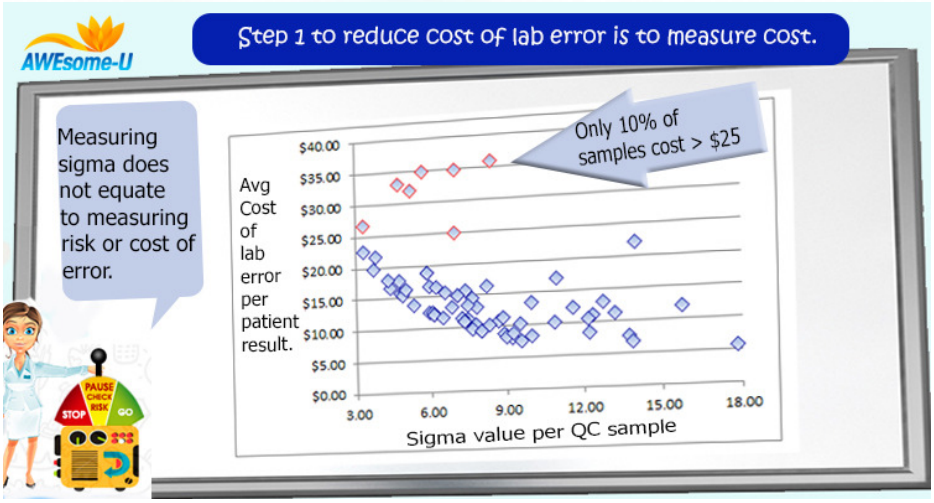
Welcome! Oct. 18, 2018

Agenda Oct. 18, 2018

Agenda:

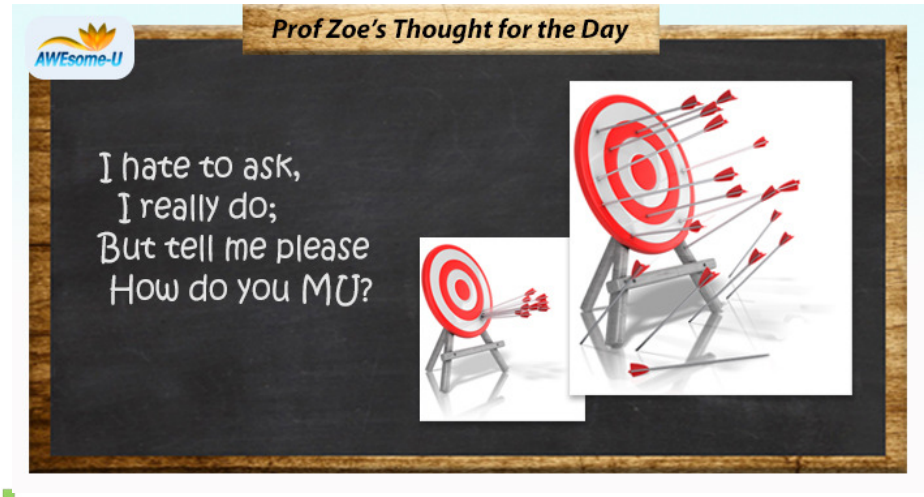
- Introductions
  - Personal Objectives
- Risk Metrics
- Uncertainties about measurement uncertainty
- Does anyone care?
- Analytical Run and Bracketed QC



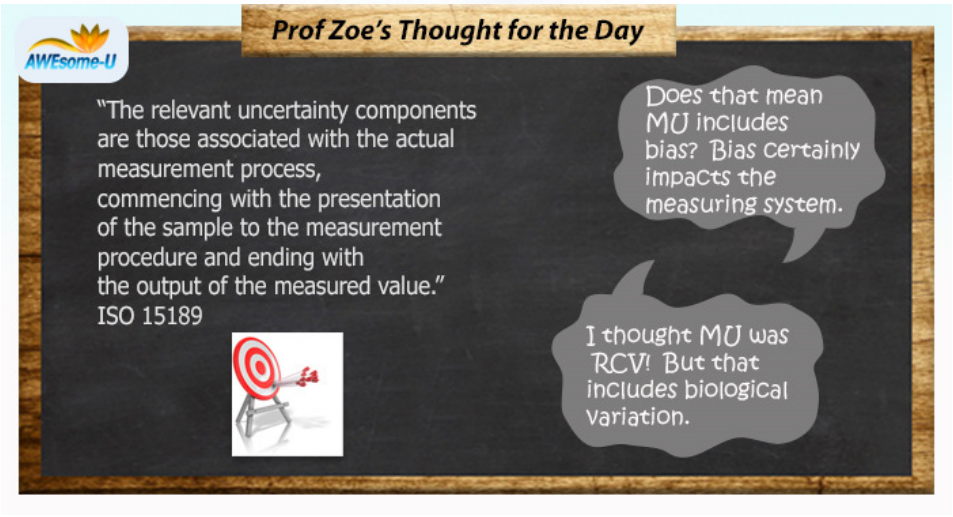
Risk Metrics for Routine Analytical Performance Review (not Trouble-Shooting or QC Evaluation)

