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RISK-BASED MONITORING: AFTER YEARS OF TALKING ABOUT IT, WHERE ARE WE NOW?

Ross Rothmeier,
Vice President, Technology Solutions and Innovation Labs
Medidata Solutions

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Presentation Topics

- What is essential to meet ICH standards?
- What are the technology requirements for a scalable RBM solution?
- How can we tackle the challenges of RBM implementation?
- How can we work across strategic partnerships?

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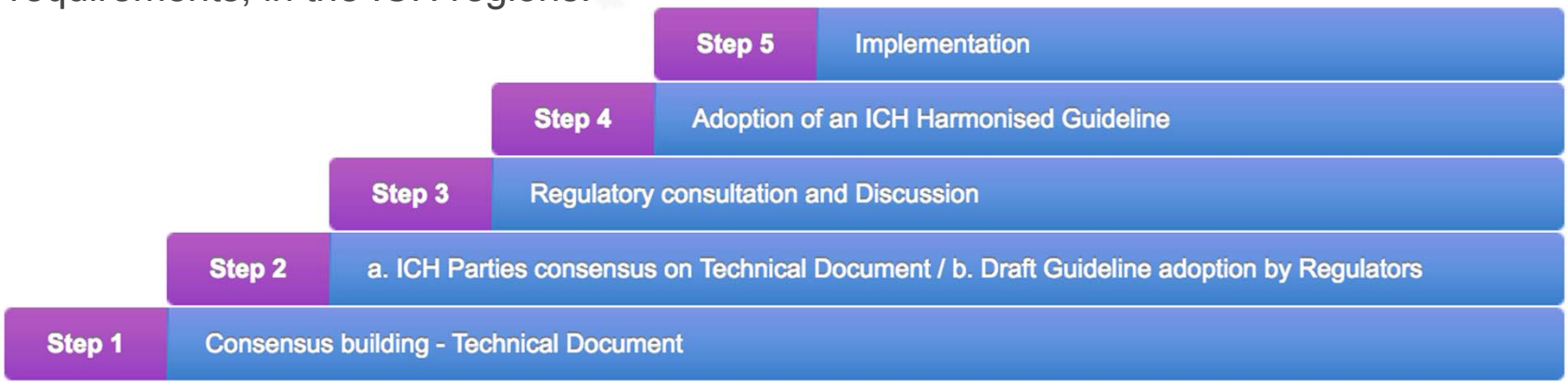
Formal ICH Procedure - ICH E6 (R2)

http://www.ich.org/products/process-of-harmonisation

Step 5: Implementation

Having reached Step 4, the harmonised Guideline ***moves immediately*** to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the ICH regions.



Completion Date	Deliverable
June 2015	*Step 1* Technical Document
June 2015	*Step 2a* Technical Document
June 2015	*Step 2b* Draft Guideline
June 2016	*Step 3* Expert draft Guideline
November 2016	*Step 4* Final Guideline

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Is Centralized Monitoring Mandatory?

- ICH E6 (R2) draft
  ADDENDUM of 5.18.3 Extent and Nature of Monitoring
  - The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. … A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).
  - Centralized monitoring is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.

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New ICH Risk Assessment Requirements?

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to assure human subject protection and the reliability of study results.

5.0.2 Risk Identification

Risks to critical study processes and data should be identified. Risks should be considered at both the system level (e.g., facilities, standard operating procedures, computerized systems, personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording).

5.0.3 Risk Evaluation

The identified risks should be evaluated by considering:

(a) The likelihood of errors occurring, given existing risk controls.

(b) The impact of such errors on human subject protection and data integrity.

(c) The extent to which such errors would be detectable.

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Methods of Centralized Monitoring Mentioned in ICH E6 (R2) draft 5.18.3 ADDENDUM

Methods	Data, Docs and/or Systems Related
(a) Routine review of submitted data.	EDC, eSource, TMF docs
(b) Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems.	EDC, eSource
(c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites.	EDC, eSource, Analytics
(d) Analyzing site characteristics and performance metrics.	EDC, eSource, CTMS, eTMF
(e) Selection of sites and/or processes for targeted on-site monitoring.	RACT/IQRMP, KRIs, Analytics, CTMS

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Biggest Challenges with Implementing RBM

Cost to Implement & Scale

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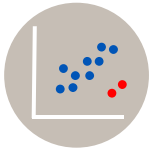
Org Change Management

Aversion to Increased "Risk"

