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Inspect what you Expect

Risk Management Programs and Implementation

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Agenda

- Understanding ICH E6 (R2)
- Risk Based Quality Management
- Centralized Data Analytics
- Finding a Platform that work for you

PCMG

Wartime Fighter Bomber: Illustrating the Point

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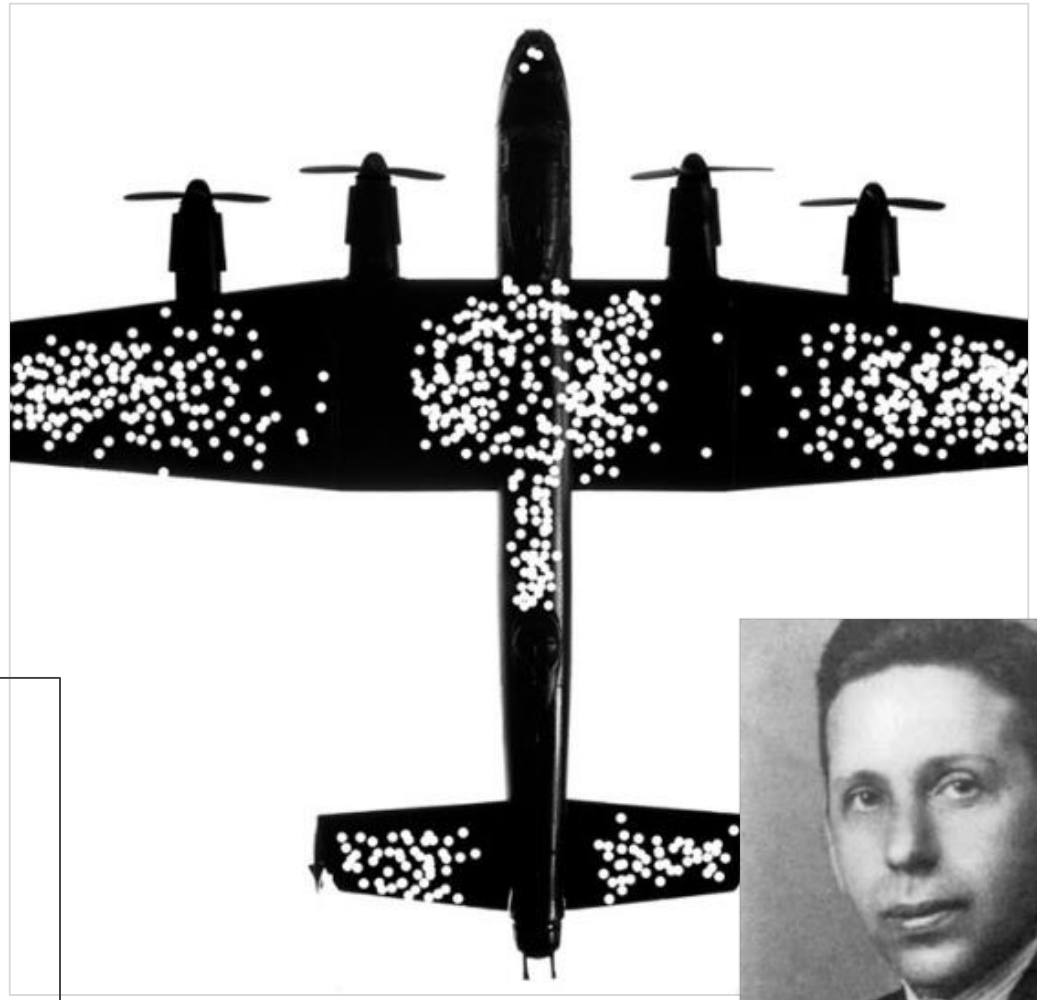
- Bullet hole data, planes returning from combat
- “Clearly, we need more armor in areas with pattern”
- Abraham Wald*, *“Where are the ones that didn’t make it back?”*
- Completely flips the analysis



*Hungarian mathematician

Survivor Bias / Data Bias

- Are you only looking at part of the picture, a.k.a. the ‘survivors’?
- Solutions emerge when you investigate what you cannot easily see.

History of Risk- Based Regulations

- Dec 2012: OECD Recommendation on the Governance of Clinical Trials
- Mar 2013: FDA Guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.
- Nov 2013: EU GCP IWG Reflection paper on risk-based quality management in clinical trials
- Apr 2014: regulation (EU) No. 536/2014
- Apr 2017: Risk proportionate approaches in clinical trials – EU recommendations
- Jun 2017: ICH E6 (R2) becomes effective in the EU
- Mar 2019: FDA Draft Guidance: A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers.

ICH GCP E6 R2 RBM REQUIREMENTS

- **Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased.**

- **Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches.**

- **Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results.**

- **Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.**

*This ICH GCP Guideline Integrated Addendum provides **a unified standard for the European Union, Japan, the United States, Canada, and Switzerland** to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions.*

ICH GCP E6 (R2) RBM REQUIREMENTS

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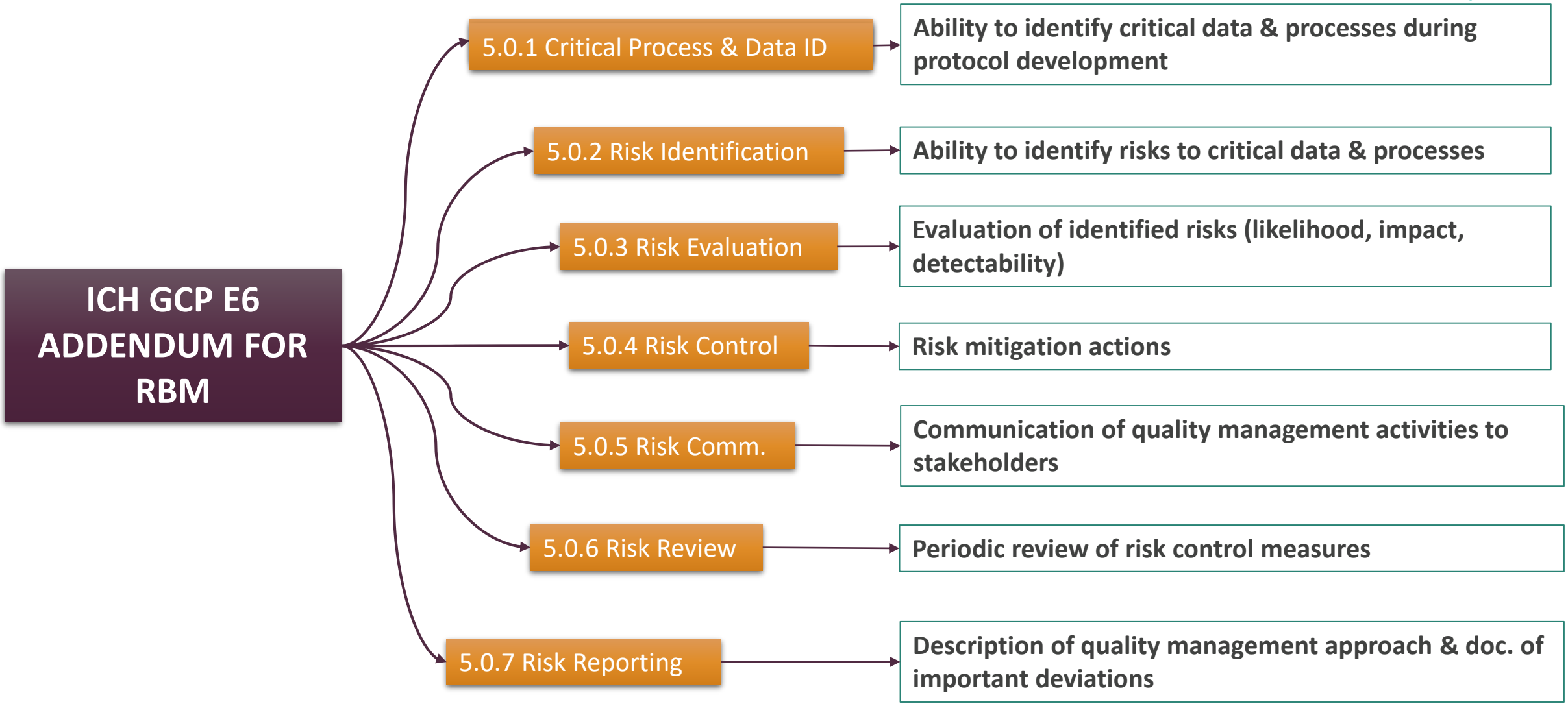


5.2.2 Sponsor Oversight and 5.18.3 Action Items

FDA RBM Workshop

https://www.youtube.com/watch?v=xp8Wp0Upuvo

- Held on 17 July 2019
- Regulatory Agencies – FDA, EMA
- Pharmaceutical Companies
- Academics
- Service Providers – CRO, Consultants, Service Companies

FDA RBM Workshop
FDA Comments – David Burrow

Risk Based Quality Management is NOT JUST risk-based monitoring

Why?

- Quality, reliability, interpretability
- "The absence of errors that matter"
- Regulatory requirements to ensure proper monitoring

} **APPROVABILITY**

How?

- Risk assessment → Protocol Development → Risk-Based Monitoring
- Monitoring in a risk-based manner
- Pre-specified plan, **based** appropriate assessments, **with** mitigation, escalation & remediation strategies

What? Varied monitoring activities (**can be risk based or NOT**)

- On-site
- Remote
- Centralized

FDA RBM Workshop
EMA Comments – Camelia Mihaescu

Monitoring Tools

- Type and combination of monitoring should be **trial specific**
  - On-site
  - Remote
  - Centralized
- On-site monitoring with high SDV is **not the only means** to ensure patient safety
- Monitoring strategies that involve **central tools** to identify the need targeted monitoring visits based on assessment of accrued data and information
- Monitoring activities should be **documented**
- Monitoring plans should be **reviewed and updated**, based on updated risk assessment and mitigation plan.

