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KEYNOTE ADDRESS: OVERVIEW OF RISK BASED MONITORING AND A CASE STUDY OF IMPLEMENTATION WITHIN A MIDSIZE CRO

21 JUL 2016

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PRESENTERS

Cheryle Evans, SVP, Clinical & Medical Operations

- Senior executive with 27 years of research experience including 18 years in CRO project management, study start-up, clinical monitoring and document management
- Member of Drug Information Association and ACRP

Patricia Wozniak, PhD, Sr. Dir., Biostatistics

- Over 20 years of industry experience and over 25 years of statistical consulting experience
- Published over 60 journal articles
- Member of the American Statistical Association, Drug Information Association, and CDISC Questionnaire Sub-team

Katie Obermeyer, Manager, Biostatistics

- 10 years of industry experience in both large pharma and CRO
- Member of the American Statistical Association

RISK BASED MONITORING INITIATIVE - AGENDA

- Overview of Advanced Group
- A Perspective on RBM
- The AC RBM Initiative
- AC RBM End-to-End Process
  - Policy
  - Tools
    - Key Risk Indicators (KRIs)
    - Risk Assessment Tools
    - Data Monitoring Plan
- Considerations for RBM Readiness
- Q&A

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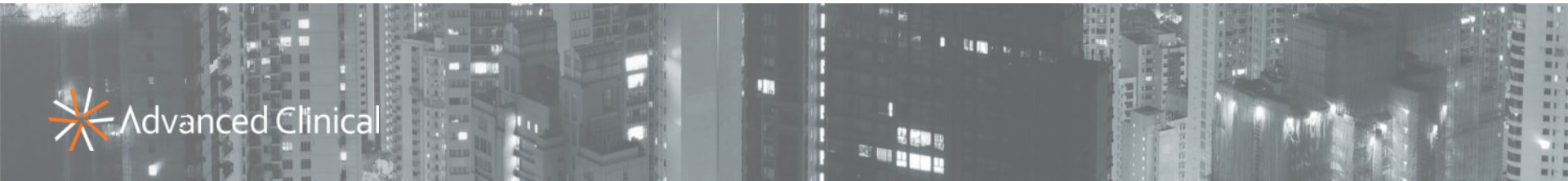
ADVANCED GROUP



THE ADVANCED GROUP OF COMPANIES

- Parent – Advanced Group, established 1988
  - Experts in talent acquisition and management, consulting, outsourcing and professional services
  - 4 Business Segment Specialties
    - **Wunderland** - Marketing/Creative staffing business
    - **Advanced RPO** - Recruitment Process Outsourcing solutions (RPO)
    - **Advanced Resources** - Staffing services for office support, accounting/finance, and healthcare positions (Temporary, temp-to-hire, direct hire and executive search)
    - **Advanced Clinical** - Contract staffing, FSP solutions, and full service CRO services for the Clinical Research Industry
  - Profitable with 2015 revenues of ~$150M
  - Company focused on philanthropic activities

Advanced Clinical offers global outsourcing solutions inclusive of staffing, FSP, and full-service CRO models

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ADVANCED CLINICAL IS AWARD WINNING

- Privately-held organization founded in 1995
- Best-in-class leadership
  - Leader of DM SCDM Board Member
  - Leader of Statistics holds position on CDISC COA sub-team
  - Experienced clinical leadership working together for over 15 years
    - Panel leaders/speakers at Industry forums on CRO/FSP strategies
  - Patient recruitment experts average 12 years experience
- Award-winning organization

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ONLY MID-SIZE CRO OFFERING ALL DELIVERY MODELS

- Global Feasibility
- Project Management
- Patient Recruitment & Retention
- Clinical Monitoring
- Data Management
- Biostatistics
- Medical Monitoring
- Pharmacovigilance
- Medical Writing
- Quality & Validation

Full Service CRO

- FSP teams across projects
- Functional services by project
- Gap augmentation
- Quality oversight
- Study rescue management

Functional Outsourcing

- On-Demand Staffing
- Staff Augmentation
- Direct hire
- Temp-to-perm
- Asset transfer
- Payrolling

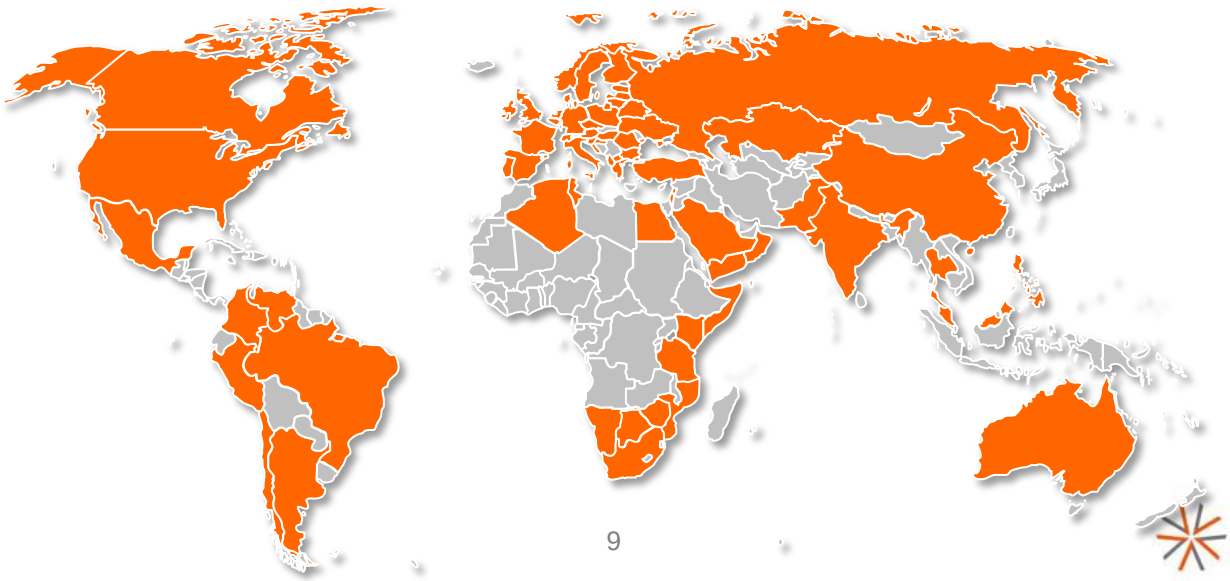
Strategic Staffing

Our Services are Customized for Long-Term Client Benefits!

GLOBAL REPRESENTATION IN OVER 50 COUNTRIES

- We have a strategic partnership to enhance our global offering providing access to more than 50 countries
- Formal relationship inclusive of:

Governance Structure	Operational Guidelines	Quality Manual	Bi-annual Audits	Face-to-Face Meetings



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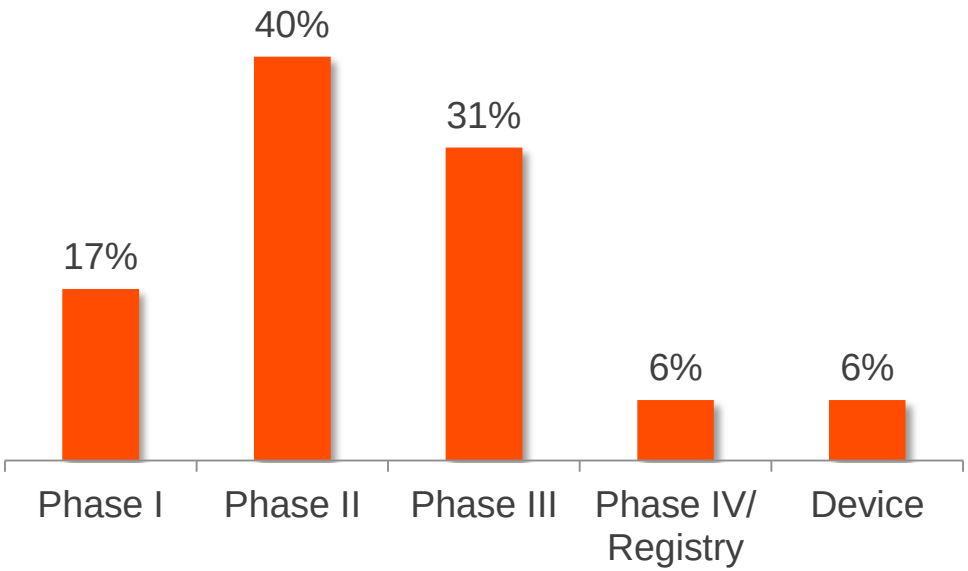
STUDY PHASE & THERAPEUTIC AREA EXPERIENCE

Advanced Clinical has experience across all Phases, in all major therapeutic areas including drug, biologic, generic, and device.



- Anti-Infectives
- AutoImmune
- Cardiology
- CNS
- Dermatology
- Gastroenterology
- Genitourinary
- Inflammation/Musculoskeletal
- Metabolic Disorders/Endocrinology
- Oncology/Hematology
- Ophthalmology
- Pediatrics
- Pulmonology/Respiratory
- Rare Diseases/Special Populations
- Women's Health

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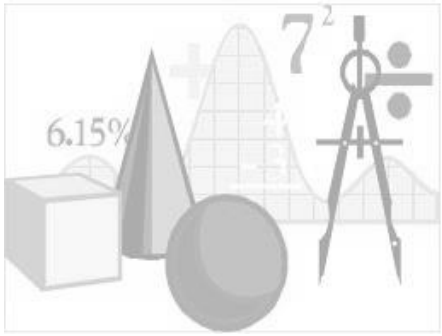
A PERSPECTIVE ON RBM

RBM: DEFINITION & RATIONALE



RBM Definition

- Risk-based monitoring is the process of ensuring the quality of clinical trials by identifying, assessing, **monitoring** and mitigating the risks that could affect the quality or safety of a study

FDA RBM Guidance: "The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trials by focusing Sponsors on the most important aspects of study conduct and reporting."

Rationale

- Human subject protection & quality
- Centralize a complex, labor-intensive & expensive decentralized process
- Improved management based on predetermined core risk indicators and data
- Focus onsite activity on source data review

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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WE ALL AGREED 100% IS BEST: BUT WERE WE RIGHT?

- The mantra of 100% SDV was/is ubiquitous in the industry

~~100% SDV is Best Practice~~

Practice not Valid

- Only 1.1% of eCRF fields were corrected based on SDV

- 100% SDV persists

High Cost

Lost Focus

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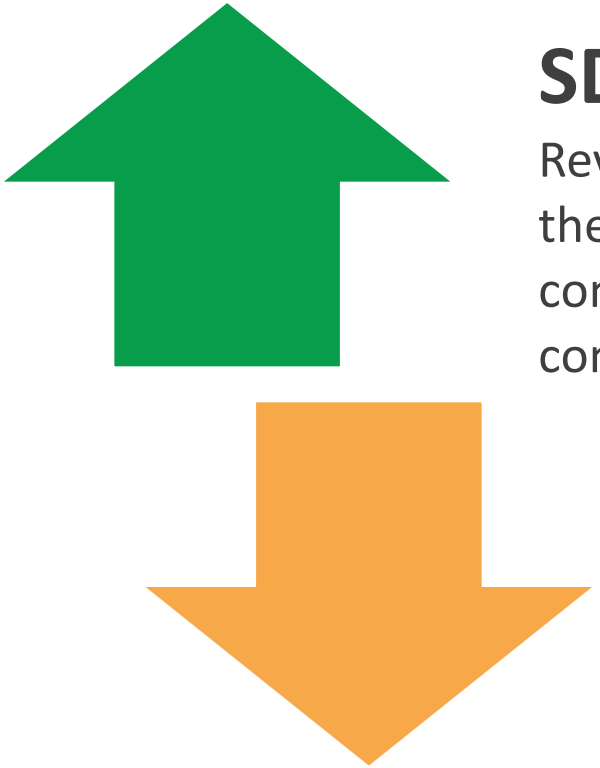
SOURCE DATA REVIEW (SDR) AND SOURCE DOCUMENT VERIFICATION (SDV)



SDR - High Value Activity

Review of the source documents to check the quality of the source, protocol compliance, Investigator involvement, compliance with own SOPs

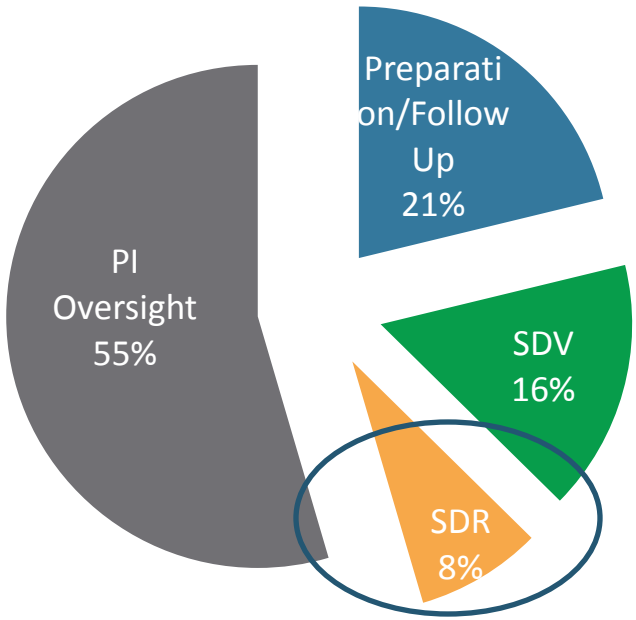
SDV - Low Value Activity

Transcription checking – comparison of source data and CRF

RBM reduced SDV: Transcription checking on a sampling of subjects in combination with centralized and remote data monitoring review.