Number of New Solutions

Advanced Statistical Methodology



Strategic Partnerships

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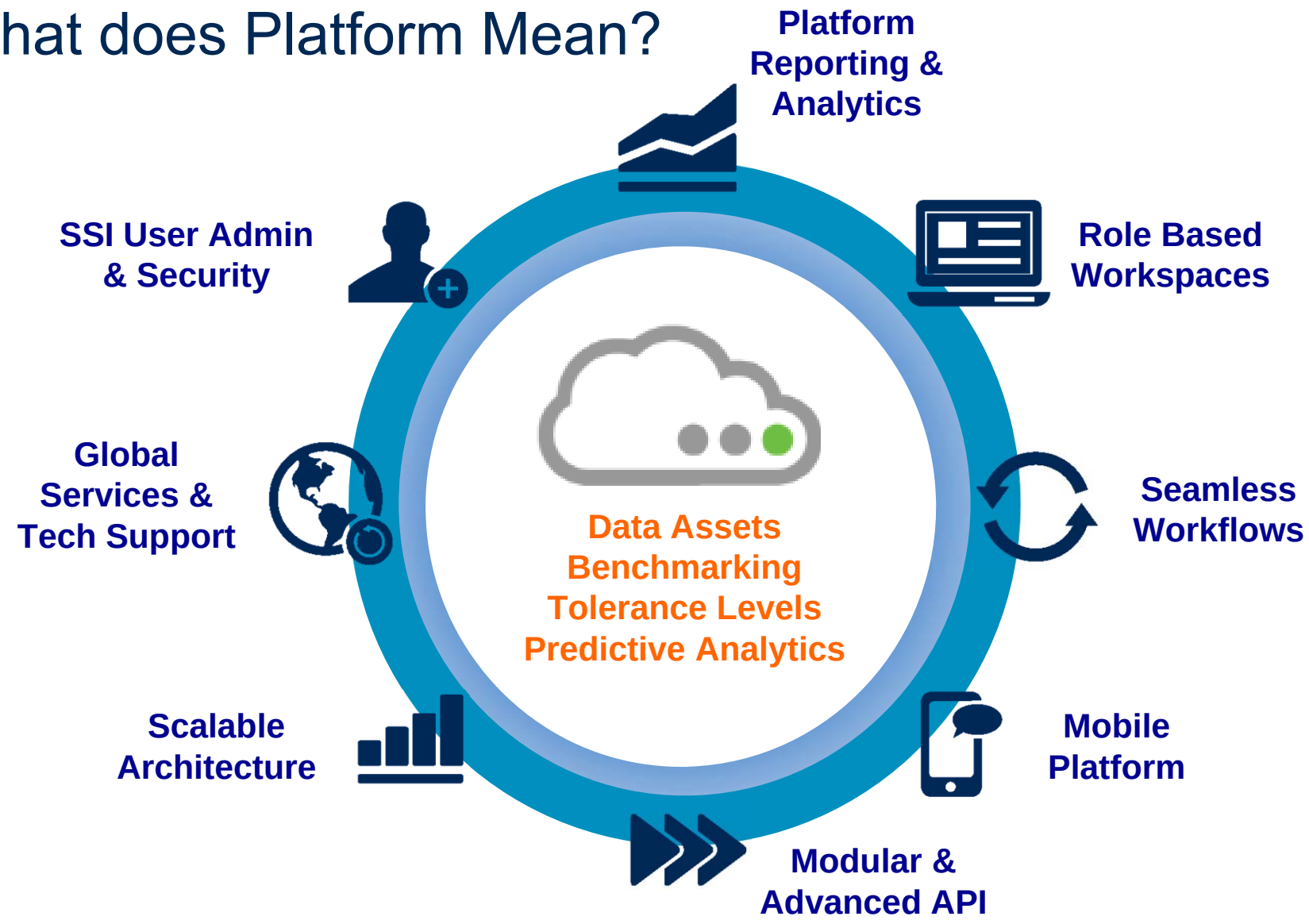
What does Platform Mean?