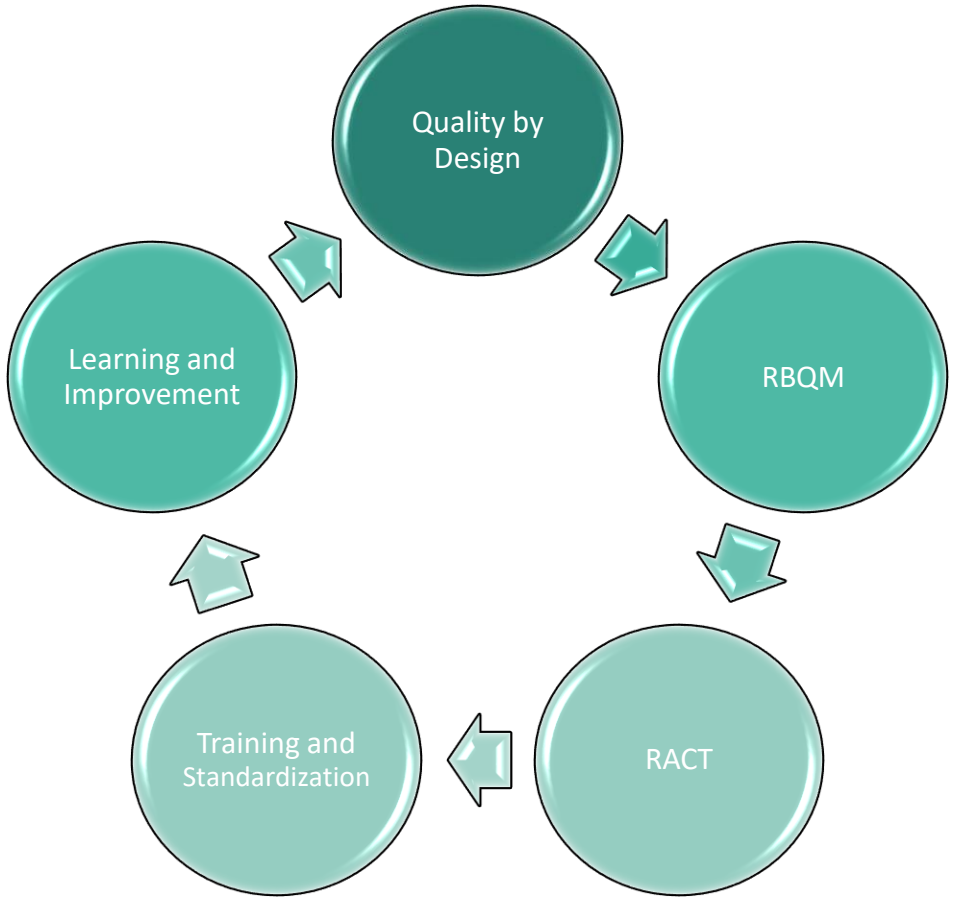
QbD (Quality by Design)

- Quality is designed into the study protocol and processes
- Focus on critical factors -> ensure protection of study subjects and data reliability
- Proper management of the risks to critical quality factors (Risk Based Quality Management)

Risk Based Quality Management

ICH GCP E6 (R2): *The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.*

Basics of Risk Based Quality Management



- *Quality by Design* is proactive
- RBQM as data-driven process to support risk identification, analysis, management and reporting
- RBQM can be supported by manual and automated tools
- Constant adaptation to changing environment and improvement
- Ensure quality of data

Dynamic Process

Key Terminology for RBQM

What is a RISK?

A RISK is any **uncertain** event or situation that has the **potential** to adversely impact subject safety, integrity of data that is essential to decision making or the study objectives

How is a RISK different from an ISSUE?

An ISSUE is an event or situation that **already exceeds** predefined tolerance levels and adversely impacts subject safety, integrity of data that is essential to decision making or the study objectives

[A risk that already happened]

What is RISK-BASED QUALITY MANAGEMENT (RBQM)?

RBQM is an **adaptive methodology** which **focuses on the quality** of data by continually assessing the inherent risks and the importance of the data collected, and implementing the **appropriate mitigating** strategies

Key Terminology for RBQM (cont.)

What is a RACT?

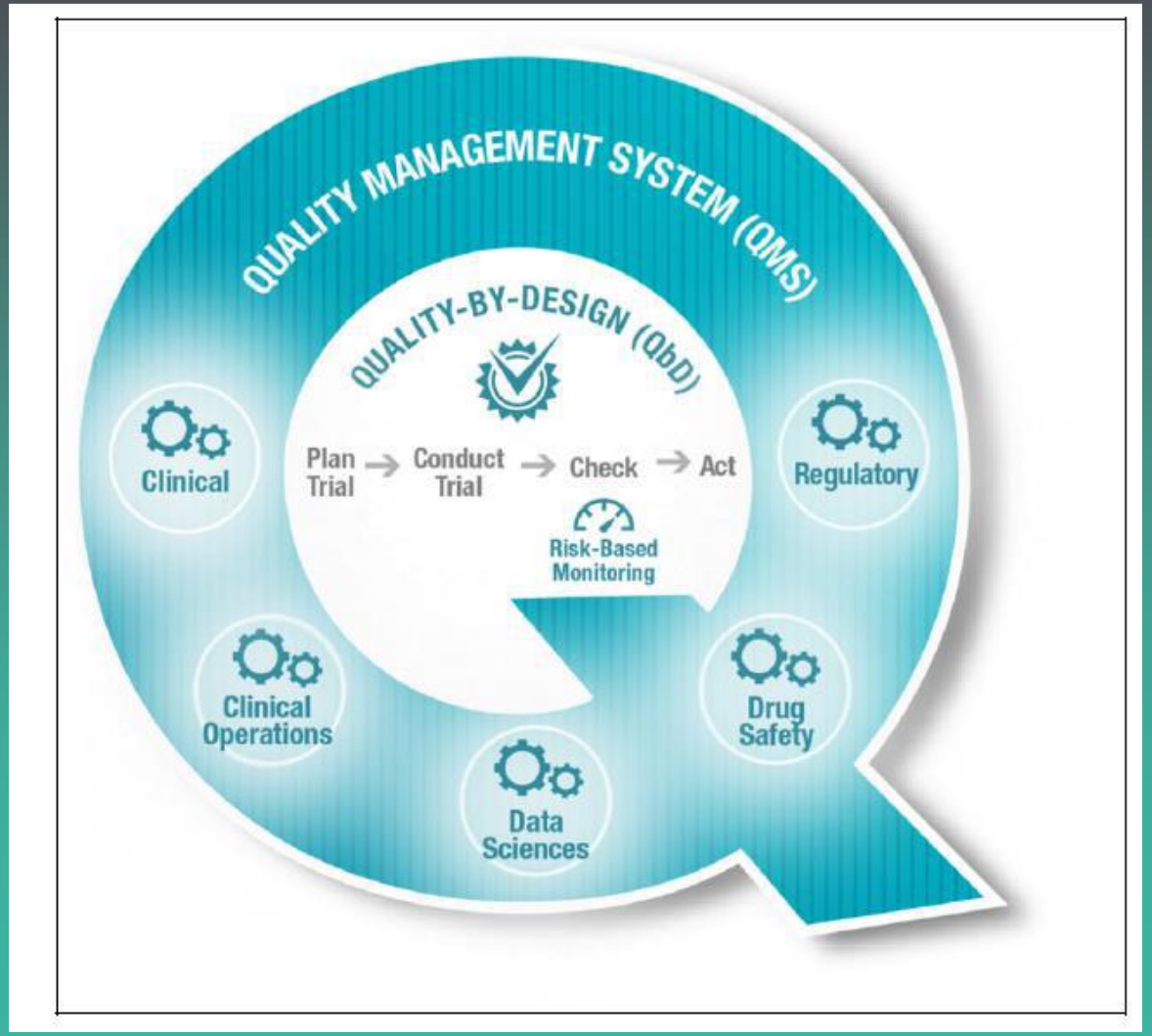
Risk **A**ssessment and **C**ategorization **T**ool (RACT) used to help identify, evaluate and manage risks during a study. The RACT is a tool based off TransCelerate guidance which assesses study risk in a **structured and standardized** manner

What is a KEY RISK INDICATOR (KRI)?

- KRIs are **metrics** used in management to indicate the **level of risk of an activity**
- It differs from a Key Performance Indicator (KPI) in that a KPI is meant as a measure of **how well** something is being done while a KRI is an **indicator of the possibility of future adverse impact**

Effective KRIs should be:
Measurable - metrics should be quantifiable (e.g., number, count, percentage, etc.)
Predictable - provide early warning signals
Comparable - track over a period of time (trends)
Informational - measure the status of the risk and the associated control(s)

Relationships across Quality Management Systems, Quality by Design and RBM



Establishing Risk-Based Monitoring within a Quality-Based System as "Best Practice" for Clinical Studies https://www.acrohealth.org/rbqm-report/

Meeker-O'Connell A et al. Ther Innov Regul Sci. 2016;50:397-413.