- Clinical cost of lab errors per year
- Number/proportion of lab errors/year
- Sigma (#SD to 50% failure)
- Margin for Error (#SD to unacceptable risk)
- Total Error
- MU (Measurement Uncertainty)
- RCV (Reference Change Value)
- Risk-Based Quality Grade

Does Anybody Care??

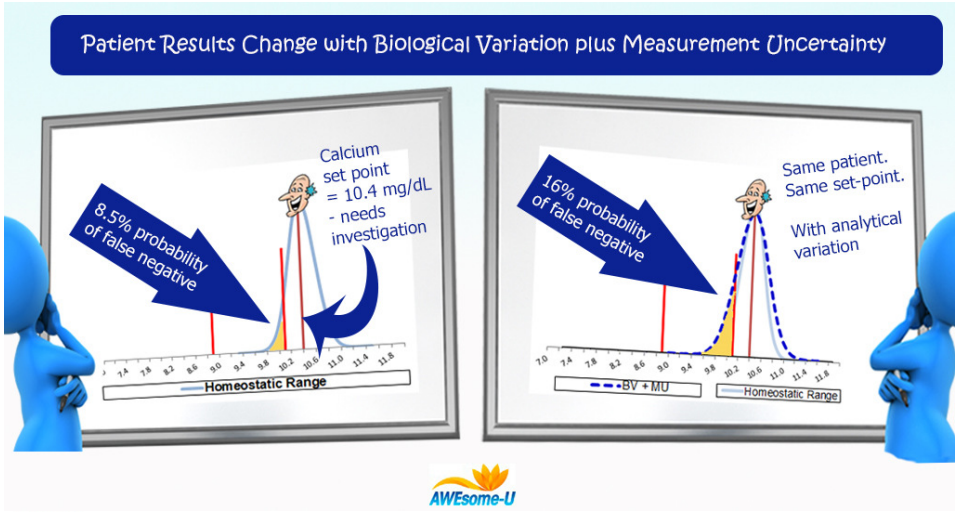


What MU shall we do?



The RCV helps doctors interpret results vs prior results or decision limits.

It has uncertainty from the CV_a and CV_i



Can we just do this? Report RCV?

To begin, simply square the value of each **uncertainty** source. Next, add them all together to **calculate** the sum (i.e. the sum of squares). Then, **calculate** the square-root of the summed value (i.e. the root sum of squares). The result will be your Combined **Uncertainty**.
Jul 16, 2015

Proposal: MU = RCV?

- For a change between consecutive measurements to become significant, the difference must be larger than the change that can reasonably be expected due to normal biological and analytical variation. This threshold value is termed the Reference Change Value (RCV). The RCV can be calculated for each laboratory test and depends on the biological within-person variability (CVI) and the analytical variability (CVA). [2]
- RCV= √2 * Zscore* √(CVa^2 + CVi^2)
- In this formula, the Z-score represents the number of standard deviations and correspond to the desired probability.
- Commonly used Z-scores are 1.96 and 2.56.
- These Z-scores calculate the percentage increase or decrease that is required to become statistically significant, with a false positive rate of 5%, ($p < 0.05$) and 1% ($p < 0.01$) respectively.

Or … MU = CV_T

Measurement Uncertainty as
(CV_T = 1.96* √(CVa^2 + CVi^2)

WHY
Do we MU?
WHAT does
MU do?

You cannot assume they are comparing to another result.

"Thus for serial result to be significantly different, the difference must be greater than the combined variation inherent in the two results." Fraser. Biological Variation from Principles to Practice

RCV= √2 * Zscore* √(CVa^2 + CVi^2)

Which CVi?

Clin Biochem. 2013 Oct;46(15):1548-53. doi: 10.1016/j.clinbiochem.2013.05.055. Epub 2013 Jun 1.

Estimation of biological variation and reference change value of glycated hemoglobin (HbA(1c)) when two analytical methods are used.

RESULTS:

- The within subject (CV(I))-between subject (CV(G)) biological variations were 1.17% and 5.58%, respectively for HPLC. The calculated CV(I) and CV(G) were 2.15% and 4.03%, respectively for boronate affinity chromatography. Reference change value (RCV) for HPLC and boronate affinity chromatography was 5.4% and 10.4% respectively and individuality index of HbA(1c) was 0.35 and 0.93 respectively.

