MyRBQM Approach to Risk Based Quality Management

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Trust in Data

Recently,
at a Novo-Nordisk Global Data Management Conference

Question:

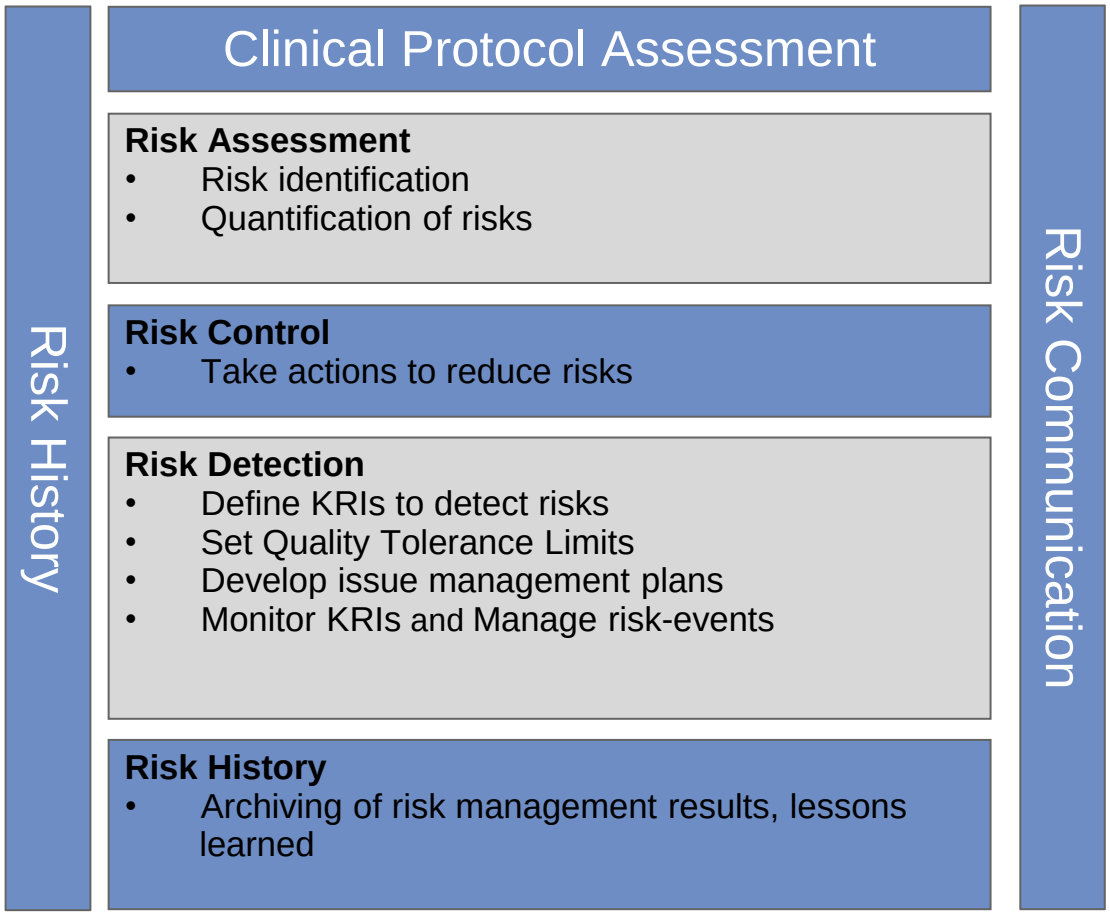
What is the greatest challenge for clinical data management ?

Answer:

To manage and understand the many systems and the many copies of the study databases

…… and that is probably true for many other functions as well

Holistic Risk-based Quality Management (RBQM)



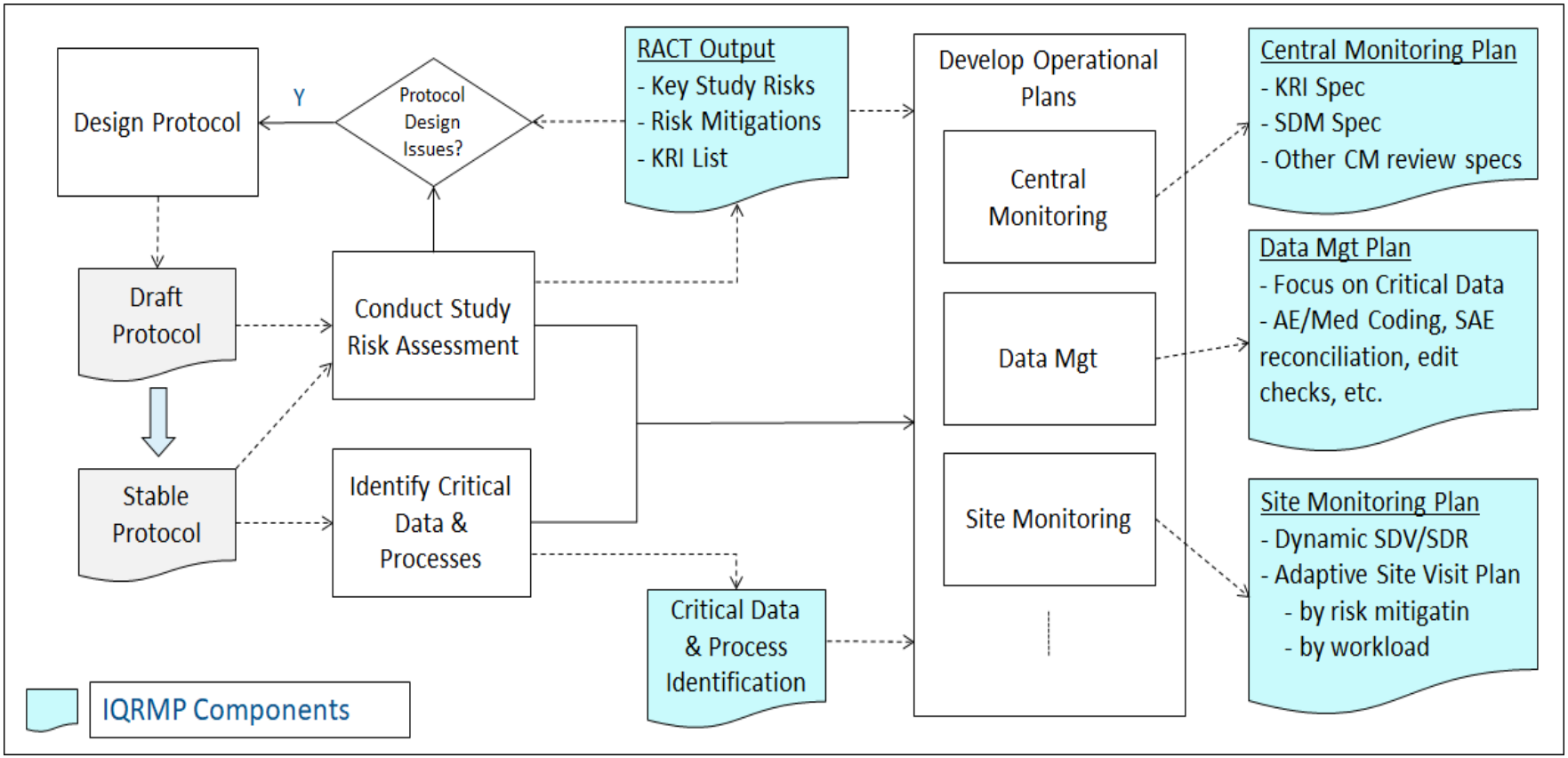
RBM - focuses on optimization of clinical monitoring only.

