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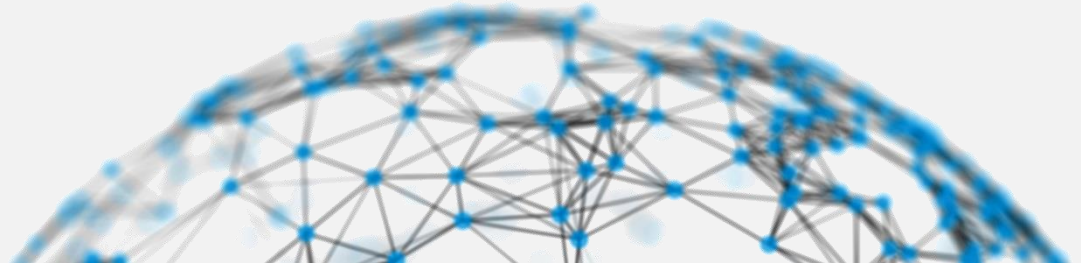
Risk-Based Monitoring – Its Not Complicated!

Rich Davies
Executive Director Of Business Solutions
OmniComm Systems

The EDC of choice for more than
4,000 clinical trials around the world



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Agenda

- The Growing Case for RBM
- RBM Keys to Success

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Strong Regulatory Endorsements for RBM …

FDA Final Guidance (August 2013): A Risk-Based Approach to Monitoring

"There is a growing consensus that risk-based approaches to monitoring … are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality."

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Strong Regulatory Endorsements for RBM …

EMA Reflection Paper (Sep 2013): Risk-Based Quality Management in Clinical Trials

"There is a need to find better ways to make sure that limited resources are best targeted to address the most important issues and priorities …"

"… Risk based quality management is the identification of the risks on a continuous basis … throughout the design, conduct, evaluation and reporting of clinical trials."

We've been here before …

Remember when …

- Remember when we collected data on …..

PAPER !!!

- Accepted quality management approach was to perform Double Data Entry.
- Not everyone thought so – several companies performed QC checks without DDE

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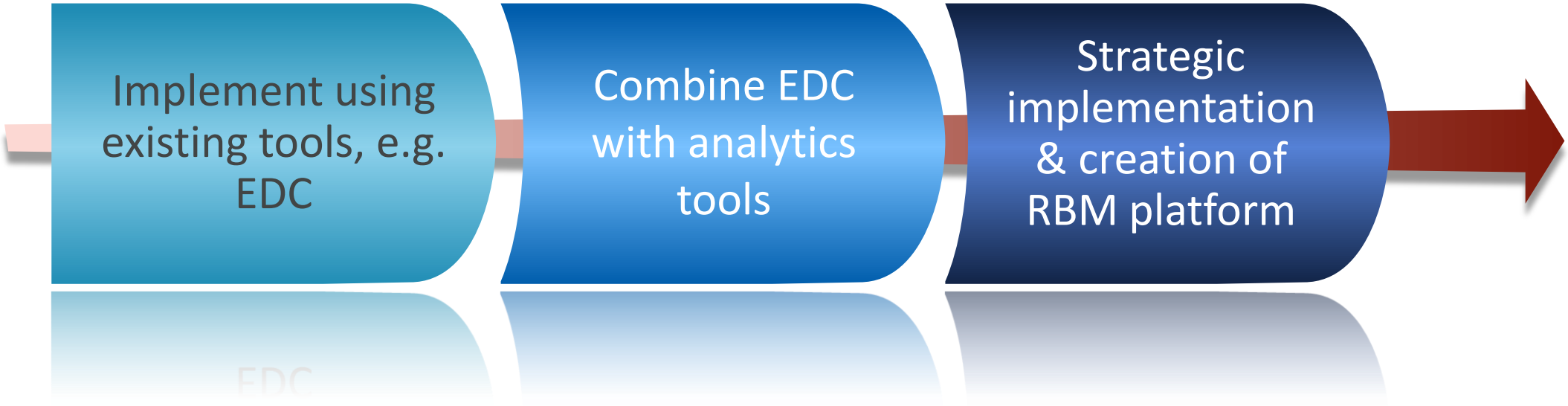
Risk/Adaptive Monitoring Strategy