Risk Based Study Execution

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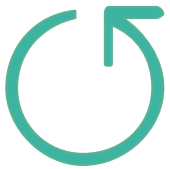
Risk Assessments	Integrated Quality Risk Management Plan (iQRMP)	KRI Programming	Monitoring Plan (MP)	Monitoring Execution
▪ Complete Risk Assessment including identifying critical data and processes that would impact the study results ▪ Define the risk mitigation plan ▪ Define the key risk indicators ▪ For a program of studies, ensure assessments are program and study focused	▪ Defines the outcome of the risk assessment ▪ Defines the workflow for Risk Based Study Execution	▪ Programming of key risk indicators ▪ Creation of analytics to support centralized monitoring	▪ Define On-site, Off-site and Central Monitoring activities for study ▪ Define the visit schedule how it can be altered based on the data review	▪ Review Analytics and Visualizations ▪ Review Execute Monitoring Activities ▪ Determine what actions to take based on risk management plan ▪ Conduct on-site monitoring per CMP

RBQM Requirements

People

- Trained people
- Collaborative approach on data integrity and patient safety
- Mitigate when possible after identifying risks
- Use best practices to monitor further risks
- Target interventions based on quality problems



Process

- Robust process
- Perform early and ongoing risk assessments
- Fixate on critical processes and data
- Employ risk indicators, action strategies, and thresholds
- Alter monitoring activities in response to risks

Technology

- Integrated technology
- Tailored to unique needs of RBM
- Dynamic, nimble, data-driven
- Has ability to comprehensively manage risks
- Caters to relevant roles through advanced functionalities
- Has ability to scale with increasing maturity and complexity

Centralized Data Analytics

- Centralized monitoring
- Data Aggregation
- Analytical tools
- Predictive Analytics/Machine Learning

Centralized Monitoring

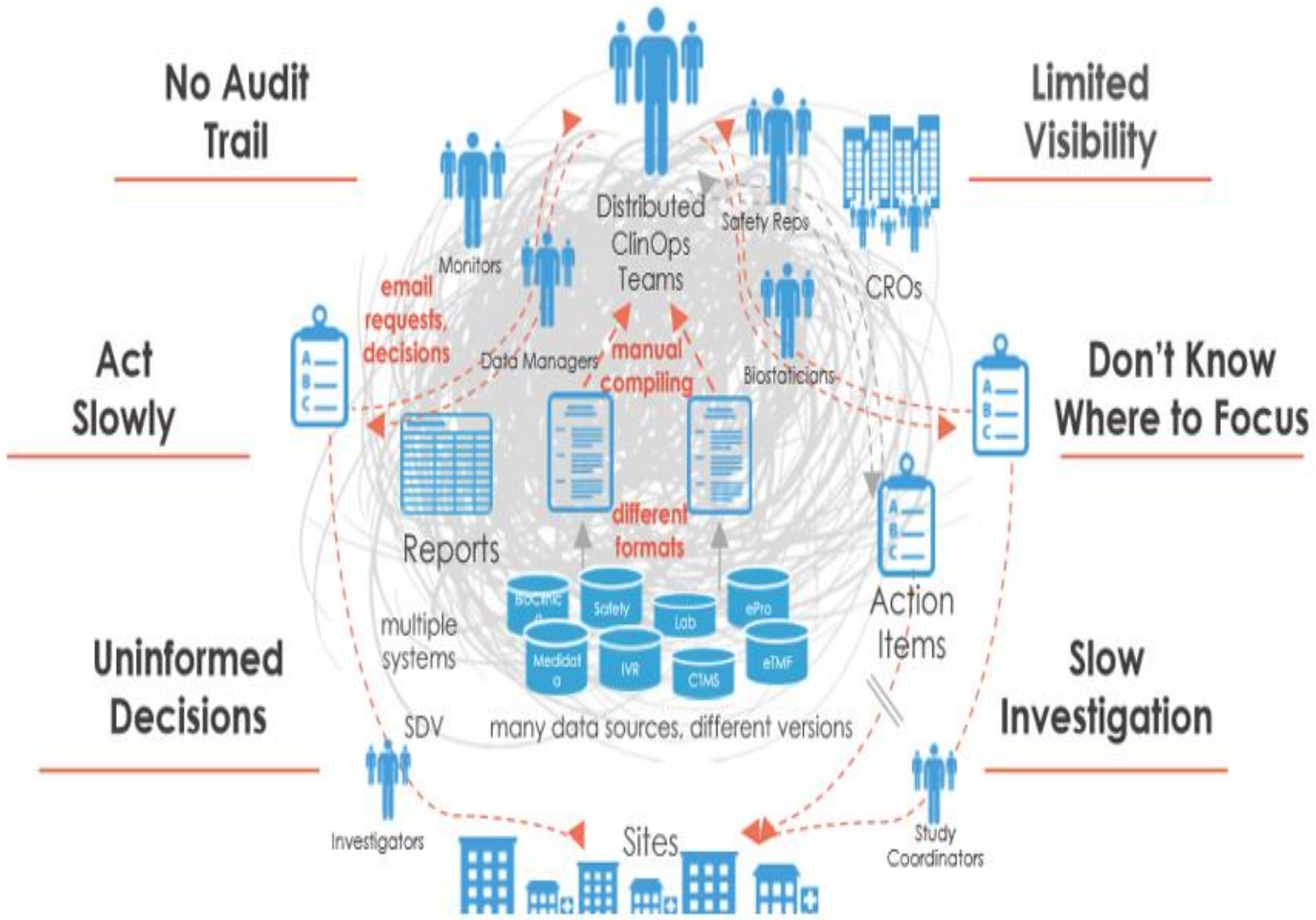
- Identification of missing or inconsistent data, data outliers, variability (or lack of) and protocol deviations
- Analysis of data trends within and across sites
- Identification of systematic errors or data integrity issues
- Analysis of site characteristics and performance metrics
- Determine need for remote or on-site monitoring
- Different skill set then the current Monitoring Staff

Central Monitor Competencies

- More technologically capable - comfortable with multiple apps, systems, and how they interact (or do not interact).
- Increased understanding of data - how to analyze, interpret, and complete a feedback loop with the study team and site regarding data.
- Better able to document and “think like an auditor” - while this should be a current skill set, with the increased of offsite data review, documentation of how we are following trends and issues will be key.
- Flexibility- the role requires more flexibility as visit schedules are not set, and based on data measures (volume, issues).
- Communication – the ability to communicate with sites, internal teams and sponsors via verbal, written, email, text and via applications. This includes WebEx and other media.

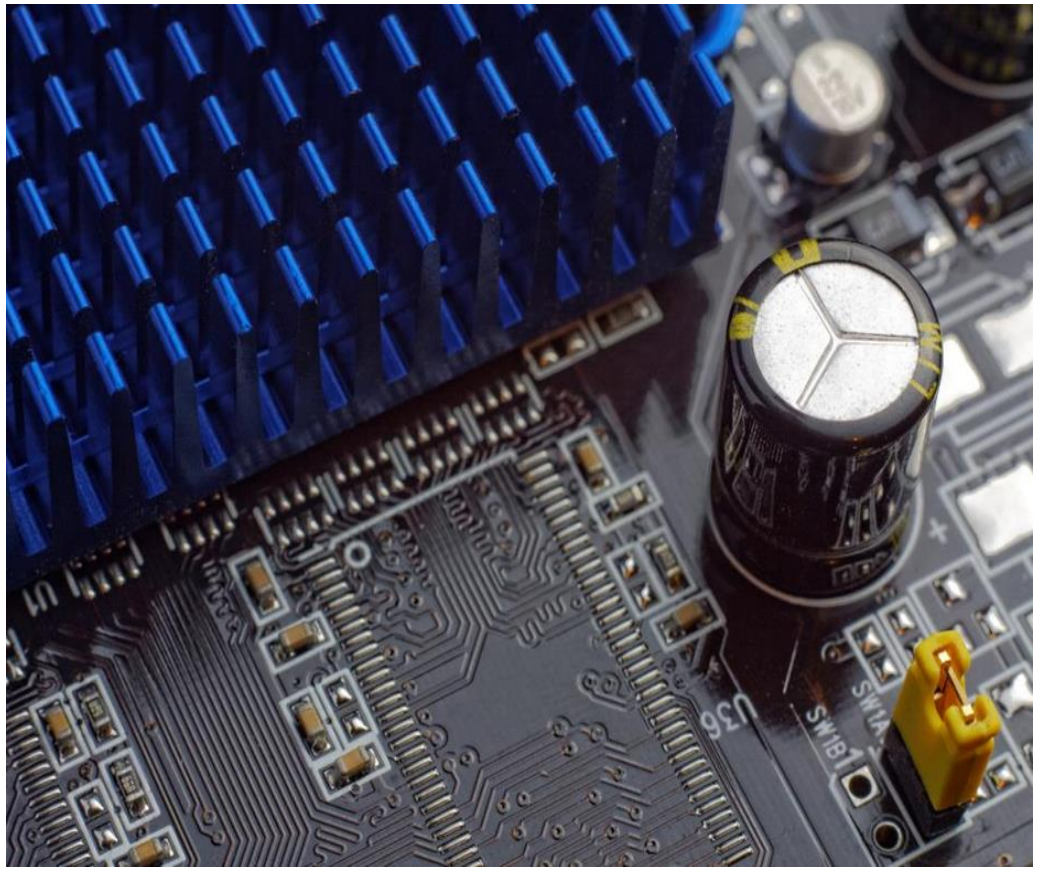
Data Aggregation

- Data availability is critical to maximizing the power of centralized monitoring.
- Data integration key
- Multiple data sources:
  - CTMS
  - EDC
  - LABS
  - IVR/ECG
  - EMR
  - Custom In house applications (we will also consume fixed format excel)
- Data Warehouse



Data Acquisition

- **Remarque Systems is agnostic to data sources.**
  - Support API and file transfer.
- **Remarque uses a time series data model**
  - Data from traditional clinical trial systems
  - Data from real life healthcare tracking or direct from device data.
- **Remarque uses a configurable data mapping model**
  - Relies on underlying JSON mapping files
  - Data ingest is not coded but configured.
  - **No need for Data Warehouse**