RBQM - incorporates whole quality management, therefore other activities, like Data Management, Biostatistics, Project Management, Regulatory , Medical writing, etc.

We speak about RBX - risk-based everything, where we can assess the risks of each process and each risk entity, like country, program, or even patient.

The overall RBQM process for a study

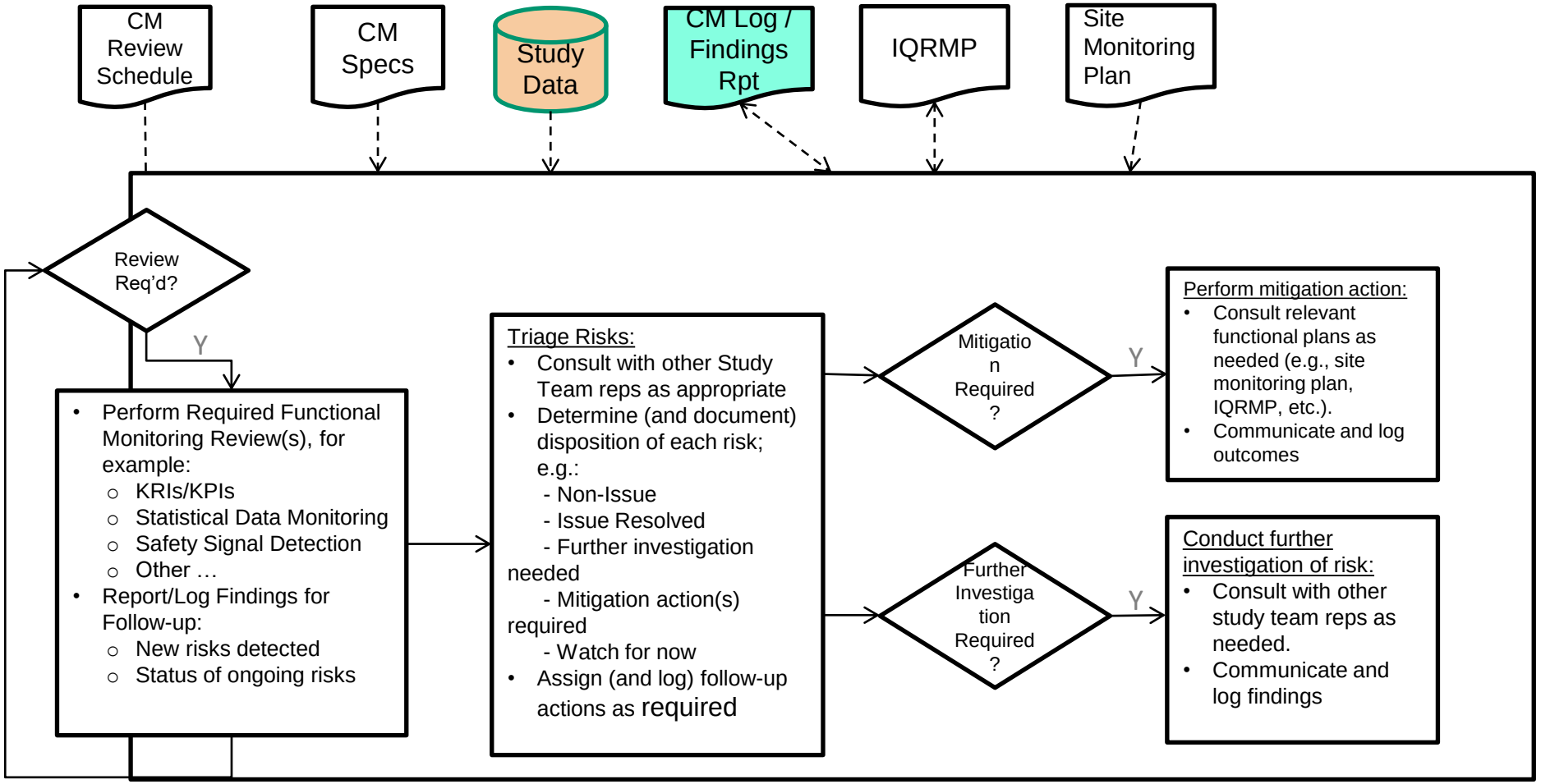
Pre-study risk planning



RBQM approach as developed by a DIA working group chaired by Steve Young

The overall RBQM process for a study

During study conduct



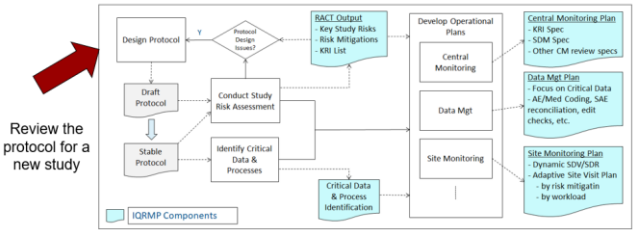
RBQM approach as developed by a DIA working group chaired by Steve Young

Transcelerate RACT

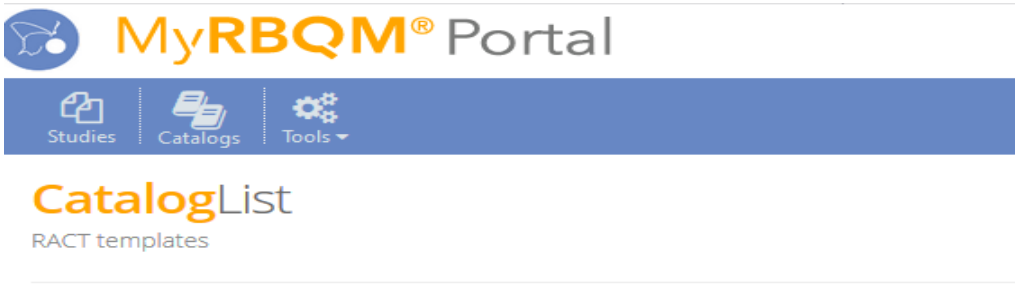
http://www.transceleratebiopharmainc.com/wp-content/uploads/2013/10/2_RACT_20140411.xlsx

Risk Categories according to Transcelerate

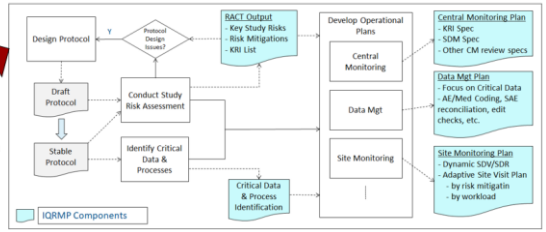
1. Safety
2. Study Phase
3. Complexity
4. Patient population
5. Technology
6. Data collection
7. Endpoints
8. Operational experience
9. Investigational Product
10. Supply chain
11. Blinding
12. Operational complexity
13. Geography
14. Your own defined area as applicable