Sliding scale of sophistication



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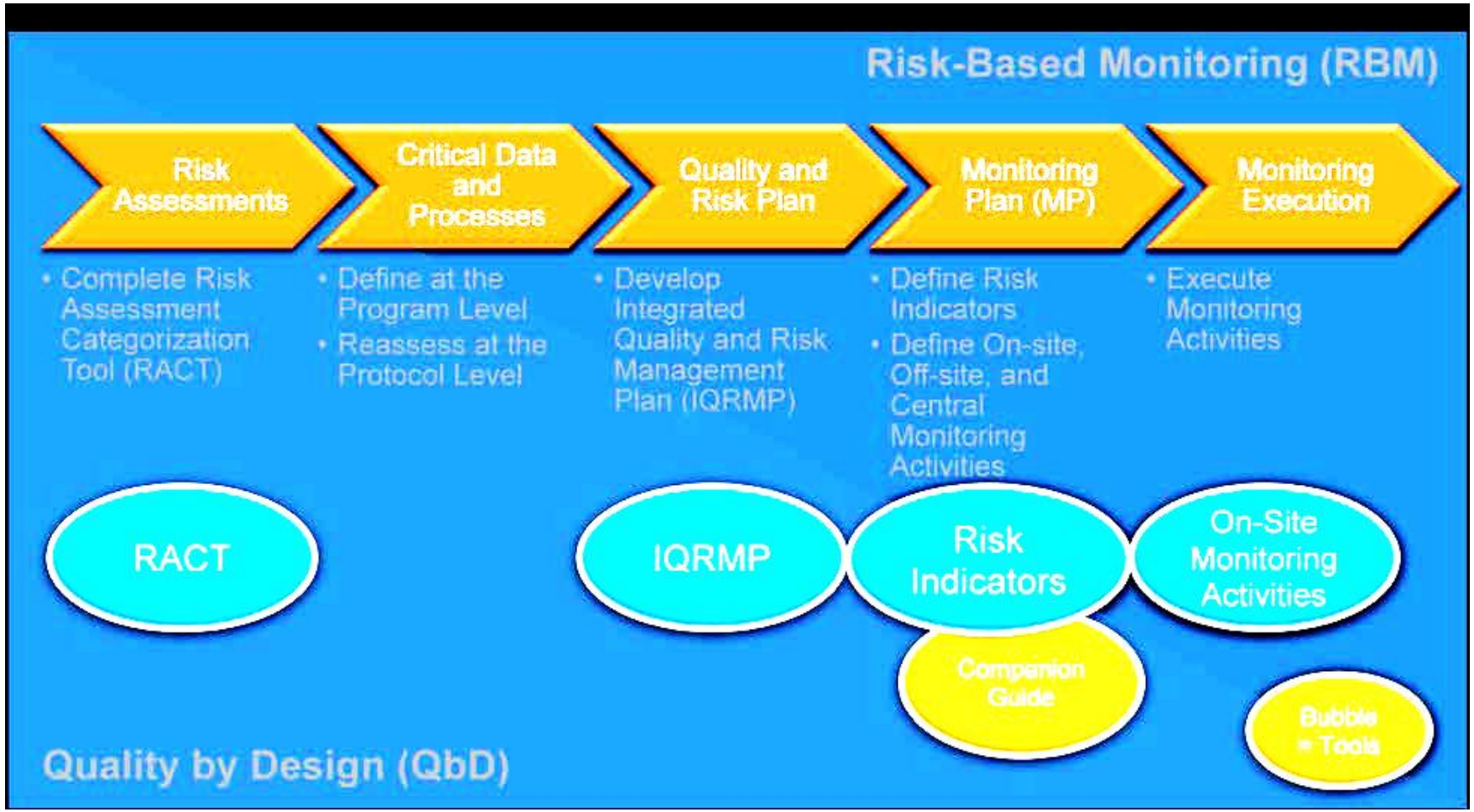
Emerging Methodology Support for RBM …

TransCelerate Position Paper on RBM (May 2013)



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Growing Quantitative Evidence for RBM …

TransCelerate Article – November 2014

- Title: “Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials”

- Authors:
- Nicole Sheetz, PharmD, Brett Wilson, BSP, Joanne Benedict, MS, Esther Huffman, BS, Andy Lawton, ASTAT, Mark Travers, PhD, Patrick Nadolny, MS, Stephen Young, MA, Kyle Given, BA, and Lawrence Florin, MBA