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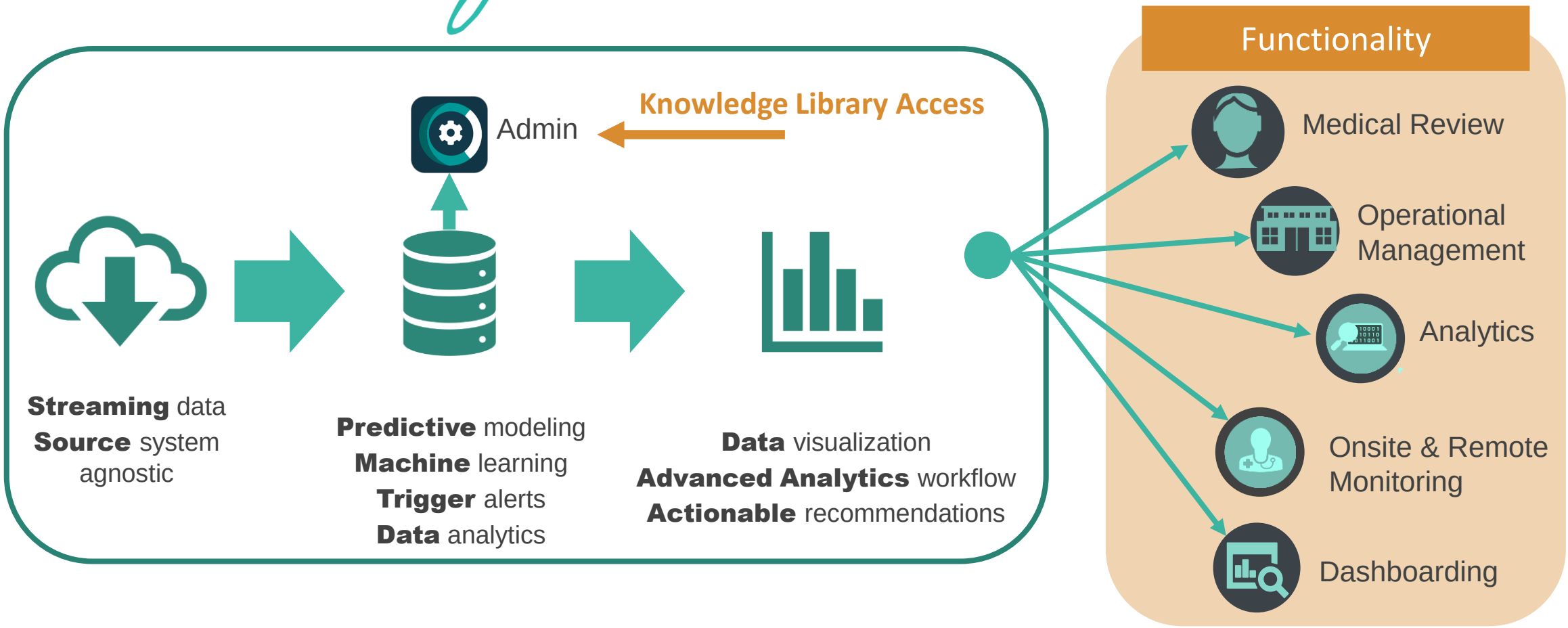
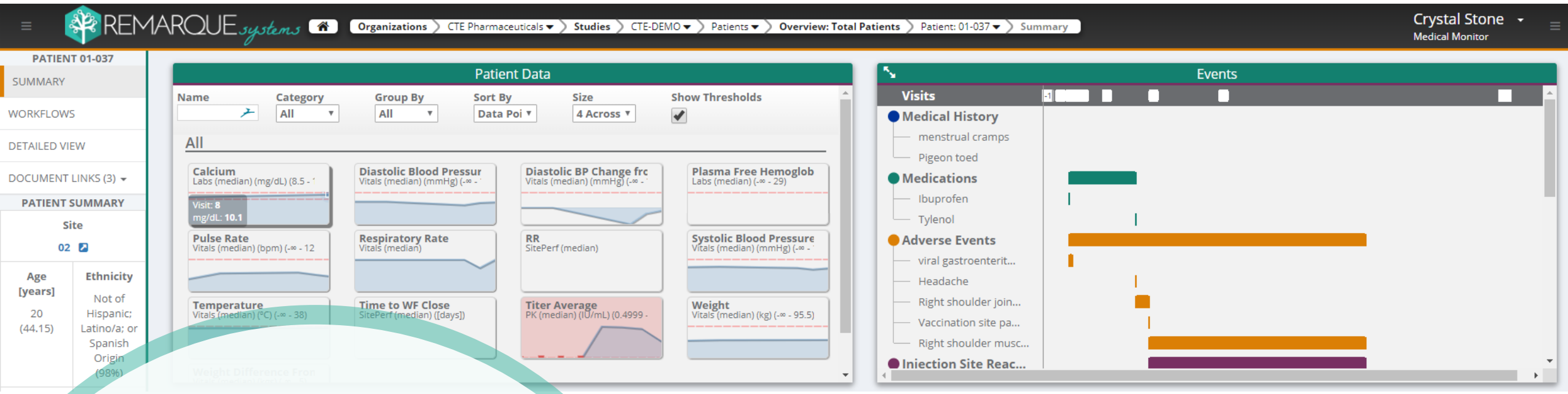
Solution offering