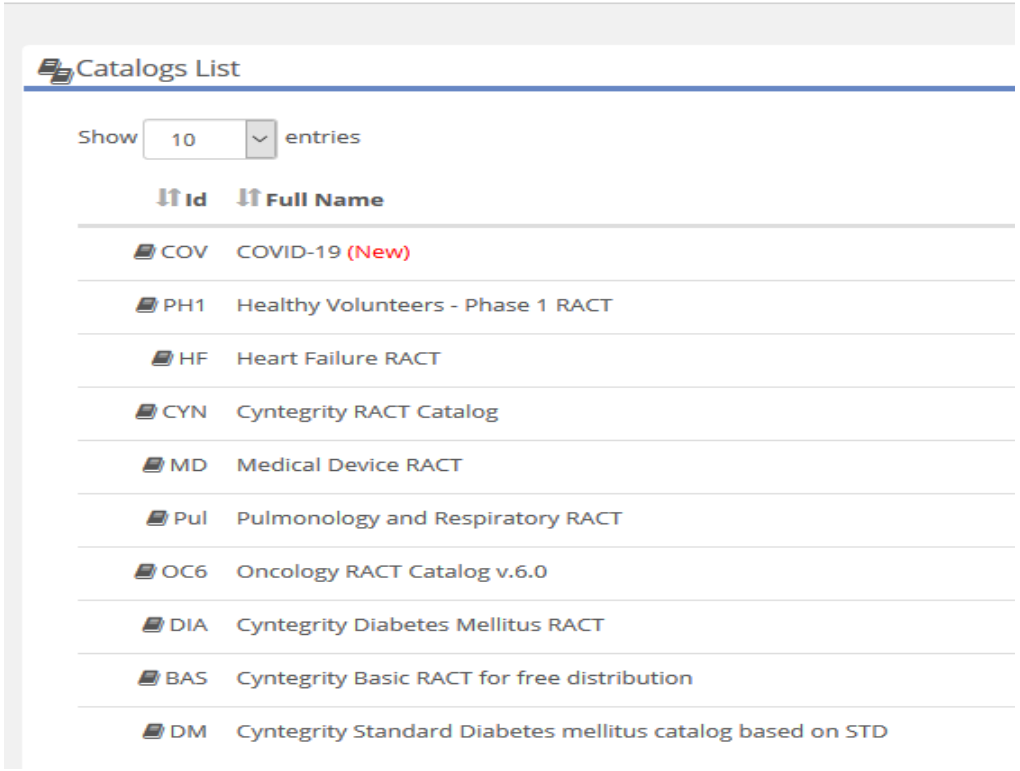


RACT catalogs

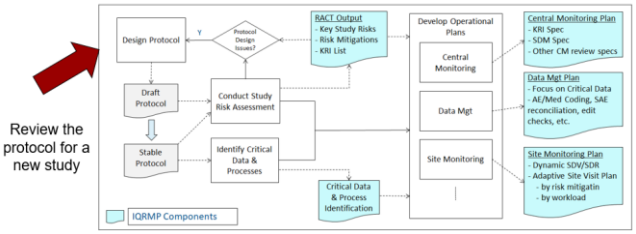


Review the protocol for a new study





RACT catalog example



Category BLI — Blinding

Delete This Category | Edit This Category's Details | Create a New Question

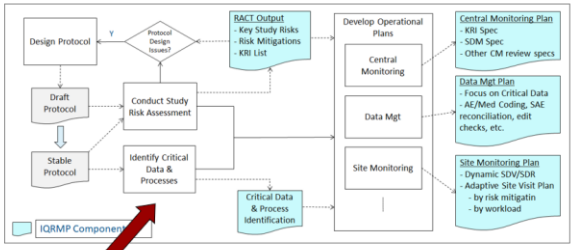
? Question BLI-1 — How is the blinding set up? 1 — Delete — Edit

? Question BLI-2 — How are the blinding assignments being administered/created? 2 — Delete — Edit

? Question BLI-3 — What is the risk of unblinding? 1 — Delete — Edit

? Question BLI-4 — Are there potential ways to unblind a patient other than through study medication? 1 — Delete — Edit

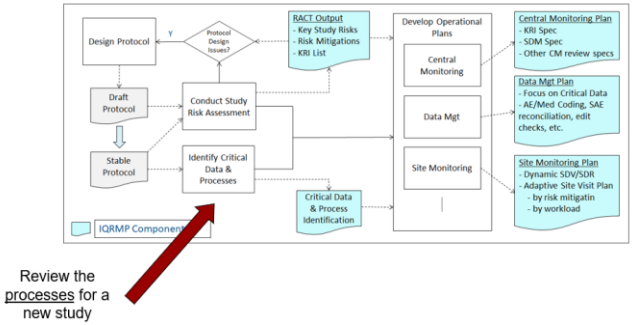
Critical processes in the study?



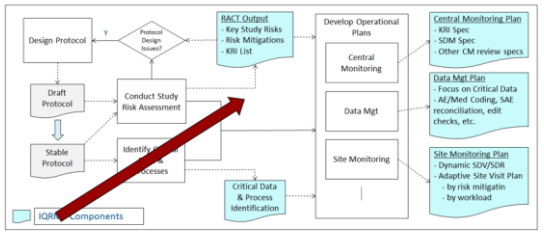
1. Under-reporting of AEs and SAEs
2. IP injection procedure
3. Delays in EDC data entry
4. IVRS not being followed, mis-randomization
5. One site enrolling many more patients than the others
6. Delays in response to queries
7. Discrepancies in the assessment by the patient and the investigator
8. CRO does not assign the ‘A-Team’ to this study
9. Changes in the regulatory requirements during study conduct
10. New state-of-the art guidelines for development of anti-infectives
11. Monitoring reports not available on time

Critical data in the study?