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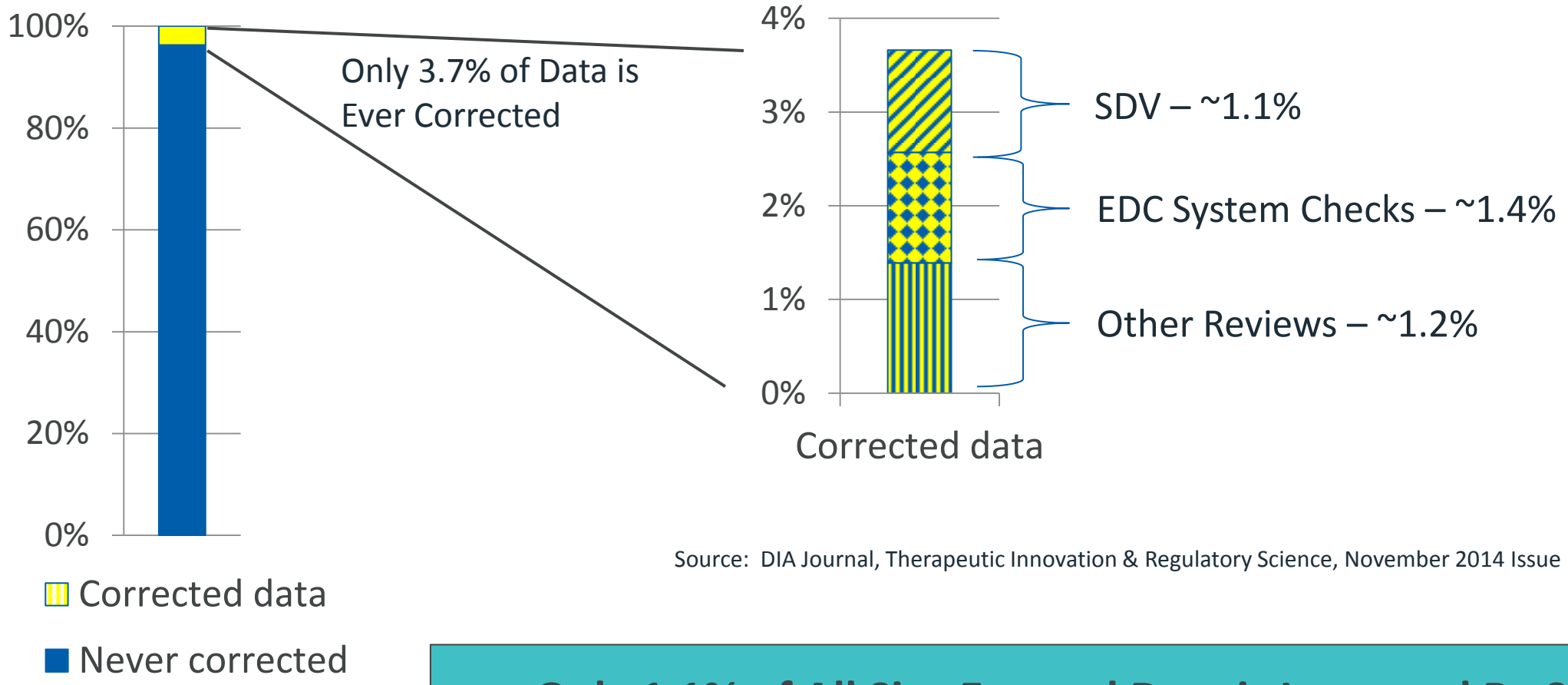
SDV Has Minimal Impact on Site-Entered Data …



Source: DIA Journal, Therapeutic Innovation & Regulatory Science, November 2014 Issue

Only 1.1% of All Site-Entered Data is Impacted By SDV!