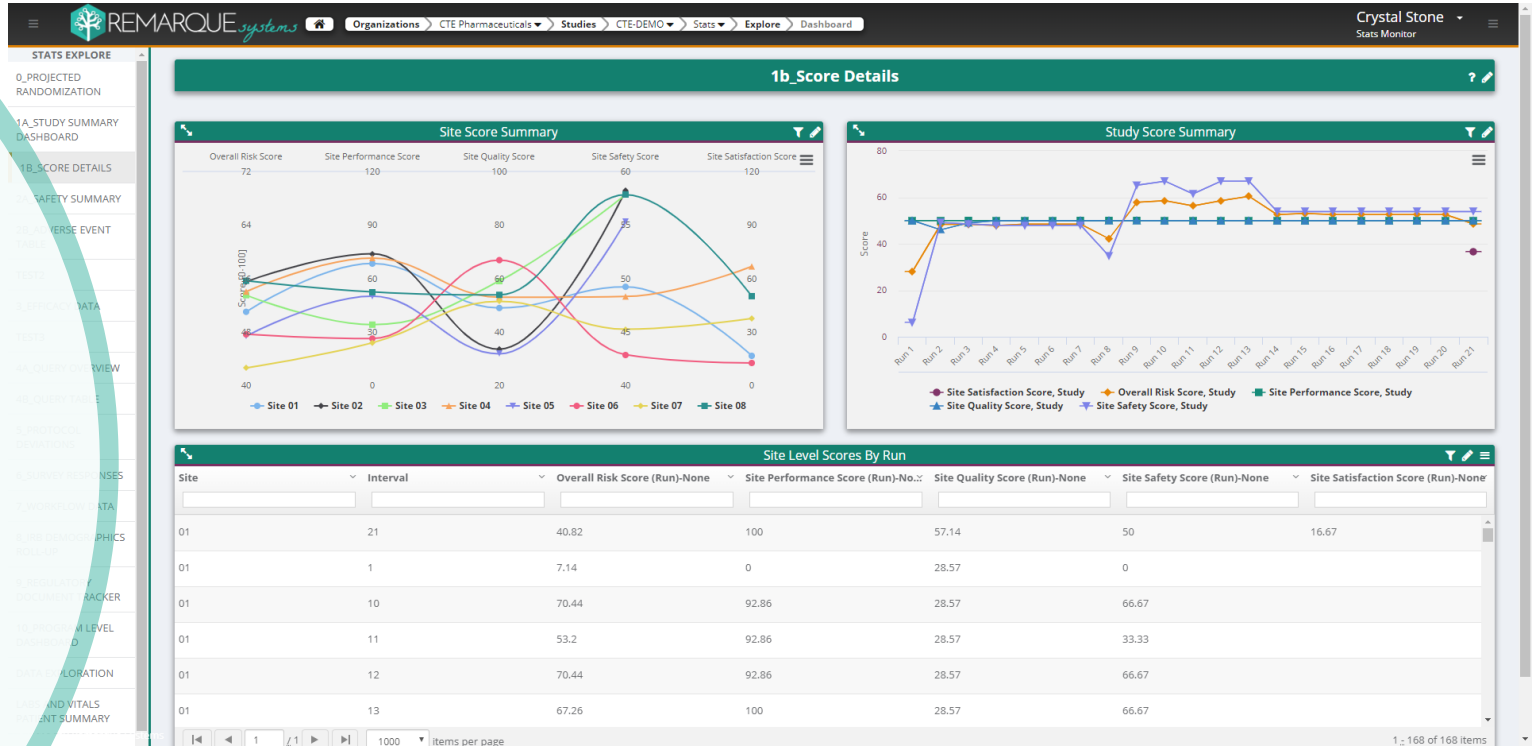
VISUALIZATIONS

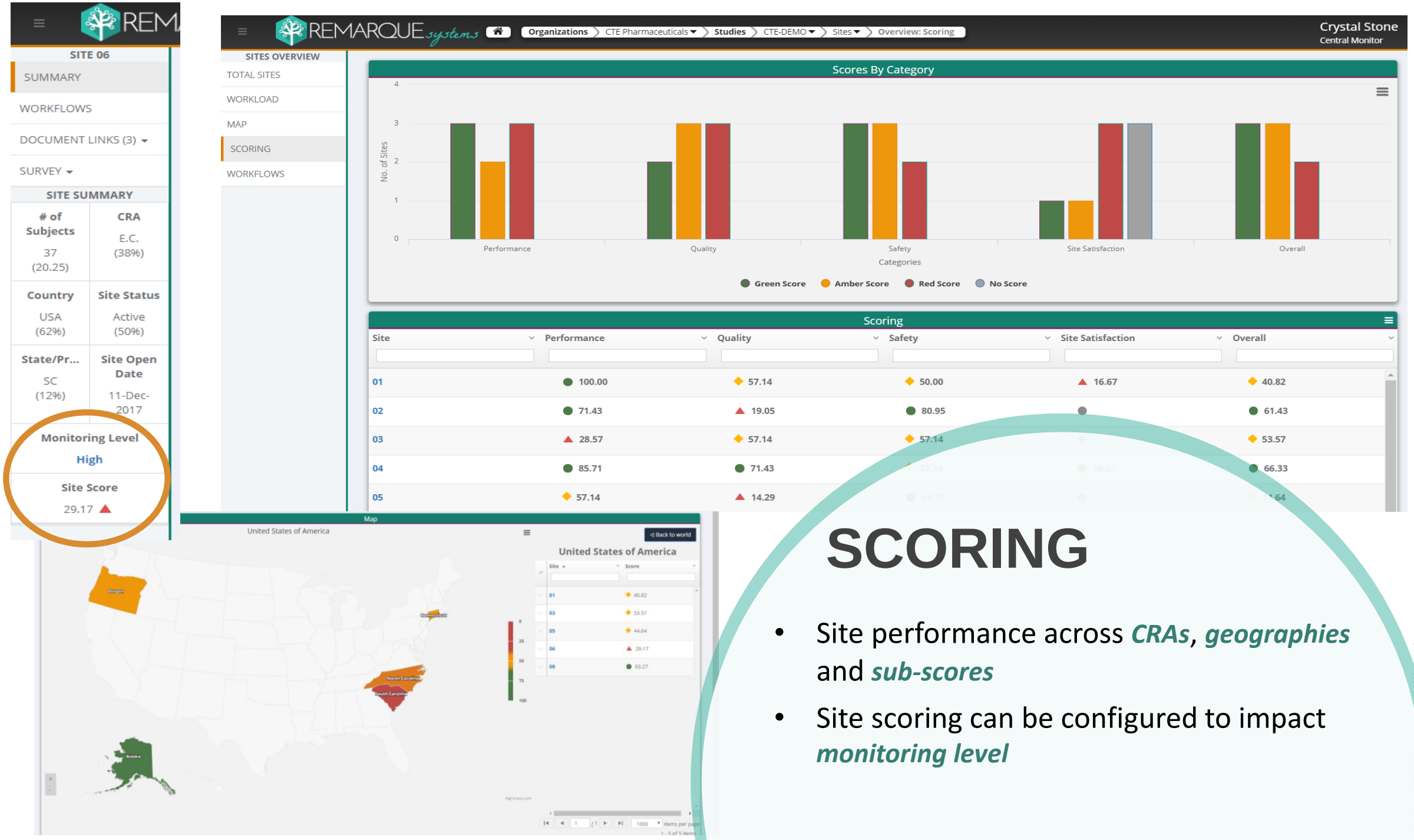
Standard visuals:

- Sparkline – out of the box line chart displaying real time data by patient or site
- Event Tree – providing view of patient summary (AEs, medications, medical history, etc.)

End user configurable visuals:

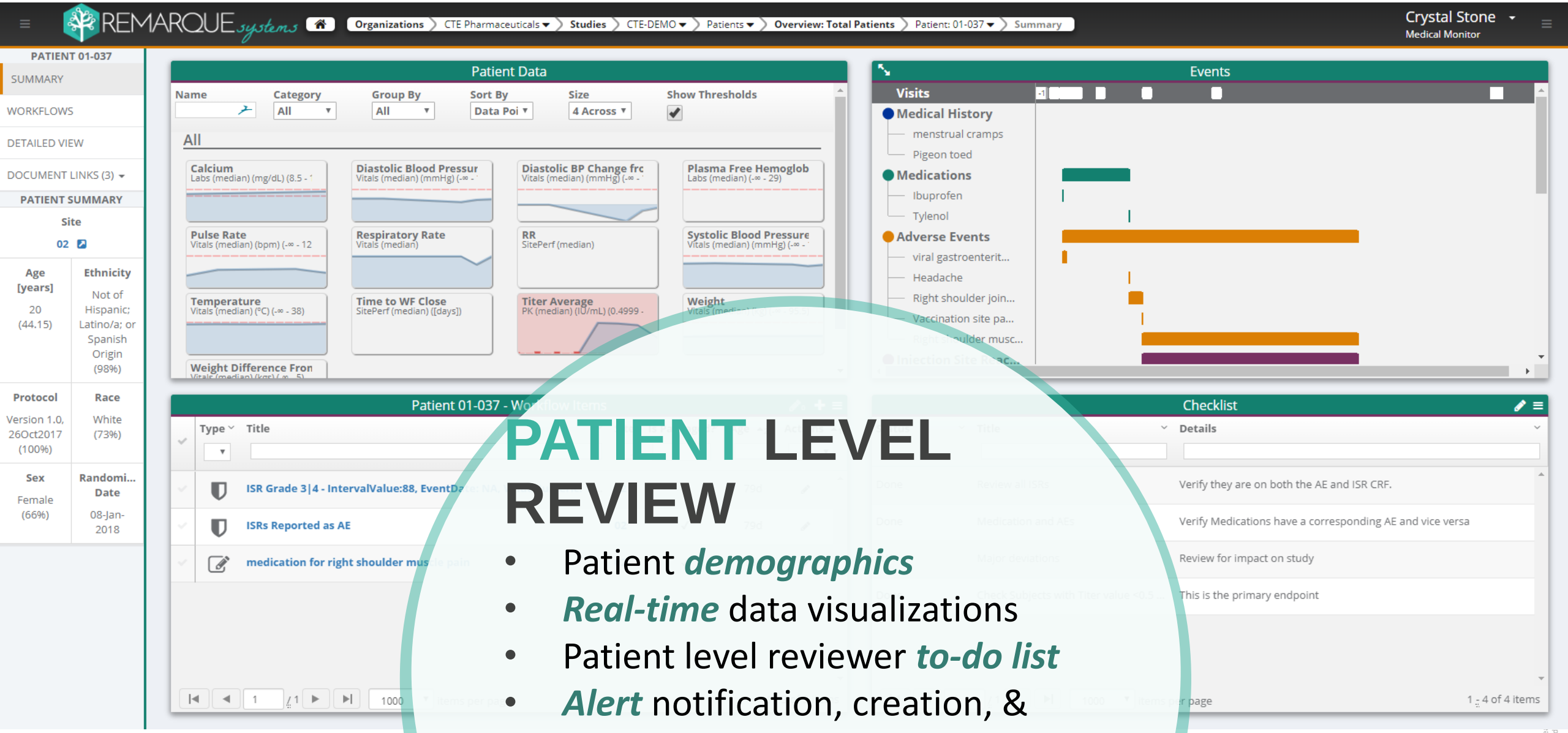
- Dashboards – real time data visualizations at the patient, site, or study level





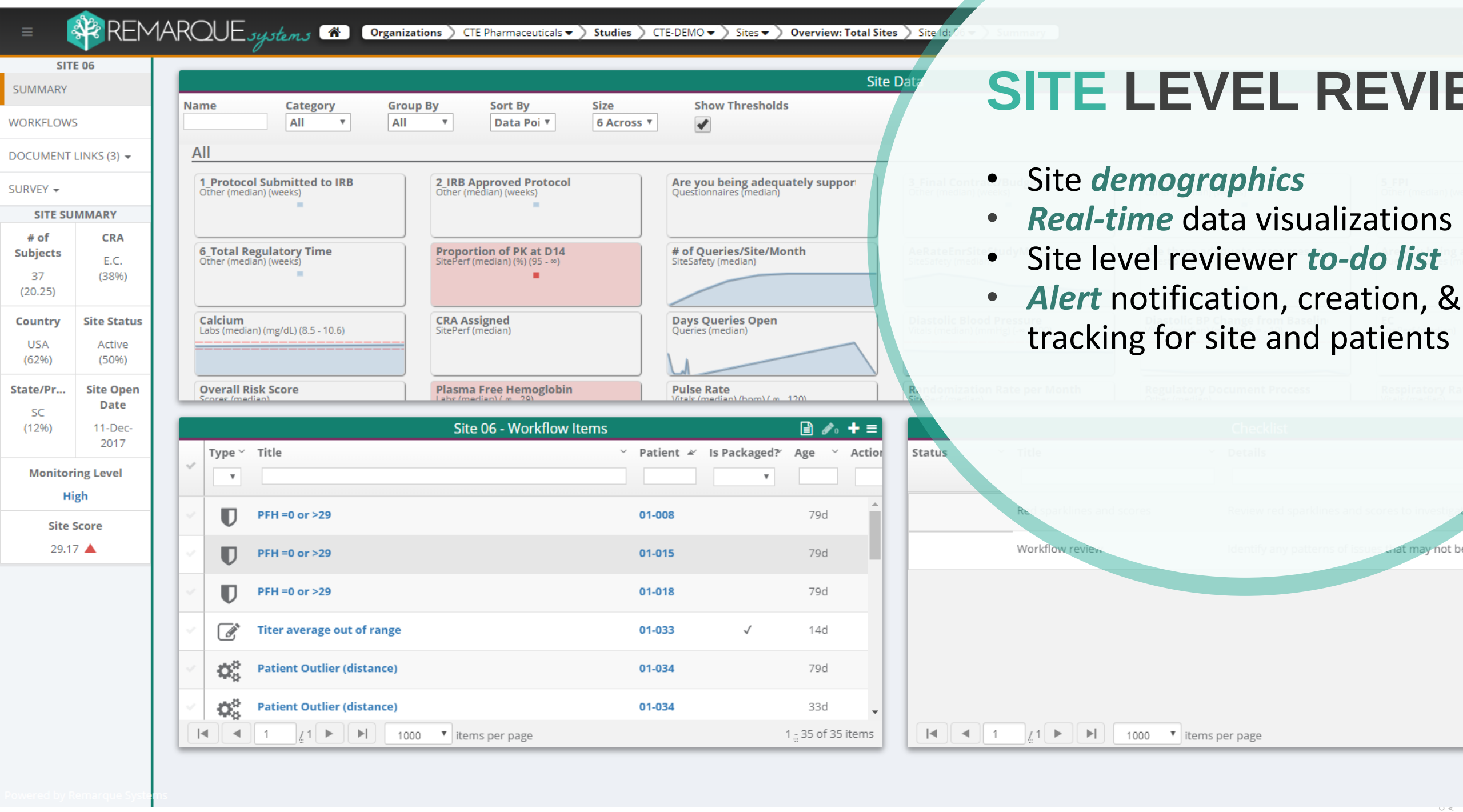
SCORING

- Site performance across ***CRAs***, ***geographies*** and ***sub-scores***
- Site scoring can be configured to impact ***monitoring level***