1. Enrollment per month
2. Injection volume per patient
3. Distribution of male / female patients
4. Number of serious adverse events
5. Number of lost to follow up patients
6. Main efficacy data completeness
7. Number of strokes / myocardial infarctions
8. Number of days with pain
9. etc



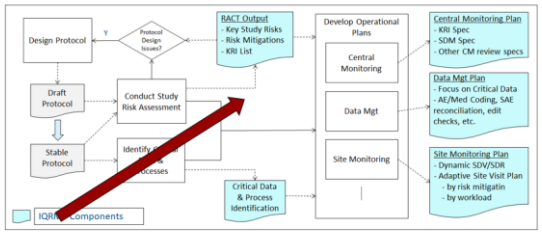
Risk scoring



Create the list of risks and the scoring for those risks

Risk	Impact	Likelihood	Detectability	Risk Score
Enrollment	3	3	1	9
Injection volume / comparability	3	2	2	12
100-200 male patients	2	3	1	6
SAE reporting	3	1	2	6
Lost to follow up	3	3	1	9

Mitigation actions for the risks



Create the list of risks and the scoring for those risks

Risk	Mitigation 1	Mitigation 2	Mitigation 3	Mitigation 4
Enrollment	Keep proxy sites in place	Review site EHRs for subject number confirmation	Continuously track enrollment	Award fast enrollers
Injection volume / comparability	Provide clear instructions for volume calculation			
100-200 male patients	Check EHRs for sites with male subjects			
SAE reporting	Create interface between EDC and PV system	Implement macro on important medical event list	Print SAE handling laminated card	

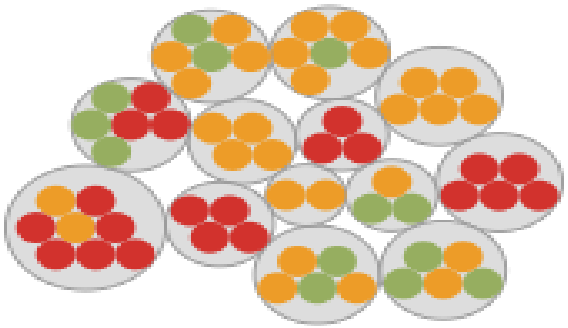
Risk-based Quality Management

Process: Design Phase, output

OCR—Ocrelizumab

RAC Mit. ...