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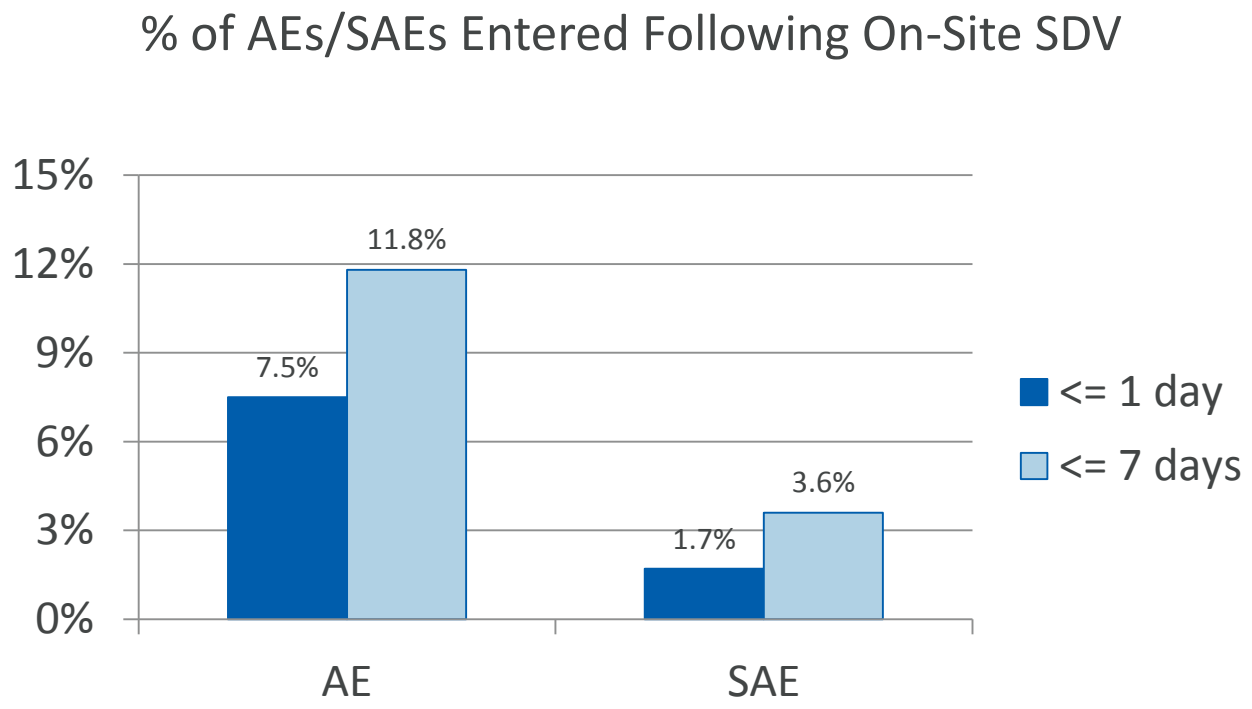
SDV More Relevant for AE Reporting …



Source: DIA Journal, Therapeutic Innovation & Regulatory Science, November 2014 Issue