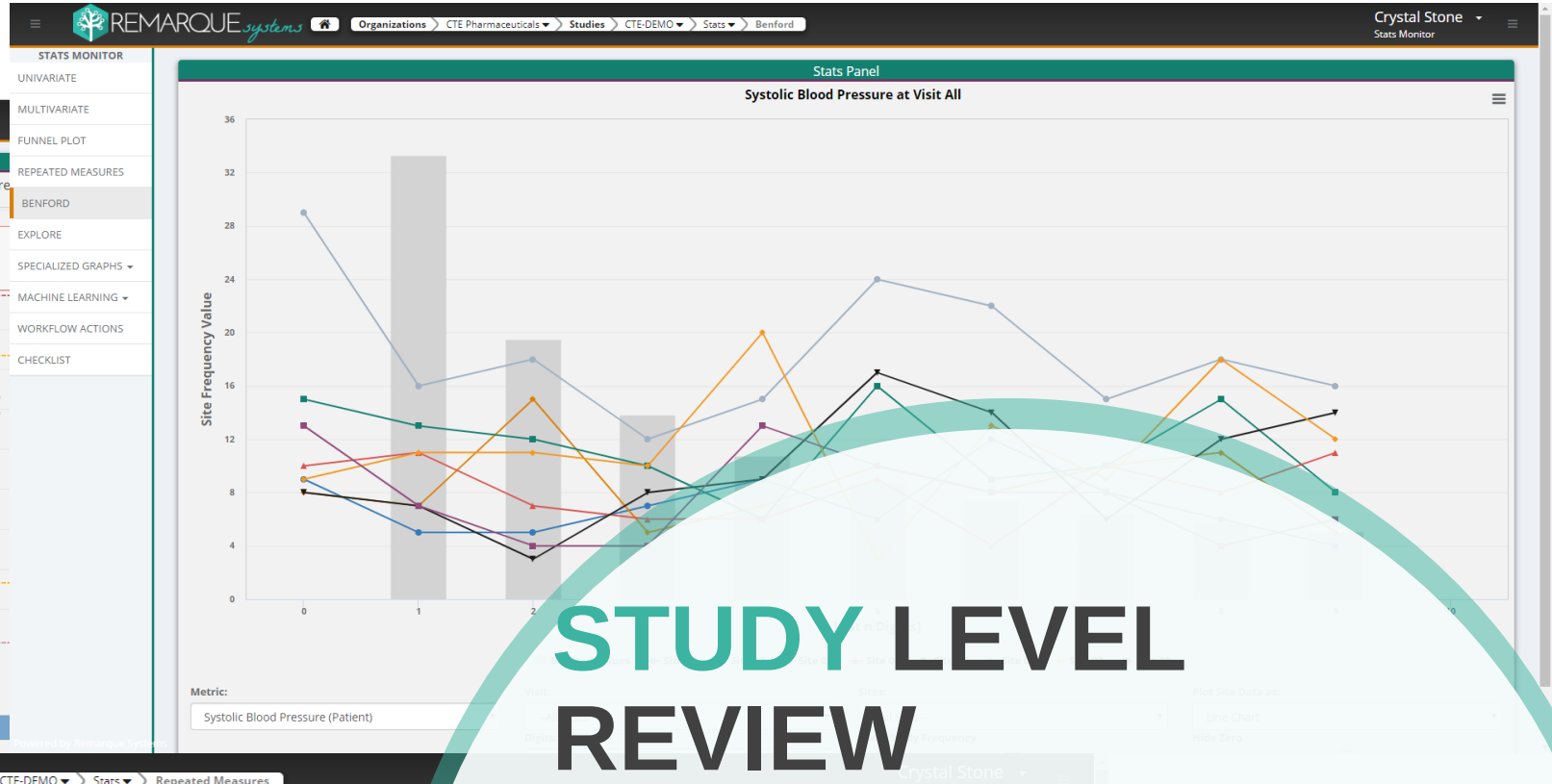
PATIENT LEVEL REVIEW

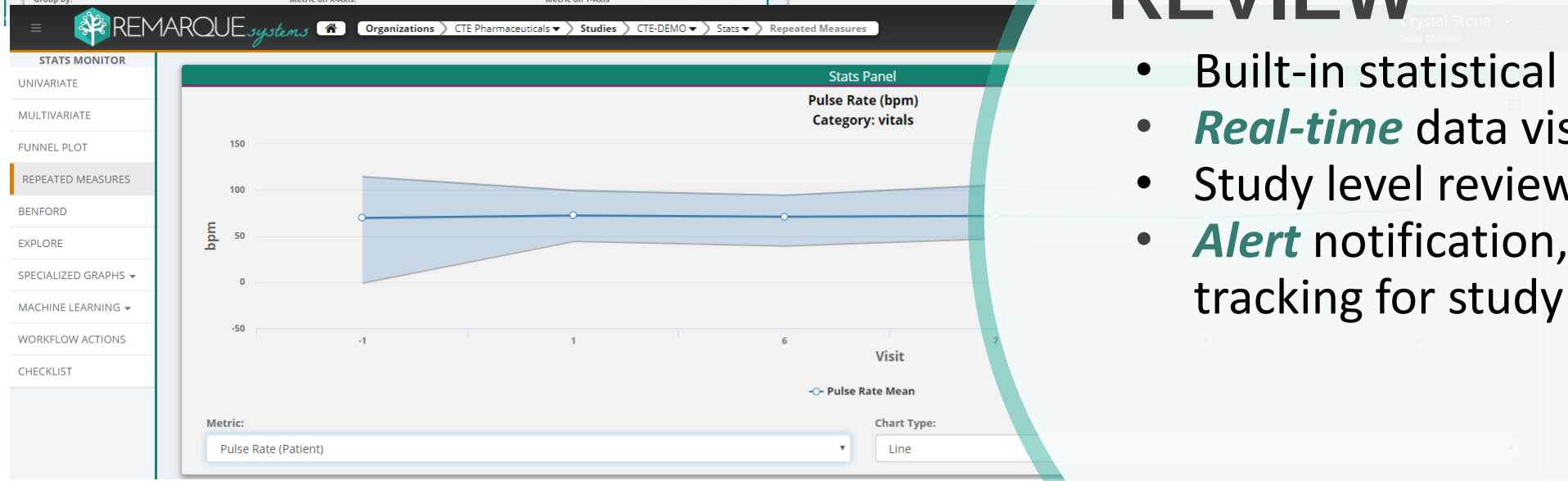
- Patient ***demographics***
- ***Real-time*** data visualizations
- Patient level reviewer ***to-do list***
- ***Alert*** notification, creation, & tracking for patient



SITE LEVEL REVIE

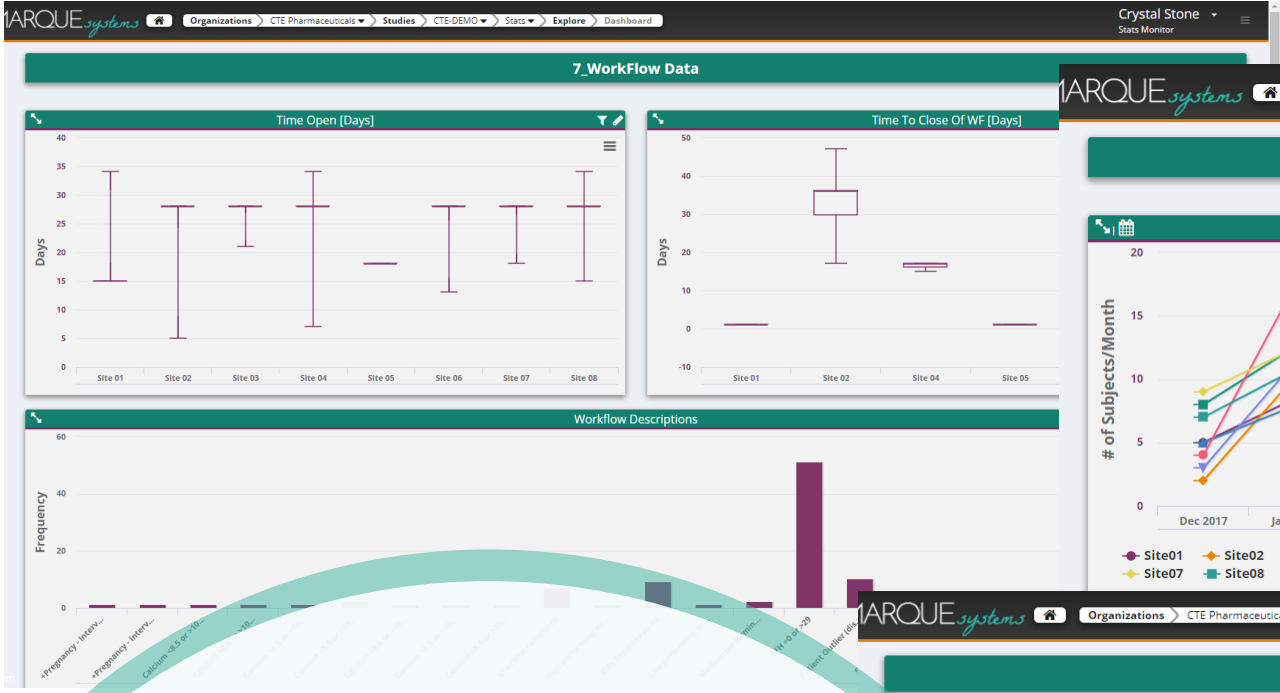
- Site *demographics*
- *Real-time* data visualizations
- Site level reviewer *to-do list*
- *Alert* notification, creation, & tracking for site and patients