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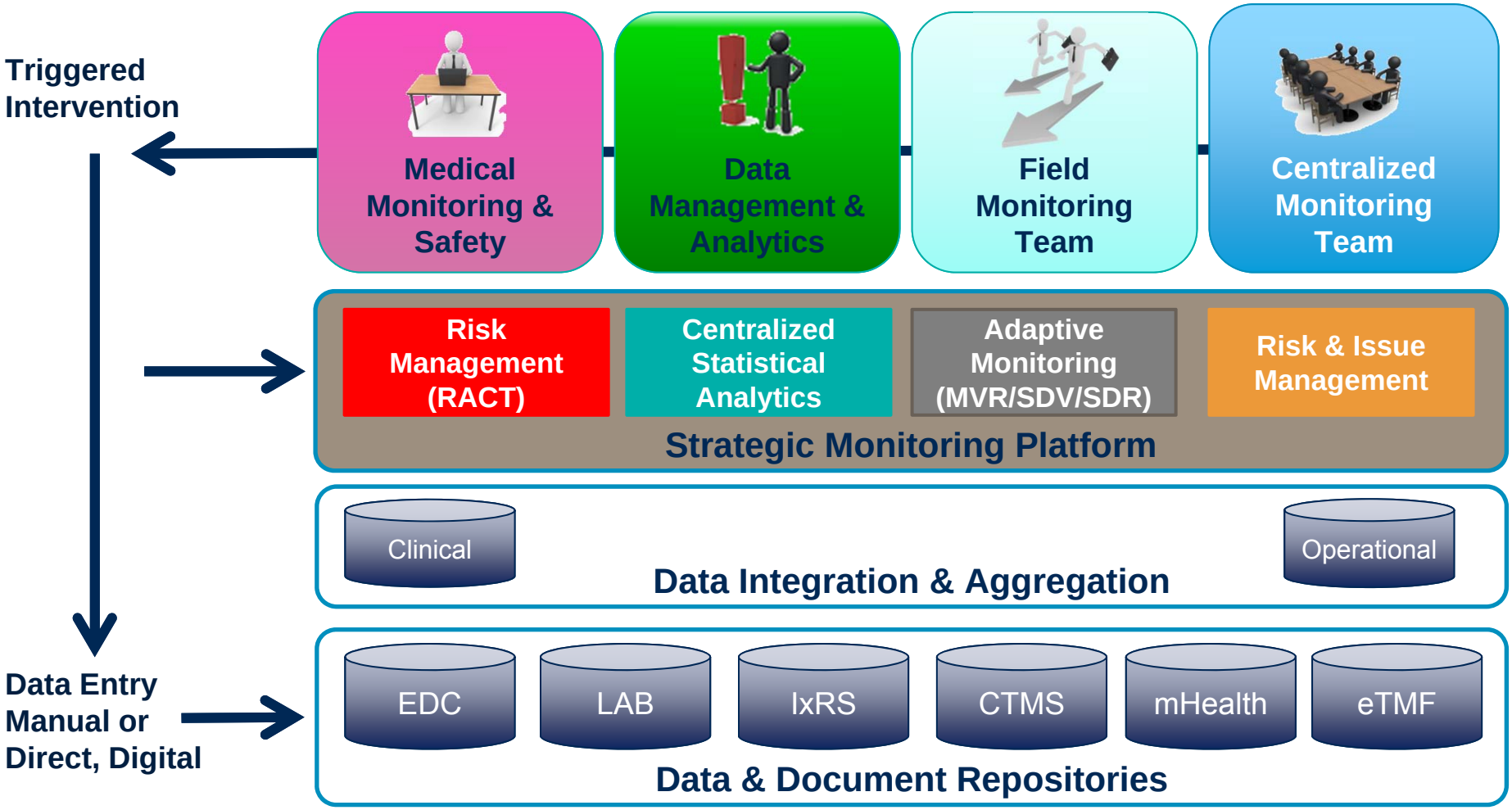
Technology Requirements for Platform RBM



Based on TransCelerate Risk-Based Monitoring Technology Considerations - Part 2 (issued Dec 2015)

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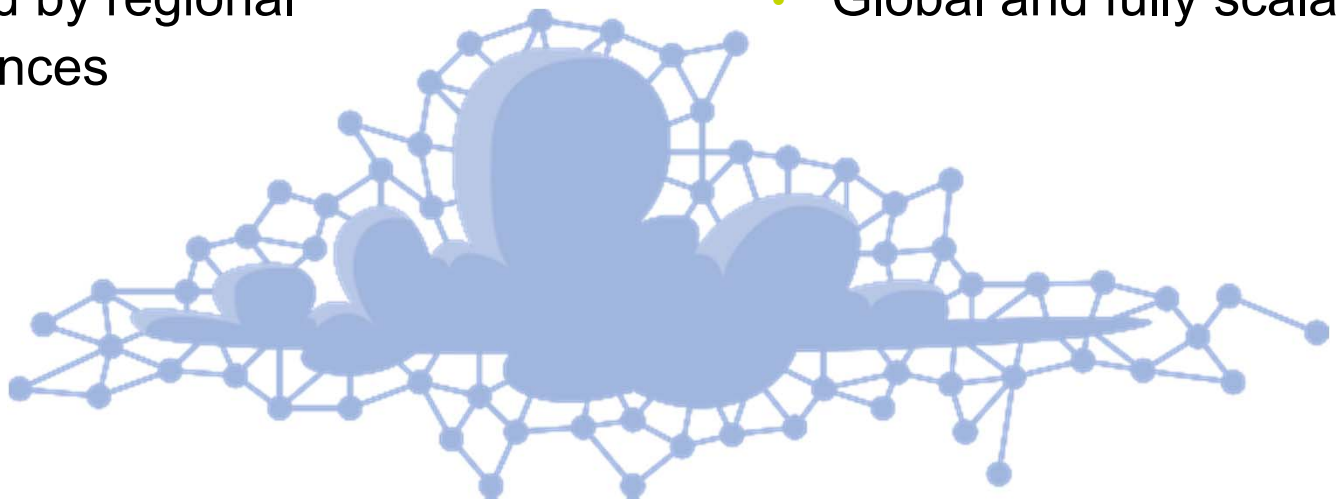
Enterprise Level Issue Management