- … But CVi = 1.9% at Westgard site

And CVi is different in this study

Table 1. View popup

Variance components for GHb and FPG.

Variance component	GHb, %	FPG, mmol/L
Between-subject S_g (CV_g)	0.20 (4.0%)	0.31 (5.8%)
Within-subject S_i (CV_i)[1]	0.08 (1.7%)	0.30 (5.7%)
Analytic S_a (CV_a)		
Between day	0.11 (2.3%)	0.09 (1.7%)
Within day[2]	0.07 (1.5%)	0.04 (0.8%)

1 Also includes within-day analytical variation.

2 Estimated from quality-control data.

Which CVa?

Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g. changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.

- The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value.
- The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples.
- The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.

How to calculate MU?

Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g. changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.

DIMS to include multiple reagent lots - or do a mean and SD apply to a single Gaussian data set?

DIMS to use mean & SD from mixed (or non-Gaussian) data sets?

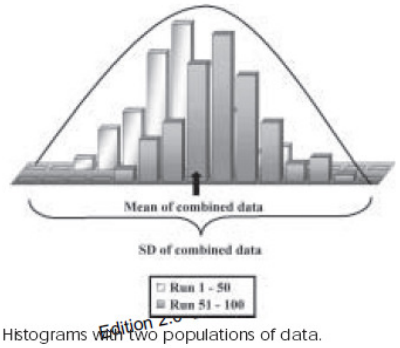


Figure 2-10. Histograms with two populations of data.

Table 2-4. Calculations from mixed data populations illustrated in Figures 2-9 and 2-10.

	Run 1 to 50	Run 51 to 100	Mixed data Run 1 to 100
Mean	100.0	103.8	101.9
Median	100.0	104.0	101.8
Mode	100.0	104.0	100.0
SD	1.9	2.1	2.8

Knowing whether method imprecision is reflected by "usual" or cumulative SD. We use the SD to assess the acceptability of method precision, to calculate total error and critical systematic error, and to set limits for QC rules. If we combine data from several populations, the SD calculated on this cumulative data is often much higher than the SD from any single data population. Figure 2-11 illustrates 360 control results from an AST method with a target or true value of 100 units and a quality specification of ± 20% based on the CLIA regulations. We might see a pattern similar to this hypothetical example if we change reagent lots or calibrators every two months, and each lot produces different, yet still acceptable, mean values.

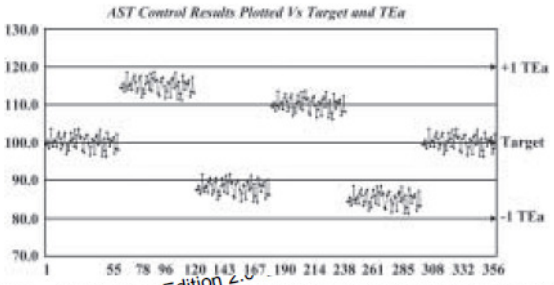


Figure 2-11. 360 AST results from 6 different reagent lots plotted against the target value and TEa limits.

Table 2-5. Calculations of mean, SD, TE and ΔSEc in six individual data populations.

Set	Run Numbers	Mean	SD	TE	ΔSEc
1	1–60	100.09	1.94	3.96	8.62
2	61–120	115.09	1.94	18.96	0.89
3	121–180	88.09	1.94	15.79	2.52
4	181–240	110.09	1.94	13.96	3.46
5	241–300	85.09	1.94	18.79	0.97
6	301–360	100.09	1.94	3.96	8.62

Zero TE > 20 or SEc zero

Table 2-6. Calculations of the cumulative mean, SD, TE and ΔSEc in six data populations.

Set	Cumulative	Mean	SD	TE	ΔSEc
1	1–60	100.09	1.94	3.96	8.62
2	1–120	107.59	7.77	23.13	0
3	1–180	101.09	11.24	23.57	0
4	1–240	103.34	10.79	24.92	0
5	1–300	99.69	11.95	24.22	0
6	1–360	99.75	10.94	22.12	0