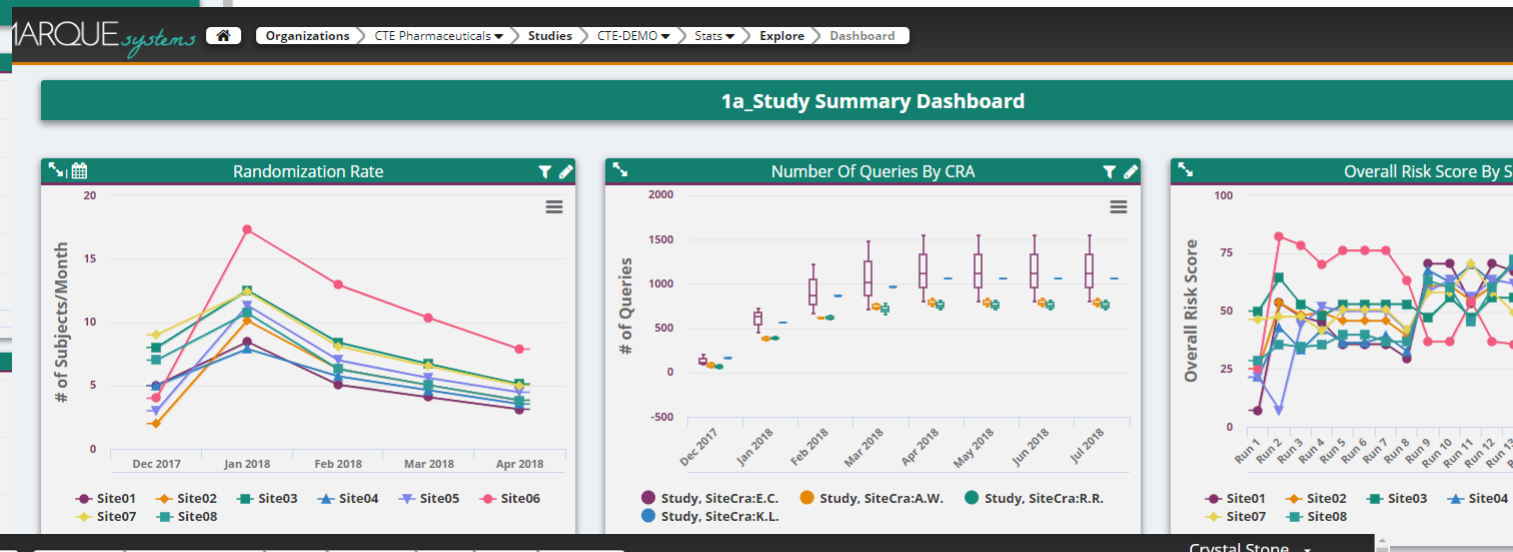


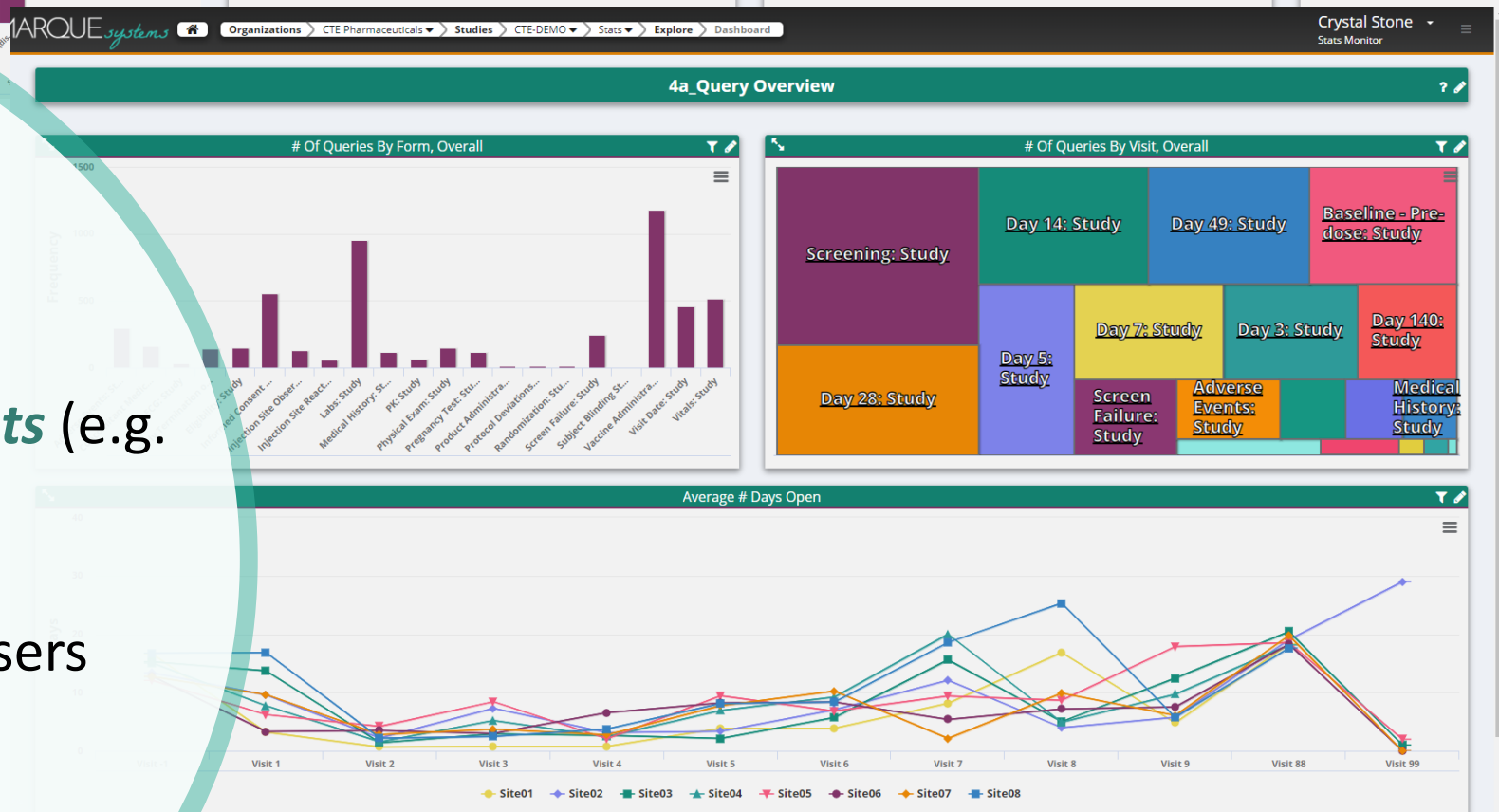


STUDY LEVEL REVIEW

- Built-in statistical ***analysis tools***
- ***Real-time*** data visualizations
- Study level reviewer ***to-do list***
- ***Alert*** notification, creation, & tracking for study





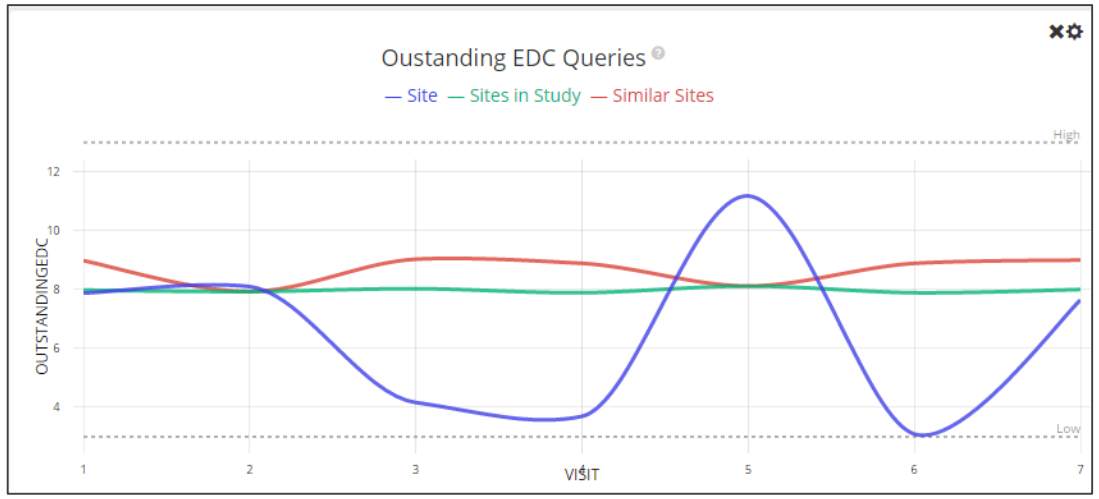


DASHBOARDS

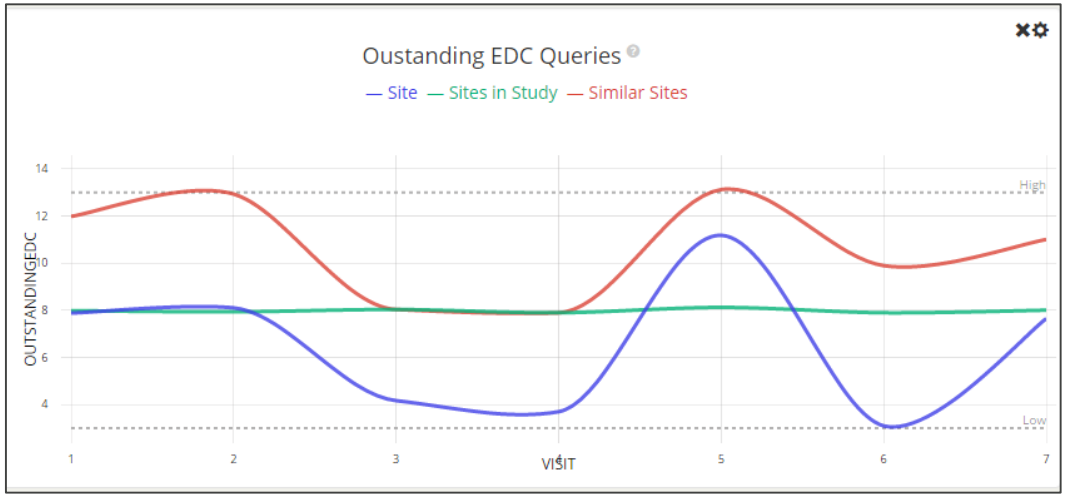
- ***Ad hoc*** reporting
- Configurable ***layout*** and ***plots*** (e.g. line, bar, pie, grid)
- ***Real time*** data
- Ability to ***publish*** to other users