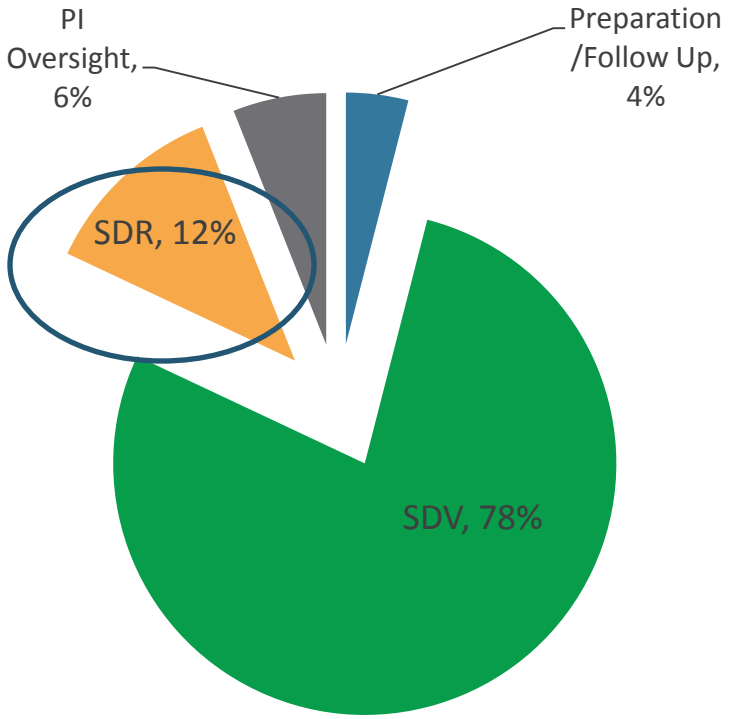
AUDIT EXPERIENCE VS. ALLOCATION OF "TRADITIONAL" ON-SITE EFFORT

Distribution of Investigator Site Audit Findings



Distribution based on 2012 findings from 289 relevant audits out of the 628 investigator site audits and applicable Country Office and vendor audits that were performed on Pfizer sponsored studies.

Traditional Allocation of On-Site CRA Effort



TransCelerate Analysis: 9 therapeutic areas, 6 companies, 380K queries → only 2.4% related to SDV of critical data

Based on industry estimates

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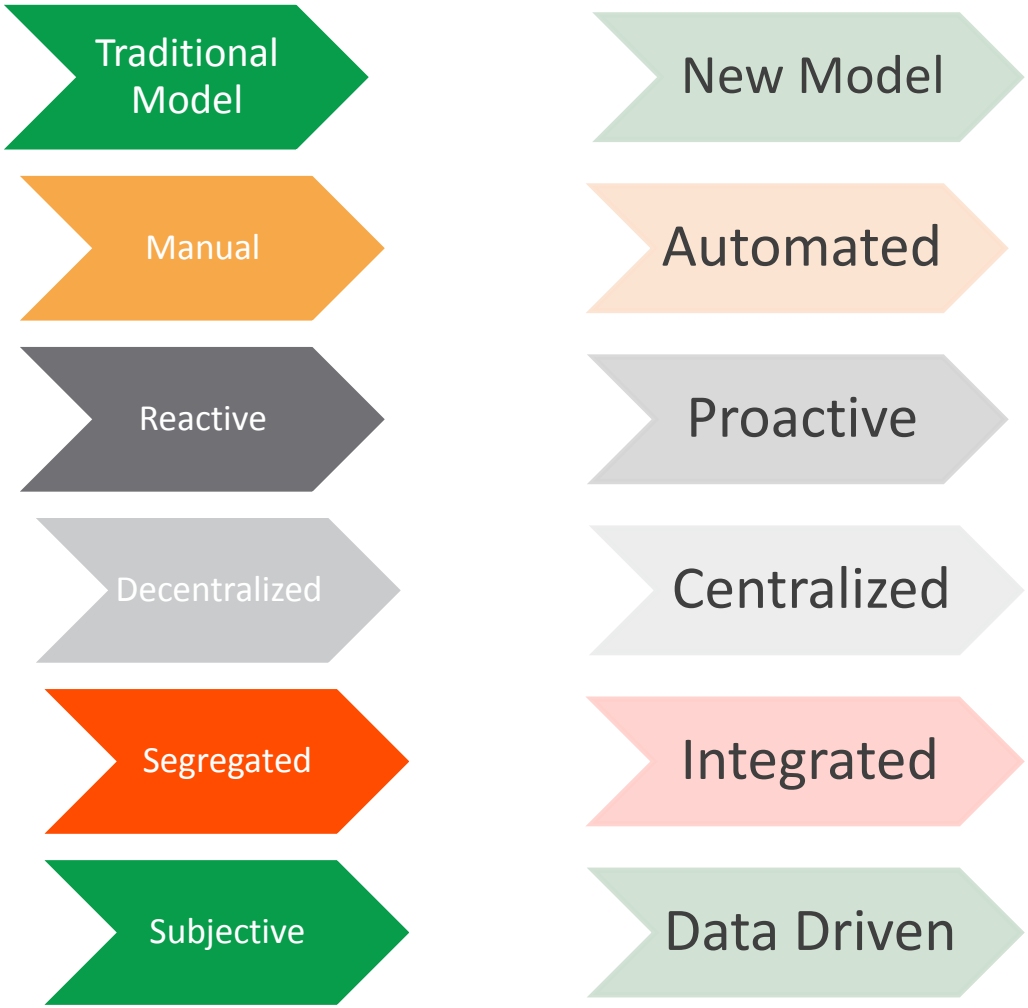
NEW MODEL ADVANTAGES



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RBM AND THE CASE FOR CHANGE: NOW IS THE TIME

A Consensus that Data Driven Monitoring (DDM) will:

- Enhance Quality
- Improve Safety
- Reduce onsite monitoring costs

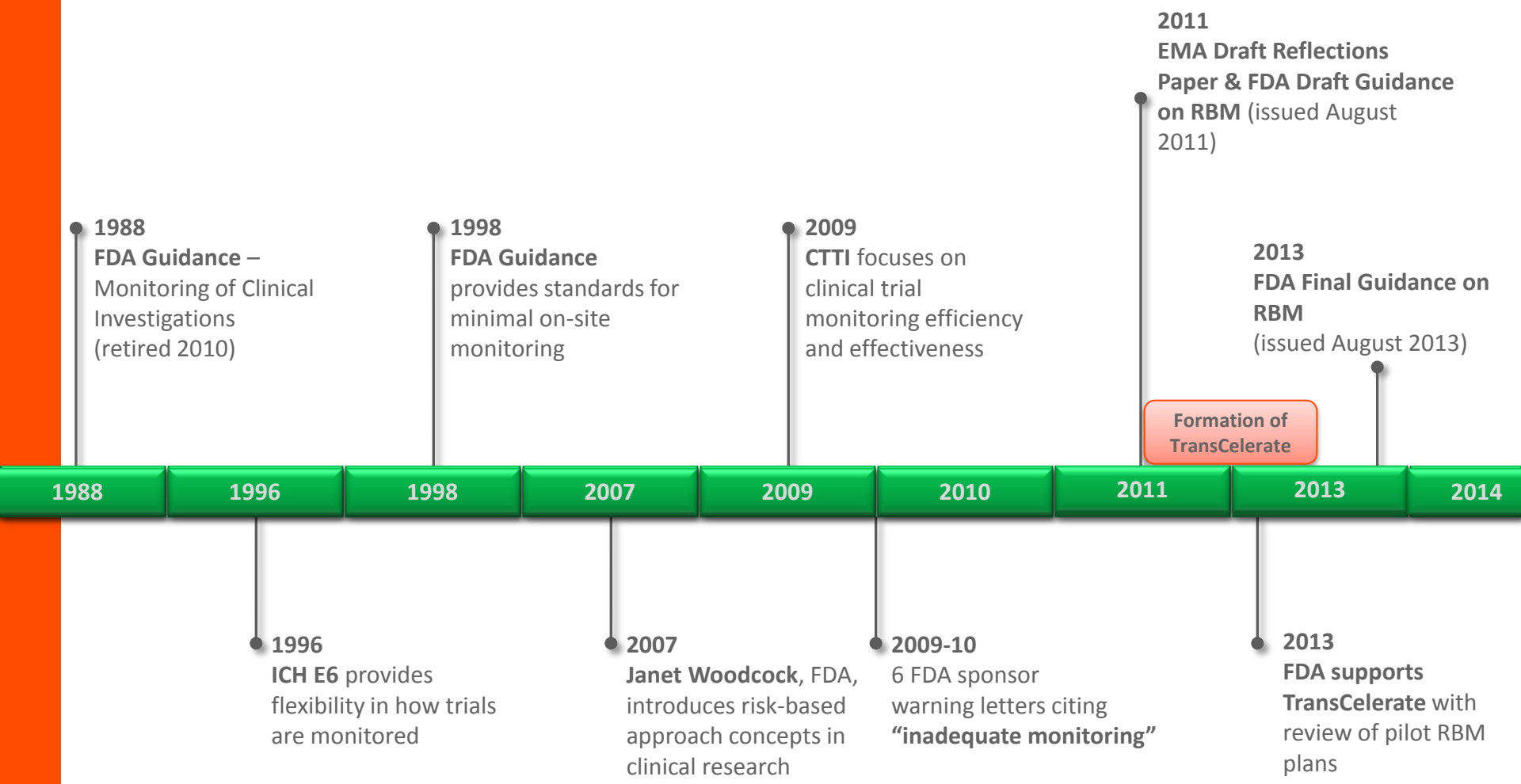
Technology Available to Assess Data

- Sophisticated technology to transform desperate data sources into meaningful dashboards
- Allow clinical teams to make observations, assess RISK & deploy focused actions

Regulators Onboard

- FDA issued final Guidance in Aug 2013
- EMA issued final Guidance in 2011, updated Nov 2013

REGULATORY AGENCIES: LEADING THE MOVEMENT



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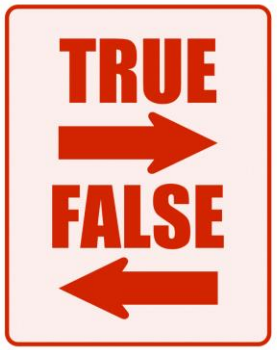
COMMON RBM MISCONCEPTIONS



- RBM is Risky Monitoring
  - 100% SDV as the gold standard ensures the highest level of quality and the lowest risk
- RBM will reduced SDR
- RBM will lower costs
  - lower costs by doing less monitoring
- Monitoring efforts are eliminated or substantially reduced
- Technology will automate monitoring and eliminate CRAs

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TRANSCELERATE QUANTITATIVE PERFORMANCE METRICS[1]

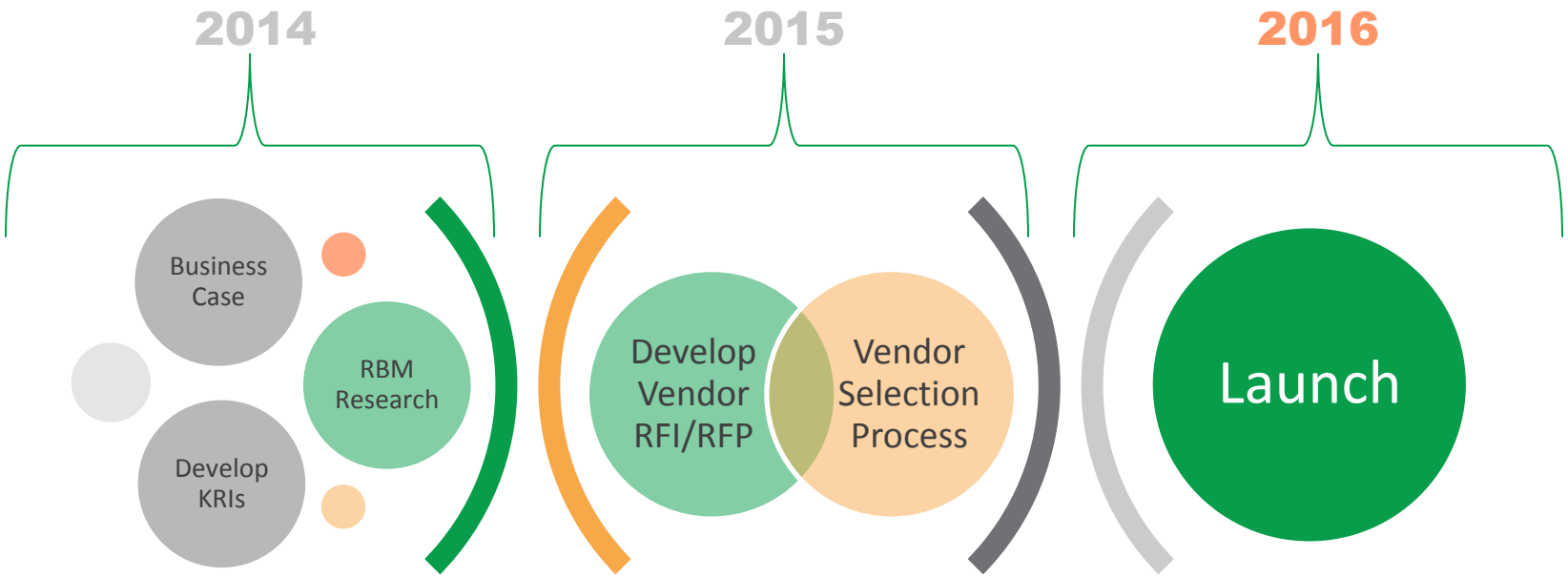
Metric	Attribute	Result
1. Average number of major/critical audit findings per audited site	Quality	Positive
2. Percentage of site unreported, confirmed SAEs compared to total SAEs	Quality	Positive
3. Significant Protocol Deviations rate per treated subject – Total number of deviations/total number of subjects for the protocol	Quality	Positive
4. Median number of days from patient visit to eCRF data entry	Cycle Time	Positive
5. Median number of days from query open to close	Cycle Time	Positive
6. Median number of days from significant/major issue open to close	Cycle Time	Positive
7. Average Monitoring (all types) cost per site	Efficiency	Neutral
8. Average interval between on-site monitoring visits per site	Efficiency	Mixed

"Seven (7) TransCelerate member companies voluntarily reported metrics on 59 RBM Trials to a blinded third party. Not all member companies provided metrics but through survey it is known that at least ten companies implemented RBM in at least 125 trials in order to evaluate the methodology."

