data and **Harvey balls** to help us see all items of concern for each site. Each project team reviews these at an internal team meeting each week. This has been successful for us in identifying areas of concern where we were able to immediately react to avoid a bigger issue.
  - Medium Sized Pharma:
    - Earlier this year, we rolled out a RACT guidance for DM in alignment with broader RBM practices, the assessment from the guidance **feeds into our DRP and Data Quality Management Plan (DQMP)**. Also building more advanced analytics to aid in other groups focus areas.



INFORMAL SURVEY OF DM LEADERS

- What about the review of audit trail data?
  - Medium Sized Pharma:
    - For the audit trail review process (at our company, but also in discussion w/ the industry via eClinical Forum), our industry is going to use the definition of critical data from RBM (RACT) to define what is reviewed in the audit trail to help detect oddities.
- Why have your organizations been slow to adopt?
    - Fear (of change, non-acceptance by regulators, missing something)
    - Risk-Averse (used to reviewing everything, even if it has limited importance to the overall study safety/efficacy)

RBM TOOLS AND METHODS

- DDC, tSDV/tSDR, Virtual/Site Less Trials
  - Direct Data Capture:
    - Many organizations are embracing collecting data directly from subjects with no transcription
    - tSDV/tSDR – using the RACT and other tools, determination is made as to where to target clinical and data review based on entered data (which triggers required form review, limited review for screen failures)
- Virtual/Site Less Trials
  - How do I monitor and ensure data integrity?
  - Drug supply and the integrity of traceability? (shipping to home)
  - What is source and how do I monitor?
  - Medication compliance

- Financial barriers (lost earnings from missing work, inability to pay for extended childcare, etc.) can also discourage patients from participating.
- Gottlieb - "As a result, only a fraction of U.S. patients—about 3 to 5% in the case of cancer patients—participate in clinical trials," he said

RBM TOOLS AND METHODS

- tSDV/tSDR
  - Forms can be required to be reviewed based on any number of criteria or triggers – this is targeted form review.
    - Specific data point; for example, all forms that contain a BMI 10% higher than the last reported BMI must be reviewed.
    - A trigger can be based on a specific user. For example, the first ADAS-COG completed by every user must be reviewed.
    - Limited review required when patient is noted as screen failure
  - When criteria is met - ‘Required’ is now a fourth review status

RBM TOOLS AND METHODS

- RWE/RWD
  - Using data from routine care of patients
  - Sources include EMR, medical claims, lab results, patient mobile device data, etc. – *critical that aggregate data analysis is employed to help identify risk*
  - Data come from actual use of products in real-life settings, they can inform in a way that controlled clinical trials have never done
- Hybrid Studies
  - Mix of brick and mortar site visits and at home visits
  - How are these managed effectively (RBM approach)?
  - How do I ensure patient privacy and protections?

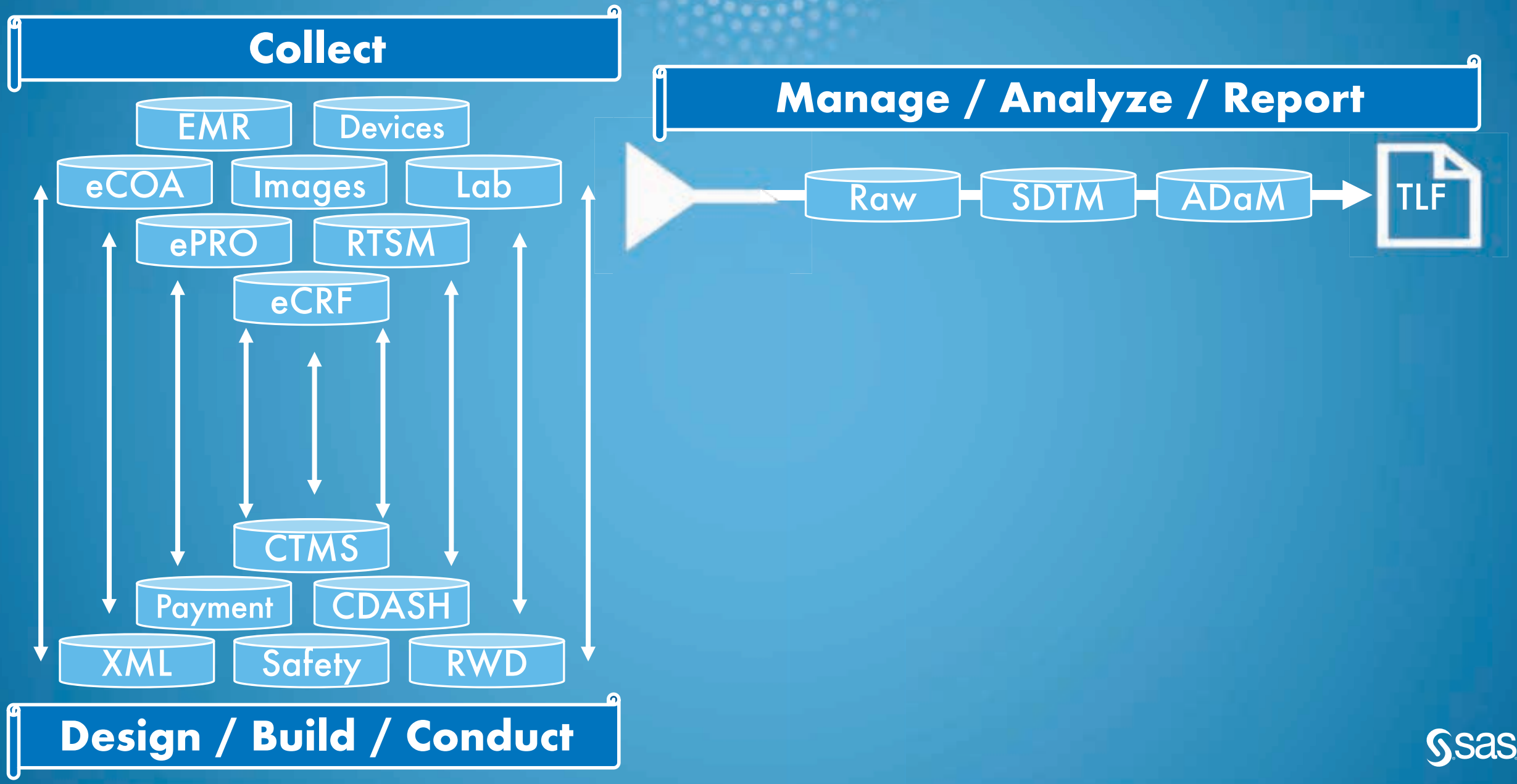
Agencies are encouraging innovative approaches as patients live, on average, over 2 hours from a research site (US data)

SUMMARY

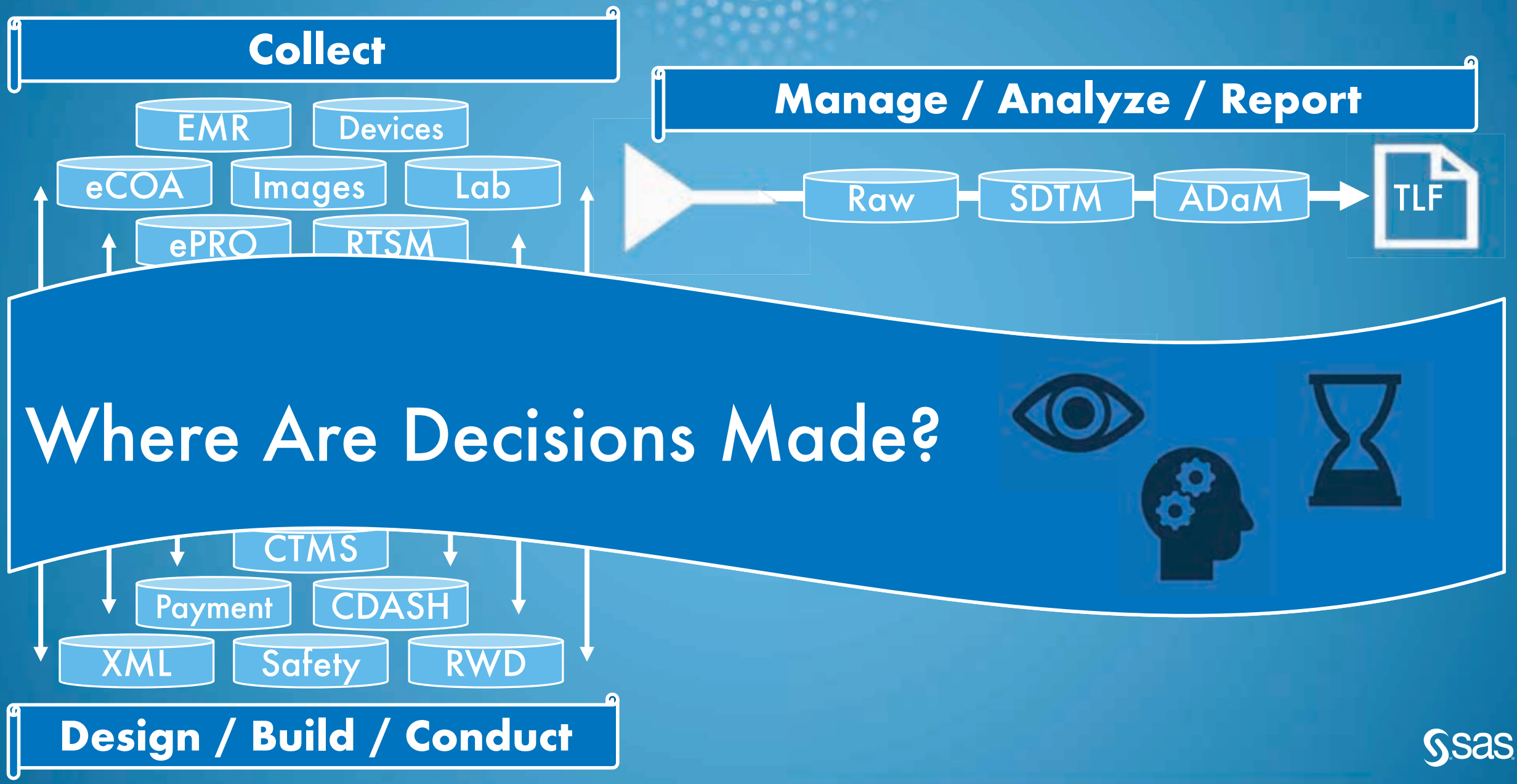
- Partnership across all of the project/program teams is critical
  - DM is poised to be the center of enabling an effective RBM strategy
- Tools, Technologies and Styles
  - Must look at how the data are collected (both from a source standpoint and method chosen (traditional sites, virtual study, etc)
  - What does that mean to the collective RBM approach and the techniques provided based on the tools/style selected?