Total Risk Score : 8



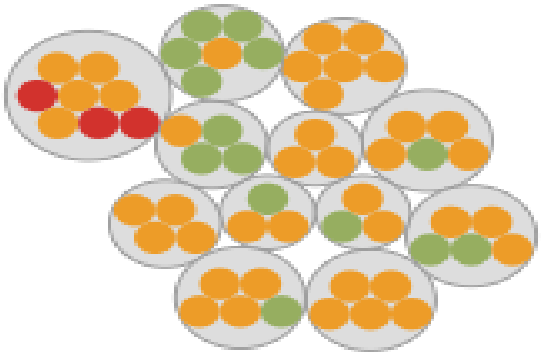
Active RAC: Release 08-03-2018

Select

SEM—Semaglutide

RAC Mit. ...

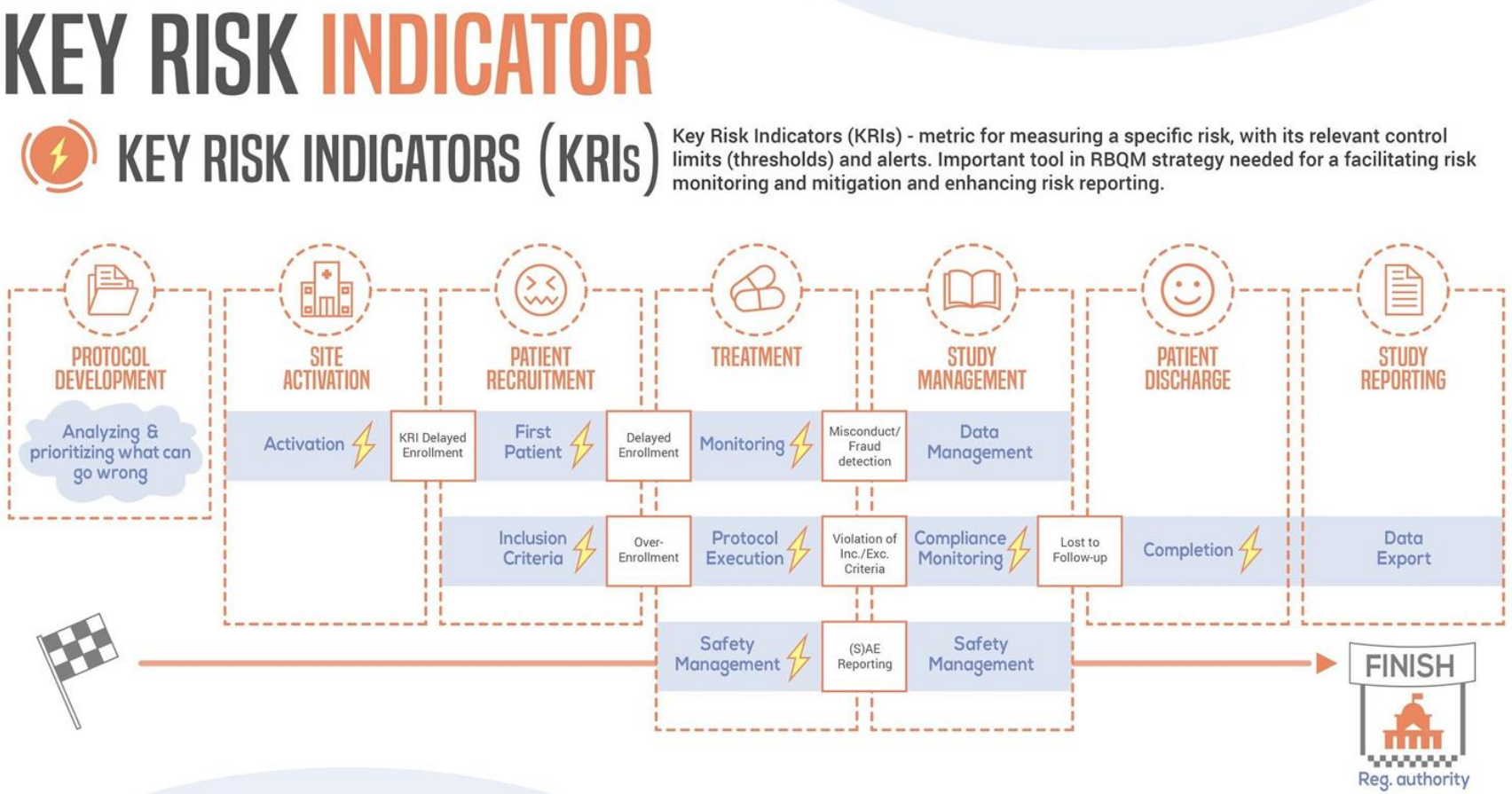
Total Risk Score : 5



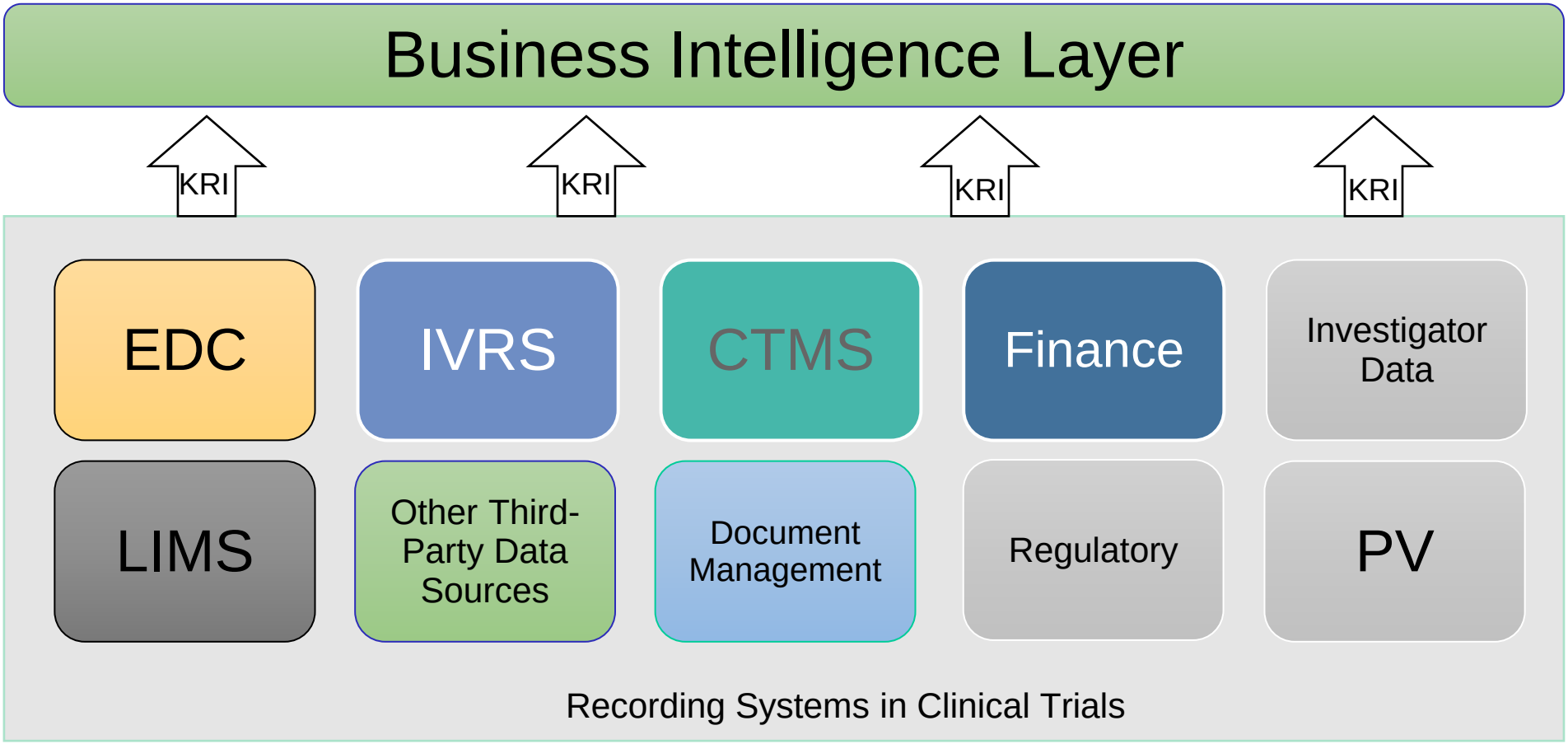
Active RAC: Release 19-02-2018

Select

Key Risk Indicators for the various steps in a study