~7% to 12% of AEs Entered Following SDV

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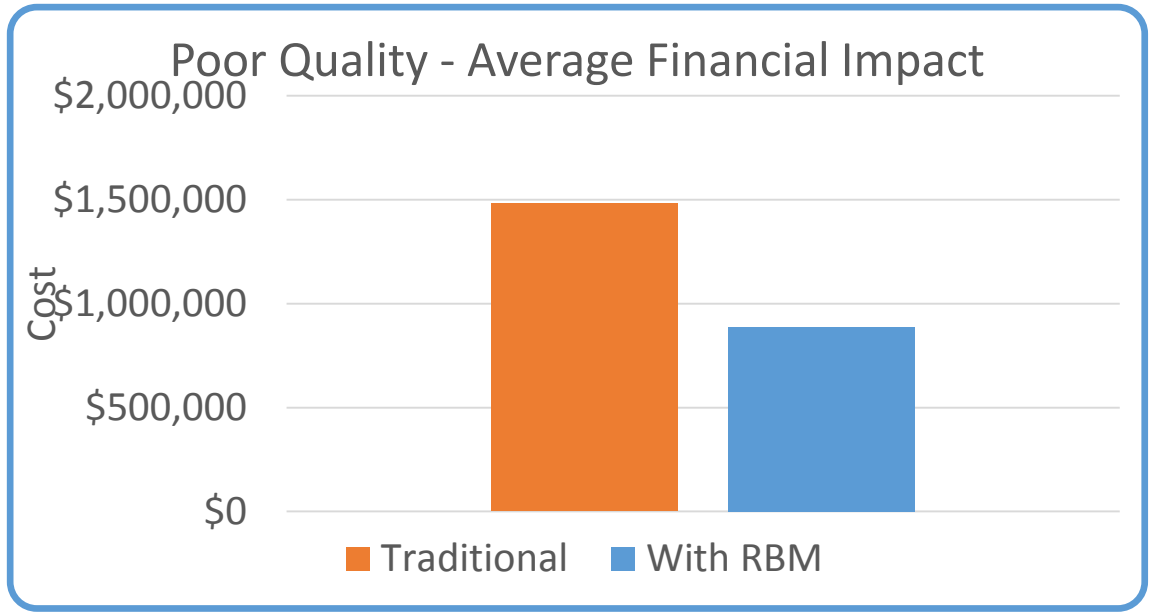
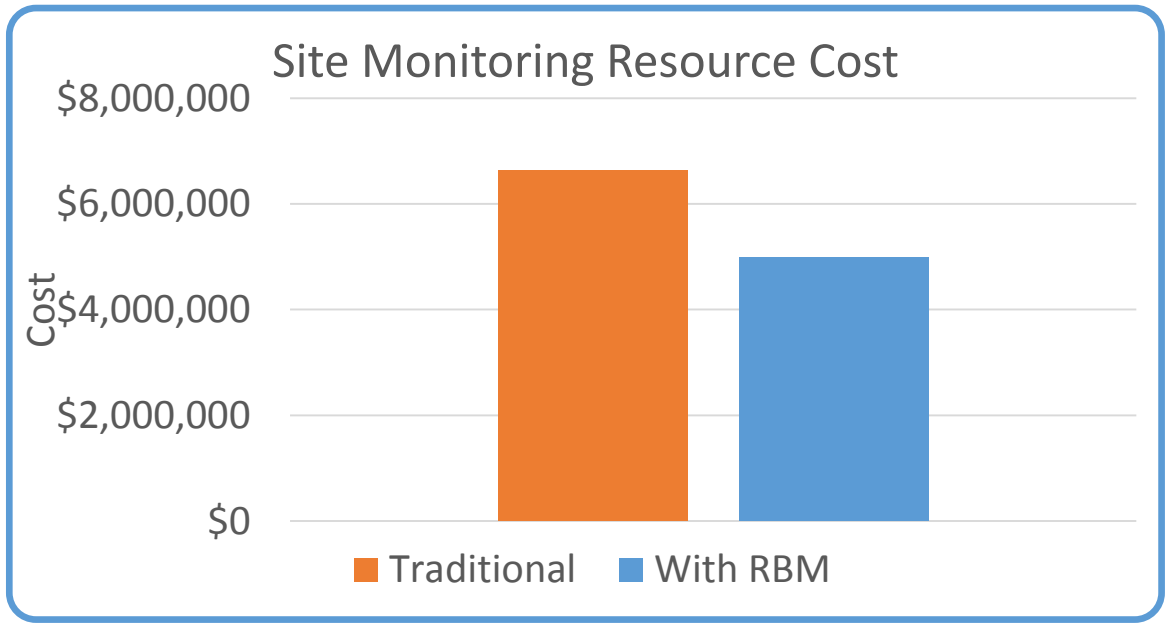
Measuring RBM's Tremendous Value Proposition

At least two significant value dimensions …

Improved Quality =>
Higher Rate of Marketing Approvals



Site Monitoring
Resource Efficiency



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Key to RBM Success – **Keep it Simple!**

RBM Does NOT need to be complex or burdensome …

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A Few RBM Keys to Success

Focus on Simplicity …

- ✓Study Risk Management Plan (IQRMP)
- ✓Dynamic (Targeted) SDV Plan
- ✓Effective KRIs – Quality over Quantity

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Study Risk Management Plan

Focus on Simplicity …

- SRMP Key Components:
  - Study Risk Assessment
  - Critical Data Identification
  - KRI Action Plan
  - Dynamic SDV Plan

Study Risk Assessment

		Key Risk Areas:			Overall Study Risk Level:	M
Assessment Category	Key Study Attributes Impacting Risk	Enrollment / Retention	Data Quality	Compliance & Patient Safety	Study Team Assessment of Applicability	Level of Applicability (L,M,H)
		H	M	M		
Study Design Complexity	Procedure Volume and Burden	x	x	x		M
	Unique/Complex Study Equipment		x	x		L
	Adaptive or Stratified Designs		x	x		L
	Complex Dose Titration			x		L
	Laboratory (e.g., local labs, specialty assessors)		x	x		M
Patient Population	Severity of Disease/Condition		x	x		H
	Vulnerable Patients (e.g., children, mentally handicapped, inmates)			x		M
	Complexity of Eligibility Criteria	x		x		H
Investigational Product	Established IP Safety Profile?					L
	Severity of Known IP Toxicity and Drug Interactions	x				H
	Complexity of IP Supply and Maintenance (e.g., Storage requirements, shelf-life, etc.)			x		L
	Complexity of IP Preparation and Administration			x		L
	Safety Profile of Comparator or Other Study Meds	x				H