Technology should enable workflow by connecting systems and analytical methods

Goal: Automating Decisions



Goal: Automating Decisions



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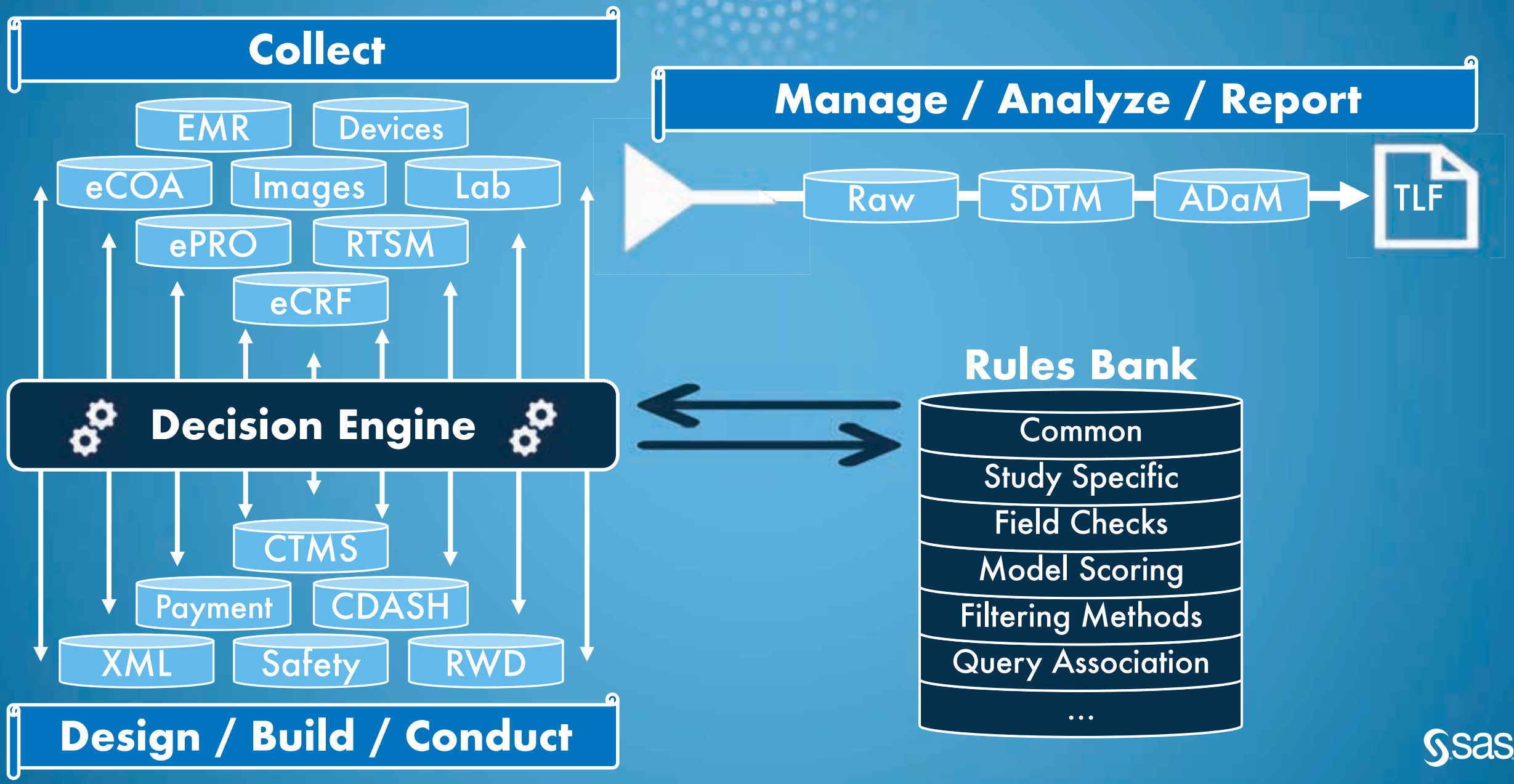
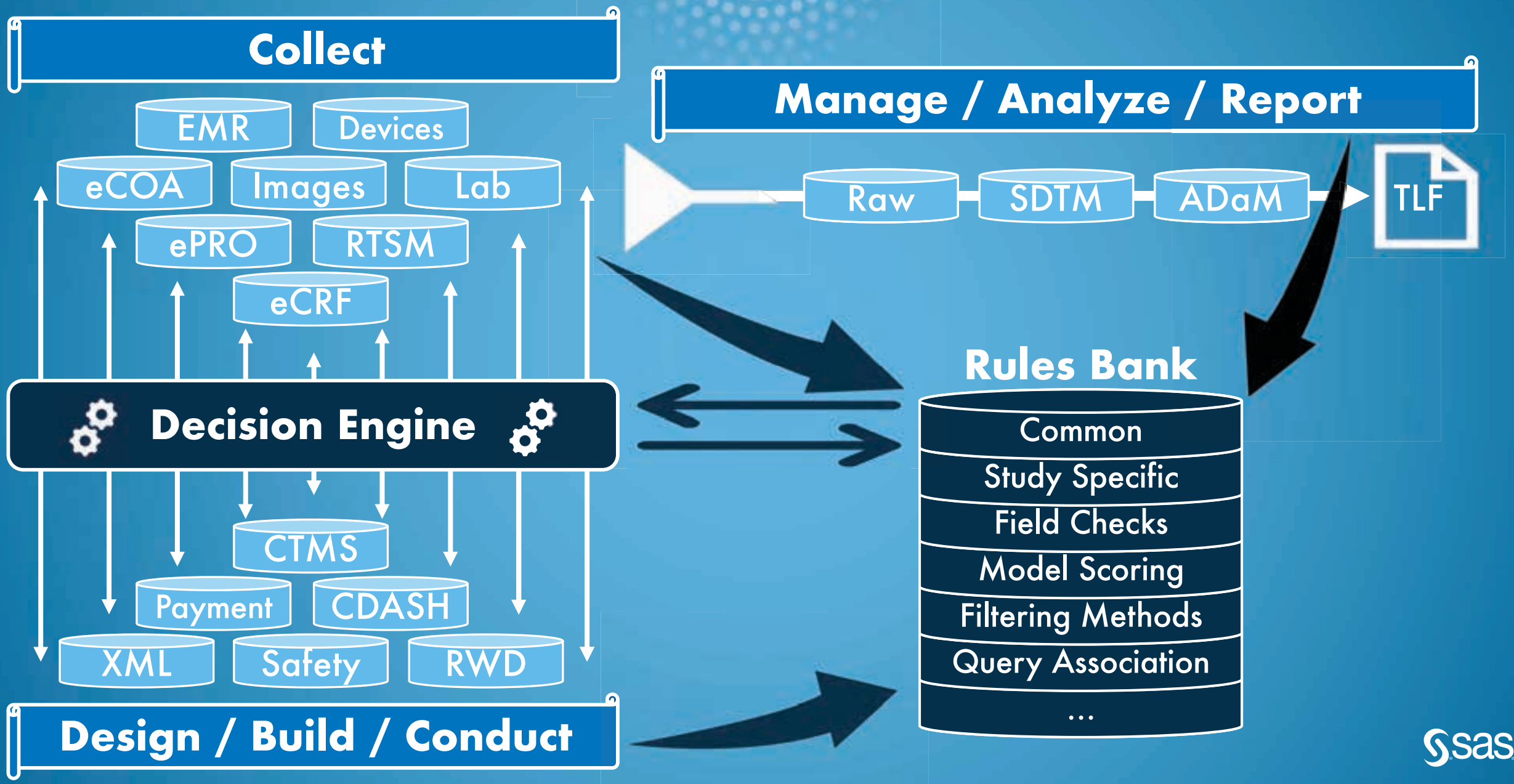
Goal: Automating Decisions



Goal: Automating Decisions



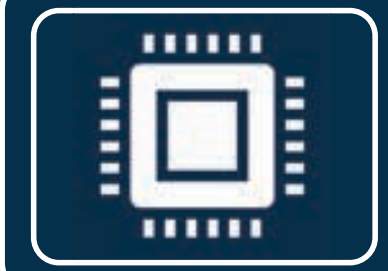
Goal: Automating Decisions

Rules Bank

- Common
- Study Specific
- Field Checks
- Model Scoring
- Filtering Methods
- Query Association
- …

Checks: Translate business knowledge to *if-then-else* rules.

Query Association: Take previous query logic and detect new entries that may also match.



Filtering Methods: Bayesian Filters for more dynamic field level edit checks. Use RWD to build priors for trial cohort (Inclusion/Exclusion).

Models: Machine Learning Techniques for anomaly detection like Isolation Forest, Support Vector Data Description, Moving Windows PCA, Clustering techniques.

Thank You!

Mike Henderson
SAS Healthcare and Life Sciences Customer Advisory Leader

Mike.Henderson@sas.com

https://www.linkedin.com/in/statmike/

https://www.statmike.com (Slides to be posted)

https://www.github.com/statmike

Session 4: Identifying Enablers to Support Implementation of Risk-Based Monitoring Approaches

TransCelerate BIOPHARMA INC.

Enablers for RBM Success

Reb Tayyabkhan
July 2019

Key Points

- It all starts at the beginning
  - RACT and associated Plans
  - The Big "M"…not the small "m"
- SDV should not be a driver for Site Monitoring
- We all play a role in educating the broader ecosystem on RBM principles

TransCelerate Member Survey To Understand SDV Trends

*Question sent in May 2019 via email to RBM Team Members**

Survey Question: Do you place any criteria on your CRO partners regarding level of SDV required for trials they conduct on your behalf? Yes or No? If yes, please elaborate.

We are looking to understand whether you provide specific SDV requirements to your CRO partners, or, do you leave SDV levels to them, or does it depend on variables such as trial phase, sites used for the trial, therapeutic areas, etc.? It is not necessary to provide all the details, but general explanatory comments or examples are fine.

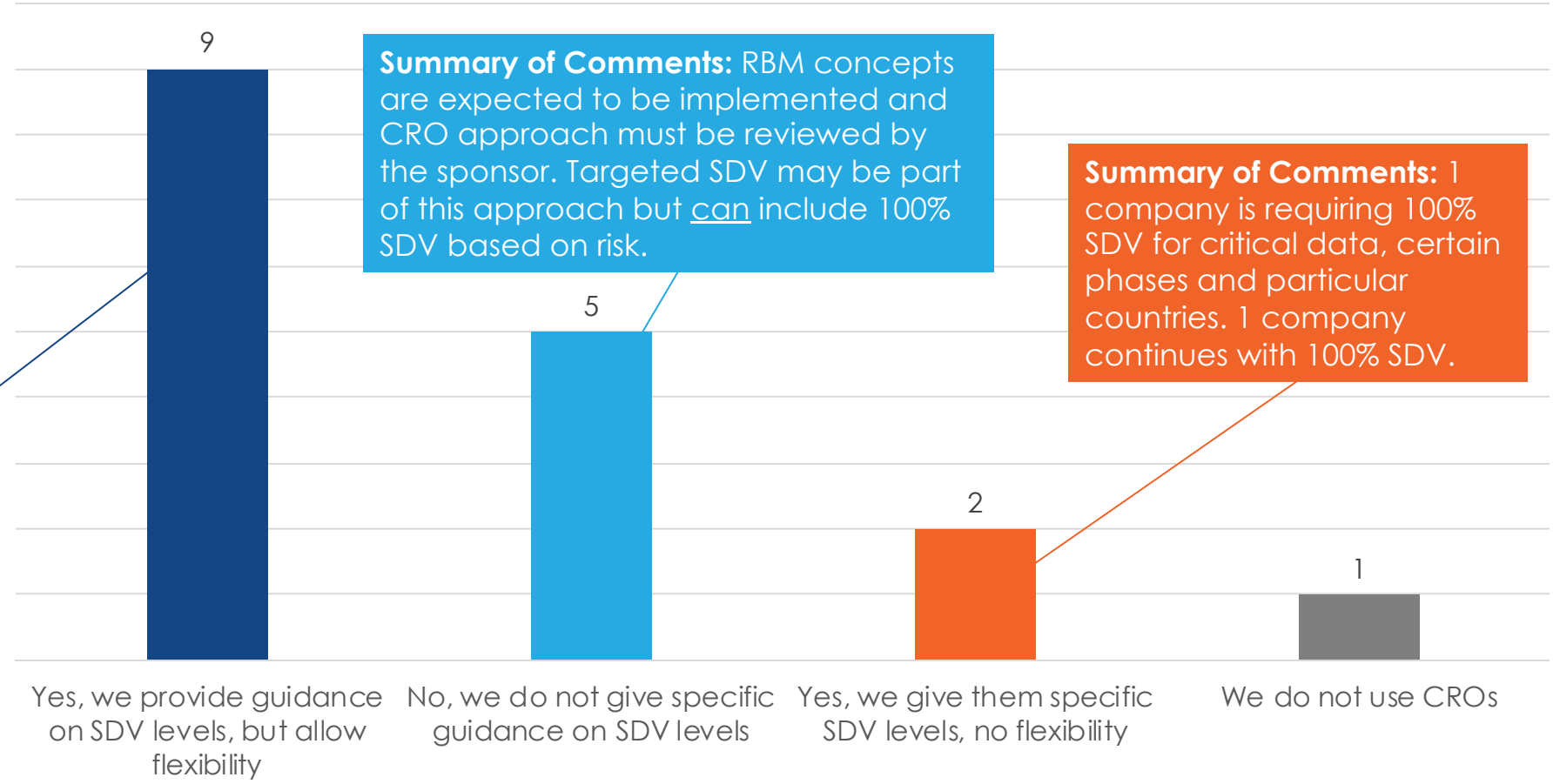
*TransCelerate membership is composed of **20 sponsor companies.** Of those member companies, **18 are currently represented on the Risk Based Monitoring (RBM) Team. 17 individual member companies** responded to this survey.

TransCelerate Member Survey To Understand SDV Trends

Summary of Responses to Survey Question

n=17

Member Company Responses, Aggregated



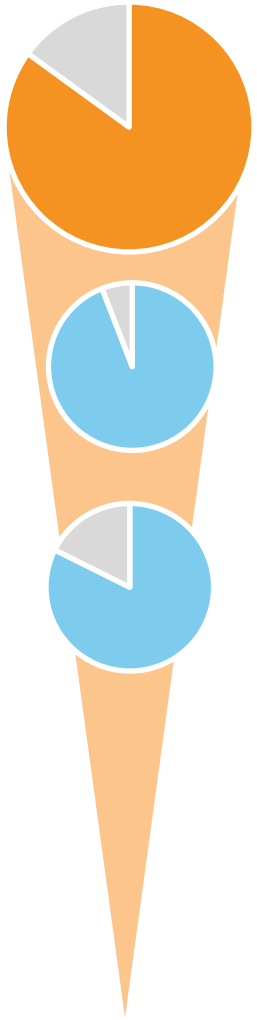
Summary of Comments: Some level of guidance is given to CROs on SDV levels. For example, targeted SDV is performed for critical data points related to safety, risk and quality. However, there are consistently study-specific discussions to agree on monitoring plans.