[1] Source: Risk Based Monitoring Update – Vol V FINAL 28Jan2016

THE AC RBM INITIATIVE

AC RBM INITIATIVE



Phase I: Discovery

(251 Team Hrs. Entered)

RBM Research & Development

- Established the RBM Initiative Committee
- Conducted Research
- Collected / Reviewed material artifacts
- 40 Key Risk Indicators Identified
- CM SoPs Drafted
- Plan Templates Drafted

Phase II: Vendor Selection

(587 Team Hrs. Entered)

Refinement

- KOM with Triumph OPRA conducted Nov 11 2015
- 17 Key Risk Indicators Defined & Usage Document finalized
- Drafted Change Management Plan
- Sources of Truth (SoT) identified and "Flat Files" development ongoing

Phase III: Operationalize & Train Teams (Estimate 200 Hrs.)

Go Live: Q216

- Submitted SoT "Flat Files" for programming
- Conducted 1st Protocol Risk Assessment
- Completed comprehensive End-to-End Operational Process Schematic
- Drafted Data Monitoring Plan
- Validation (UAT) planned for March 2016
- Branding & Marketing planned for March 2016
- **Launch – Go Live – Q216**

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ANALYTICAL TOOL SELECTION

- Developed a 12 page comprehensive RFI with input from Sponsor Partner
- Reviewed ten providers, inclusive of Medidata, and received five (5) RFIs from:
  - Comprehend
  - J-Review
  - Oracle
  - TIBCO – Spotfire
  - Triumph OPRA
- Narrowed the list to three (3) and conducted F2F presentations
  - Comprehend
  - TIBCO - Spotfire
  - Triumph OPRA
- Final Choice → Triumph OPRA
  - System agnostic
  - Only provider with a closed system that documents
    - Risks (Observations)
    - Mitigations and F/U (Actions)
  - Consultants that are SMEs in RBM → currently working with clients in RBM
  - RBM is their core competency

TRI – OPRA SYSTEM CAPABILITIES

Audit trail

Cloud based

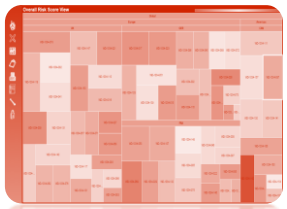
CFR compliant

Activity management

Zero footprint
web client access

OPRA

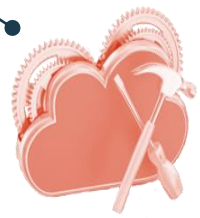
Trend
analysis



Data visualization

$$SD=\sqrt{\frac{\sum(x-\bar{x})^2}{n}}$$

Statistical analysis



User configurable

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OPERATIONALIZING RBM

ASSESSING RISK

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OPERATIONALIZING RBM

Risk: Understand RISK in the context of a clinical trial

- Level of uncertainty vs. immediate hazard

KRIs & Risk Mitigations: Identify Key Risk Indicators (KRI)s & Set Mitigation Plans

- Transcerlate's RACT
- MCC's RAMMT
- Data Monitoring Plan

Data: Identify where the data is located

- Sources of Truth (SoT)
- Import files

Dashboard: Consolidate the SoT electronically and generate a RBM Dashboard

- Identify an analytical tool provided (TRI OPRA)
- Establish a set of KRIs and Usage Definitions

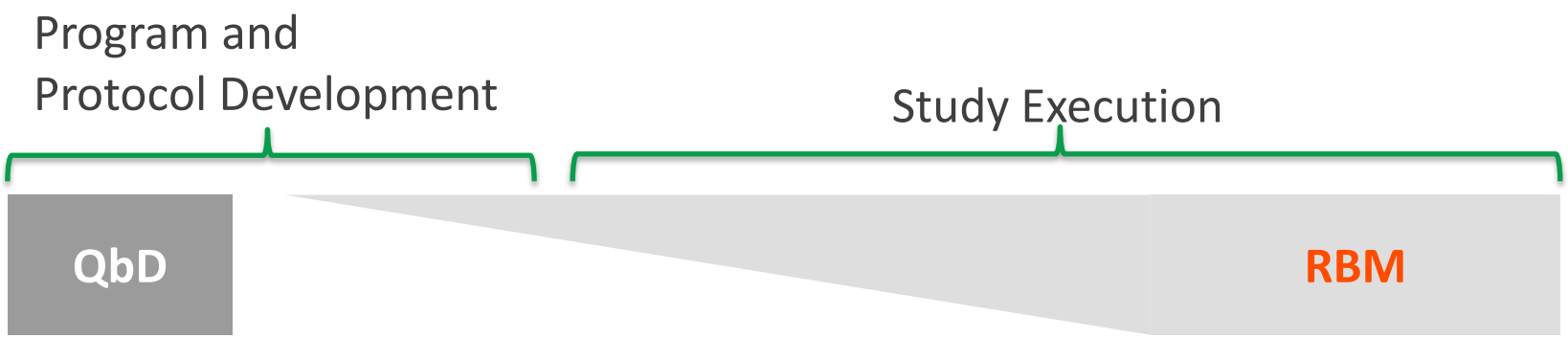
Infrastructure: Team Roles & Responsibilities

- Defined task ownership and processes

Quality: Set a quality processes that will stand up to a regulatory audit

- Meet regulatory guidance requirements with prospective plans, SOPs, processes and documentation

QUALITY BY DESIGN (QBD)



Quality built into the scientific and operational design and conduct of clinical trials

- Focus on what matters
- Critical Data AND Critical Processes that impact on:
  - Patient safety or
  - Data Integrity
  - GCP / Regulatory Compliance

Identify risks at the program, study, and site level in order to employ the appropriate level of monitoring

- Map the risks to appropriate monitoring plans
- Employ mechanisms to monitor important parameters (inclusive of Central monitoring activity)
- Use of technologies that enable effective oversight
- Targeted on-site interventions

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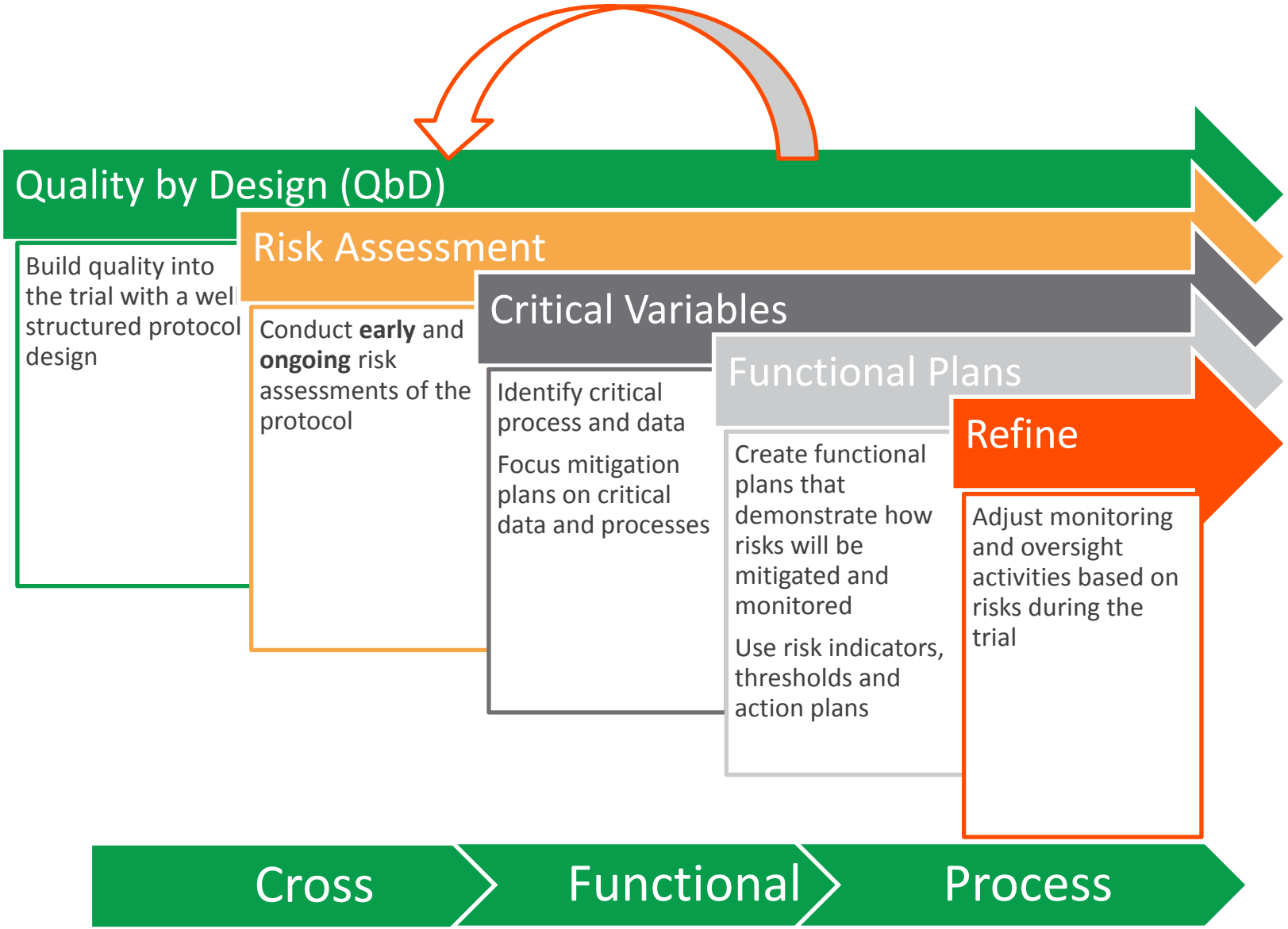
QUALITY RISK MANAGEMENT



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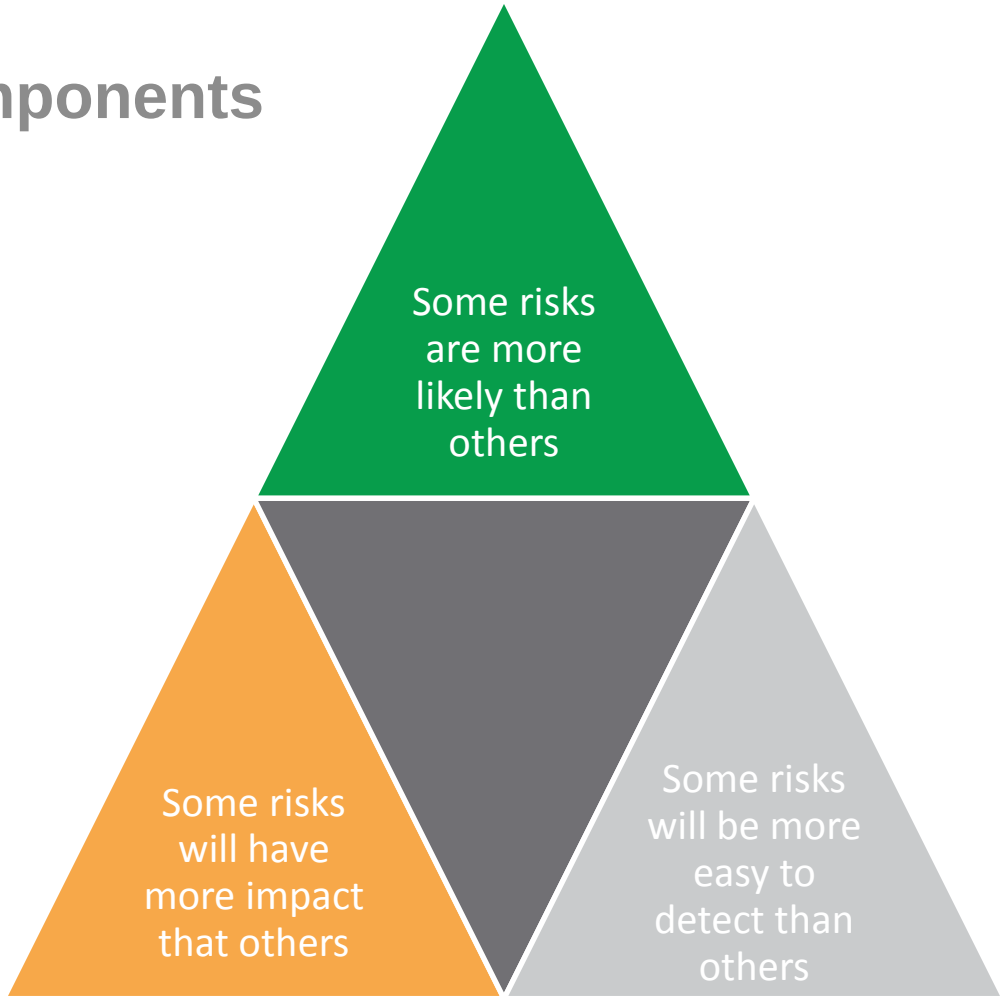
DISSECTING RISK

Three important components of Risk:

- **Probability**
- **Impact**
- **Detectability**



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MITIGATING RISK

If we can identify risk, we can plan strategies to detect and mitigate the risk and the impact

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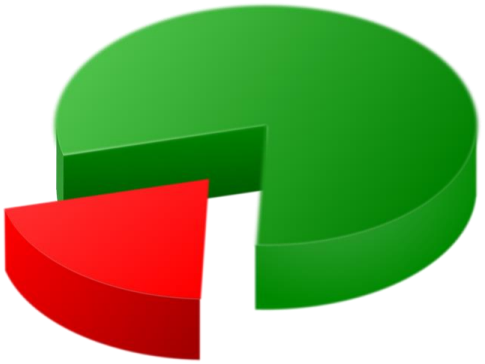
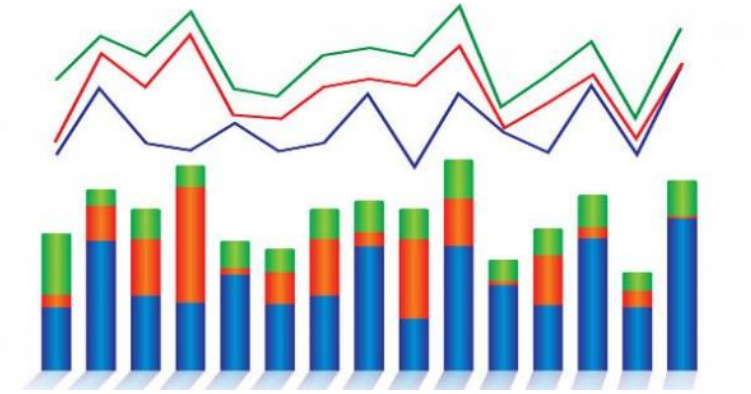
OUTCOME OF THE RISK ASSESSMENT

