How to Limit Patient Harm from Erroneous Results, QC Strategies Based on Risk Management

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Learning Objectives

- Identify the steps in patient risk managed QC strategy design
- Explain how to set the Severity of Harm category for an analyte
- Describe 2 components of the QC design that can be changed to minimize patient risk

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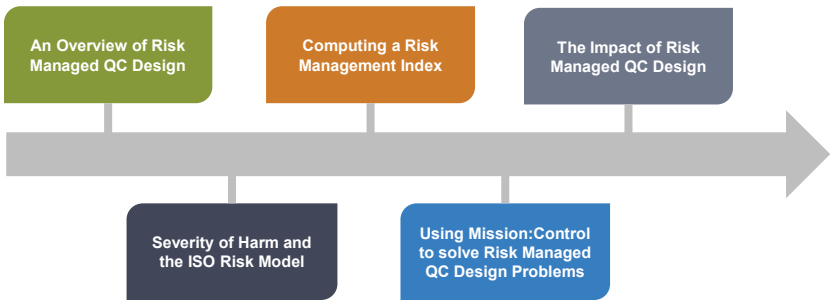
Agenda



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The Benefits of Risk Managed QC

Risk Managed QC focuses on the patient – not the instrument.

- The primary metric is the probability that an erroneous result will be produced.
- The goal of Risk Managed QC is to keep the probability of producing erroneous results below an acceptable minimum.
- This approach considering the quality specification, test method performance, reliability, clinical utility and patient volume.
- This approach does not assume uniform precision across the analytical range.

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Risk Managed QC Strategy Design

Risk Managed QC Strategy Design:

1. Use the clinical utility of the test method to determine an acceptable level of patient harm.
2. Considering the quality specification, test method performance, reliability, clinical utility and patient volume, compute the predicted probability of producing patient harm.
3. Find a QC strategy that has predicted probability of patient harm less than the acceptable level of patient harm.

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The ISO Model for Acceptable Risk

ISO 14971 - Application of Risk Management To Medical Devices

- Model for risk management and determining acceptable levels of risk.

BS EN ISO 14971:2012

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The CLSI EP23 Model for Acceptable Risk

This same approach was used in CLSI EP-23 Laboratory Quality Control Based on Risk Management

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Using The Risk Models

Use the risk model by assigning a Severity of Harm category to each analyte, based on how the analyte is used in the clinical setting

Each Severity of Harm category has an associated maximum acceptable probability of patient harm

The acceptable probability of patient harm be used to determine the maximum probability of producing erroneous patient results

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Severity of Harm Categories

Severity of harm is described in terms of the severity of the consequence to the patient

Consequence to patient	Severity of Harm Category
Inconvenience or temporary discomfort	Negligible
Temporary injury or impairment not requiring professional medical intervention	Minor
Injury or impairment requiring professional medical intervention	Serious
Permanent impairment or life-threatening injury	Critical
Patient death	Catastrophic

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Acceptable Probability of Harm

Severity of Harm Category	Acceptable Probability of Harm	Maximum Acceptable Rate	Maximum Acceptable Probability
Negligible	Frequent	1 in 100	0.01
Minor	Probable	1 in 1,000	0.001
Serious	Occasional	1 in 10,000	0.0001
Critical	Remote	1 in 100,000	0.00001
Catastrophic	Improbable	1 in 1,000,000	0.000001

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Severity of Harm in QC Strategy Design

In Risk Managed QC Strategy Design, the Severity of Harm is used to set the limit of erroneous result production.

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The Probability of Producing Erroneous Results

- Given a TEa, test method performance, a QC strategy, and test method reliability, we can estimate our probability of producing erroneous results.

- Probability of Erroneous Results (P_U) =
  Probability of In-Control erroneous results +
  Probability of Out-of-Control erroneous results.