Summary of Comments: RBM concepts are expected to be implemented and CRO approach must be reviewed by the sponsor. Targeted SDV may be part of this approach but can include 100% SDV based on risk.

Summary of Comments: 1 company is requiring 100% SDV for critical data, certain phases and particular countries. 1 company continues with 100% SDV.

TransCelerate Member Survey To Understand SDV Trends

Summary of Themes



85% RESPONSE RATE

17 of 20 member companies responded

Of those, 94% indicated that 100% SDV of all data points is not required of their CRO partners. 6% (1 company) does require it.

82% indicated that they either do not provide specific guidance on SDV levels or allow for some level of flexibility. For example, targeted SDV, which may include 100% SDV of some data points, is performed for critical data points related to safety, risk and quality. Others ask their CRO partners to simply follow RBM methodology.

In general, member companies appear to be supporting flexibility for CROs in RBM implementation. Additional work may be needed to more fully understand CRO challenges to full implementation.

IMPROVING THE IMPLEMENTATION OF RISK-BASED MONITORING APPROACHES OF CLINICAL INVESTIGATIONS

17 July 2019

Marriott Marquis • Washington DC

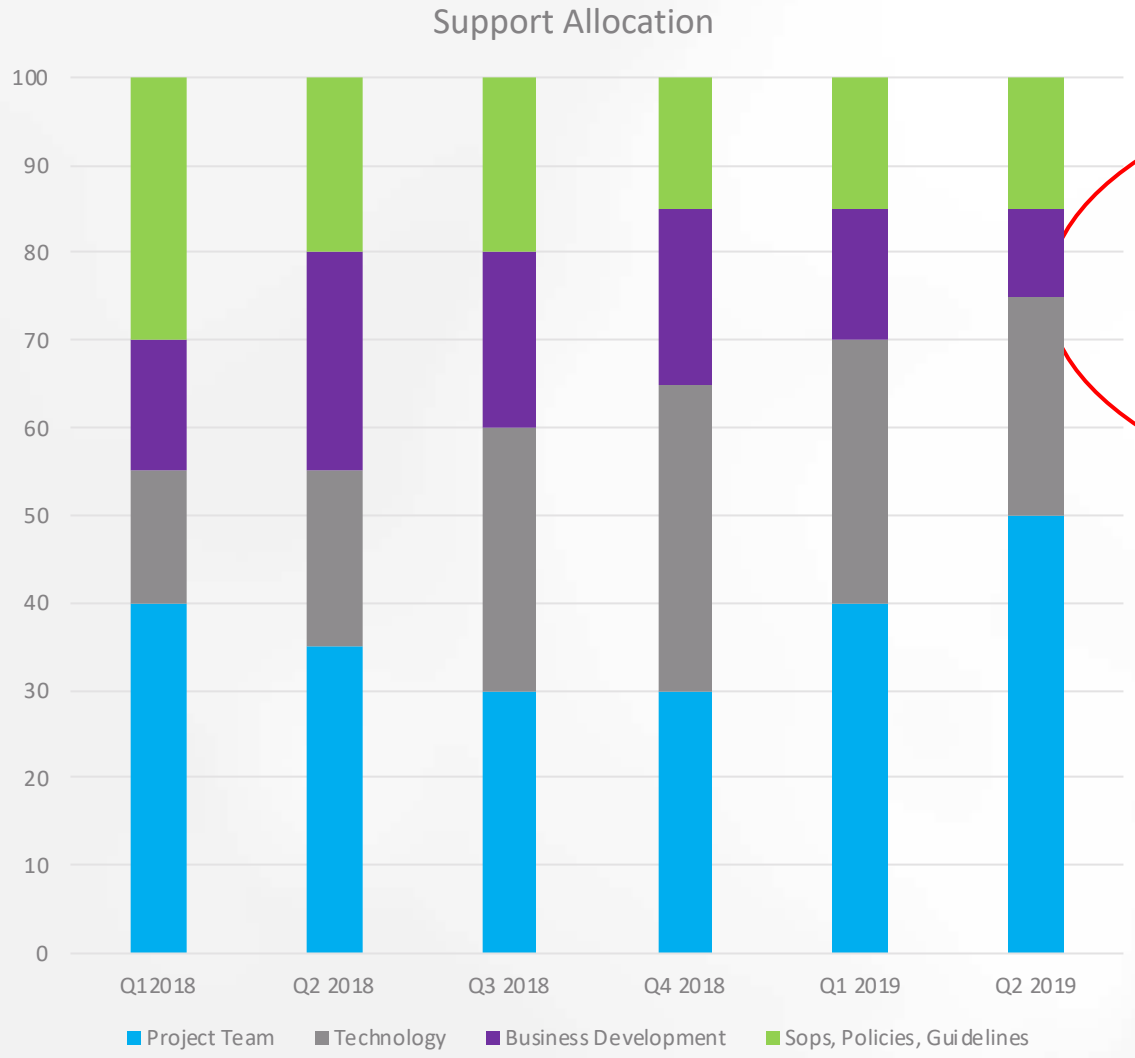
Rosanne Petros, Merck, Panel 4

- What factors influence the successful uptake and implementation of RBM?
  - Acknowledgement that RBM is an adaptive, integrated/holistic methodology (not just site monitoring) from program start to program end
  - Destigmatize perceptions of risk and risk = bad
- How can organizations apply change management best practices when adopting RBM?
  - It is not a single assessment, but a continuous improvement concept applied throughout the clinical program and trials
- How, and under what circumstances, might approaches to RBM vary? When is centralized RBM appropriate?
  - With RBM we are tailoring monitoring to match risks, rather that use blanket monitoring no matter the type of risk we are facing.
  - Study design and risk factors should dictate the use of different monitoring techniques (Central Monitoring as a better way to spot certain risks)

- What are the challenges of implementing risk-based monitoring in multi-national trials?
  - Some countries less experienced with trials/GCP place a lot of reliance on monitors to do quality control
  - Regulatory requirements sometimes differ globally which precludes having one RBM global development program
- Are there remaining challenges to implementing RBM fully within organizations? If so, what resources are needed to overcome these challenges?
  - RBM implementation faces challenges with regards to modification of old ways of working, conflict with existing workload of study teams, breaking organizational silos and need for diverse expertise limited on the job market
- What is FDA's role in supporting the implementation of RBM
  - More clarity on the implementation of RBM to encourage Sponsors to find innovative ways in conducting clinical trials.
  - Regulators should accept that RBM is still evolving and there will be differences among Sponsors in terms of RBM process.

Factors that Influence the Uptake of RBM

Support Effort Cannot be Under-Estimated



- **Support (PM)**
  - iQRMP
  - Risk definition
  - Client presentation/ discussion on Risk Management
  - Attending meetings for PM related activities
  - Determining Thresholds / Developing Analytics
  - Assisting with UAT
  - Team Review Cycles
  - Adjustments / Questions after Go Live
- **Support (Technology)**
  - Supporting AD PM 044 document
  - Learning functionality of Technology
  - Technology Testing for new releases
- **Business Development**
  - Prepare and Discuss Pre-Award RACT with Team
  - Bid Defense Team Prep
  - Presentations / Meetings with client pre-award
- **SOPs, Policies, Guidelines**
  - **Initial SOPs**
  - **Initial Policies**
  - **Guidelines / Guidances - updates**

Challenges

- Risk is complex
  - Learning as we go / changing as we Learn
  - Project Team: steep learning curve
- Changes to EDC database
- Managing Client requests for updates
- Working from Draft protocol
- Distractions
  - Vendor data, capabilities, and quality issues
    - Unexpected requirements
    - Inconsistent transfers
    - Out of window transfers

Change Management Needed
RBx Adoption Campaign and Training

- Goal is to create a baseline awareness with specific attention to groups who must implement it immediately on their studies or speak to this strategy at bid defense meetings
- Following the ADKAR Methodology:
  - Awareness
  - Desire
  - Knowledge
  - Ability
  - Reinforcement
- All departments/functions addressed through 1 or more of the following 4 sections depending on role:
  - Identify Risks – What? Who? How?
  - Monitor Risks – Who? How? When?
  - Take Action – Who? How?
  - Track Resolution – Who? How?

- RACT workshops conducted
  - Business Development
  - Business Unit Leadership
  - Central Monitors
  - Project Management
- Monthly Central Monitor Technology Updates
- TechnologyTraining
  - Data Managers
  - Sponsor Staff
  - Data Requirements

RBQM – A Very Simple Idea …

Quality

Study Design

Quality by Design

- Patient and Site-Centricity
- Remove non-core procedures
- Well-thought out study design

Risk

Study Planning

Risk Mitigation Planning

- Critical Processes & Data
- Risk Assessment
- Risk Control

Monitoring

Study Execution

Targeted Quality Management

- Central Monitoring
- Remote Monitoring
- On-Site Monitoring

Think

Act

CluePoints

Keep it Simple …

- Risk Assessment and Mitigation Planning
  - Critical Thinking vs. Box Checking
- Centralized Risk Monitoring
  - Quality over Quantity
  - Key Tools: Statistical Data Monitoring, KRIs, QTLs
  - Effective Risk Triage
- Site Monitoring
  - Targeted – focus on what matters most
  - SDV vs. SDR?

Organizing for Success …

- Risk Assessment and Mitigation Planning
  - Risk Facilitator
  - Cross-functional study team experts
- Centralized Risk Monitoring
  - Central Monitors (Data Analysts)
  - Risk Coordinator
  - Cross-functional study team experts
- Site Monitoring
  - Focus on critical thinking

Session 5: Measuring the Impact of Risk-Based Monitoring Approaches

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Measuring The Impact Of Risk Based Monitoring:

The PAST, PRESENT & FUTURE of RBM METRICS

Justin Stark, Novartis
Innovation Director, Global Development Operations

TransCelerate's Initiatives deliver practical solutions to overcome inefficiencies in research & development

OUR MISSION:

Collaborate across the global biopharmaceutical R&D community to identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high-quality delivery of new medicines

HARMONIZE PROCESS AND SHARE INFORMATION

- Clinical Data Standards
- Common Protocol Template
- Common Statistical Analysis Plan Template
- Comparator Network
- DataCelerate™
- eSource
- Digital Data Flow
- Placebo Standard of Care
- Toxicology Data Sharing
- Common Clinical SAE
- Modernization of Statistical Analysis
- Data Standards

IMPROVE THE PATIENT AND SITE EXPERIENCE

- Clinical Research Access and Information Exchange
  - Common Registry Data Packet
- Clinical Research Awareness
- eConsent
- eLabels
- Investigator Registry
- Patient Experience
- Patient Technology
- Site Qualification and Training
- Shared Investigator Platform

ENHANCE SPONSOR EFFICIENCIES & DRUG SAFETY

- Advancing Safety Analytics
- Clinical Data Transparency
- Data Monitoring Committee
- Intelligent Automation Opportunities in Pharmacovigilance
- Interpretation of Guidance and Regulations
- Protocol Deviations
- Quality Management System
- Risk-Based Monitoring
- Value of Safety Information Data Sources

TransCelerate's 5 original initiatives

The Reach of our Global Membership is Expanding

Membership is available to biopharmaceutical research and development organizations that engage in innovative discovery, development and manufacturing of new medicines*.

There are
over
1,000
people
from Member Companies that design and develop TransCelerate solutions.

* to be eligible for membership, companies must meet specified eligibility criteria.

Timeline of Risk Based Monitoring Initiative

- 8 Methodology Framework Papers
- Multiple Supporting Tools and Resources for Industry Use
- **TransCelerate collects, anonymizes and aggregates RBM metrics data from member companies. Implementation increases most significantly from 2015-2016.**

2012
TransCelerate forms. One of its first initiatives is Risk Based Monitoring, in response to FDA guidance.

- Focus on Facilitating Awareness, Adoption and Best Practice Sharing
- Ongoing High Visibility Engagements across Industry (Healthcare Authorities, Conferences, Site Advocacy Groups, Contract Research Organizations)
- **Perception is that RBM is improving quality and efficiency, however quantifying the magnitude of improvement remains challenging**

2019
TransCelerate Metrics Survey. 18 member companies are invited to participate in an anonymous survey to better understand how the value of RBM implementation is defined and assessed.

2020 on …
Risk Based Monitoring continues to evolve. Multiple factors including ICH E6, E8 revisions, evolving quality management systems, and technology advances have the potential to impact Risk Based Monitoring

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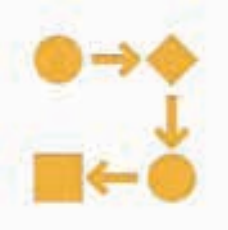
Collecting RBM Data Quarterly | Methods

- **Data was collected from participating member companies quarterly from 2013-2017, resulting in >1000 observations.**
- **Guided by a defined set of RBM metrics, member companies voluntarily reported data to TransCelerate on clinical trials where they were implementing RBM.**
- **Member companies were asked to rate change over time for each metric as "better," "worse" or "about the same" (as compared to each company's internal baseline expectation).**
- **Data was blinded, aggregated and reported by TransCelerate each quarter.**

METRICS
Average number of major/critical audit findings
Percentage of unreported, confirmed SAEs as compared to total SAEs as discovered through any method
Number of Significant Protocol Deviations
Average Monitoring (all types) cost per site
Average interval between on-site monitoring visits per site
Median number of days from issue open to close
Median number of days from patient visit to eCRF data entry
Median number of days from query open to close



In 2018 & 2019, we have further aggregated the data to analyze risk based monitoring trends and produce cumulative observations.