What it's not

- Excel-based
- Single point of origin
- Point-to-point
- Source of regulatory risk
- Limited by regional differences

What it is

- Cloud-based
- Multiple points of origin
- Multifactorial
- Regulatory compliant
- Global and fully scalable



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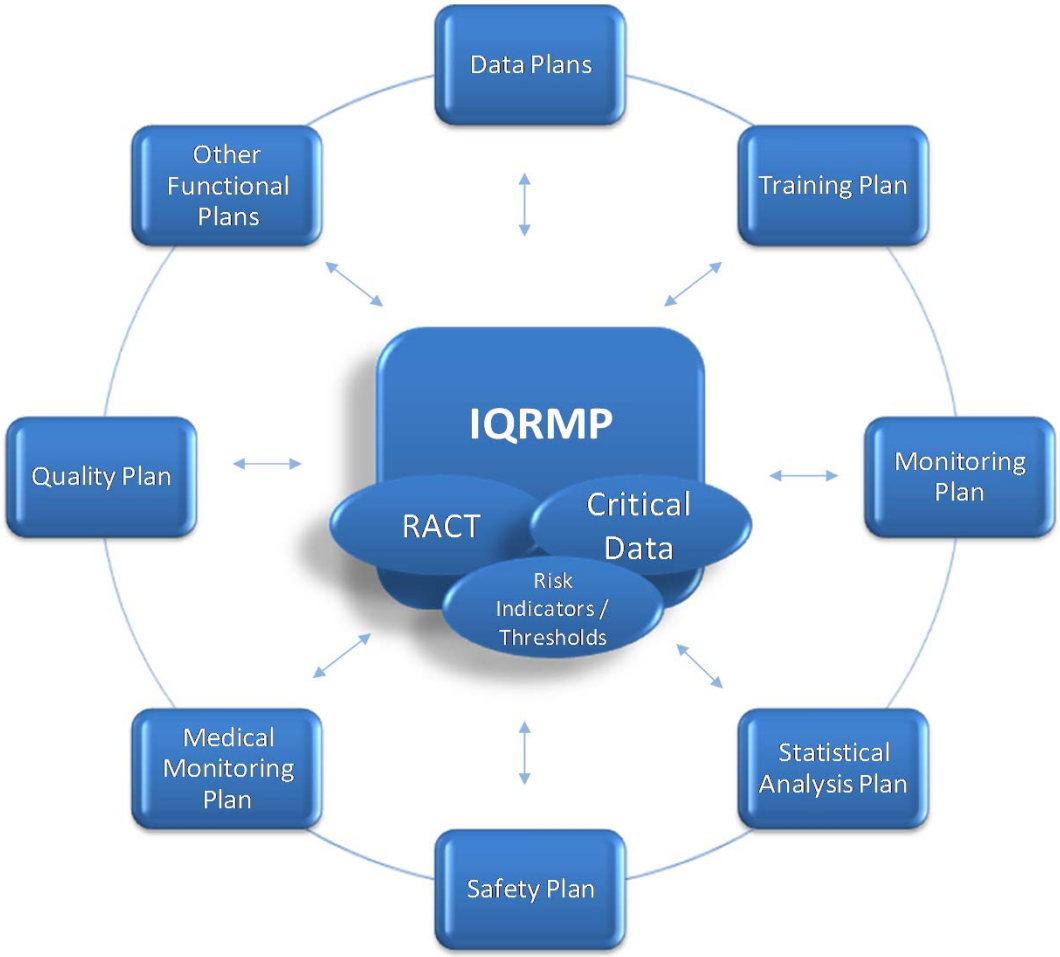
Risk Based Management Approach