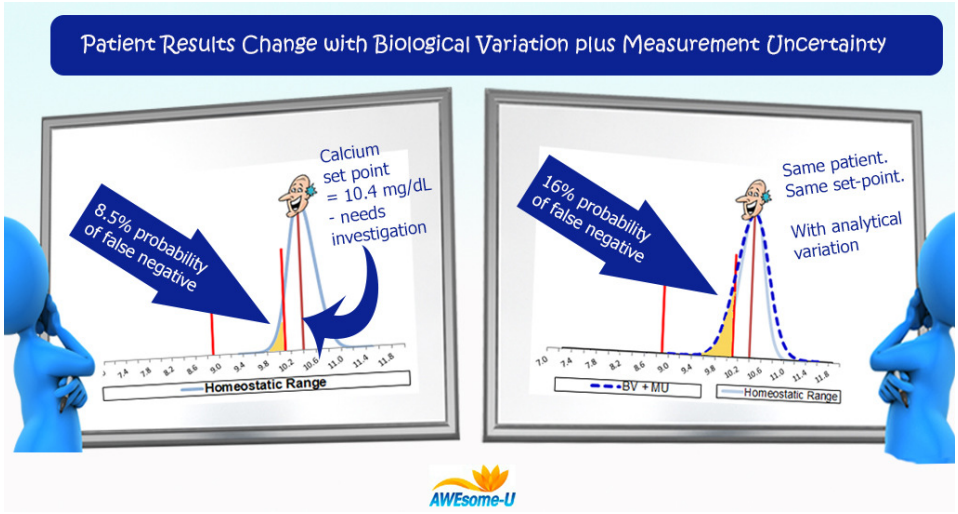
5 of 6 > 20 And SEc zero

Final Answer Report 101 MU = ??

What uncertainty impacts "Bob" today?

"The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty."
ISO 15189-2012

We could report the probability that the result reported exceeds a decision limit and/or differs clinically from a prior result



Is this a case of the senseless being proclaimed because nobody wants to say "I do not understand"?

George Sweeney

HOW do we convince them they are wrong?

Evaluation of Analytical Process

CatalystQC™ Risk Manager Overview

5	1	1
	2	
6	3	
7	Test Case to Model Calculations	
8	4	

Evaluation of Analytical Process

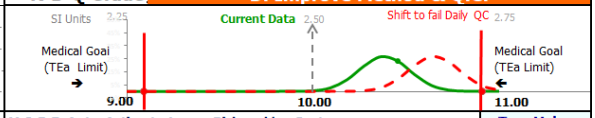
CatalystQC™ Risk Manager Overview

Instrument A, Calcium, Level 2, Lot: 222222

Test Calcs 3, Chemistry, 1-Sep-18 To 30-Sep-18

Evaluation of Analytical Process Quality:	PASS
True Value of this QC Sample	10.00
Measured Mean in this time period	10.42
Measured SD in this time period	0.150
TEa Limit (ACCEPTABLE Medical Error) (Limit of Medical Utility)	1.00
Total Error (as |Bias| + (2*SD)	0.72
# Patient Samples /Yr. controlled mainly by this QC sample	36,500
ACCEPTABLE # Results / year failing TEa Limit	830
# Results / year failing TEa Limit (with quality at this time)	2
Clinical/Legal cost of failure at TEa Limit. (Max Medical Goal)	$100
ACCEPTABLE Average Clinical/Legal cost of error per Result	$50.00
Average Clinical/Legal cost of error per result (at this time)	$47.01
Margin for Error (# SD to Unacceptable Risk as # errors/year)	1.87
z-value (sigma as [(TEa – |bias|)/SD] to TEa Limit	3.87
Biological Variation (within individual)	1.70%
Measurement Uncertainty as (CV_T = 1.96* √(CVa^2 + CVi^2)	4.37%
Maximum ACCEPTABLE Measurement Uncertainty	10.0%

R-B-Q Grade: D. Improve Method & Q.C.



M.O.R.E. Auto-Action to Lower Risk and/or Cost:

Improve method accuracy & precision

Use OptimiZed QC Process

Increase QC frequency

Consultant or Risk Manager Comments:

Test Case to Model Calculations

$1,825,000	**Acceptable Risk** per year from average cost of error.
$1,715,705	Total Cost of Lab Error/Year with current performance
$20,516	**Annual Saving/Cost of QC + Clinical Savings /Failure**

True Value	Peer - Method
TEa Source	CLIA USA
Acceptable Risk Method Review	Sigma=2
Daily QC	%=5
Bracket QC?	No

AWEsome NUMBERS

Rate Risk Metrics for Routine Analytical Performance Review (vs Trouble-Shooting or QC Evaluation or to meet Accreditation Requirements)

- Clinical cost of lab errors per year
- Number/proportion of lab errors/year
- Sigma (#SD to 50% failure)
- Margin for Error (#SD to unacceptable risk)
- Total Error
- MU (Measurement Uncertainty)
- RCV (Reference Change Value)
- Risk-Based Quality Grade

AWEsome NUMBERS