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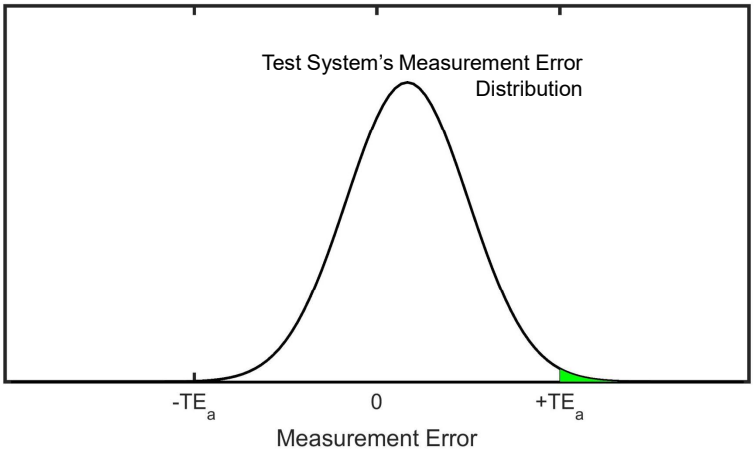
Measurement Error Example



TE$_a$ – Total Error Allowable

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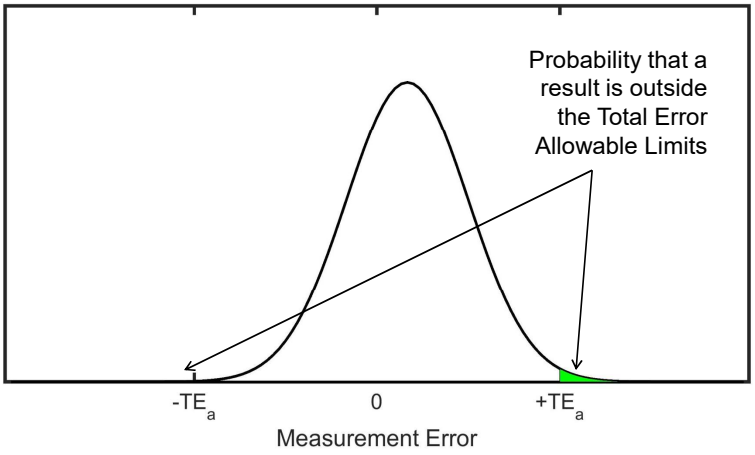
Probability of an Erroneous Result



TE$_a$ – Total Error Allowable

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Estimating the In-Control Erroneous Results

- Given a test method's performance metrics (means and SD's), and the TE_a, we can estimate what the probability is that a patient result will be erroneous (outside the TE_a).
- This gives us a "rate" of producing erroneous results when the test method is working properly, and everything is In-Control.
- Expressing the probability of producing an erroneous result as a percentage gives us the %Unreliable Results.

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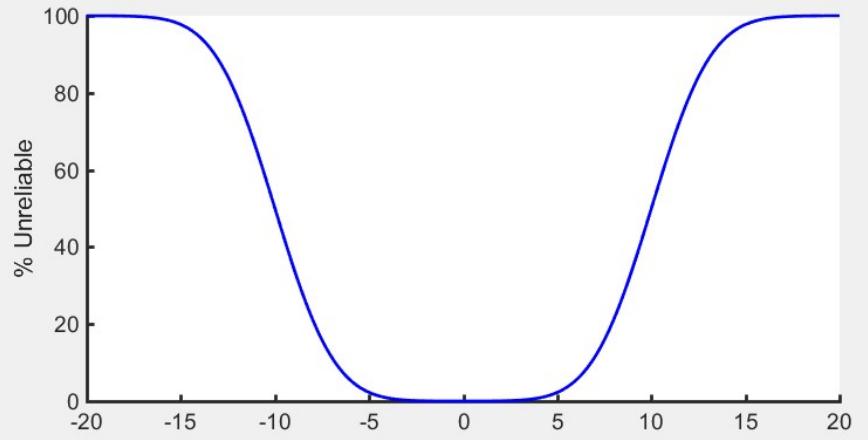
% Unreliable vs. Size of Error Condition



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Estimating Out-of-Control Erroneous Results

- Estimating the probability of producing erroneous results when Out-of-Control is more complicated than the In-control condition.
- In addition to the performance metrics and the TE_a, we need to know the QC strategy, and the reliability of the test method (how frequently the test method goes Out-of-Control).
- The QC strategy consists of:
  - The number of patients tested between QC's
  - The number of QC's tested
  - The QC rule

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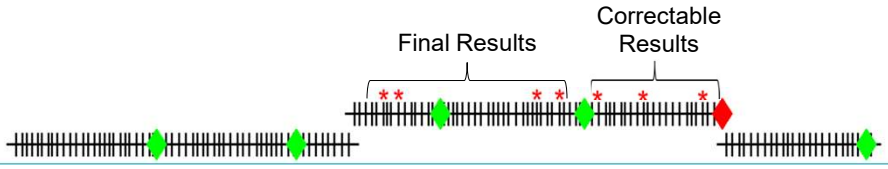
Correctable Results vs. Final Results

- When an Out-of-Control condition is detected (usually a function of the QC strategy), the lab has the opportunity to identify erroneous results and correct them – Correctable results.
- If the Out-of-Control condition is not detected with the first QC event after it started, erroneous results may be produced while the QC is accepted – Final erroneous results.