- The IQRMP includes the (RACT), Critical Data (EDC), and Risk Indicators (CSA)
- Each function or role will leverage patient data and/or centralized analytics to perform their data validation & monitoring activities
- Issue management and workflows create the cross-functional communication platform for a ***scalable, inspection-ready solution***



Visual Source: Position Paper: Risk-Based Monitoring Methodology FINAL 30May2013

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Persona Driven Workspaces

Centralized Monitoring Team

Primary Purpose: Review analytics to identify trends or areas of risk within the clinical trial

Focused Tools: EDC, Operational & Clinical KRI Dashboard, Decision Making Workflow, and **Issue Management**

Workflow: 1) Review observations flagged by KRIs
2) Hold – flag observation for ongoing follow-up
3) Action – close observation, generate query in EDC or create issue management record
4) Follow-up issues until resolved
5) Confirm positive trending of KRIs over time

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Persona Driven Workspaces

Field Monitoring Team

Primary Purpose: Perform off-site and on-site monitoring activities
Focused Tools: Site Performance Dashboard, Adaptive Monitoring Workflow (SDV/SDR), **Issue Management** and MVR generation
Workflow:
1) Schedule visits based on data volumes or associated risk levels
2) Review site performance KRIs on planned frequency
3) Utilize patient profiles to identify clinically relevant data
4) Perform and track SDV and SDR per Monitoring Plan
5) Perform assigned actions within Issue Management
6) Generate new issues identified during visits
7) Complete Monitoring Visit Reports (MVR)

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Persona Driven Workspaces

Data Management & Analytics

Primary Purpose: To perform deep dive data analytics across all study related data sources

Focused Tools: EDC, Centralized Statistical Analytics, Machine Learning Algorithms, **Issue Management**

Workflow: 1) Leverage advanced analytics and pattern detection to identify "unknown" data anomalies and clinical trial risks
2) Tag new risk visualizations for ongoing monitoring by Centralized Monitoring Team
3) Perform analytics driven root cause analyses
4) Document potential sources of risks
5) Generate data queries in EDC
6) Generate and assign new Issues

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Persona Driven Workspaces

Medical Monitoring & Safety

Primary Purpose: To review critical medical and safety risks
Focused Tools: Patient profiles, Clinical KRIs, Pattern Detection for Missing Endpoints, **Issue Management**
Workflow: 1) Review patient profiles flagged as meeting critical safety tolerance limits
2) Evaluate AESI incident rates
3) Identify targeted risks and create issues
4) Generate data queries to clarify medical discrepancies
5) Identify potential missing endpoints or safety signals and document follow-up

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What about your Investigators?

Principal Investigator & Delegates

Primary Purpose: To enroll subjects and conduct protocol defined procedures in accordance with regulatory

Focused Tools: EDC, Patient profiles, Site Performance Metrics, **Issue Management**

Workflow: 1) Enroll subjects and enter data into eCRFs
2) Identify & report all safety events using patient profiles
3) Generate issues regarding study requirements
4) Resolve and document actions regarding potential quality issues or GCP non-compliance
5) Review performance metrics to identify opportunities to improve study conduct