KRIs Sources



Frequency of KRI measurement

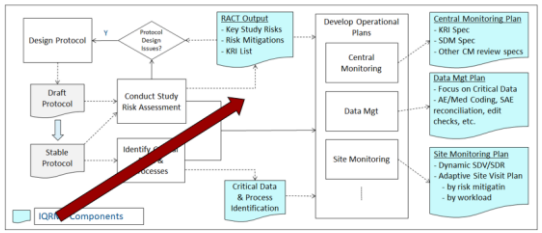



frequency

risk of not getting the picture

much data noise

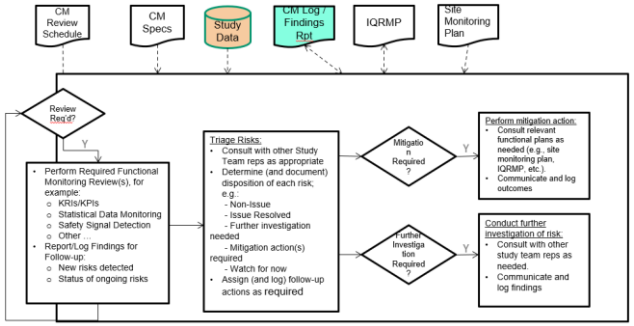
Identify the key risk indicators for the risks



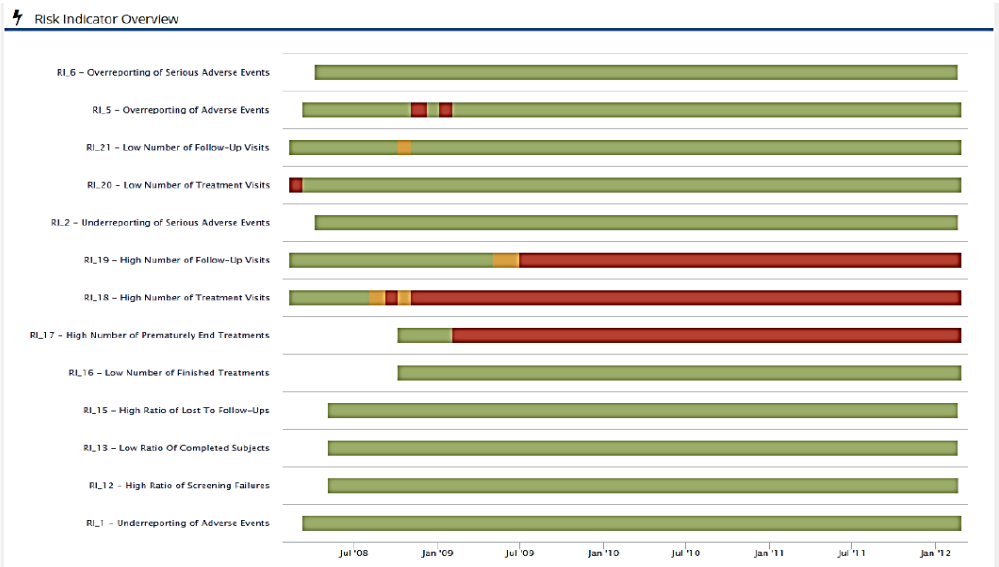
Create the list of risks and the scoring for those risks