The risk assessment process should:



- **Identify and prioritise risk (score)**
- **Result in actionable outcomes**
  - **Mitigations**
  - **Plans**
- **Continuous, connected, traceable process**



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CORE AND STUDY KRI'S

	KRIs	Examples	Design Impact
Core KRIs	• Many KRIs used to detect site quality risk will be standard. • Core KRIs are often associated with safety and performance, but they can also be surrogate markers for quality risk and should be monitored and managed.	• AE rates • Inclusion/ exclusion deviations • Recruitment ratios • Early term rates • Data entry timeliness • Query rates	• Availability of historical data • Ability to determine thresholds based on historical data • Use of companion data
Study KRIs	• Designed to assess and monitor the critical data and processes for a study. • KRIs may also change during the course of a study, due to risk factors changing as the study progresses e.g. once enrollment is complete.	• Image quality assessment • Therapy specific assessment scores • Dose changes	• Threshold may be influenced by therapeutic area • Thresholds likely to be based on population • More likely to be exploratory

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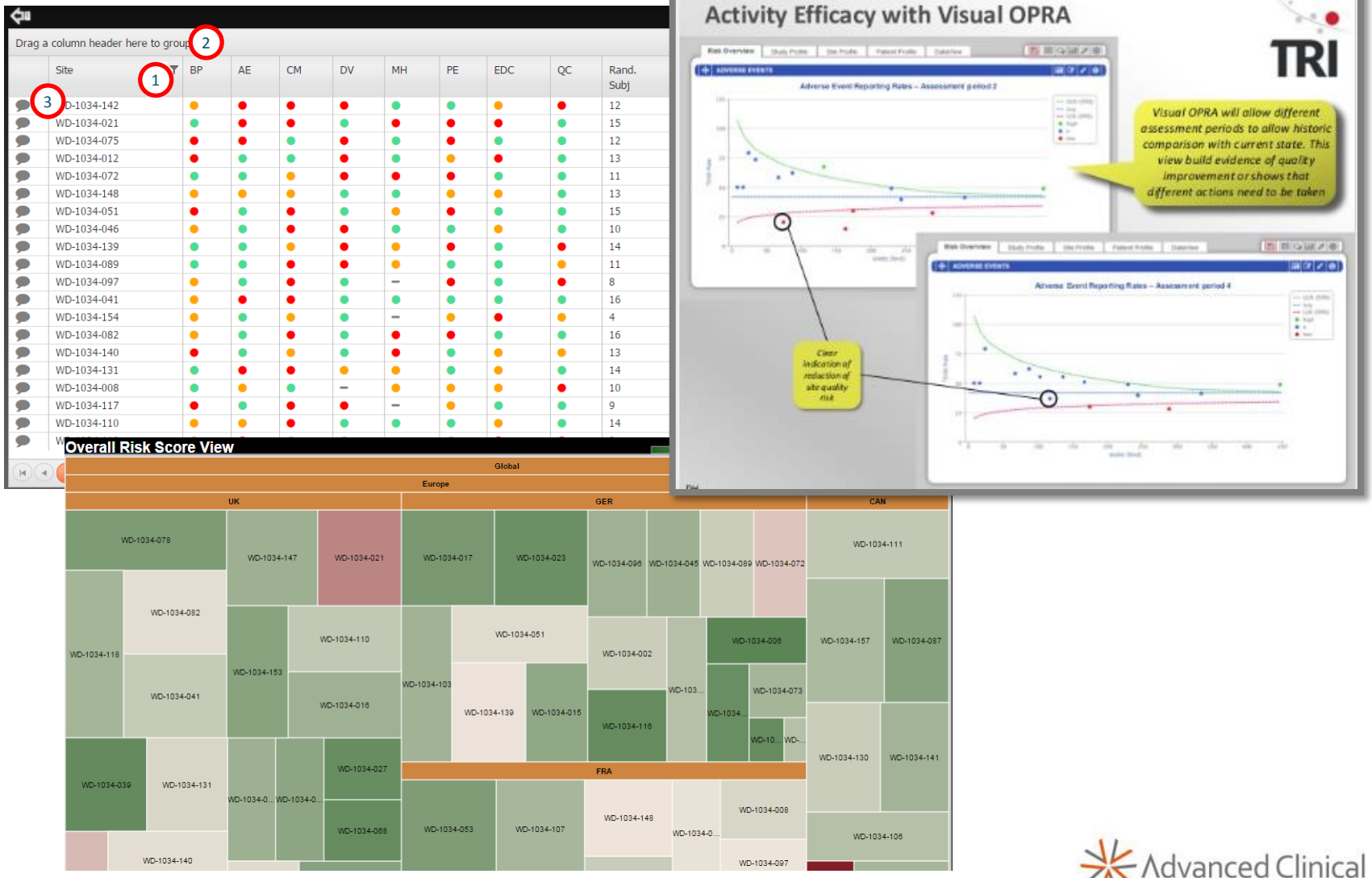
CENTRALIZED DATA MONITORING

		Risk Signal				
KRI Category	KRI Description	Data Quality	Protocol Compliance	Subject Safety	Site Engage-ment	Subject Retention
Enrollment	• Enrollment Rates • Screen Failure (SF) Rate • Reasons for SF • Discontinuation Ratio • Discontinuation Reasons	√			√	√
Safety	• AE Reporting Rate	√	√	√	√	
Data Quality	• Query Rate • Query Response Time	√	√		√	
Study Plan Compliance	• Data Entry Timeliness	√	√	√	√	
Protocol Compliance	• Protocol Deviation Rate • Protocol Deviation Type • Subject Visit Compliance	√	√	√	√	
Misconduct	• Digit Preference • Mean Value	√	√	√		
Unreliable Assessment	• Laboratory Sample Quality	√	√		√	

RISK-BASED MONITORING KRI'S



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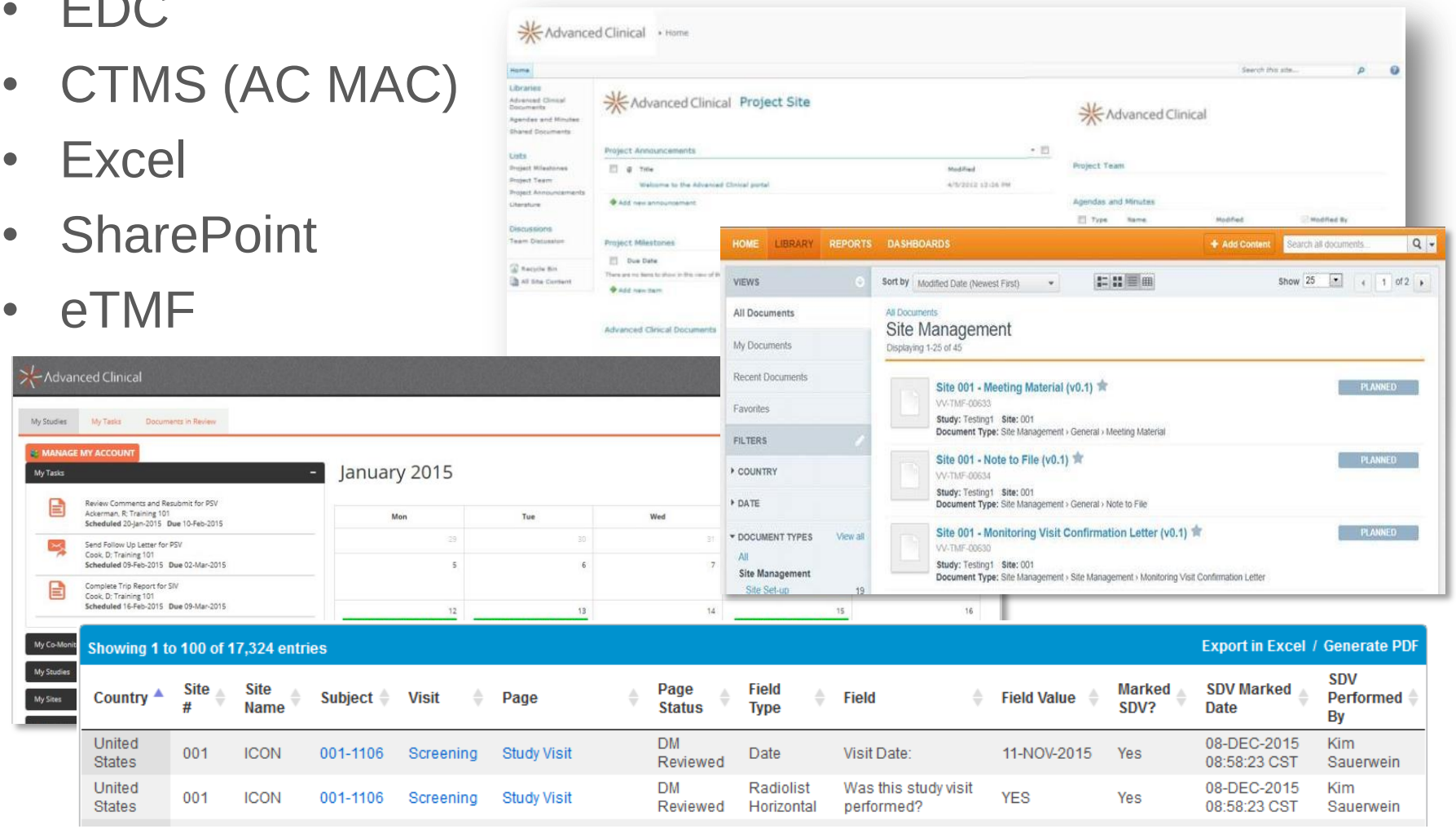
SOURCES OF TRUTH (SOT)

- EDC
- CTMS (AC MAC)
- Excel
- SharePoint
- eTMF



Country	Site #	Site Name	Subject	Visit	Page	Page Status	Field Type	Field	Field Value	Marked SDV?	SDV Marked Date	SDV Performed By
United States	001	ICON	001-1106	Screening	Study Visit	DM Reviewed	Date	Visit Date:	11-NOV-2015	Yes	08-DEC-2015 08:58:23 CST	Kim Sauerwein
United States	001	ICON	001-1106	Screening	Study Visit	DM Reviewed	Radiolist Horizontal	Was this study visit performed?	YES	Yes	08-DEC-2015 08:58:23 CST	Kim Sauerwein

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ELEMENTS OF FUNCTIONAL PLANS

	Central Monitoring	Clinical Monitoring Critical Data	Clinical Monitoring Critical Process
What will be reviewed?	KRIs	AE Term, start date	Sample Management
How it will be reviewed?	OPRA	On site	Remote contact [change in staff] Onsite [SIV] Remote/onsite [Response to trigger]
Frequency of review	Monthly	per guideline for study risk level	At SIV on change of site staff following observations from CM
Level of review	KRI and Data review	SDR/SDV - per guideline study risk level	Discussion with site Facility review
Response to triggers	Green rising Amber rising Amber static/ decreasing Red	As direct observation: defined as part of guideline (e.g. increase level of SDR if errors found) In relation to KRIs – aligned with CM	As direct observation :- Dependent on observation – covered either by Guidelines or Monitoring Plan In relation to KRIs - aligned with CM
Traceability of review	Actions documented in OPRA	Actions documented in CTMS	Actions documented in CTMS