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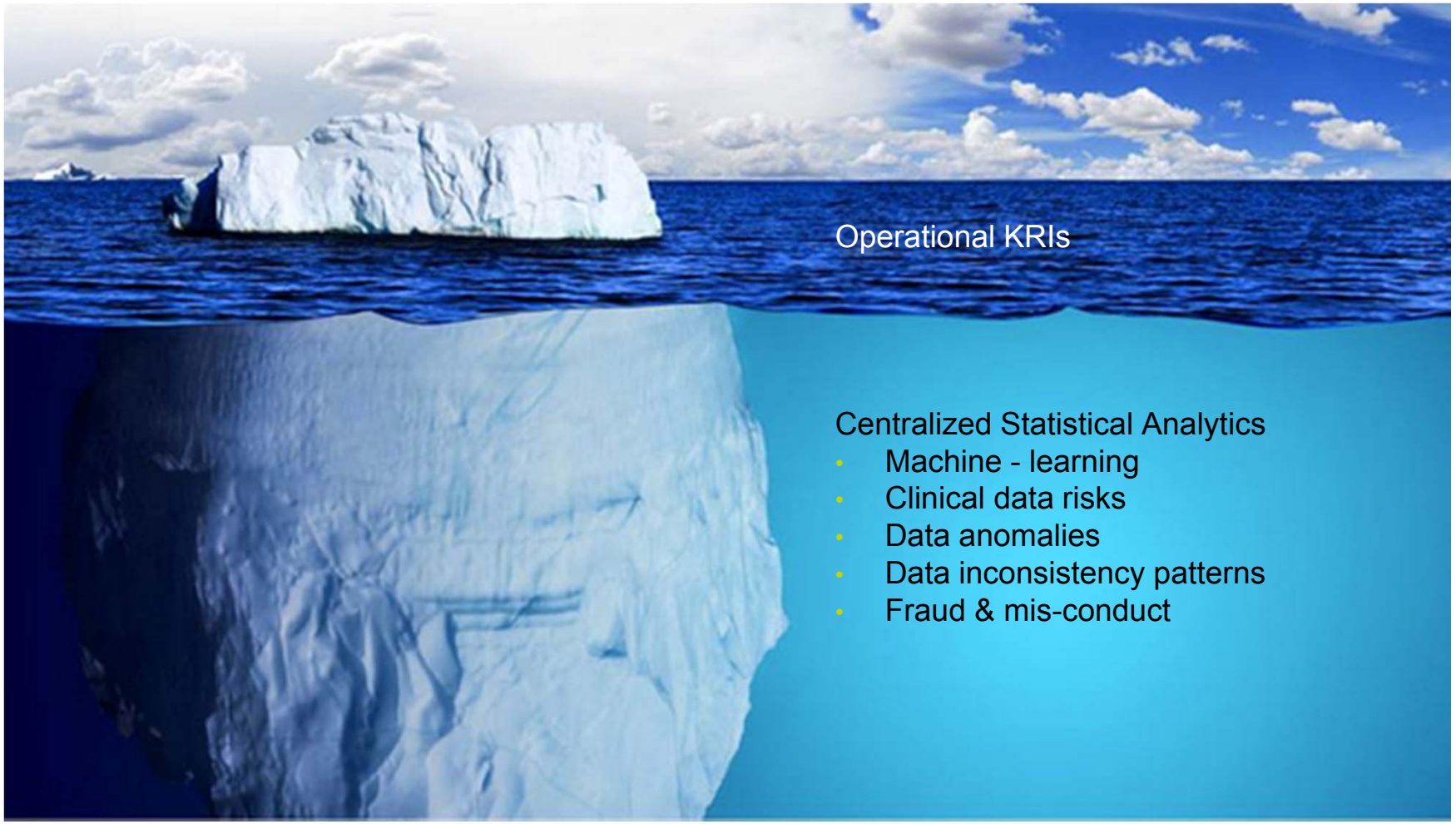
Deeper, More Advanced Analytics!



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Example Finding # 1 - Zero Variability in Diastolic BPs

Issue Description

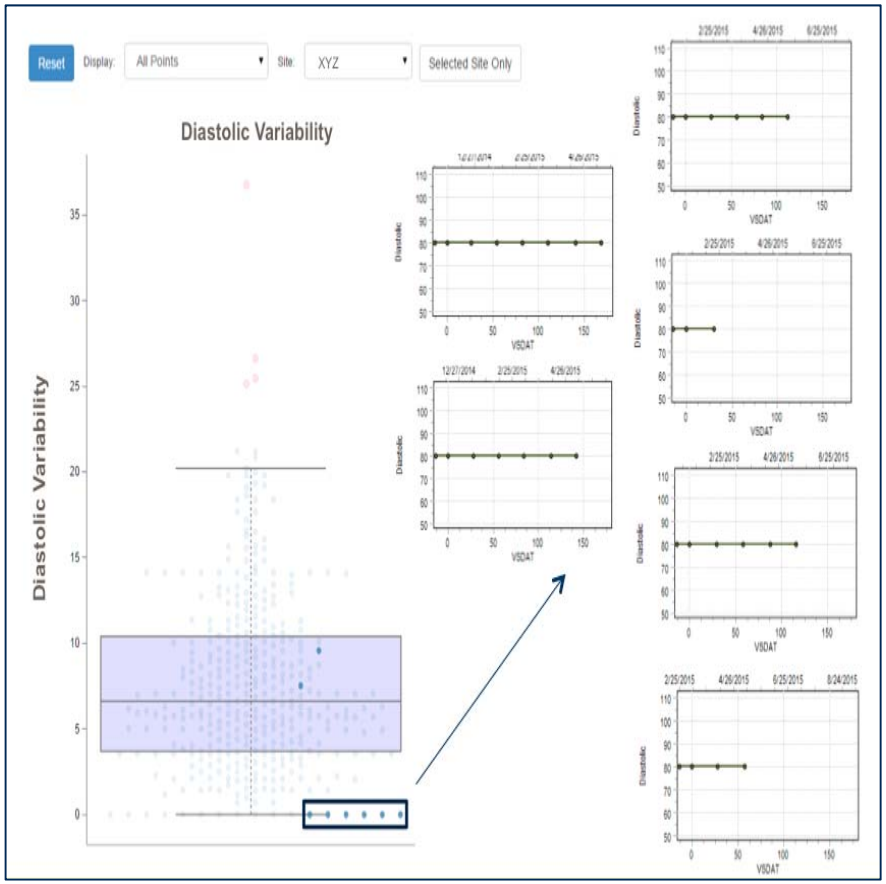
- Data algorithms calculate variability metrics for data collected over multiple visits (machine learning)
- Sites with no variability (zero slope) may indicate poor diagnostic procedures or mis-conduct
- Other vitals for this site had similar zero variability issues