Risk	Indicator 1	Indicator 2	Indicator 3	Indicator 4
Enrollment	# of subjects / month	# of subjects / site	Length of break in Sept. in China	
Infusion volume / comparability	Volume infused / subject	Infusion duration	Infusion interruptions	
100-200 male patients	# of male subjects	% of male / female subjects	% of male/ female subjects per site	
SAE	# of SAEs	# of AEs that should have been SAEs	# of SAEs / subject	Ratio of SAEs / site and subject
Lost to follow up	# of lost to follow up subjects	# of informed consent withdrawn	# of drop out due to AE	

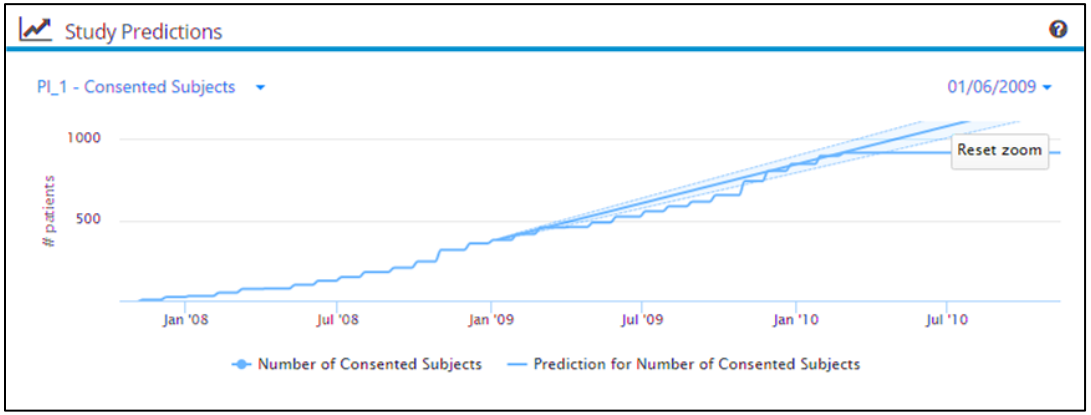
Rules for targeted monitoring



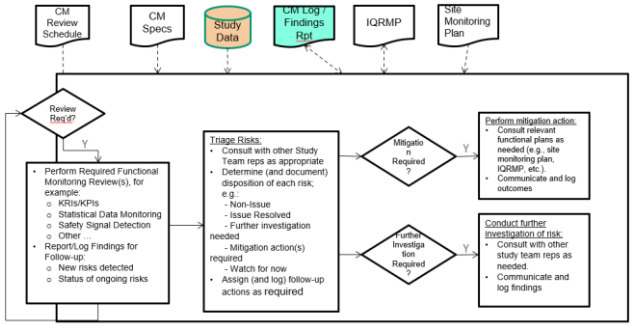
1. Define thresholds triggering monitoring activities
2. Review extremes for plausible explanations (vacation time, Covid-19, end of season)
3. Decide on sending site monitor
4. Decide on activating audit group
5. Deciding on closing site and what to do with the data