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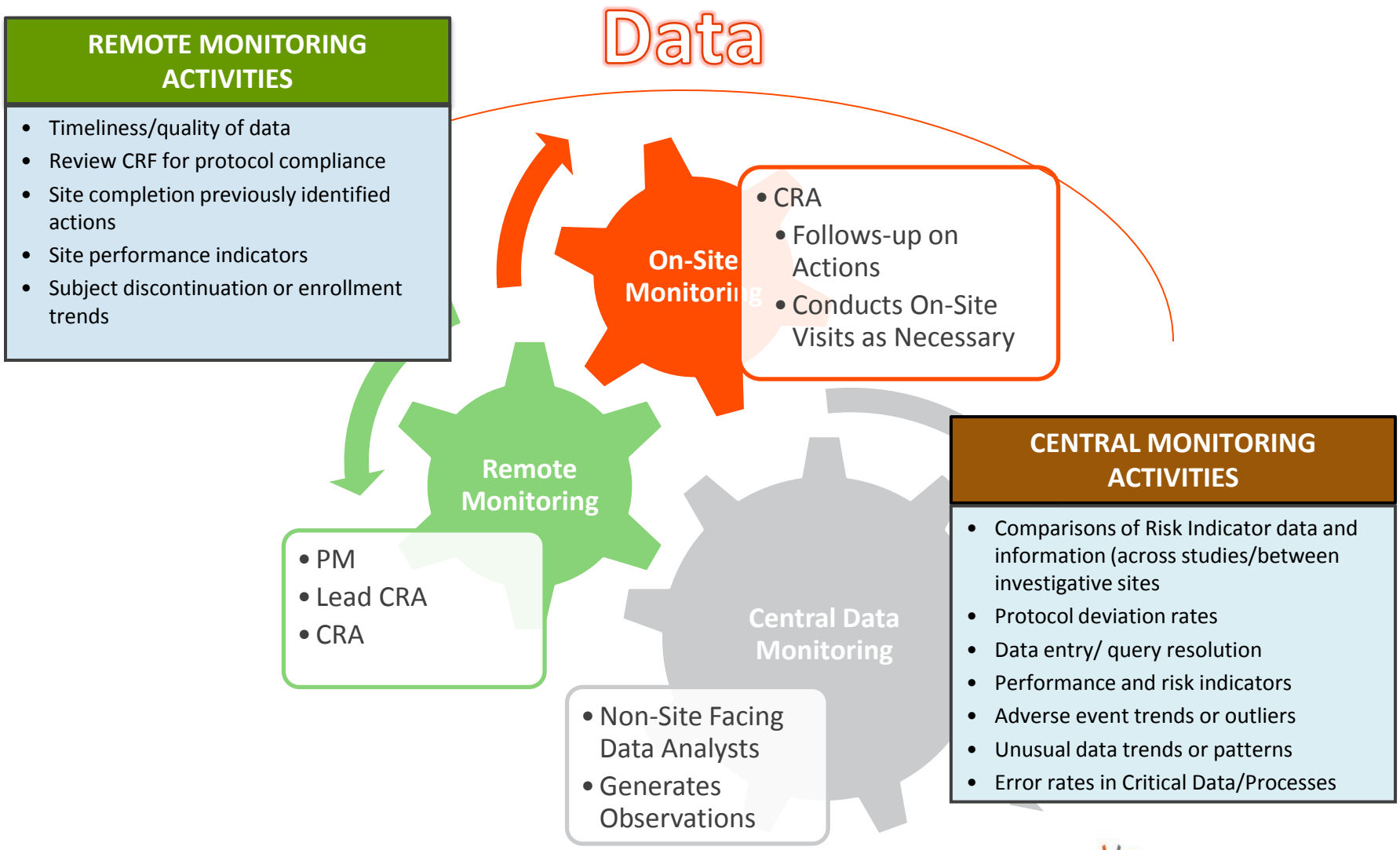
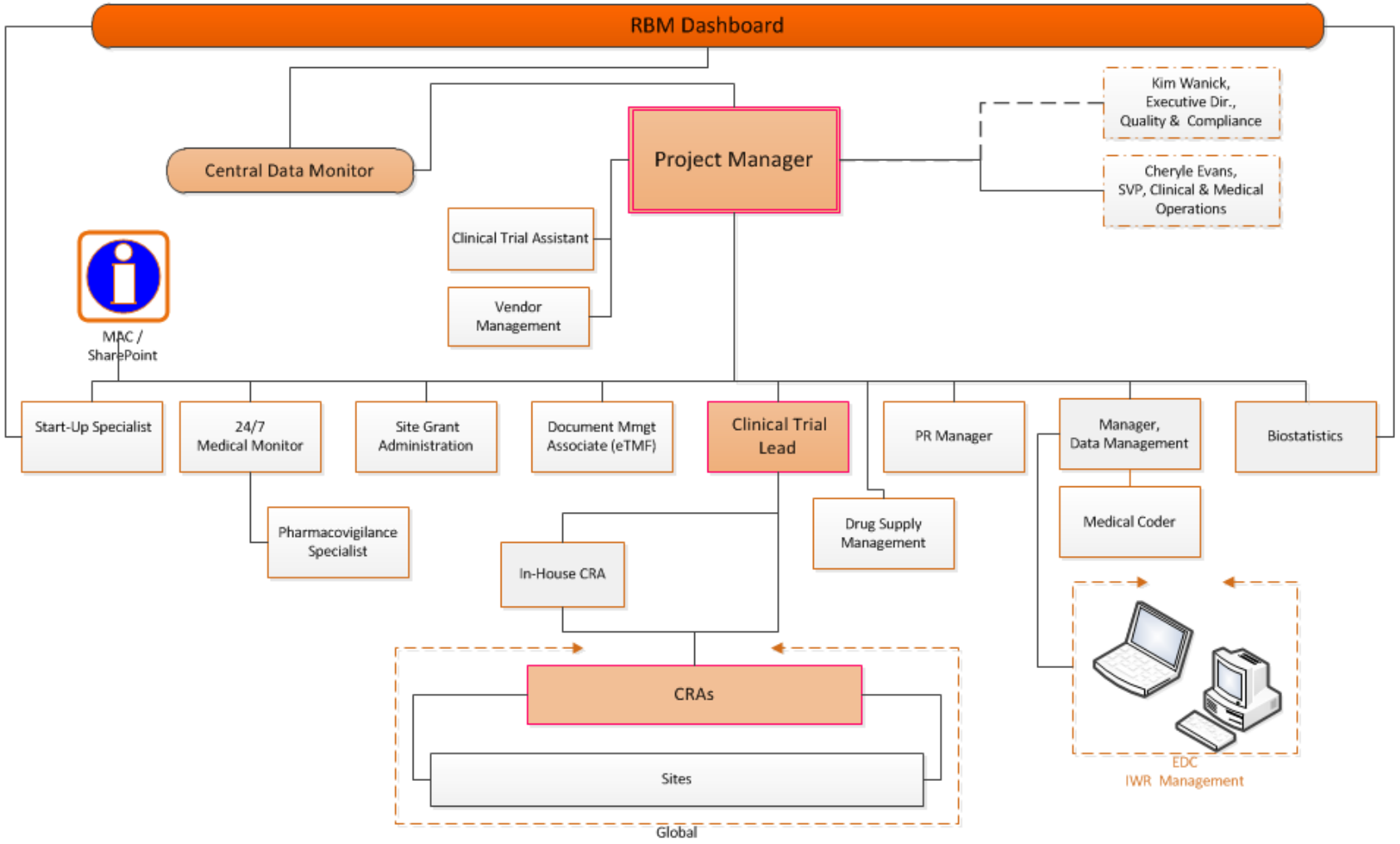
RBM STRUCTURE & FUNCTIONAL ROLES



PROJECT TEAM SCHEMATIC



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CENTRAL DATA MONITORING

What is it?

The ongoing review and trend analysis of data across sites and studies to support a dynamic, flexible and targeted site monitoring strategy and high quality study execution

How does it work?

- Monitor risk signal detection with OPRA KRI reports
- Report data issues to site monitors to support site monitoring strategy

Who does it?

- Central Data Monitor – A functional role filled by research staff with analytical skill sets by training and experience

Technology

- Alerts and triggers
- Visualizations that support efficient reviews
- Workflow manager

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ADVANCED CLINICAL RISK BASED MONITORING ACTIVITIES

Clinical Risk Management	•Risk oversight throughout the entire study •Indirect site relationship •Direct relationship with Centralized Monitoring, Remote Monitoring and On-site Monitoring
Centralized Monitoring	•Analytics data monitoring from FPI to database lock •Indirect site relationship •Direct relationship with Clinical Risk Management , Remote Monitoring and On-site Monitoring
Remote Monitoring Visit	•Subject level data and site metrics review from FPI to database lock •Virtual site relationship (telephone and email) •Direct relationship with Clinical Risk Management and On-site Monitor*, Centralized Monitoring
Remote Site Contact	•Triggered follow-up and site management from FPI to database lock •Virtual site relationship (telephone and email) •Direct relationship with Clinical Risk Management and On-site Monitor* and Centralized Monitoring
On-site Monitoring Visit	•Informed consent and IP and source document review •Direct site relationship •Direct relationship with Clinical Risk Management and Remote Monitor* and Centralized Monitoring

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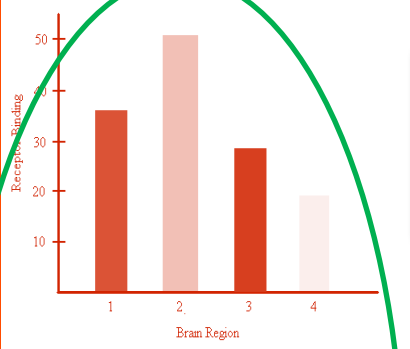
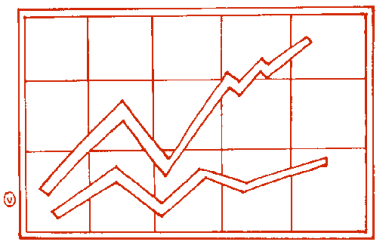
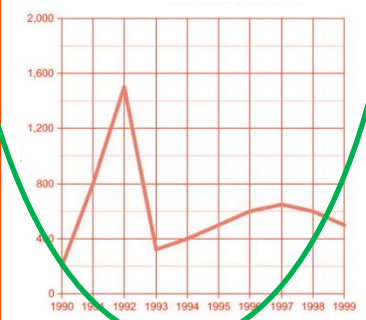
TRI OPRA ANALYTICAL TOOL: OBSERVATIONS & ACTIONS







KRI - Site by Site Data

Create observations against site or indicator

Create actions required to address noted issues and assign

Complete tasks detailed in action

Update action with findings/resolution

Close action when complete

Review action updates and create new if applicable

When all actions have been closed and no further action is deemed necessary close the observation

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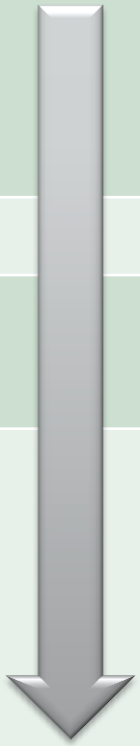
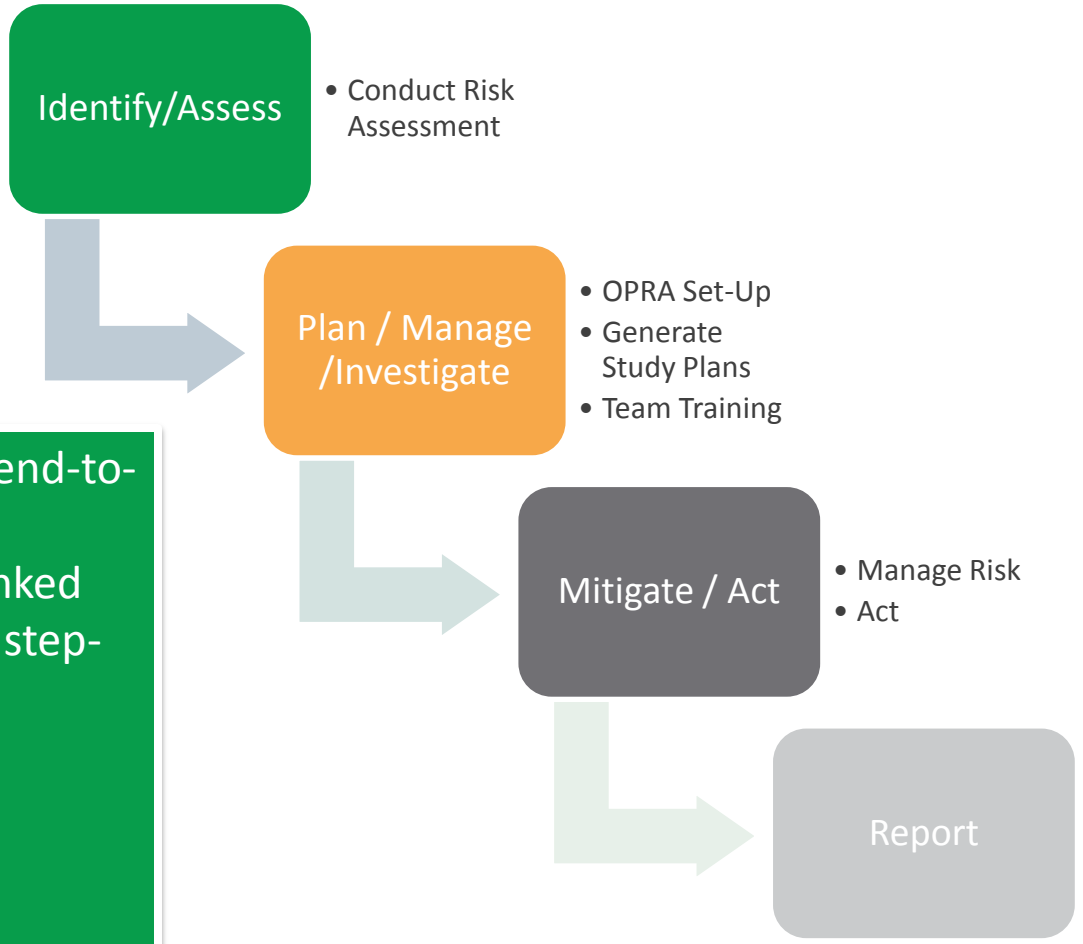
MINIMUM REQUIREMENTS FOR ONSITE VISITS AND SDV AND SDR

Minimum Requirement	High Risk (e.g., Ph I/II)	Moderate Risk (e.g., Ph III)	Low Risk (e.g., Ph IV)
Site Contact/Oversight • 1st On-site Visit • Max window for On-Site Visit • Remote Monitoring Schedule • Central Monitoring Schedule			
Individual Subject Review			
Core Critical Processes • Consent • IMP Supply Management			
Core Critical Data • SAE • AE • Eligibility • Prohibited Con Meds • IP Accountability • Non-Critical Data			

AC Policy will require a minimum SDV and SDR On-Site Monitoring determined by study Risk Assessment

END-TO-END PROCESSES



Developed detailed end-to-end process map schematic with 20 linked processes to outline step-by-step procedures:

- ✓ Assess
- ✓ Plan
- ✓ Manage
- ✓ Investigate
- ✓ Act

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RBM: SITE CONSIDERATIONS

Site Implications

- Increased involvement with the quality control of data capture and entry
- More time spent on quality management, process improvements, and corrective actions
- High priority on data entry timelines
- Communication method flexibility

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RBM: IMPACT TO INDIVIDUAL STAKEHOLDERS

Regulators

- Increased patient safety by earlier or remote data review
- Improved data quality

Clients

- Early detection of issues via a suite of monitoring methods (central, remote, onsite)
- Data visualisation to help identify trends and outliers which compliments existing medical review processes
- Enables targeted data collection
- Lowers overall risks associated with studies by enhanced monitoring capabilities
- More efficient distribution of study budget

AC

- Efficient and focused use of resource
- Delivery of better quality studies

Investigators

- Early detection of issues means fewer queries downstream
- Focused attention of CRA while onsite
- Access to CRA at defined timepoints during remote monitoring and other site calls

Patients

- Remote and centralised review increases patient safety while participating in trials
- Better quality trials to support new medicines coming to market