Potential Impact

- Validity of site data
- Regulatory delays to investigate
- Fraud/mis-conduct

Recommended Action

- Escalation to Quality Assurance
- Follow SOP for potential mis-conduct



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Example Finding # 2 - Swollen Joint Count Differences

Issue Description

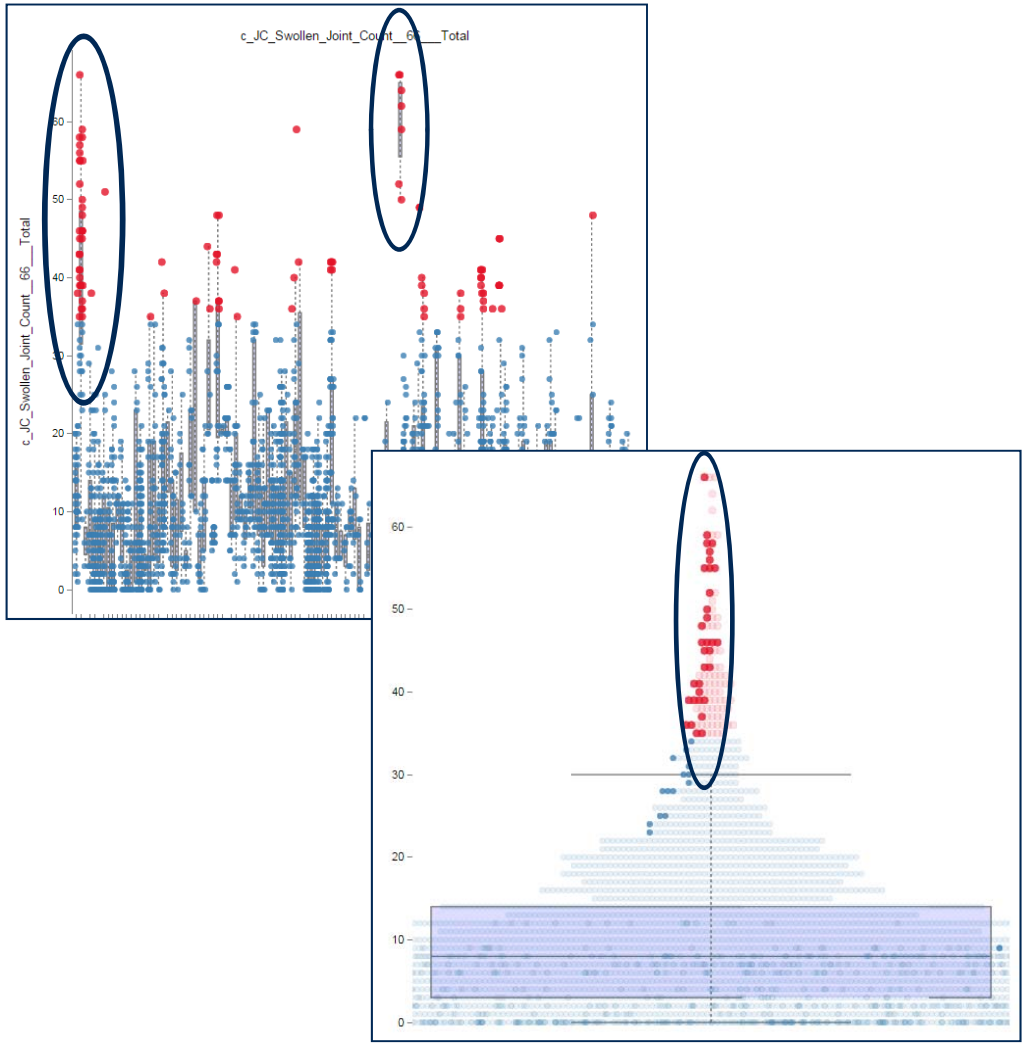
- Univariate analysis evaluating all swollen joint counts by data point
- Statistically improbable high values highlighted and then grouped by site
- Two sites identified with most JC values in anomalous data range