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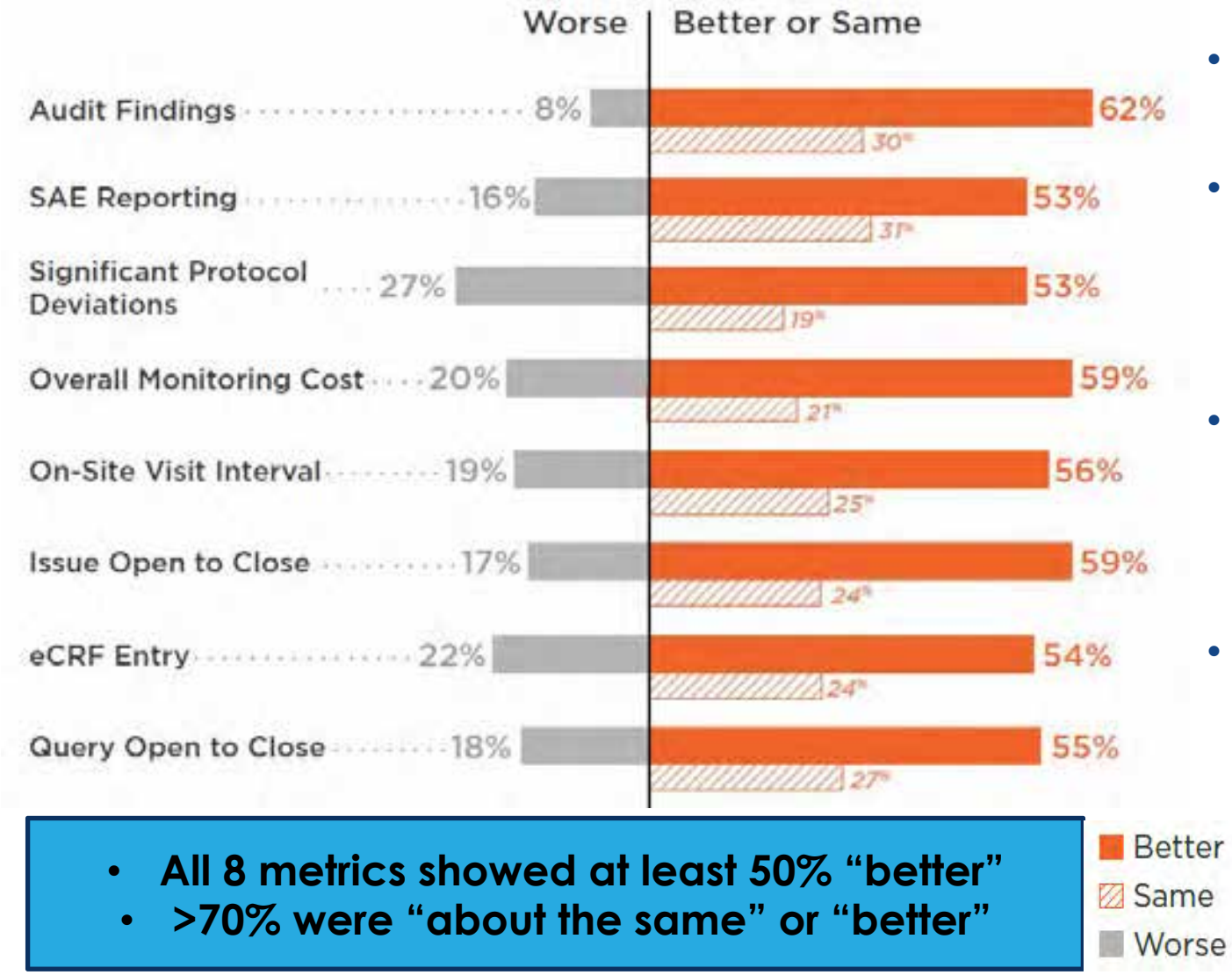
Cumulative Data Observations (Relative %)



- **All 8 metrics showed at least 50% "better"**
- **>70% were "about the same" or "better"**

- **Audit Findings:** Quality appears to increase in more mature studies.
- **SAE Reporting:** Early on in studies, there appears to be an initial rise in SAE reporting, but as the study progress, SAE reporting appears to improve, overall.
- **Significant Protocol Deviations:** Compliance appears to improve during the study; however, data becomes too limited in later maturities to prove this.
- **Overall Monitoring Cost & On-Site Visit Interval:** Cost and On-site Visit Intervals are highly correlated.

Issue Open to Close, eCRF Data Entry, Query Open to Close: Those implementing took care to focus on data flow, recognizing it is critical to success.

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Understanding Current State | What do RBM metrics look like today?

2019

RBM Metrics Survey

of Member Companies

(n=18)

Objectives:

(1) analyze current use of the original metrics

(2) assess how benefits of RBM are currently measured

(3) determine whether new metrics have been developed by members to further define the value of RBM

Results:

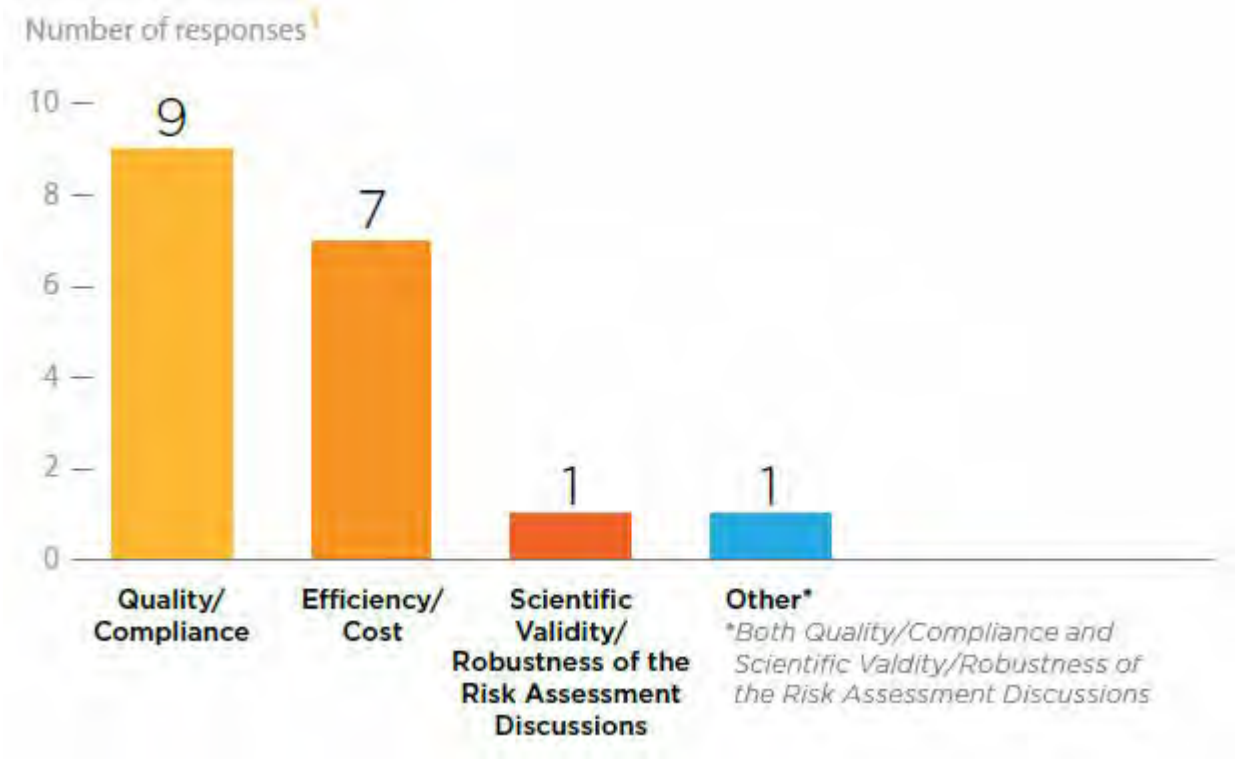
(1) Interpretation of experiences of member companies

(2) Not "one-size-fits-all"

Understanding Current State

2019 Member Company Survey Results

Key Decision Drivers Behind RBM Adoption



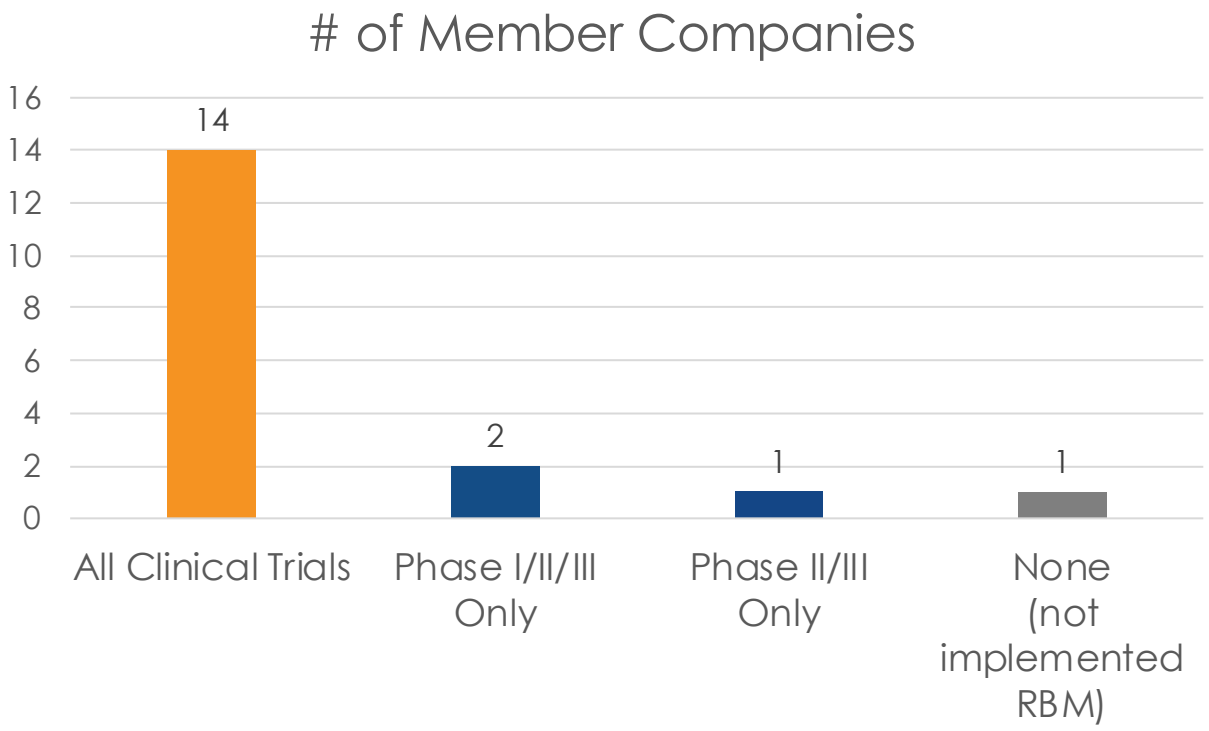
Both Quality/Compliance and Efficiency/Cost are primary drivers for implementing an RBM model.