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FINANCIAL CONSIDERATIONS

Direct Service Costs

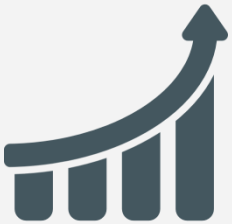
- Cost Neutral vs. Traditional costing

Pass Through Costs

- Cost Efficiencies related to reduced number of on-site visits

CONSIDERATIONS FOR RBM READINESS

RBM STUDY CONSIDERATIONS



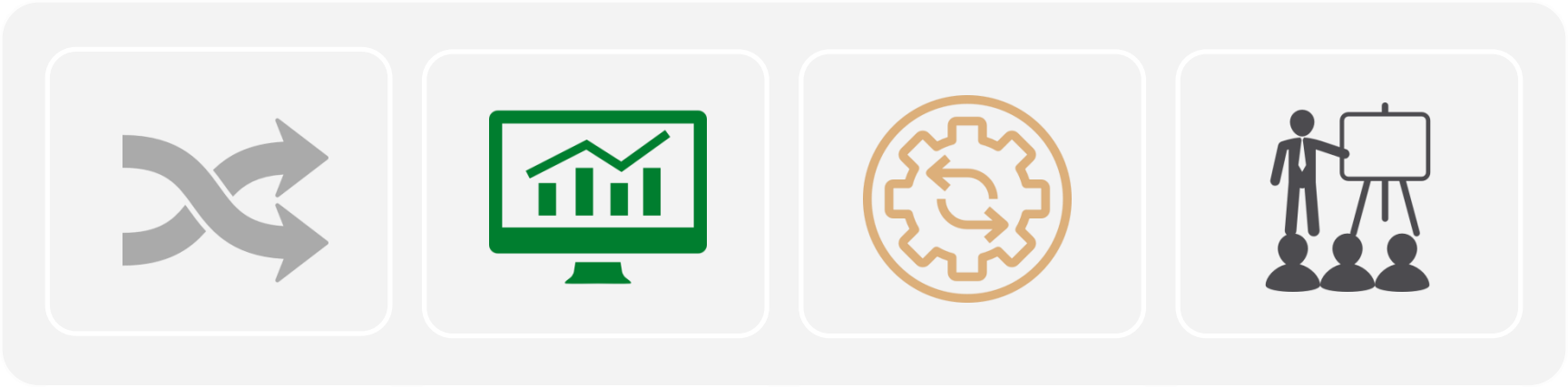
Study Phase

Global Study(ies)

Country Mix

High Volume of Data

RBM READINESS CONSIDERATIONS



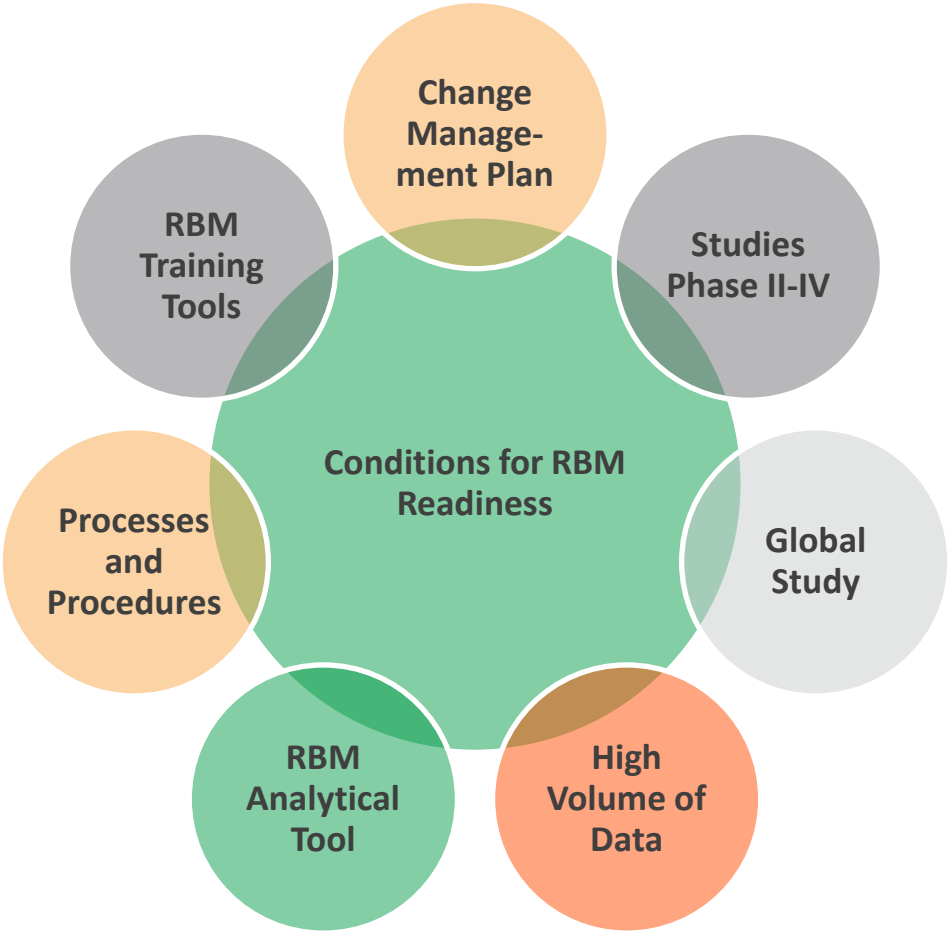
Change Management

RBM Analytical Tool

Process & Procedures

RBM Training Tools

CONDITIONS FOR RISK BASED MONITORING READINESS



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IN SUMMARY

- RBM is here to stay
  - Consensus that DDM will enhance quality, improve safety & reduce onsite monitoring costs
  - Technology is now available to assess data
  - Regulators onboard and providing guidance and support
- Change Management is a hallmark of achieving success
- Stakeholders are in every area of the clinical research arena
- Sites are an integral part of implementing a successful RBM program

QUESTIONS/COMMENTS/THOUGHTS

ADDITIONAL LINKS

- http://www.transceleratebiopharmainc.com/resources/
- http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf
- http://www.icr-global.org/crfocus/2012/23-1/understanding-risk-based-monitoring/
- http://assets1.csc.com/dvc/downloads/DIA_Defining_Risk_Based_Monitoring_Program.pdf
- http://www.cognizant.com/InsightsWhitepapers/Risk-based-Monitoring-Strategies-for-Improved-Clinical-Trial-Performance.pdf

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Advanced Clinical Contact:
Cheryle Evans, SVP, Clinical & Medical Operations
T: 847.943.2954
cevans@advancedclinical.com

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OPERATIONALIZING KEY RISK INDICATORS

KATIE OBERMEYER

21 JULY 2016

DEERFIELD, IL

INTRODUCTION

- KRI Selection
  - Process and considerations
- Defining KRIs
- Combining Data Sources
- Creating Flat Files

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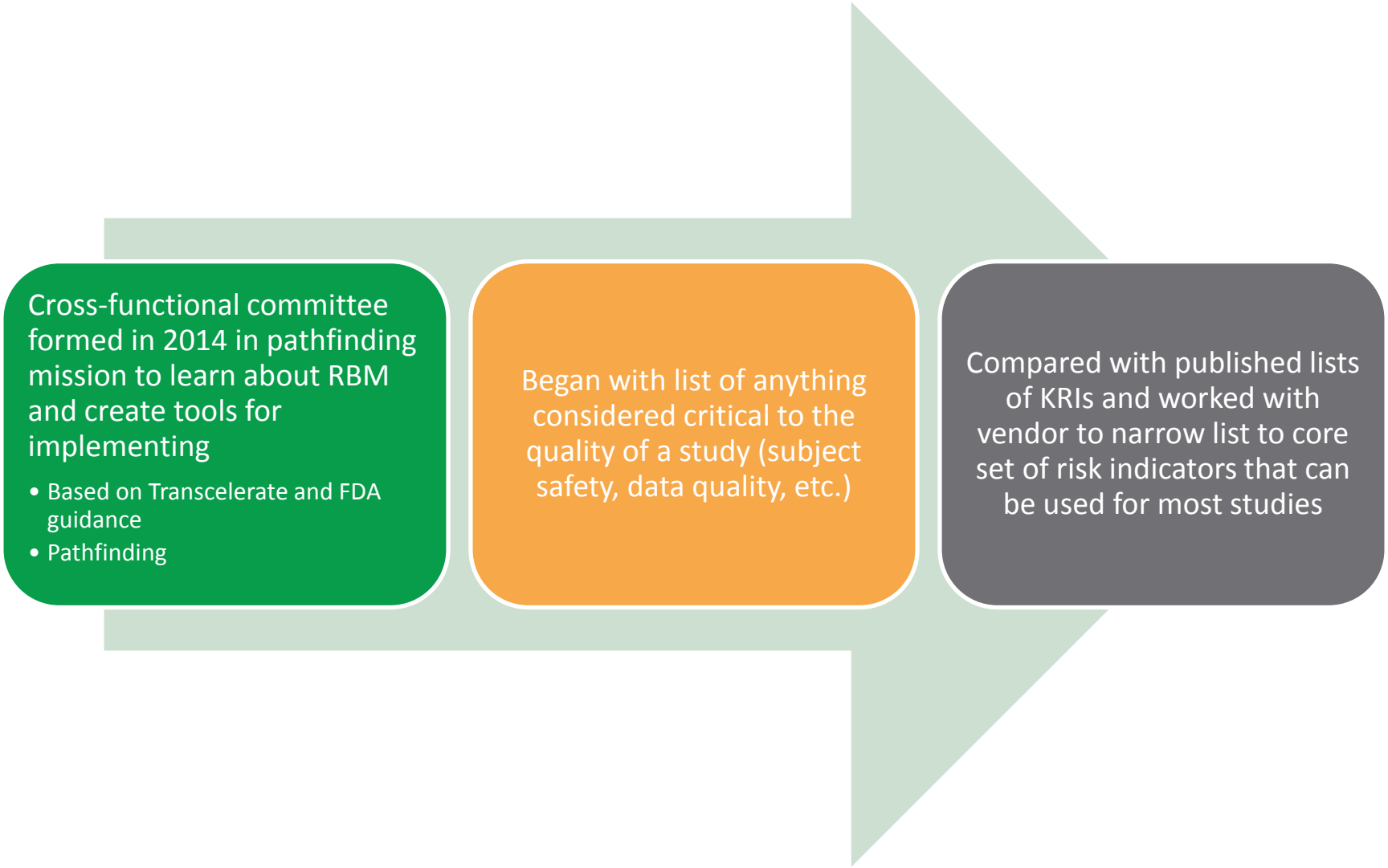
KRI SELECTION PROCESS



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KRI SELECTION CONSIDERATIONS

- Overall Goal – looking for trends at site level (not patient level)
- Ability to collect data to support KRI consistently across studies
  - May need to change current processes
  - e.g. protocol deviations may be collected in different sources (EDC, CTMS, CRA trackers), able to determine visit out of window
- Risk indicator vs. performance indicator
  - Risk indicators are variables considered to influence the quality of a study and can be used to detect potential issues or risk.
  - Performance indicator measures how well something is being done, may or may not indicate risk
    - e.g. site personnel turnover
- Core KRIs can be used for most studies. Study specific KRIs may be identified during a risk assessment of the study

CORE KRIs

KRI Category	KRI Description	Definition
Enrollment	▪ Enrollment Rates ▪ Screen Failure (SF) Rate ▪ Reasons for SF ▪ Discontinuation Rate ▪ Discontinuation Reasons	➢ Number enrolled per unit of time ➢ % of screened subjects who SF ➢ Box plot of reasons for SF (if captured) ➢ % of enrolled subjects who discontinue ➢ Box plot of reasons for discontinuation
Safety	▪ AE Reporting Rates ▪ SAE Reporting Rates	➢ Number of AEs (or SAEs) per time on study
Data Quality	▪ Query Rate ▪ Query Response Time	➢ Number of queries per 1000 data points ➢ Mean number of days from query issue date until resolved
Study Plan Compliance	▪ Data Entry Timeliness	➢ Mean number of days from subject visit until data entry
Protocol Compliance	▪ Protocol Deviation Rate ▪ Protocol Deviation Type ▪ Subject Visit Compliance	➢ Number of deviations per time on study ➢ Box plot of reasons for deviation ➢ % of visits out of protocol-defined window
Misconduct	▪ Digit Preference ▪ Mean Value	➢ % of values (systolic BP) ending in 0 ➢ Mean value for given variable (BP, age, lab)
Unreliable Assessment	▪ Laboratory Sample Quality	➢ % of non-evaluable lab samples

DEFINING KRIs

KRI Description	Formula	Considerations
AE Reporting Rate: Number of AEs per time on study, compared to study population.	A = Total # of AEs for all subjects at the site B = Total time on trial for all subjects at the site (Sum of (date of last (most recent) visit for each patient - Date first dose) X Axis = Subject Months Y Axis = AEs/subject Month	▪ How to define time on trial? o Use discontinuation date? Most recent visit date? o Subject months vs. years
Query Rate: Cumulative queries / 1000 data points / Site	A = Total # of queries accumulated to date for a given site B = Total number data points submitted for that site /1000 X axis = datapoint (1000s) Y axis = query rate	▪ How to get total number of data points for subject or site? Not standard report in some EDC systems (e.g. Rave) ▪ Consider all queries? System vs. manual