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Probability of Error Detection

- Unfortunately, Statistical QC is a probabilistic process, and there is no certainty that an Out-of-Control condition will be immediately detected.
- Each QC Rule has a characteristic “Power Curve” which relates the probability of error detection (P_{ed}) to the size of the Out-of-Control condition.
- Small errors are hard to detect and will likely require multiple QC events prior to detection
- Large errors are easy to detect and have a higher probability of being detected quickly.

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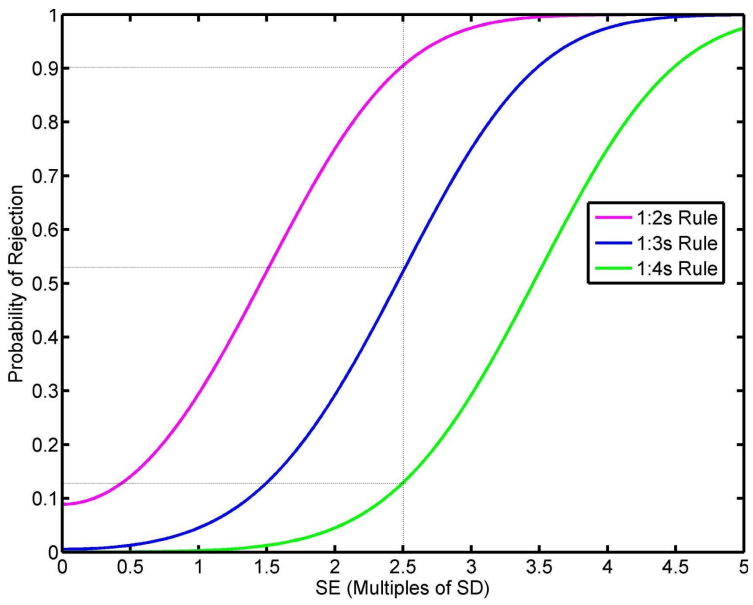
Power curves for 1:2s,1:3s, 1:4s



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Expected Number of QC Events to Detection

- The Expected Number of QC Events to Detection – E(QCE) is how may QC Events are expected to be required to detect an error of a given size.
- This can be estimated as 1/Probability of Error Detection (P_{ed})
- For our previous case for detecting a 2.5S error with:
  - 2 QC's 1:2s rule: Ped = 0.905, E(QCE) = 1.1
  - 2 QC's 1:3s rule: Ped = 0.522, E(QCE) = 1.9
  - 2 QC's 1:4s rule: Ped = 0.129, E(QCE) = 7.7

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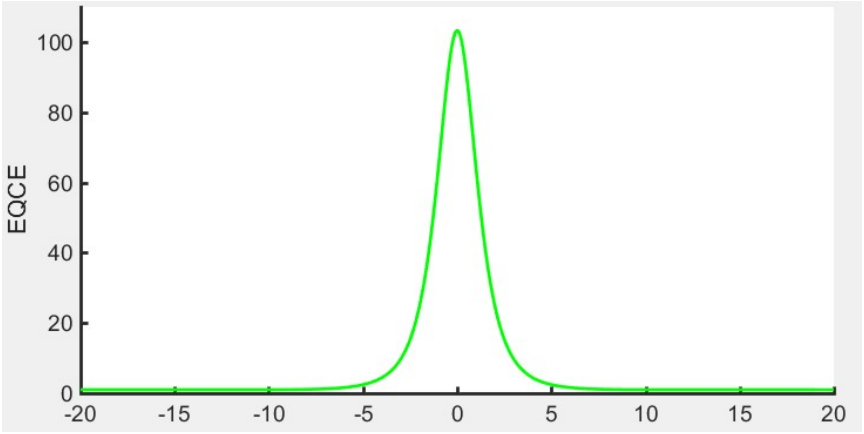
EQCE vs. Size of Error Condition



Expected number of QC Events to Error Detection - EQCE

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Probability of False Rejection

- The Probability of False Rejection (often called FRR – False Rejection Rate) is the probability that a QC Event will reject during the In-Control State.
- This is a False Positive from the QC Strategy.
- The FRR should be as low as possible due to the trouble and costs incurred by the lab from a False Rejection.
- On the QC Rule Power Curve, the FRR is the probability of rejection when the size of the error condition is zero.