[1] Participants could select only 1 response

Understanding Current State

2019 Member Company Survey Results

Types of Trials in Scope of RBM

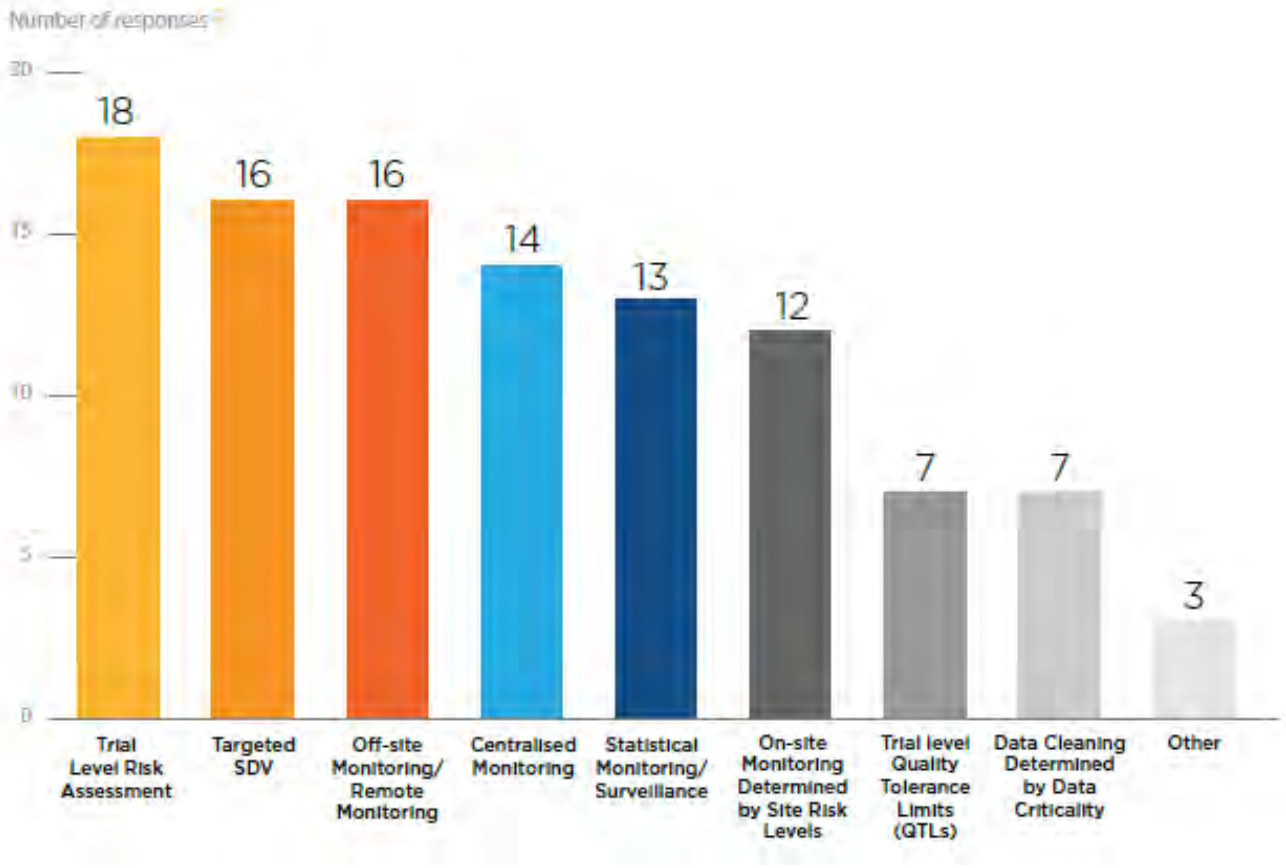


- Implementation of RBM is now seen across **all phases of Interventional Clinical Trials**.
- 14 companies report utilizing RBM in all phases of their studies currently. The others have taken various, staggered approaches.
- Member companies approaches to implementation have evolved over time to expand to current state.

Understanding Current State

2019 Member Company Survey Results

Components Implemented with RBM



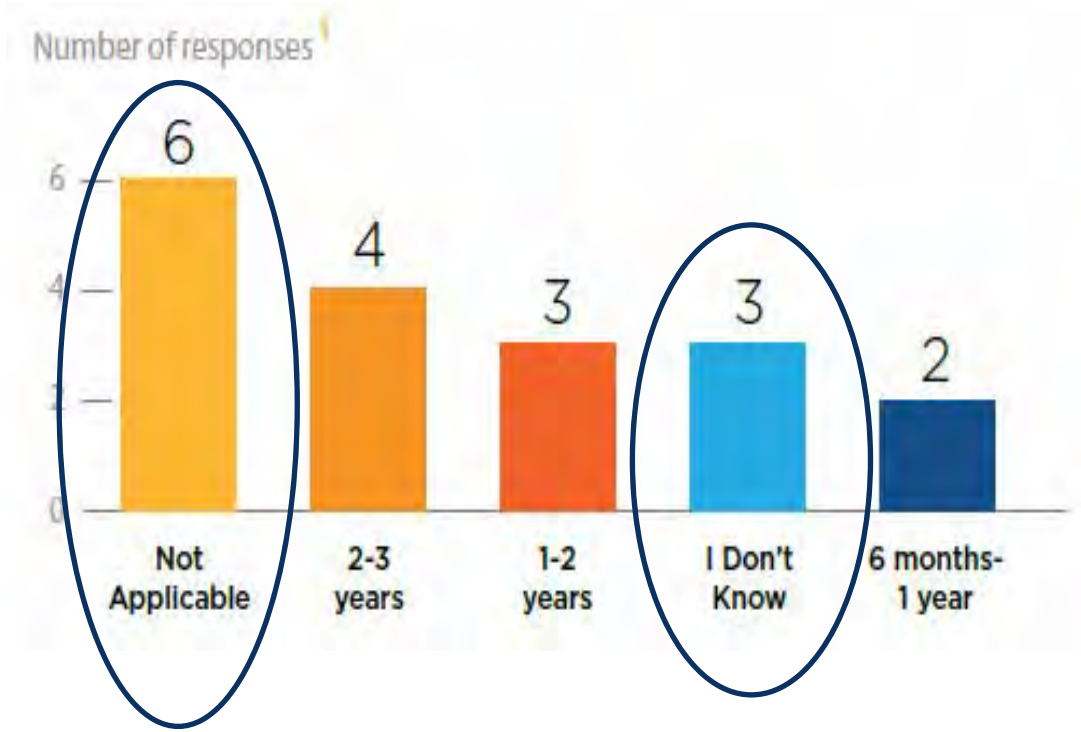
- **Risk assessments, reduced Site Data Verification (SDV) and a more remote approach to analysis and monitoring** are the major components consistently seen across companies who have adopted a RBM model.
- The original focus areas of the TransCelerate RBM model (e.g., **site focused**) appear to be well-established.
- The risk-based approach appears to be **spreading to other, related areas** (e.g. data cleaning).

[2] Participants could select more than one response

Understanding Current State

2019 Member Company Survey Results

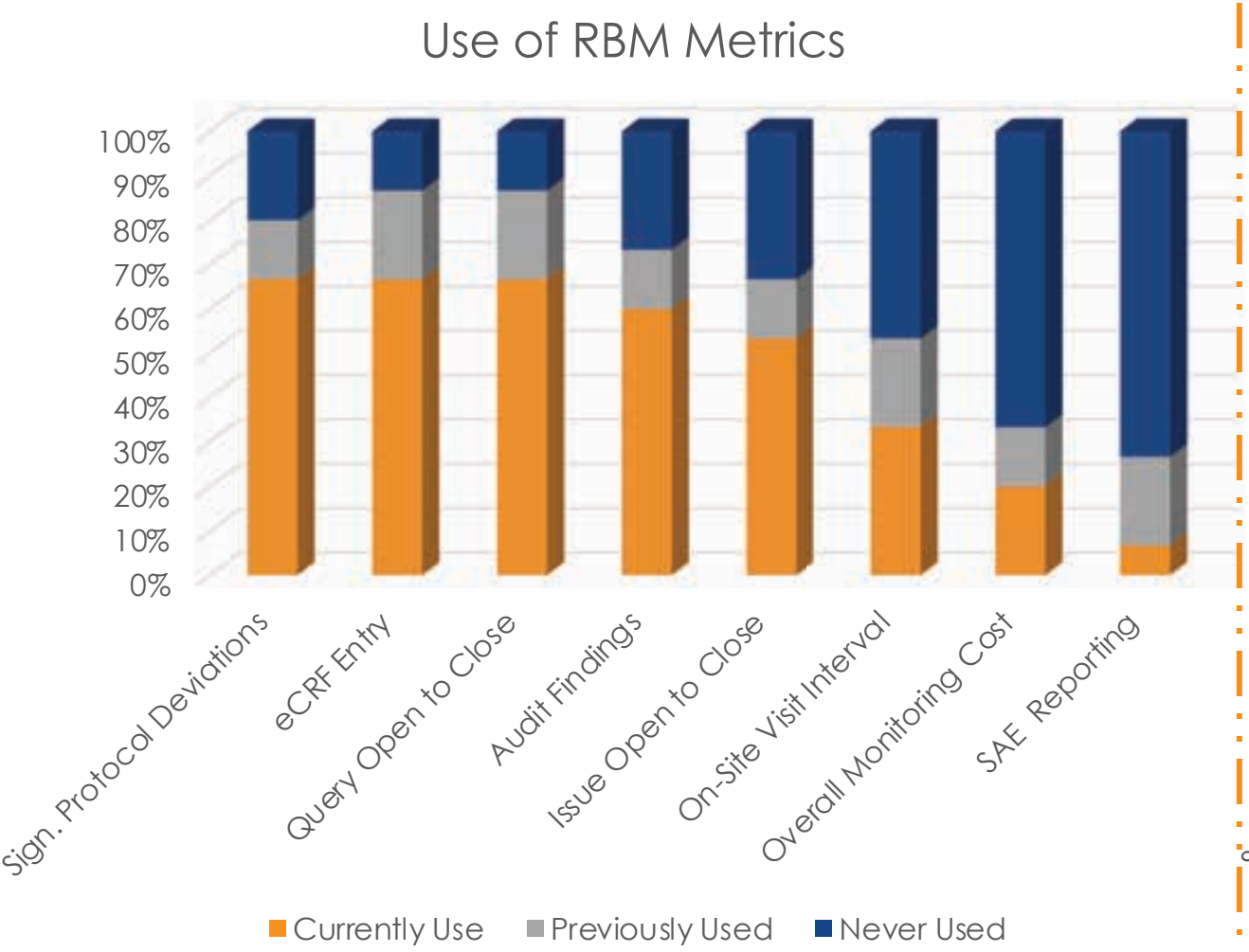
How long did it take to see/measure the impact(s) of RBM implementation?



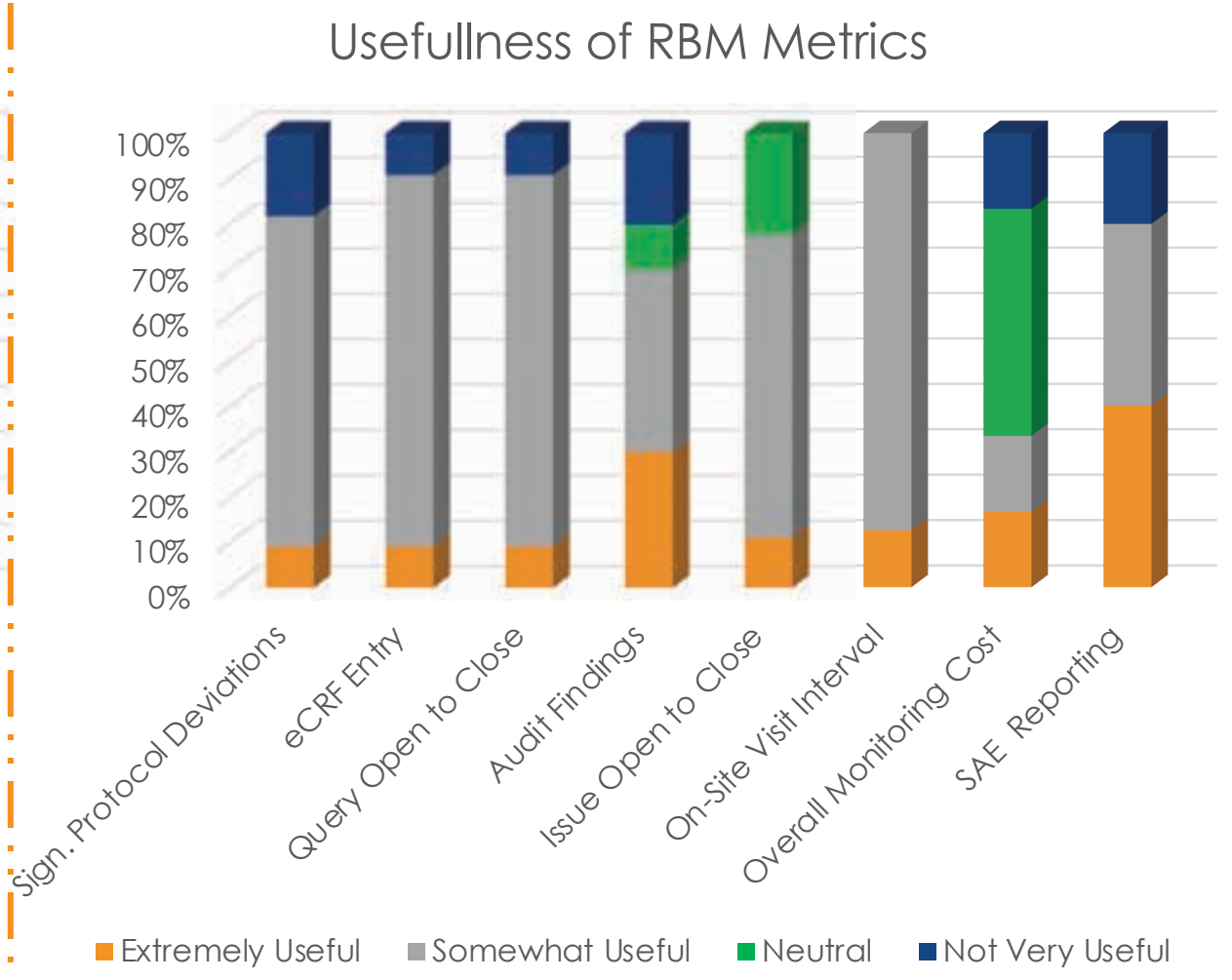
- Whilst it appears that RBM contributed positively to the development process **within 1-3 years of implementation**, few companies are tangibly measuring its direct impact through metric analysis, with many are still developing their metrics and collecting data.
- While quality is a key decision driver for implementation, **organizations struggle to measure quality directly** and note **significant change management efforts are necessary to support the process.**

[1] Participants could select only 1 response

Are the original metrics being used to evaluate the implementation of RBM?