Potential Impact

- Variability in primary efficacy endpoint
- Poor diagnostic data in other efficacy areas

Recommended Action

- Impact analysis on final study results
- Schedule on-site review to conduct root cause analysis and retrain site



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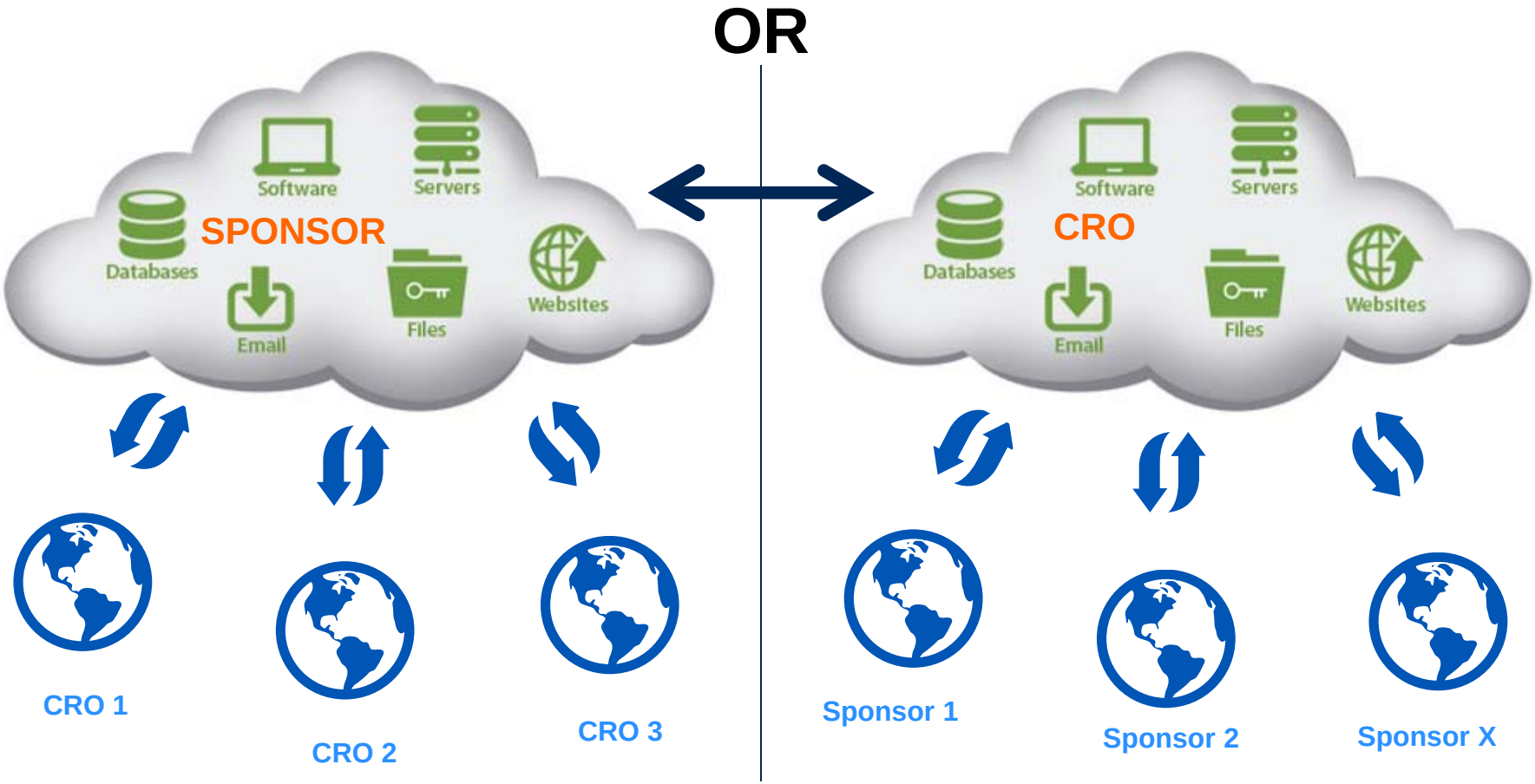
Potential RBM Technology Ecosystems



Most likely some combination of the two…

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Thank You