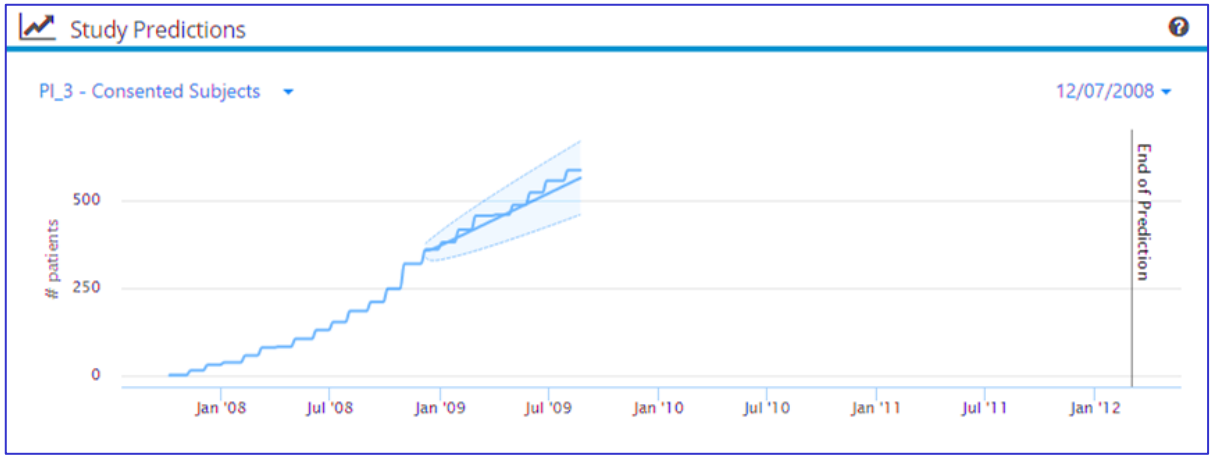


Proactive Approach: trends, patterns, and outliers Predictions



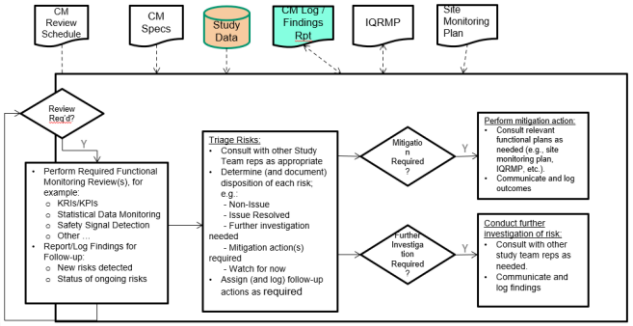
Source: Cyntegrity's MyRBQM Portal

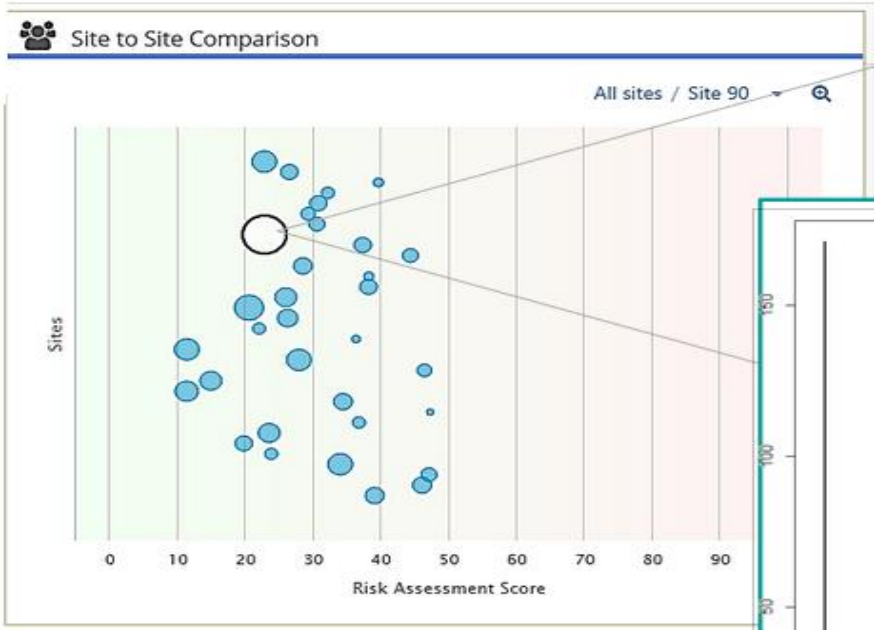




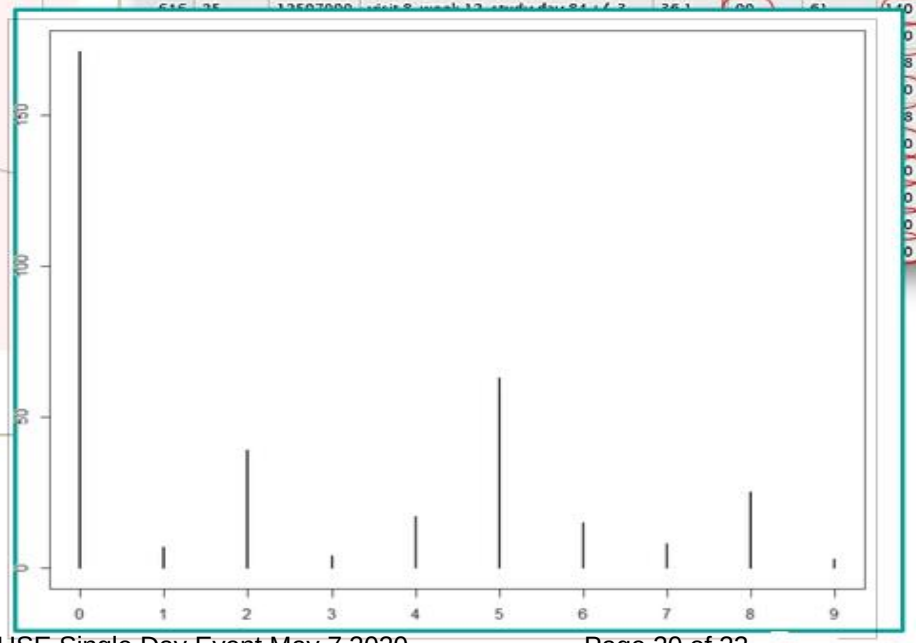
Source: Cyntegrity's MyRBQM Portal

Centralized statistical monitoring: Look for digit preference, Strange distributions, Outliers, Patterns





609	25	12507009	visit 17, week 44, study day 308 +/- 4	36	70	60	110
610	25	12507009	visit 18, week 48, study day 336 +/- 4	35.5	70	62	95
611	25	12507009	visit 19, week 52, study day 364 +/- 4	35.5	90	64	120
612	25	12507009	visit 2, baseline, study day 01	36	78	72	118
613	25	12507009	visit 3, week 02, study day 15	36.2	70	61	130
614	25	12507009	visit 4, week 04, study day 28 +/- 3	35.5	66	68	100
615	25	12507009	visit 6, week 08, study day 56 +/- 3	35.8	80	86	130



In conclusion

1. When implementing RBQM, consider analyzing the data on an ongoing basis once you got them from the respective system(s)
2. Assess all the steps necessary to create a holistic RBQM environment
    1. Risk assessment
    2. Critical data
    3. Critical processes
    4. May be even critical people
    5. Risk categorization
    6. Key risk indicators
    7. Thresholds
    8. Access to many different data source systems
    9. Accountability / Escalation
    10. Targeted monitoring
    11. Centralized statistical monitoring
    12. Predictions
    13. Link to CAPA
    14. Creation of an IQRMP by the system
    15. Documentation of all decisions made during the course of a study
3. Do not copy the data every time you want to run an analysis

In conclusion

Once such an approach has been implemented, users shall be able to manage all RBQM related activities within such a system