Are the original metrics considered useful?



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KEY PERFORMANCE INDICATORS (KPIs)

Examples* of new/novel Key Performance Indicators for Risk Based Monitoring developed by member companies. The member companies also ranked the usefulness of these KPIs.

Rank	Process	Compliance	Data
Extremely Useful	• Time from data "cut" to Action • Ratio of on-site to off-site monitoring visits • SDR & SDV backlog • % queries resolved in 7 days • % pages submitted in 7 days	• Important Protocol Deviation Incidence	• Missed Assessments • Dosing Deviation Incidence
Somewhat Useful	• Reports for centralised monitoring - user statistics to indicate frequency and duration of use • Ratio of Data correction XX days after initial data entry • RBM user satisfaction survey • Query rates • Qualitative interviews with HQ trial teams • Survey for use and usefulness of site risk indicator report	• TMF Compliance	• SAE/AE Rates • Query rate (per 1000 data points)
Neutral	• Action item aging • External data review status	• CAPAs close on time (site) • CAPA # overall • eTMF status • Ratio of number of AE emerging per subject	• Query aging • Ratio of number of AE emerging per subject
Not Very Useful	• On-site vs. remote visit ratio: Ratio calculated as number on-site to remote visits	• Ratio of Missing data for the primary endpoint	• Ratio of Missing data for the primary endpoint

Qualitative Indicator
Quantitative Indicator
Multiple responses

*These are the direct answers from survey respondents, we have not summarized, word-smithed, or tried to categorize them. Some information may be contradictory since it was submitted by different companies.

Risk Based Monitoring | How are companies evaluating value?

Selections from the 2019 Member Company Survey

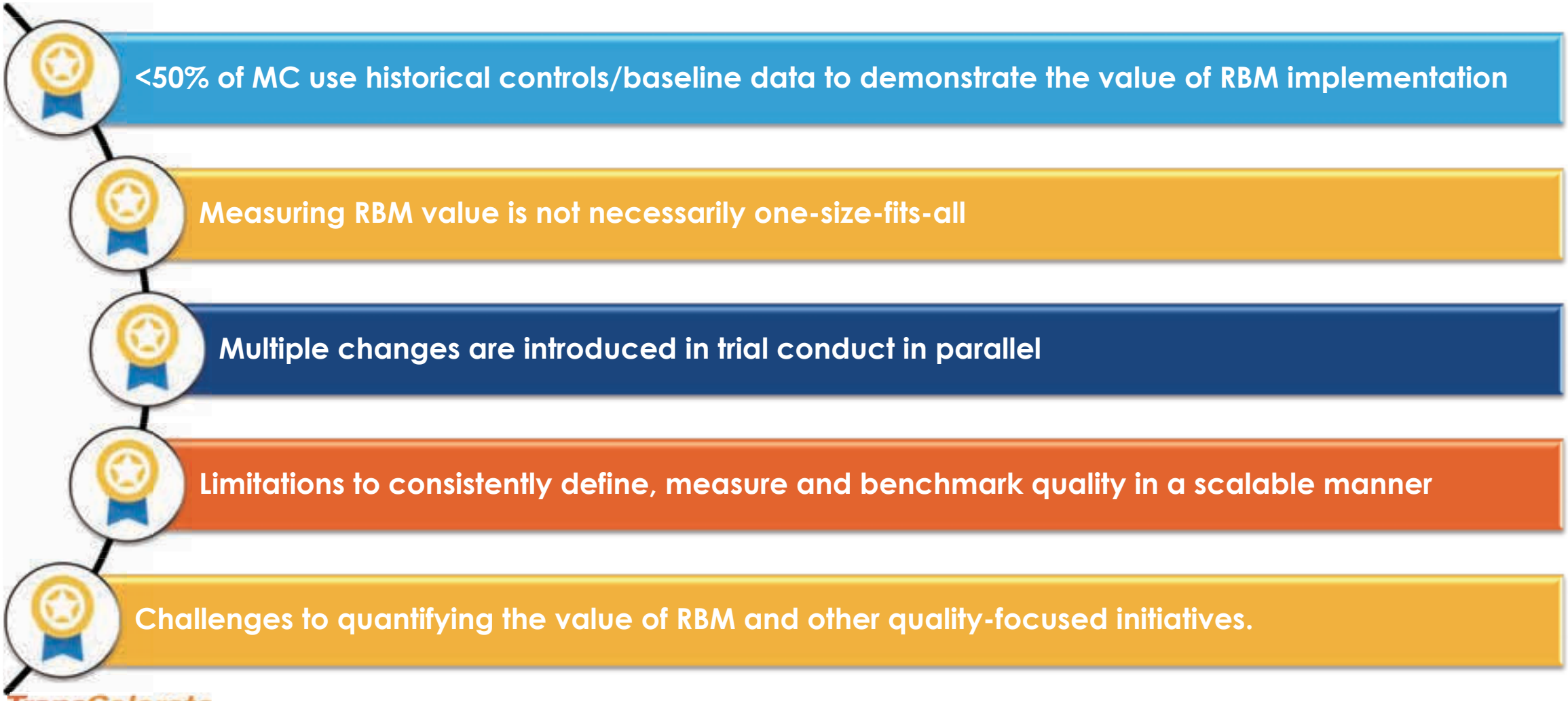
*"The benefit seen so far is…'**knowing data better**', more smooth data base lock etc".*

***"Information from the RBM model will feed into a broader, more complex risk management model** to determine what mitigation efforts provide the most value for the respected cost. We will attempt to standardize as much as possible so we can focus on the minimal trial specific risks that will greatly impact the trials."*

*"[The value of RBM] could be **value of the process, value of the people, and value of a tool.** This is likely both quantitative and qualitative with different value stories for the different audiences (study team, functions, leadership, sites, regulators)"*

*"Our biggest challenges going forward, as we evolve the model – **how do we objectively establish that the comparative quality of the trial data that is submitted in our filings is as good if not better**[?]."*

Current Challenges



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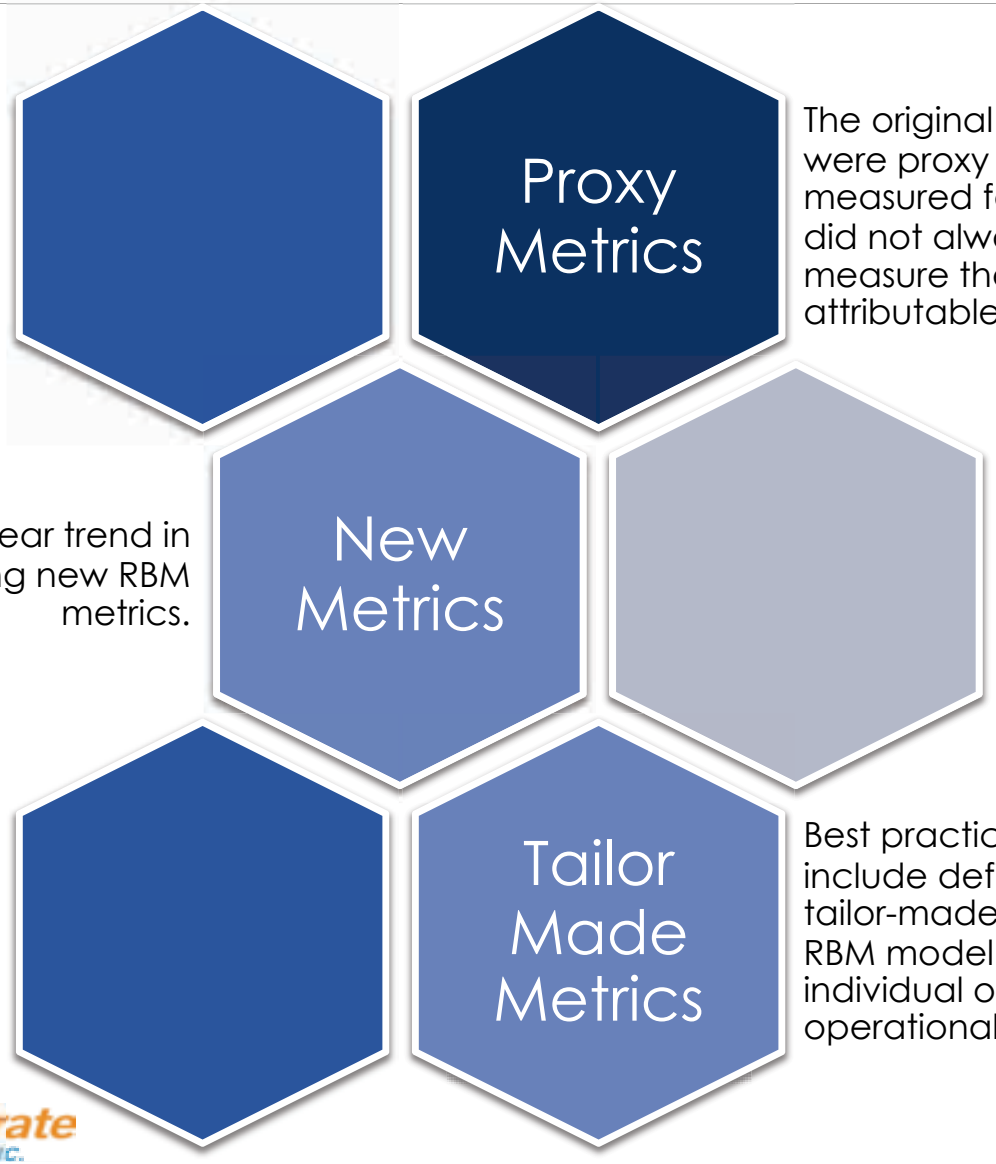
How Are RBM Metrics Evolving?



The original RBM metrics were proxy metrics that measured for quality but did not always directly measure the impact attributable to RBM

There is no clear trend in defining new RBM metrics.

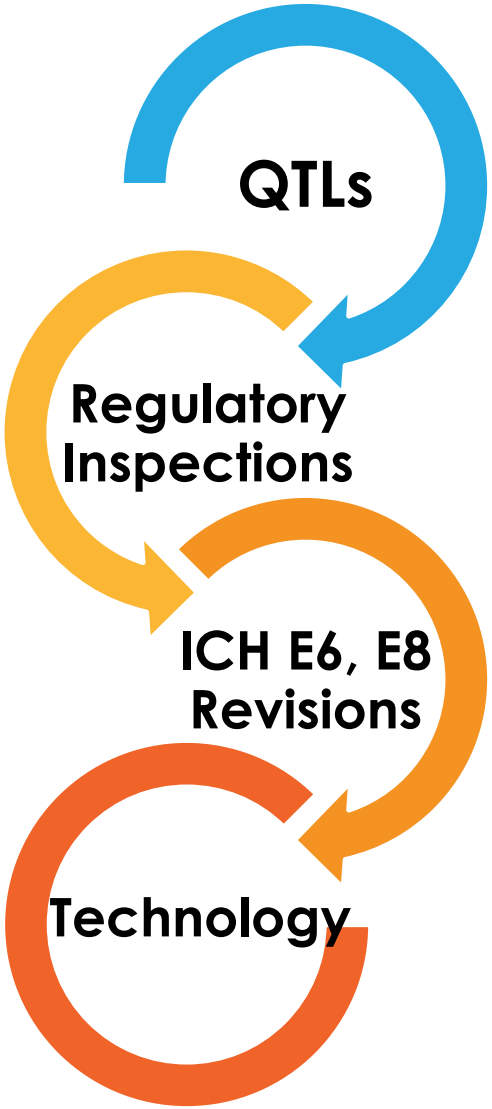
Best practices appear to include defining measures tailor-made to the chosen RBM model and the individual organization's operational design.

The art and science of measuring & demonstrating the benefits of RBM are still evolving

What's Next For Risk Based Monitoring Metrics?

Insight & experience needed

Continued industry communications to share learnings



Guidance needed

Continued evolution

Increasing levels of data intelligence & capability for feedback loops

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Thank you

For more information on the TransCelerate Risk Based Monitoring Initiative, visit us:
https://transceleratebiopharmainc.com/assets/rbm-assets/

For more information about TransCelerate, visit us:
www.TransCelerateBioPharmaInc.com

Watch our "About Us" Video

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Accelerate to Innovate

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TransCelerate BioPharma Inc.