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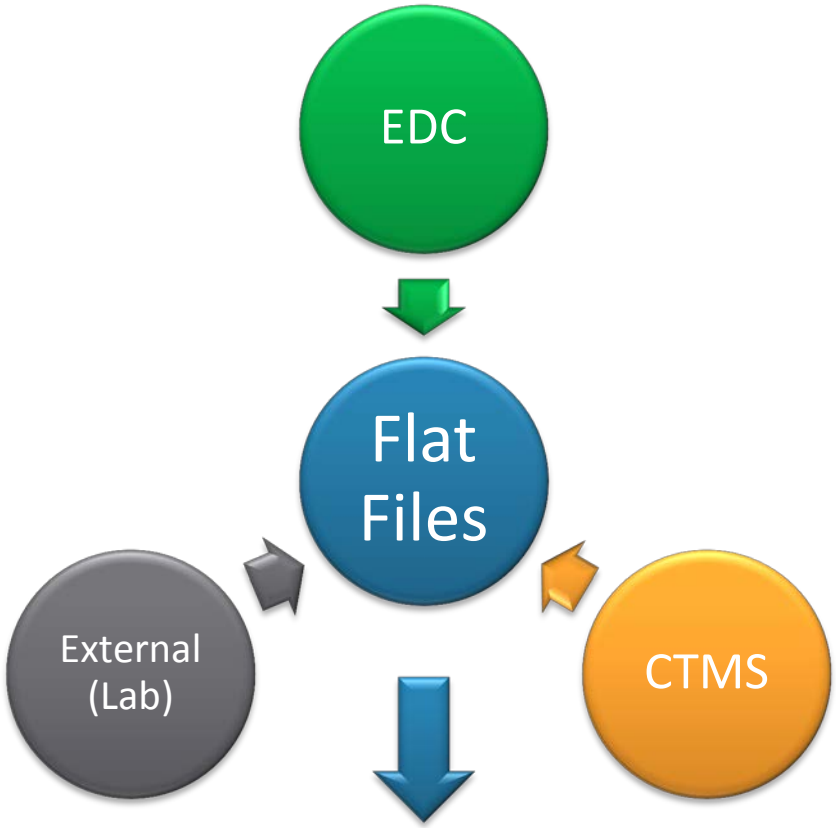
DATA SOURCE CONSIDERATIONS

DATA SOURCE CONSIDERATIONS

- Data from multiple sources
  - EDC, CTMS, external vendor data
  - Identify person or function responsible for
  - Coordinate with different functional areas (DM, clinical, stats, safety)
- Consistent subject ID, site ID, etc. across sources
- Ensure needed data captured in order to use KRI (e.g. deviation categories)

FLAT FILES



- Comma, tab, or pipe-delimited files used for calculation of KRI and Data Review
  - 11 flat files supported 16 KRIs
- Programmed majority of datasets in SAS and modified external CSV files
- Flat file contents (variable names, formats) must stay same during course of study
- Test data used to develop and validate KRIs in OPRA

SUBJID	STUDYID	SITEID	COUNTRY	AGE	SEX	RFSTDTC	STATUS	Etc.
1001	ABC-001	001	USA	34	M	10JUN2015	COMPLETED	

TAKEAWAYS

- Be open to pathfinding
- Cross-functional collaboration very important
- When selecting KRIs, focus on the big picture
- Technology is changing rapidly

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VISUAL/ANALYTICAL TOOL DEMO

PATRICIA WOZNIAK
PHUSE SINGLE-DAY EVENT
21 JULY 2016

GOAL OF THE DEMO

- Demonstrate functionality of a visual analytic tool for RBM
- Identify sites with high overall risk scores
- Drill down to KRI visualizations
- Identify outlier sites
- Evaluate level of risk (prioritize)
  - Red = outlier, not necessarily bad
- Decide on action plan
- Note: Central data reviewer must have strong analytic skills

OPRA from Triumph Research Intelligence (TRI)

SOME POINTS TO CONSIDER

- The goal tool is to identify outlier sites, not subjects
- Data are typically refreshed monthly
- Why not real-time?
  - There is a cost associated with each update. The data files have to be downloaded and massaged, then uploaded into the tool.
  - Once an update is run, the central data reviewer needs time to review the new results and create observations, and the CRAs need time to perform any needed actions.
  - Unless a study enrolls very quickly, results will not change much from day to day or even week to week.

OPRA can show changes over time: Are interventions working to reduce risk?

THE CLINICAL TRIAL FOR THE DEMO

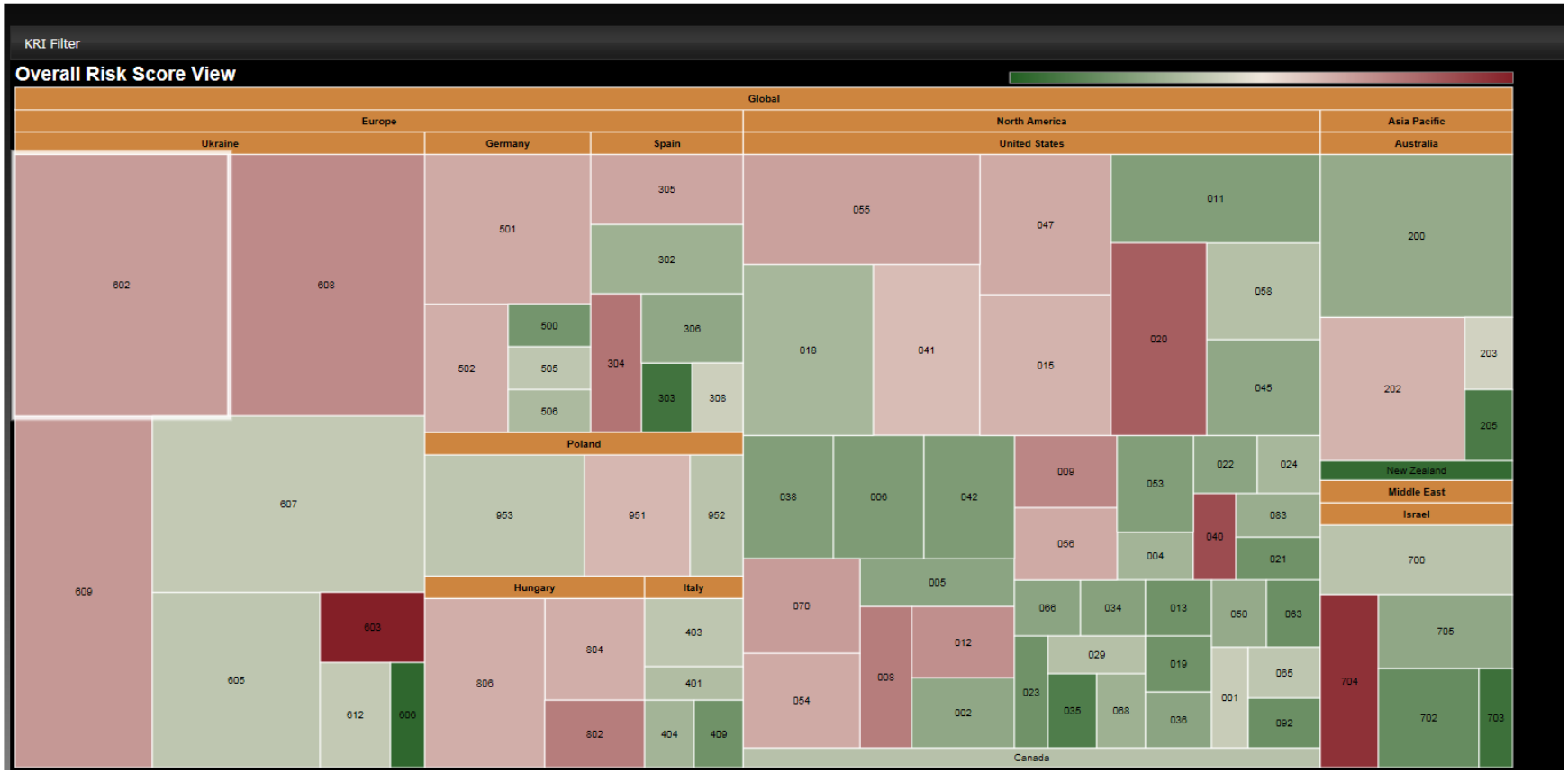
- Global multi-center Phase 3 ongoing clinical trial
- Randomized, placebo-controlled, parallel group
- 2:1 randomization
- Sample size: 240 completers

HEAT MAP (STUDY PROFILE)

- Rectangle for each site
- Organized by region, country
- Sites with more subjects have a larger area
- Dark red = high risk score
- Dark green = low risk score

Is there a region that stands out?

HEAT MAP (STUDY PROFILE)



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RISK OVERVIEW REPORT

- Sites are sorted by risk score, with highest risk at the top
- Information for each site:
  - “Risk” By KRI (red, amber, yellow, green)
  - Number of randomized subjects
  - Overall Risk Score
  - Country

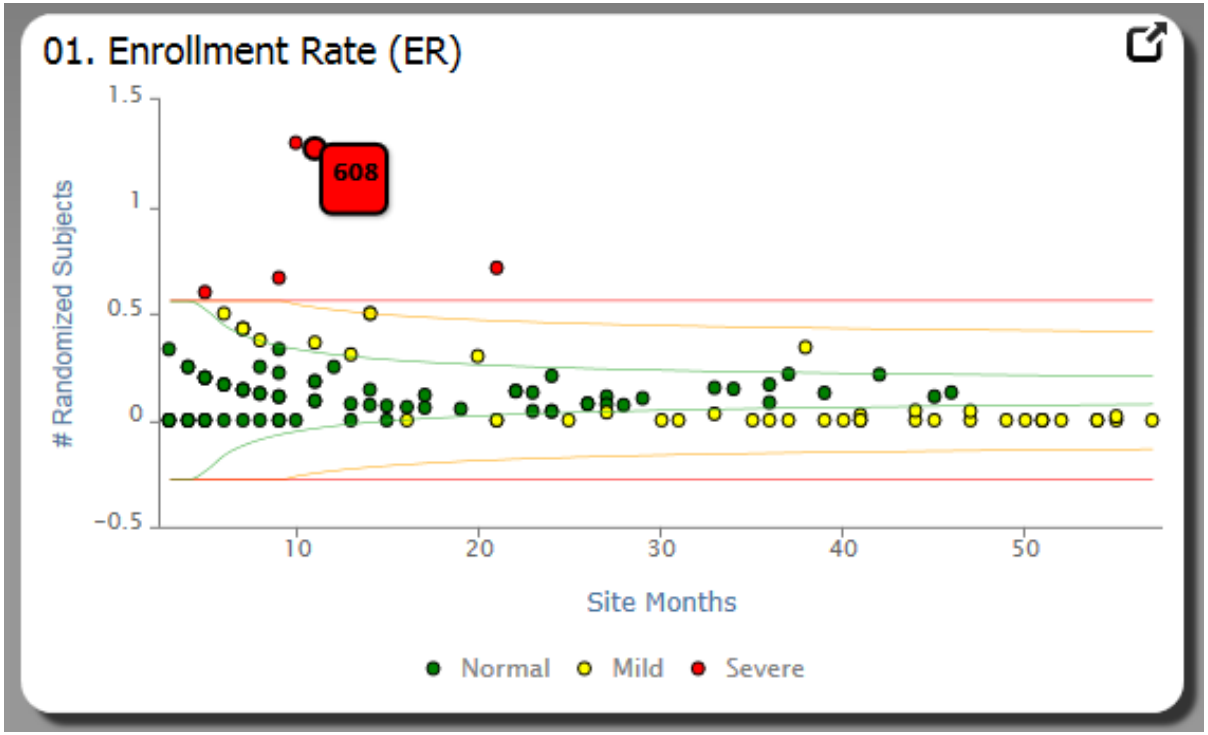
Focus on sites with some minimum number of subjects

RISK OVERVIEW REPORT

Site	ER	SFR	DR	AE	PD	DET	SAE	QRT	EDP	LSQ	MVO	Rand. Subj	Score	Country
603	-	-	-	-	●	-	-	●	●	-	-	2	89	Ukraine
704	●	●	●	-	●	-	-	●	●	●	●	3	85	Israel
040	●	●	-	-	-	-	-	●	-	●	-	1	79	United States
020	●	●	●	●	●	●	●	●	●	●	●	5	75	United States
304	●	-	-	●	●	●	●	●	●	●	●	2	70	Spain
008	●	●	-	-	●	-	-	●	●	●	●	2	68	United States
802	●	-	-	-	●	●	-	-	●	●	●	2	68	Hungary
009	●	-	-	-	●	●	-	●	●	●	●	2	66	United States
608	●	●	●	●	●	●	●	●	●	●	●	14	65	Ukraine
012	●	●	-	-	●	-	-	●	●	●	●	2	64	United States
609	●	●	●	●	●	●	●	●	●	●	●	13	62	Ukraine
070	●	●	●	●	-	●	●	●	●	●	●	3	61	United States
602	●	●	●	●	●	●	●	●	●	●	●	15	61	Ukraine
055	●	●	●	●	●	●	●	●	●	●	●	7	60	United States
305	●	●	●	●	●	●	●	●	●	●	●	3	59	Spain
056	●	●	-	●	●	●	●	●	●	●	●	2	58	United States
047	●	●	●	●	●	●	●	●	●	●	●	5	58	United States
054	●	●	●	●	●	●	●	●	●	●	●	3	58	United States
501	●	●	●	●	●	●	●	●	●	●	●	7	58	Germany
804	●	●	●	-	●	●	-	-	●	●	●	3	57	Hungary
502	●	●	●	●	●	●	●	●	●	●	●	3	57	Germany

FUNNEL PLOTS

- The KRI thresholds move closer together as the volume increases (increased sample size→reduced variability)
- Can filter so we see all sites or a subset based on color of circles