Predictive Analytics / Machine Learning:
Clustering & Distance

- Goal:
  - Build profiles of patients and sites based on their properties including demographics, medical history, Site Performance etc.
- Approaches:
  - Unsupervised (initial approach) – cluster analysis (e.g. k-means, hierarchical clustering)
  - Semi-supervised (as more users are using the systems) - interacting with users to improve performance
  - Supervised (once historical annotated data available) – ensemble approaches (e.g. random forests), regression, Neural networks, etc.



- Site's trend is different than: other sites and similar sites
- Should inspect site



- Site's trend is different than other sites but close to similar sites
- Should inspect other sites as well

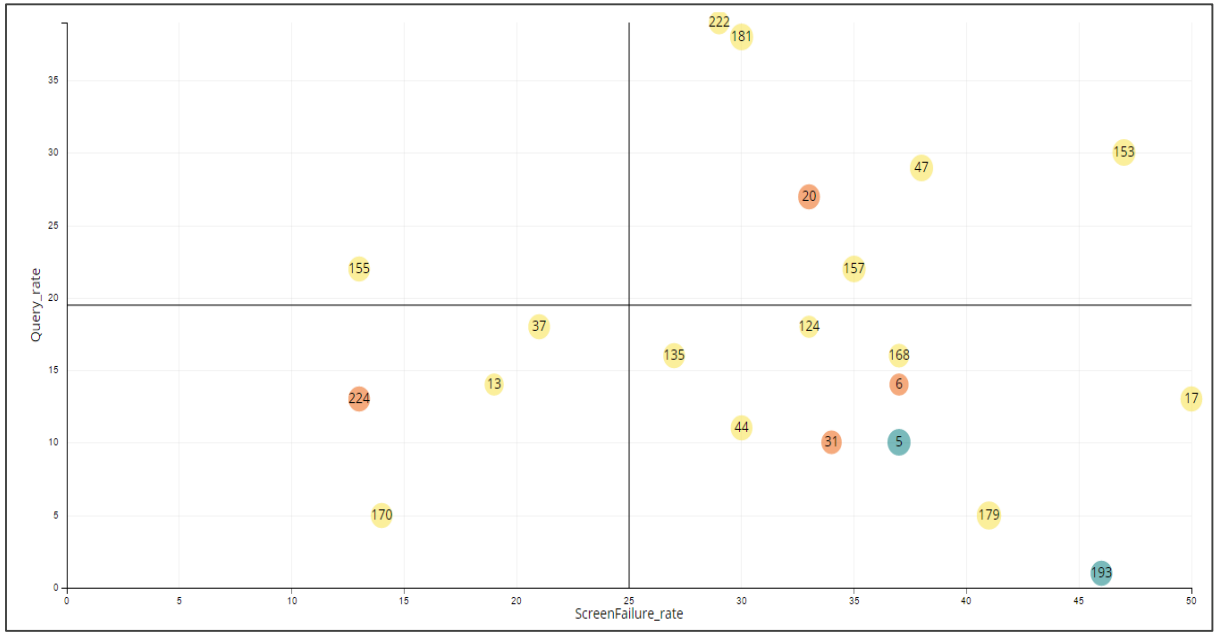
Predictive Analytics / Machine Learning:
Outlier Detection

Goal:

- Identify anomalies behavior of sites/patients

Approaches:

- Use similarity matrix (from similar patients/sites) to identify which data points don't belong to any specific model
- Use more constrained similarity measures like robust estimators (M-estimators)
- Interactive visualization



Predictive Analytics / Machine Learning:
Missing Data

Goal is to identify missing data using historical information

Use time series analysis to Identify missing visits and/or missed metrics at certain visits

Use binary recommendation systems to identify missing data based on:

- Patients (collaborative filtering)
- Metrics (content-based)
- Or both (Hybrid)

Examples for Patient 1, which other metrics does the system recommend/suggest that should be taken but are missing

Techniques used for recommendation:

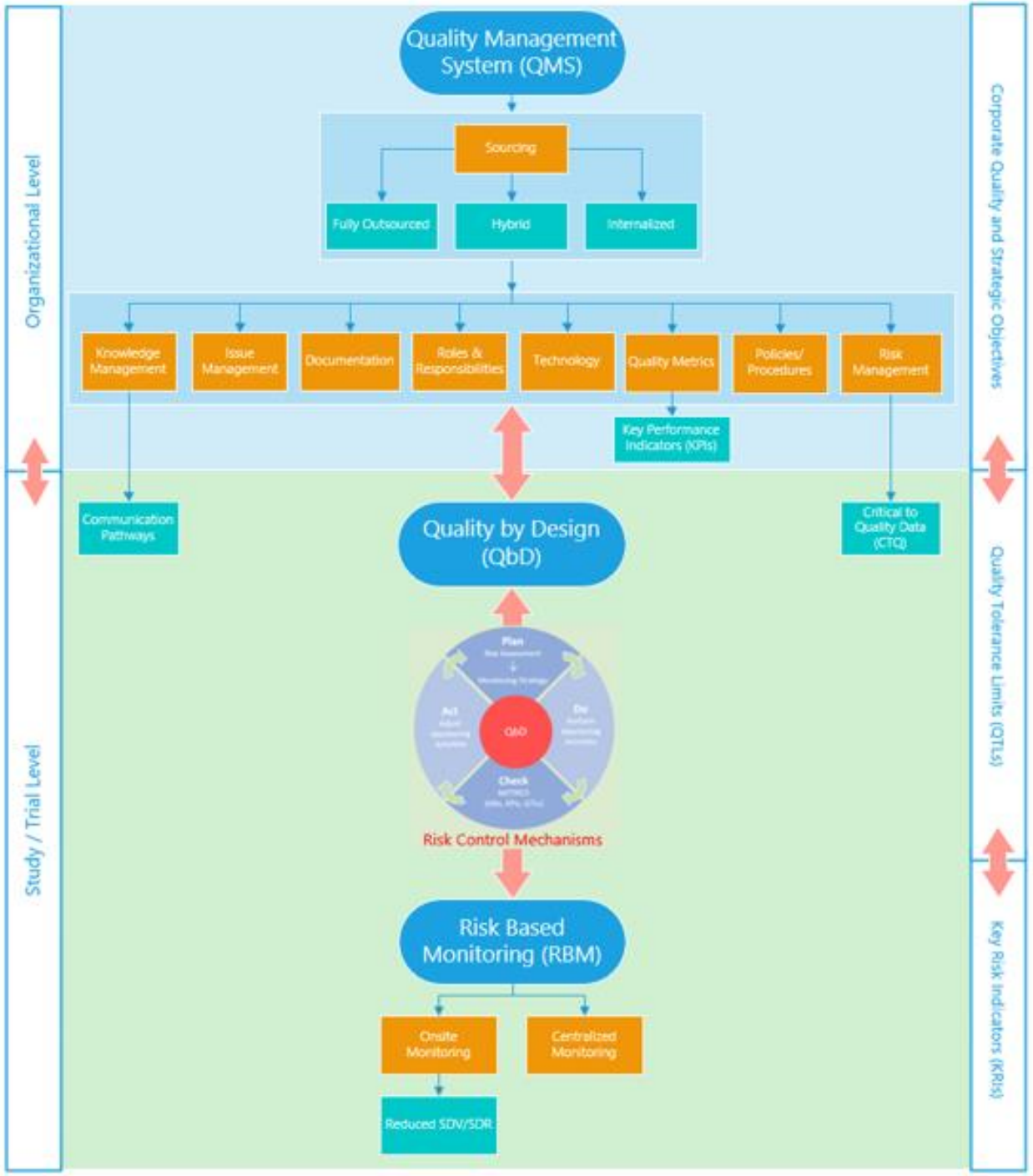
- Cluster analysis
- Non-negative matrix factorization

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Patient 1	X	X	X	X		X	
Patient 2	X	X		X	X		
Patient 3		X	X			X	X
Patient 4	X		X	X	X	X	
Patient 5	X	X	X		X	X	

	Blood Pressure	Heart Rate	ECG	Sodium
Patient 1	X	X		X
Patient 2	X	X		X
Patient 3		X	X	
Patient 4	X			X
Patient 5	X	X		

Machine identifies missed visit/metric and raises FLD

Machine waits to confirm pattern before raising FLD



How it all ties together

What Platform is Right for You?

- ✓ ICH E6 (R2) – level of compliance and audit ready
- ✓ Do you have the right people and processes?
- ✓ Risk assessments need to be cross functional
- ✓ Dynamic process
- ✓ Outsourcing model: Who is doing what?
- ✓ Where is the data? How can you get it? What is the frequency?
- ✓ Technology: Buy or Build or use CROs
- ✓ Balancing cost versus quality
- ✓ Change management is critical at all levels: Sponsor, CRO and Sites

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