LIMITATIONS

The authors acknowledge the following limitations to this work.

- Lack of a control group for comparison (Non-RBM studies) makes the interpretation of the data less complete. However, it should be noted that many member companies no longer have control groups, as risk based monitoring has been fully-embedded across clinical trial portfolios.

- Change over time was measured using a non-numerical assessment. Member companies assigned a value to each metric using "better, worse or about the same" as compared to each companies internal baseline expectation. This measurement does not allow for precise comparisons, as each member company defined relative values differently.

- This commentary is based on observed trends, as there is not sufficient data to draw robust conclusions. Quarterly data collection ended in 2016 and the number of trials reported with long maturities (greater than 1-2 years) is limited. However, the team has aggregated all data available to analyze potential trends and observations.

- Not all companies reported data each quarter. Over the course of the reporting periods, the number of companies reporting data ranged from 4 to 11.

METRICS AND EXPECTED/POTENTIAL OBSERVATIONS

The 8 original metrics below were developed in 2013 to measure the impact of RBM and guided the collection of data from member companies on a quarterly basis from 2013-2017.

METRIC Developed in 2013	Expected Observations	Potential / Alternative Observations
Average number of major/critical audit findings	• Average number of major/critical findings per audited site will decrease	• Audit findings may initially rise due to focus on critical data and processes
Percentage of unreported, confirmed SAEs as compared to total SAEs as discovered through any method	• Unreported, confirmed SAEs will decrease	• Percentage of unreported, confirmed SAE findings may rise initially due to shift in focus from SDV to SDR
Number of Significant Protocol Deviations	• Significant Protocol Deviations will decrease	• Significant protocol deviation findings may rise initially due to shift in focus from SDV to SDR
Average Monitoring (all types) cost per site	• Average monitoring costs will decrease	• Costs may remain flat until second quarter of analysis or later
Average interval between on-site monitoring visits per site	• Interval between on-site monitoring visits will increase	• Average interval between on-site monitoring visits may remain flat until second quarter of analysis or later
Median number of days from issue open to close	• Median number of days from issue open to close will decrease	• Findings initially may rise if issues management process is new to the organization
Median number of days from patient visit to eCRF data entry	• There are no expectations to improve the median number of days from patient visit to eCRF data entry	• The site may delay performing a crucial function that empowers central monitoring due to the potential decrease in on-site visits
Median number of days from query open to close	• There are no expectations to improve for the median number of days from query open to close	• The site may delay performing a crucial function due to the potential decrease in on-site visits

PAPERS and TOOLS

STATISTICAL MONITORING/SURVEILLANCE

- Statistical Monitoring in Clinical Trials: Best Practices for Detecting Data Anomalies Suggestive of Fabrication or Misconduct

CENTRALISED MONITORING

- Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's Approach, Part I
- Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's Approach, Part 2

OFF-SITE / REMOTE MONITORING

- See Table 2 in the RBM Methodology Position Paper

ON-SITE MONITORING DETERMINED BY SITE RISK LEVELS

- Site Level Risk Assessment Considerations

TRIAL LEVEL RISK ASSESSMENT

- TransCelerate Risk Assessment and Categorization Tool (RACT)

QUALITY TOLERANCE LIMITS

- Risk-Based Quality Management: Quality Tolerance Limits and Risk Reporting

Session 5: Measuring the Impact of Risk-Based Monitoring Approaches

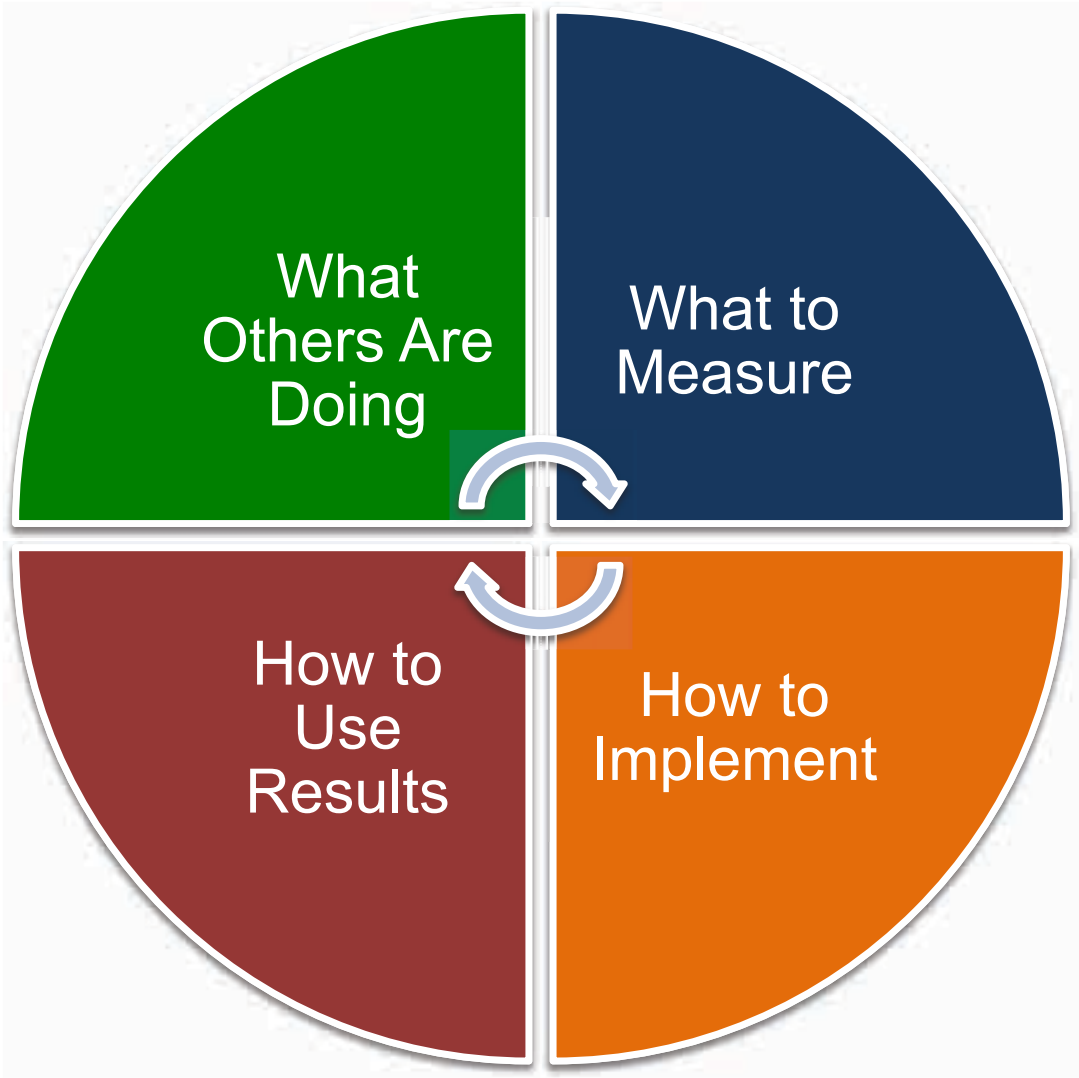
Measuring the Impact of Risk-Based Monitoring Approaches

Linda Sullivan, MBA
Co-Founder & Executive Director
lsullivan@metricschampion.org

www.metricschampion.org

MCC
Metrics Champion Consortium

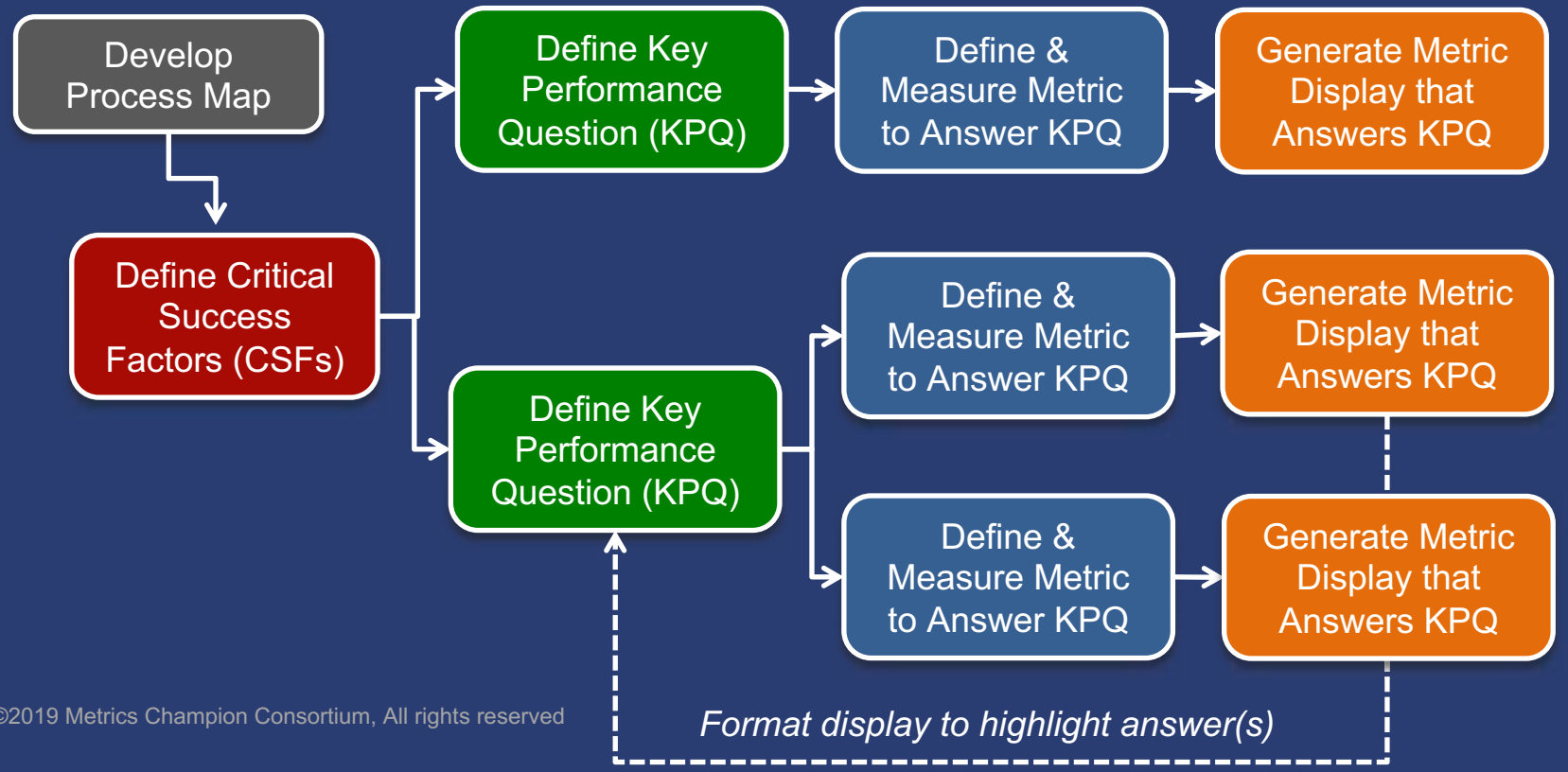
MCC's Clinical Trial Performance Management Approach



Metrics Champion Consortium

Measure What Matters Most – Metrics That Answer Important Questions

MCC Metric Development Framework



Risked-based Monitoring Pilot Success Factors

How do you decide if your pilot was successful enough to implement across programs?

It depends … how do you define success?

- ✓ Faster timelines?
- ✓ Cost savings?
- ✓ Quality improvement?
- ✓ Improved patient safety?
- ✓ Earlier issue detection?

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Risked-based Monitoring Pilot Success Factors

How do you decide if your pilot was successful enough to implement across programs?

It depends … what programs you implemented and why (what are you hoping will happen!)

If we do activity “X”, we should see the “Y” occur.
What happened?

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Risked-based Monitoring Pilot Success Factors

Key Performance Questions
Risk-based Quality Management (QbD, ICH-E6(R2) section 5.0)
Does implementation of new risk/quality management processes lengthen study start-up cycle time? Does the time decrease after teams get better at doing risk assessment and mitigation?
Does implementation of new risk/quality management processes improve subject retention in trials?
Does implementation of new risk/quality management processes reduce the number of non-substantial protocol amendments?
Does implementation of new risk/quality management processes reduce the time from LPLV to DB lock?

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Risked-based Monitoring Pilot Success Factors

Key Performance Questions
Risk-based Monitoring (centralized, remote, onsite monitoring)
Does implementation of Central Statistical Monitoring (CSM) reduce the number of non-evaluable patients?
Does implementation of CSM reduce the number of protocol deviations?
Does implementation of CSM reduce the number of data queries?
Does implementation of CSM identify “issues that matter” more quickly?