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ENROLLMENT RATE

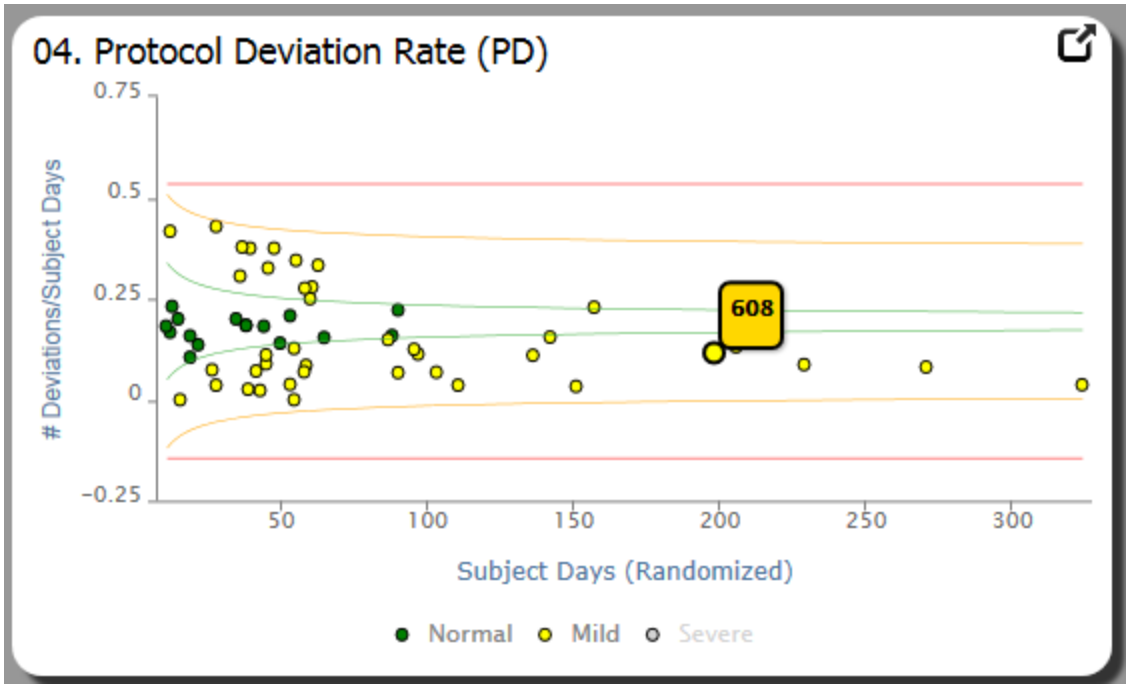
- Enrollment Rate: x-axis is number of months of enrollment for the site, y-axis is number of subjects randomized per month
- Site 608 is red for enrollment rate, indicating that the site is an outlier, with 1.27 randomized subjects/month
- Although Site 608 is an outlier, it is not necessarily a problem site
- What actions might be taken for Site 608?
  - Find out what the site is doing differently that might be implemented by other sites
  - Trigger a site visit to assess compliance with the protocol (e.g., inclusion/exclusion criteria) and data quality

ENROLLMENT RATE

- Note that there are no red outliers at the bottom of the plot—the threshold is negative, and enrollment rate is always positive
- Many sites have not yet randomized subjects in up to 5 years, which accounts for the 0's at the bottom of the funnel plot
- Consider closing long-term non-enrolling sites due to inactivity

PROTOCOL DEVIATION RATE

- Volume = total number of days in study for randomized subjects
  Rate = # deviations/subject day
- Site 608 has 198 subject days and 0.12 deviations/subject day, for a total of 23 deviations



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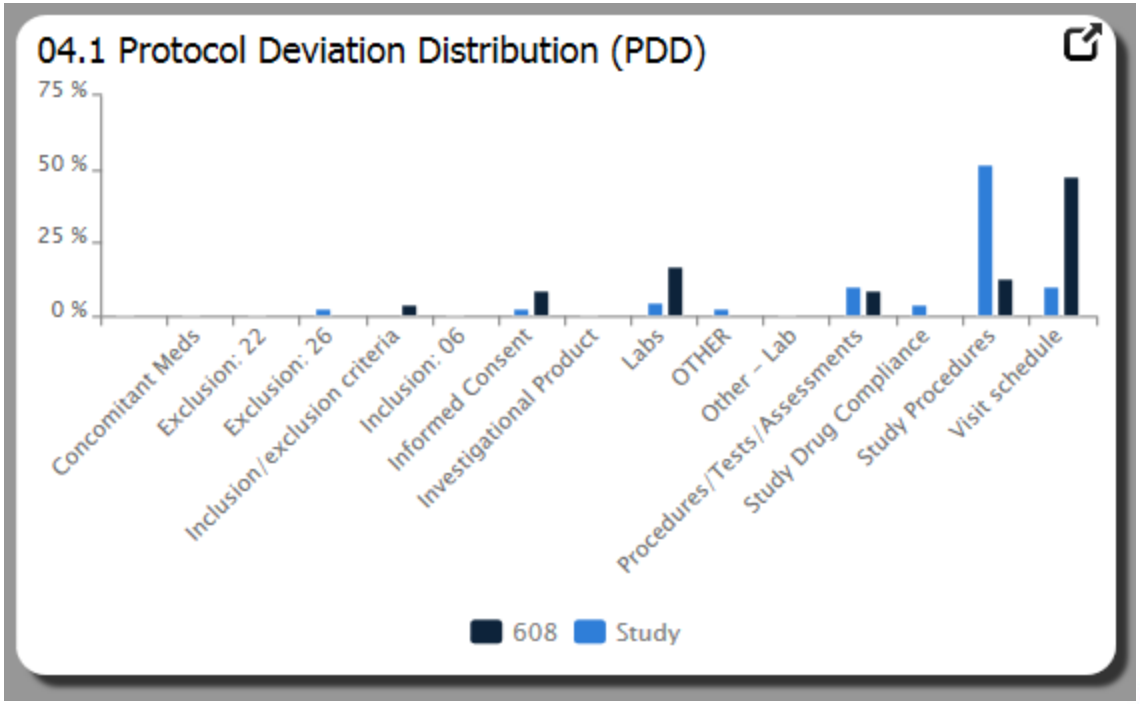
PROTOCOL DEVIATION RATE

- The bar chart shows the distribution of protocol deviation categories for Site 608 compared to all sites combined
- The most common deviations for Site 608 are related to the visit schedule, while the most common deviations for the study as a whole are related to study procedures



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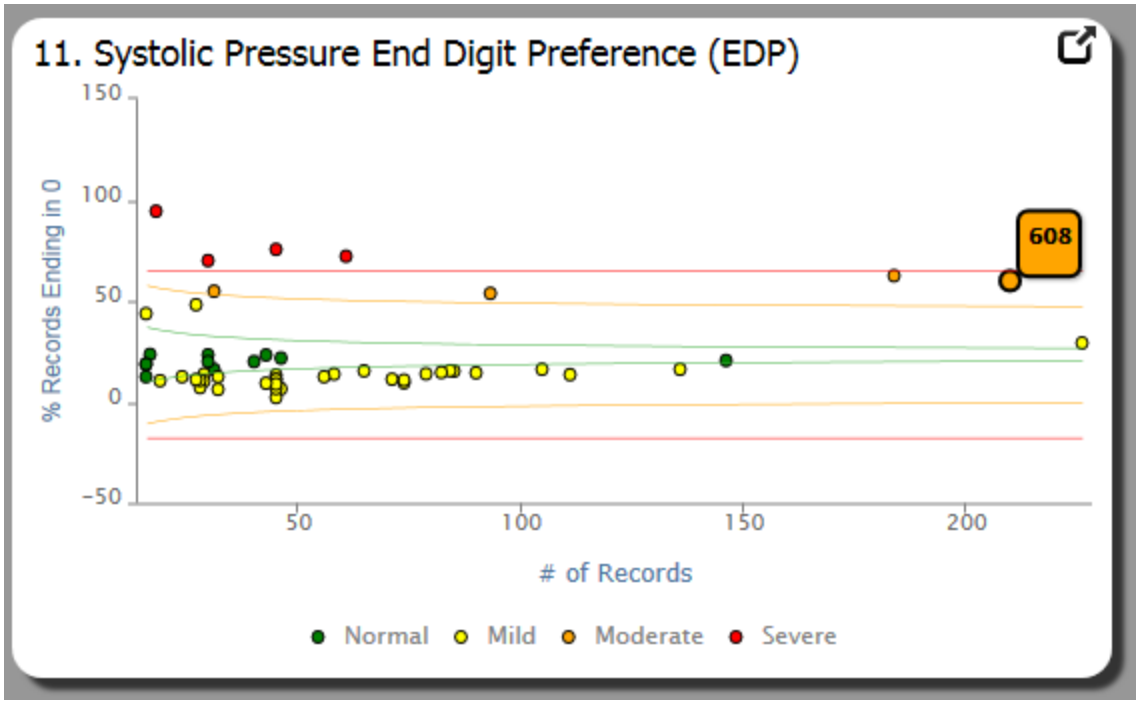
END DIGIT PREFERENCE

- Volume = Number of systolic blood pressure measurements
- Rate = % of blood pressure measurements ending in 0
- Site 608 is amber, with 60% of SBP values ending in 0



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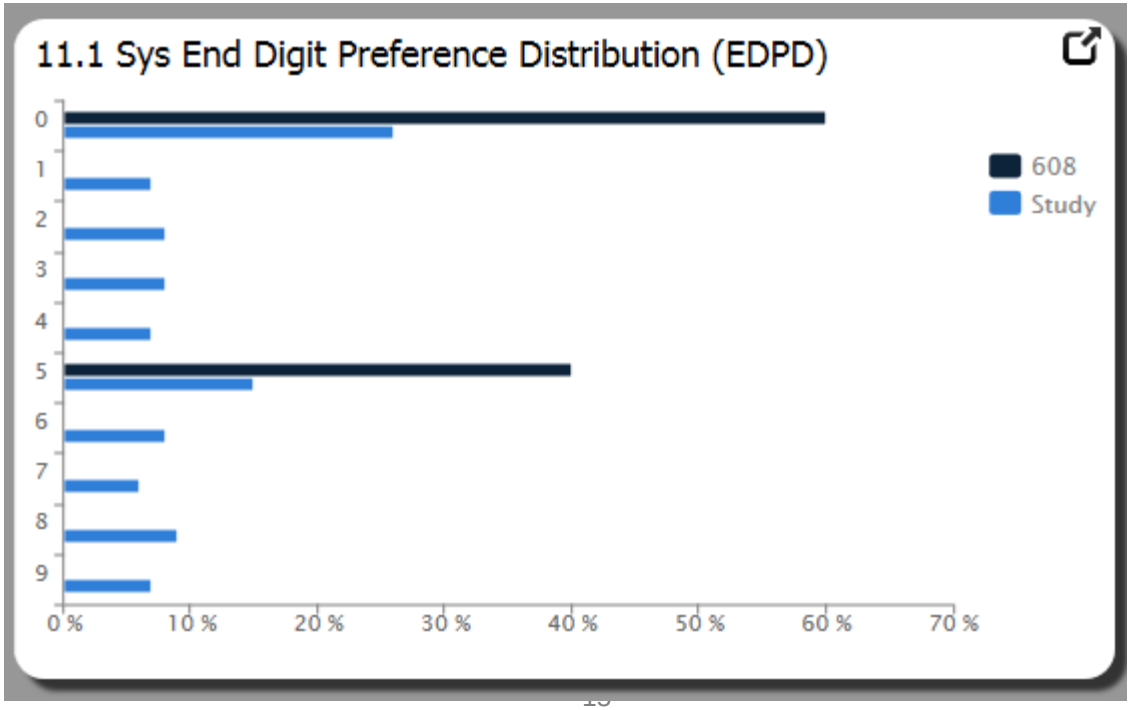
END DIGIT PREFERENCE

- Overall, 26% of SBP values end in 0, and 15% end in 5
- For Site 608, 60% of SBP values in in 0 and 40% end in 5
- What might be going on at the site?
- What actions might be taken?



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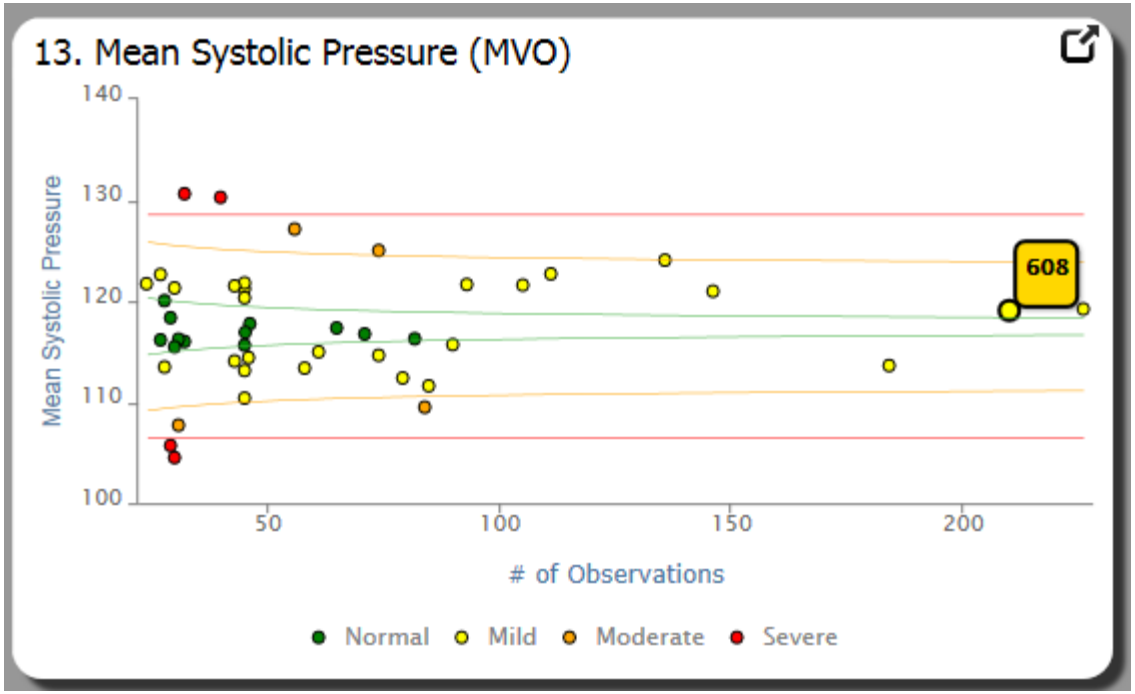
MEAN SYSTOLIC BLOOD PRESSURE

- Volume = Number of SBP measurements
- Rate = Mean of all SBP values
- Outliers in both directions
- Site 608 has a value of 119.10, which is yellow
- The funnel plot narrows at the right so that the range for normal values is small



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SUMMARY

- The central data reviewer needs to have strong analytical skills.
- The central data reviewer identifies outlier sites for each KRI and creates observations in OPRA
- Each outlier is investigated to determine what action if any, will be taken and notes the action in OPRA
- Once an issue is resolved, the action is closed out
- An outlier may or may not signal a problem (red is always bad)
- The visual/analytic tool is just one of many components of a successful RBM program

QUESTIONS/COMMENTS/THOUGHTS