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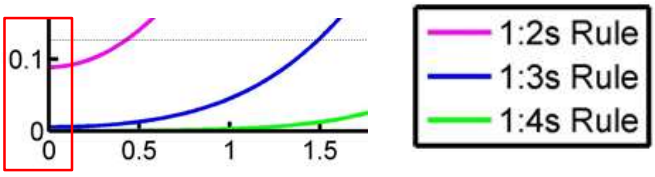
Probability of False Rejection



The False Rejection Rates for 2 QC's are:
1:2s - 0.0889 or ~ 1 in 11 QC Events
1:3s - 0.0054 or ~ 1 in 188 QC Events
1:4s – 0.0001 or ~ 1 in 7892 QC Events

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Estimating Erroneous Final Results for an Error

- Given a QC strategy, test method performance, and a quality specification, we can estimate how many erroneous Final results will be produced for a given error.
- If we do this across a range of error conditions (usually ± 2*TE_a), we get a Final Erroneous Results curve.
- The area under this curve can be used to compute the probability of producing erroneous Final results for Out-of-Control conditions if we adjust for the frequency of Out-of-Control conditions (the reliability).

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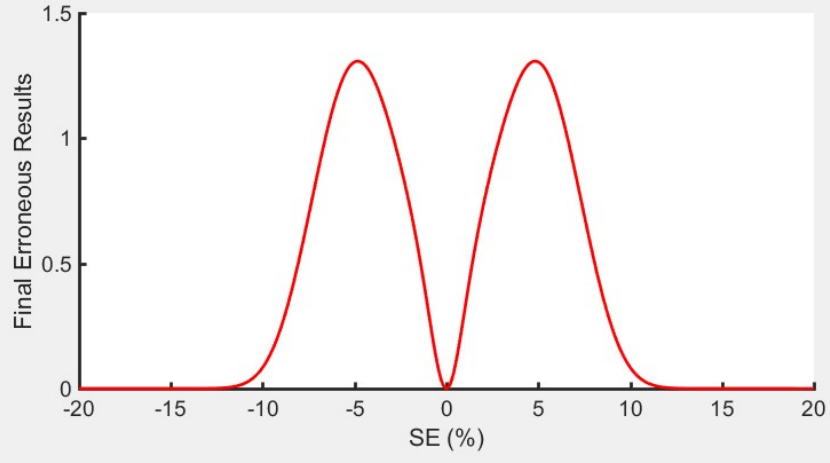
Final Erroneous Results vs. Size of Error



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Computing the Predicted Probability of Harm

The Predicted Probability of Harm is computed by:

$$P_H = P_U * P_{h|u}$$

Where:

- P_H is the predicted probability of harm
- P_U is the probability of producing an erroneous result or the rate of producing erroneous results
- $P_{h|u}$ is the conditional probability that an erroneous result causes patient harm. If $P_{h|u}$ is 1 then the assumption is that every erroneous result causes patient harm.

Does every erroneous albumin result cause patient harm?

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Computing a Risk Management Index: RMI

- We define the patient risk management index as:

$$\text{RMI} = \frac{\text{Predicted PH}}{\text{Acceptable PH}}$$

- RMI ≤ 1 implies acceptable risk.
- RMI values permit easy assessment and comparison of multiple analytes
  - with different frequencies of test system failure
  - with different probabilities of harm given an incorrect result
  - with different severities of patient harm

RMI – Risk Management Index | PH – Probability of Harm

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Risk Managed QC Strategy Design Example 1

Glucose procedure:

- CLIA Quality Specification: 10%
- 100 patients per day
- 2 QC Events with 2 levels per day
  - QC Means: 60, 130 mg/dL
  - QC SD's: 1.4, 2.7
  - 1:3s/2:2s/R:4s QC Rule
- Severity of Harm Category: Serious
  - Maps to Occasional Probability of Harm or 1/10,000
- Mean Time Between Failures is 90 days