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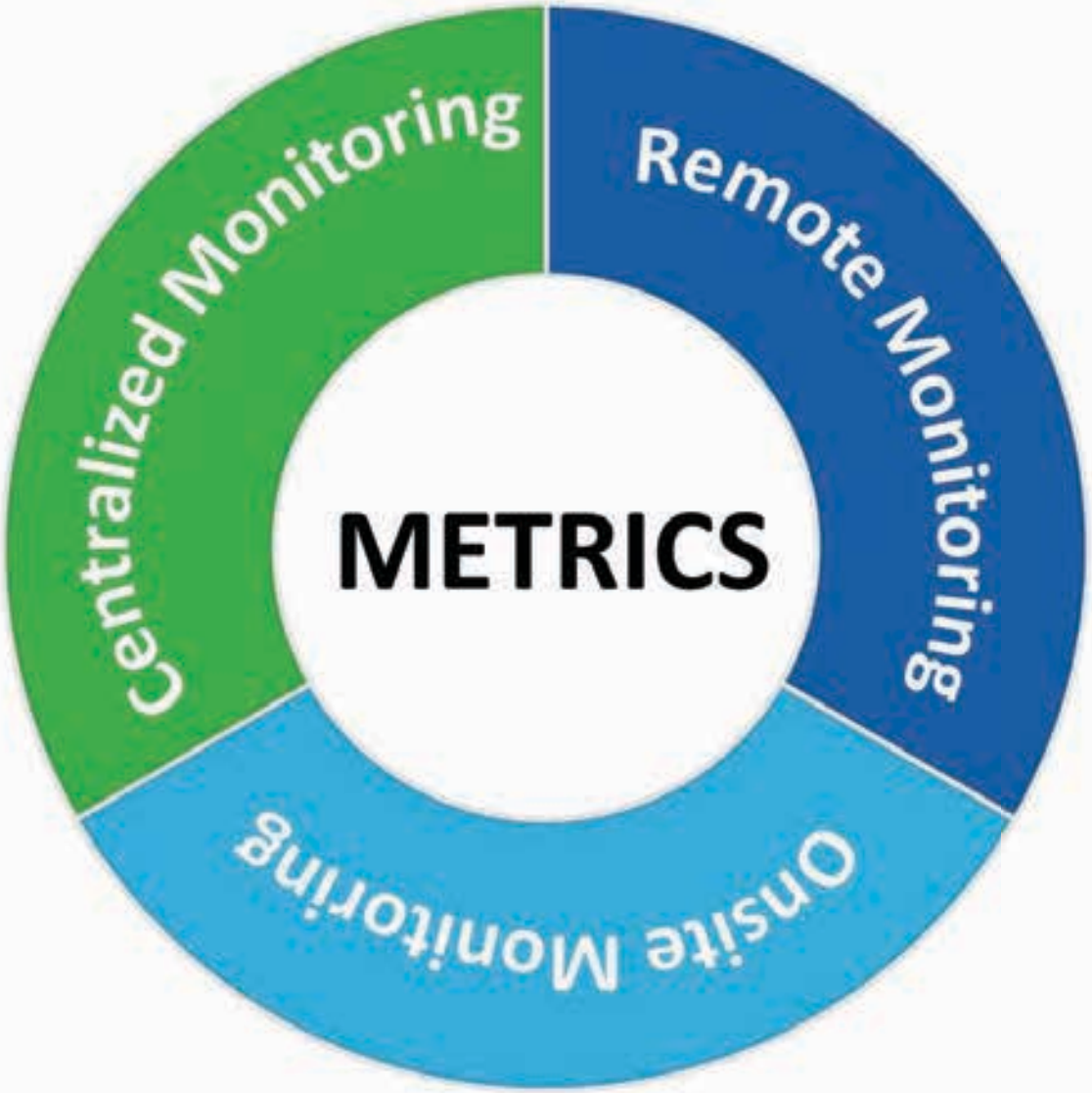
Risked-based Monitoring Pilot Success Factors

Key Performance Questions
Risk-based Monitoring (centralized, remote, onsite monitoring) – cont'd
Does implementation of Centralized Monitoring + Risk-based Onsite Monitoring enable you establish root cause of issues and put effective resolutions in place in earlier?
Does implementation of Centralized Monitoring + Risk-based Onsite Monitoring enable you reduce the cost of site monitoring?
Does implementation of Centralized Monitoring + Risk-based Onsite Monitoring enable you improve relationships with sites?
Does implementation of Centralized Monitoring + Risk-based Onsite Monitoring enable you to allocate onsite monitoring resources to high risk sites?

Defining How to Oversee/Manage RBM Processes!



MCC Metric Work Group begins October 2019

Visit www.metricschampion.org to learn more and take online ***Monitoring Process Metrics*** survey

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MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

Measuring RBM – TEMPER and other research

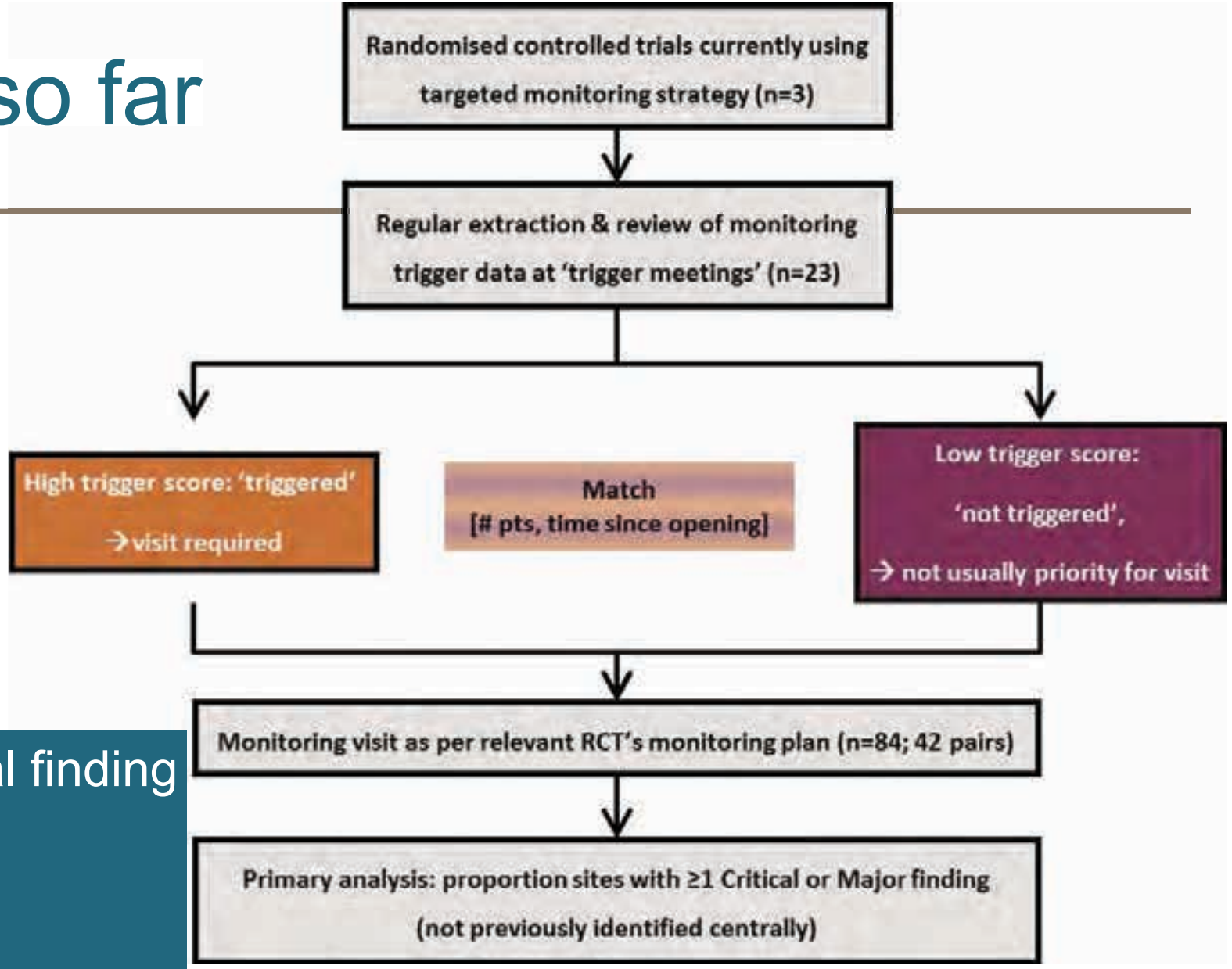
Sharon Love

MRC Clinical Trials Unit at UCL

17 July 2019

What is known so far

- Multiple SWATs
  - **TEMPER**



Site visits with ≥1 major or critical finding

High trigger score	69%
Low trigger score	45%

Difference 24% (95% CI 3%, 44%)

What is known so far

- Multiple SWATs (Study Within A Trial):
  - **TEMPER**
  - **ADAMON**
  - **OPTIMON**

→ Risk adapted monitoring was not inferior to extensive on-site monitoring

What is known so far

- Multiple SWATs (Study Within A Trial):
  - **TEMPER**
  - **ADAMON**
  - **OPTIMON**
  - **MONITORING** → 100% SDV little different to SDV of key scientific and regulatory data

What is known so far – results comparison

- Analysis comparison of triggered and 100%SDV
  - Catrin Tudur-Smith 2012, Phase III RCT multicentre advanced cancer
  - Andrew Embleton accepted 2019, Phase III Multicentre recurrent Ovarian cancer

What is known so far – results comparison

- Analysis comparison of triggered and 100%SDV
  - Catrin Tudur-Smith 2012, Phase III RCT multicentre advanced cancer
  - Andrew Embleton accepted 2019, Phase III Multicentre recurrent Ovarian cancer

Negligible difference in primary analysis results

What is known so far – potential triggers

- 8 suggested triggers (metrics) from a Delphi survey of 211 completers and 2 expert committees

Whitham et al. Trials (2018) 19:557
https://doi.org/10.1186/s13063-018-2940-9

Trials

RESEARCH Open Access

Development of a standardised set of metrics for monitoring site performance in multicentre randomised trials: a Delphi study

Diane Whitham[1], Julie Turzanski[1], Lucy Bradshaw[1], Mike Clarke[2], Lucy Culliford[3], Lelia Duley[1], Lisa Shaw[4],

What is known so far – potential triggers

- 8 suggested triggers (metrics) from a Delphi survey
  - Recruitment and retention
  - Data quality
  - Protocol compliance

What is known so far – potential triggers

- 8 suggested triggers (metrics) from a Delphi survey
  - Recruitment and retention
  - Data quality
  - Protocol compliance
- TRANSCELERATE triggers in 8 areas
  - 3 above plus safety, drug compliance, on-site workload, essential documents, staffing/supplies

What is known so far - summary

- Triggers work
- Risk-based monitoring is not inferior to 100%SDV
- Risk-based monitoring maintains primary conclusions

Research needed - how to do RBM

- Do triggers work?
- What are the best set of triggers to use and at which point in the trial?
- What outcome measure should we use for assessing if our monitoring is good enough?

Research needed - summary

Guidance underpinned by an evidence base

MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

THANK YOU

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References

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Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations

Session 5
Measuring the Impact of Risk-Based Monitoring Approaches

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Disclaimer

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Points of Consideration (1)

- RBM Benefits
  - RBM is a continuous improvement effort
  - Risk-based approaches should focus on how critical data are generated, and where, how, and why error is introduced in its lifecycle that reduces the value of that data (Critical data / processes, human subject safety, compliance)
  - Enhanced trial first-time to quality regarding minimization of errors that matter
    - Means reduced rework
      - Means reduced cost and time overruns
    - Avoiding risk, cost
      - Can be challenging to measure

Points of Consideration (2)

- RBM Impact Metrics – What to Measure
  - BMS have used these TransCelerate metrics
    - Normalized major/critical audit findings / site
    - Patient visit to data entry
    - Monitoring visit interval
    - Monitoring cost / site

    } All lagging indicators
  - Above measures good to engage stakeholders / senior leaders
  - Consider adding leading indicators
    - Risk assessment quality measure

Points of Consideration (3)

- RBM Impact Metrics - Challenges
  - Organizational RBM maturity
  - Monitoring techniques
    - How an organization
      - Interprets FDA Guidance, ICH E6, TransCelerate artifacts in their culture
      - Defines and implements RBM
    - Execution strategy – fully in-house vs. fully outsourced vs. hybrid
  - Monitoring processes
    - Data quality – systems available to effectively measure
    - Process quality – harder to effectively measure
      - Repeatability, Reproducibility
      - Measure and control process inputs to produce higher quality outputs

Points of Consideration (4)

- RBM Impact Metrics - Challenges
  - Direct controlled comparisons
    - Many influencing factors in trial conduct make this challenging
    - Therapeutic area
    - Trial phase
    - Technology
      - Applied to both RBM and non-RBM trials equivalently?