KRI Action Plan

Risk Level	Key Site Level Risks	Centralized Detection Method - KRI	Elevated Risk Alert Threshold	High Risk Alert Threshold	Remediation Options	Remediation Options
H	Enrollment / Retention:					
	Slow Enrollment	Enrollment report - by Site	0 subjects at 1 month post site initiation	0 subjects at 3 months post site initiation	a) Monitor assist site with chart reviews to identify candidates b) Monitor call/visit site to discuss enrollment issues c) Close out site	-
	High Screen Failure Rate	Screen Failure Rate	P-Score < .05	P-Score < .02	a) Monitor review screen failure records on-site to assess irregularities b) Monitor discuss high/low rate with site to explore issues	
	High Subject Drop-Out Rate (e.g., Withdrawal of Consent, Lost to Follow-up, etc.)	Subject Drop-out Rate	P-Score < .05	P-Score < .02	a) Monitor on-site investigation of drop-outs: source review, interview site staff, etc. b) Site re-training on patient mgt req'ts	
M	Data Quality:					
	Under-Reporting of AEs / SAEs	AE Rate	P-Score < .05	P-Score < .02		
	High Rate of Source-to-eCRF Transcription Errors	Auto-Query Rate				
	Poor Source Record Management	Auto-Query Rate				
		Subject Visit-to-eCRF Entry cycle time	> 14 Days Avg	> 22 Days Avg		
M	Compliance & Patient Safety:					
	High Rate of Missed Key Assessments/Procedures	Missed Assessment Rate	P-Score < .05	P-Score < .02		
	Improper or Faulty Administration of Key Assessments/Procedures	Statistical Monitoring (Outlier Detection)	TBD	TBD		
	Improper Screening/Enrollment of Ineligible Subjects	Protocol Deviations report	1 ineligible subject enrolled	>= 2 ineligible subjects enrolled		- Programmed edit checks as feasible (e.g., prohibited Med Hx, age, etc.)
	Improper IP Administration and/or Dosing (e.g., Incorrect/missed doses, improper prep/delivery)	Protocol Deviations report	2 Admin/Dosing deviations	>= 4 Admin/Dosing deviations		- Review IP Admin data listing (eCRFs) for irregularities
	High Rate of Subject Visits Conducted Off-Schedule	Visit Schedule Deviation Rate	P-Score < .05	P-Score < .02		
	Informed Consent issues (e.g., Un-signed, incorrect versions, etc.)	Protocol Deviations report	1 IC deviation	>= 2 IC deviations		
	Non-Compliance with SAE Reporting Timelines	Protocol Deviations report	1 late SAE	>= 2 late SAEs		- Review all reported SAEs for onset date vs. report date
	Missed Subject Visits	Missed Visit Rate	P-Score < .05	P-Score < .02		
	Non-Compliance with Patient Reported Outcomes (PROs)	Statistical Monitoring (Outlier Detection)	TBD	TBD		- Configure ePRO system to alert subjects re: required entries; and alert sites re: non-compliance
	Fraud and Data Fabrication (e.g., Inventing subjects, providing fabricated data)	Statistical Monitoring (Outlier Detection)	TBD	TBD		

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Dynamic SDV Plan

Focus on Simplicity …

- Do sites need different SDV levels to start?
  - Assume quality – until proven otherwise!
- Higher SDV on first subject(s), reduced afterward

Subject Number	SDV Coverage
1	100% of eCRFs
2 - 5	30% of Critical eCRFs only 100% of AEs
> 5	100% of AEs for every 3rd subject

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Effective KRIs – Quality Over Quantity

Focus on Simplicity …

- Do we need dozens of KRIs to uncover risks?
  - Avoid duplication and KRI proliferation
- Focus on KRI Reliability
  - Minimize false signals
- Focus on Early Detection
  - Leading indicators – not Lagging

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