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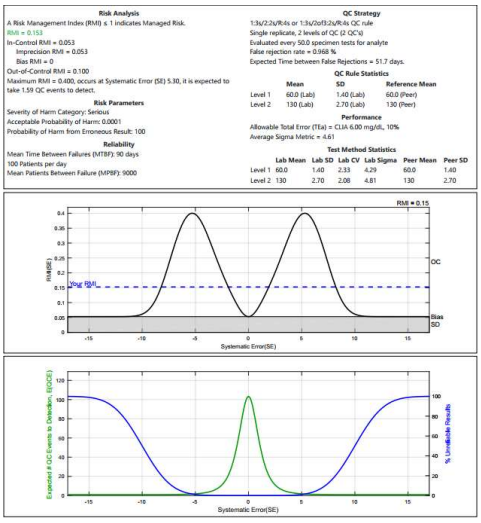
Mission:Control Analytical Risk Assessment



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Mission:Control Risk Analysis

Glucose . mg/dL
Siemens Dimension Vista (148609)

Dallas, TX, 12345
United States

Risk Analysis

A Risk Management Index (RMI) ≤ 1 indicates Managed Risk.

RMI = 0.153
In-Control RMI = 0.053
Imprecision RMI = 0.053
Bias RMI = 0
Out-of-Control RMI = 0.100

Maximum RMI = 0.400, occurs at Systematic Error (SE) 5.30, it is expected to take 1.59 QC events to detect.

Risk Parameters

Severity of Harm Category: Serious
Acceptable Probability of Harm: 0.0001
Probability of Harm from Erroneous Result: 100

Reliability

Mean Time Between Failures (MTBF): 90 days
100 Patients per day
Mean Patients Between Failure (MPBF): 9000

QC Strategy

1:3s/2:2s/R:4s or 1:3s/2of3:2s/R:4s QC rule
Single replicate, 2 levels of QC (2 QC's)
Evaluated every 50.0 specimen tests for analyte

False rejection rate = 0.968 %
Expected Time between False Rejections = 51.7 days.

QC Rule Statistics

	Mean	SD	Reference Mean
Level 1	60.0 (Lab)	1.40 (Lab)	60.0 (Peer)
Level 2	130 (Lab)	2.70 (Lab)	130 (Peer)

Performance

Allowable Total Error (TEa) = CLIA 6.00 mg/dL, 10%
Average Sigma Metric = 4.61

Test Method Statistics

	Lab Mean	Lab SD	Lab CV	Lab Sigma	Peer Mean	Peer SD
Level 1	60.0	1.40	2.33	4.29	60.0	1.40
Level 2	130	2.70	2.08	4.81	130	2.70

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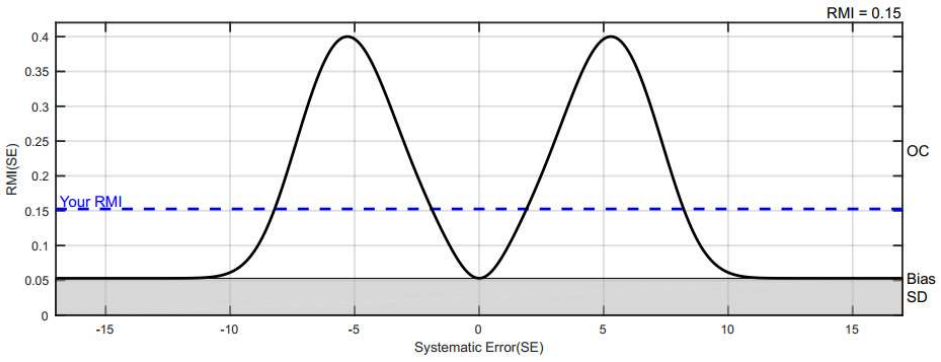
RMI Curve



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We can improve the False Rejection Rate

- This QC Strategy has a False Rejection Rate (FRR) of 0.009677 per QC Event.
- The Expected Time between False Rejections (ETFR) is 52 days.
- Given the low RMI or 0.153, we can use a rule with a lower false rejection rate.
- First, we try a 1:3s rule

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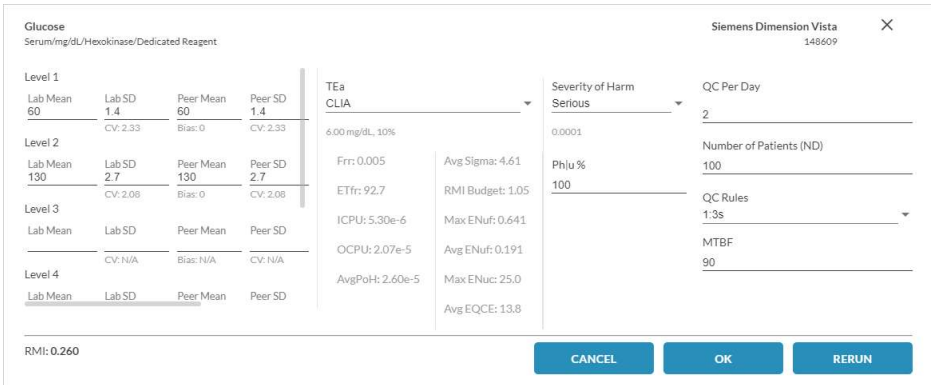
RMI of 0.26 with 1:3s Rule



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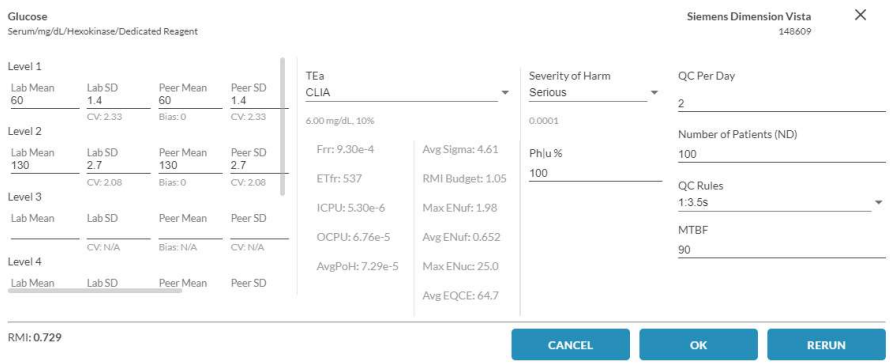
RMI of 0.729 with 1:3.5s Rule



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Final Design RMI 0.729, ETFR 537

- Using the 1:3.5s rule, we have a False Rejection Rate of 0.00093 per QC Event.
- This gives us an Expected Time to False Rejection (ETFR) of ~537 days.
- So we end with a final Risk Managed QC Strategy of:
  - 1 QC Event every 50 patients (2/day)
  - QC Means: 60, 130 mg/dL
  - QC SD's: 1.4, 2.7
  - 1:3.5s QC Rule

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Risk Managed QC Strategy Design Example 2

Sodium procedure:

- CLIA Quality Specification: 4 mmol/L
- 600 patients per day
- 2 QC Events with 2 levels per day
  - QC Means: 121.4, 153.8 mmol/L
  - QC SD's: 1, 1.1
  - Repeat 1:2s QC Rule
- Severity of Harm Category: Serious
- $P_{h|u} = 0.2$
- Mean Time Between Failures is 3 days

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RMI of 1.41 on Initial Design

Risk Analysis

A Risk Management Index (RMI) ≤ 1 indicates Managed Risk.
RMI = 1.41
In-Control RMI = 0.299
Imprecision RMI = 0.299
Bias RMI = 0
Out-of-Control RMI = 1.11
Maximum RMI = 4.70, occurs at Systematic Error (SE) 1.80, it is expected to take 2.22 QC events to detect.

Risk Parameters

Severity of Harm Category: Serious
Acceptable Probability of Harm: 0.0001
Probability of Harm from Erroneous Result: 20.0

Reliability

Mean Time Between Failures (MTBF): 3 days
600 Patients per day
Mean Patients Between Failure (MPBF): 1800

QC Strategy

Repeat 1:2s QC rule
Single replicate, 2 levels of QC (2 QC's)
Evaluated every 300 specimen tests for analyte
False rejection rate = 0.979 %
Expected Time between False Rejections = 51.0 days.

QC Rule Statistics

	Mean	SD	Reference Mean
Level 1	121 (Lab)	1.00 (Lab)	121 (Lab)
Level 3	154 (Lab)	1.10 (Lab)	154 (Lab)

Performance

Allowable Total Error (TEa) = CLIA 4.00 mmol/L
Average Sigma Metric = 3.81

Test Method Statistics

	Lab Mean	Lab SD	Lab CV	Lab Sigma	Peer Mean	Peer SD
Level 1	121	1.00	0.824	4.00	121	1.00
Level 3	154	1.10	0.715	3.64	154	1.10

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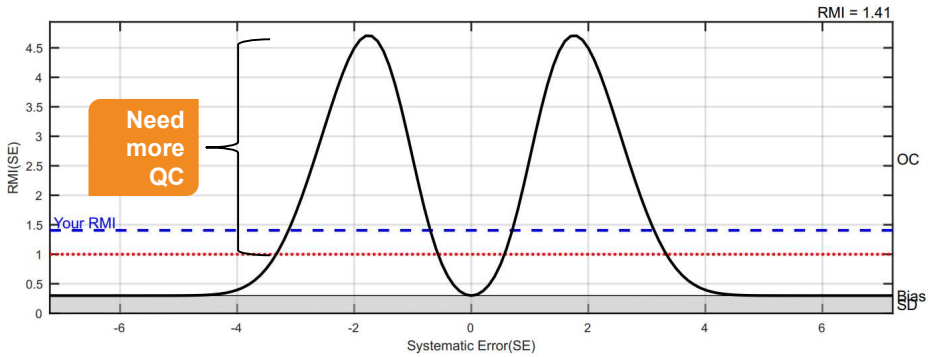
Need more QC, Out-of-Control RMI = 1.1



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We need fewer patients between QC's

- Introducing additional electrolyte control events is often necessary as electrolytes are ordered frequently and usually have tight control parameters
- In this case, we are going to add additional 2 additional QC events to bring the number of patients between QC's from 300 down to 150.

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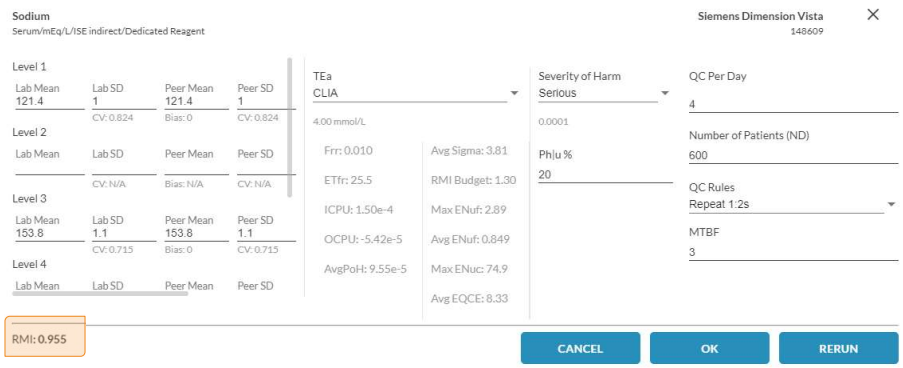
RMI of 0.955 after increasing QC frequency



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Final Design RMI 0.955, ETFR 26

- The Expected Time Between False Rejections (ETFR) is ~ 26 days with this procedure.
- So we end with a final Risk Managed QC Strategy of:
  - 4 QC Events with 2 levels per day
  - QC Means: 121.4, 153.8 mmol/L
  - QC SD's: 1, 1.1
  - Repeat 1:2s QC Rule

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The Impact of Risk Managed QC Design

- Risk Managed QC Strategy Design allows you to:
  - Use the clinical utility of the test method to assess the acceptable level of patient harm due to erroneous results
  - Estimate the probability of producing erroneous test results
  - Estimate the predicted probability of patient harm from erroneous patient results
  - Compare the predicted probability of patient harm to the acceptable level of patient harm in a Risk Management Index

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The Impact of Risk Managed QC Design

- The estimates for the probability of producing erroneous patient results consider:
  - the quality specification
  - the quality control strategy
  - test method performance
  - test method reliability
  - patient volume
- Unlike conventional QC Design, Risk Managed QC Design allows you to reduce the false rejection rate with additional QC.

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Summary

- The clinical utility of a test method determines our tolerance for producing erroneous results and can be used to determine an acceptable level of patient harm from erroneous results.
- Our QC strategy, in conjunction with test method performance and reliability, can be used to estimate the probability of producing erroneous results and predict the probability of patient harm from erroneous results for a test method.
- We can compute a Risk Management Index (RMI) as a ratio of the predicted probability of patient harm to the acceptable probability of patient harm.
- We can use the RMI to find suitable QC strategies.

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