RANDOX
QUALITY CONTROL

Improving Laboratory Performance Through Quality Control

How to Measure Uncertainty

Complete **QC** solutions for results you can **trust**

How to Measure Uncertainty

"The laboratory shall determine measurement uncertainty for each measurement procedure, in the examination phases 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."

**ISO 15189:2012
Section 5.5.8.3**

What is Measurement Uncertainty?

It relates to the doubt that exists for the result of any measurement. For every measurement there is always a margin of doubt. In everyday speech, this might be expressed as 'give or take' ... e.g. a piece of string might be two metres long 'give or take a centimetre.

Since there is always a margin of doubt for any measurement, we need to ask 'How big is the margin?' and 'How significant is the doubt?' Two values are needed in order to quantify uncertainty. One is the width of the margin, or interval. The other is a confidence level, and states how sure we are that the 'true value' is within that margin.

Measurement Good Practice Guide No. 11

For example:

We might say that the length of a piece of string measures 20 centimetres plus or minus 1 centimetre, at the 95 percent confidence level. This result could be written: 20 cm ±1 cm, at a level of confidence of 95%. The statement says that we are 95 percent sure that the string is between 19 centimetres and 21 centimetres long.

In a hospital or healthcare environment the clinician must be certain that any change identified in a patients test results is not a change to the laboratory test system but a change to the patient's status. This is especially critical at clinical decision levels.

Measuring Uncertainty

Using QC data to calculate uncertainty makes several assumptions:

- The test system is under control
- The patient samples are treated in the same manner as controls
- Gross outliers are removed (if you do not run samples when your QC is out of range then they should not be included in your calculations)

If using QC data, it is a good idea to use commutable control material with a sample matrix similar to the patient sample and analyte concentrations present at clinical decision levels.

There are two ways to measure uncertainty.

1. Uncertainty estimates from repeated readings
2. Uncertainty estimates from repeated readings and any other information e.g. previous history of calibration, bias etc.

(Regardless of the source of uncertainty, in most instances, uncertainty calculations require both measurements)

AACB recommend labs use at least 6 months QC data to calculate uncertainty.

When measuring uncertainty we look at two things intra assay precision and inter assay precision. Intra precision refers to precision within a run; it is normally measured by running 20 or more replicates of the same sample at the same time. This process will help to identify any random uncertainties within a test system. Inter precision on the other hand refers to precision over a number of different runs, it is normally measured by running 20 or more replicates of the sample over several days e.g. one replicate every day for 20 days. This process will identify any systematic uncertainties in a test system.

To measure uncertainty (u) the lab must first calculate the SEM of the intra precision (A) and the SD of the inter assay precision (B). Once we have calculated A and B we need to square them, add them and calculate the square root *(see formula below)*.

$$u = \sqrt{A^2 + B^2}$$

Since uncertainty is calculated as SD and one SD is equal to 68% confidence on the Gaussian curve *(Figure 1)* it is reasonable to multiply the uncertainty by a coverage factor (K) of 2 to attain a 2SD confidence level of 95% *(see formula below)*. This is known as expanded uncertainty (U).

$$U = 2 \times u$$

Figure 1

99.74%

95.44%

68.26%

$\mu - 3\sigma$ $\mu - 2\sigma$ $\mu - \sigma$ μ $\mu + \sigma$ $\mu + 2\sigma$ $\mu + 3\sigma$
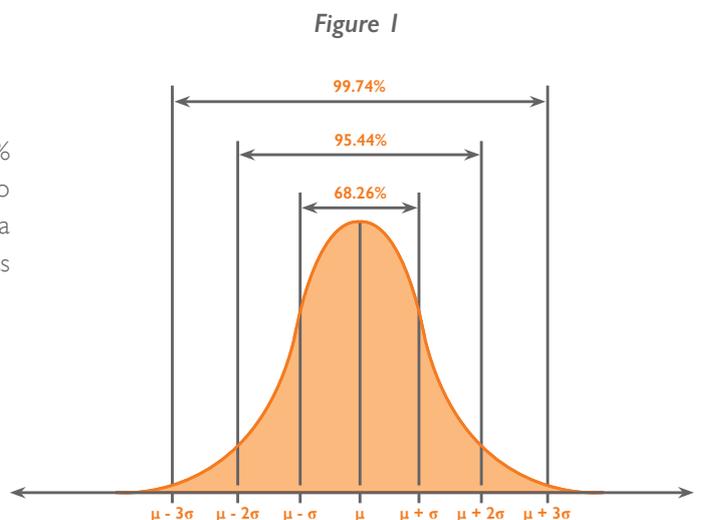
If a coverage factor (K) other than 95% is required, the table below lists the necessary coverage factors required to obtain various levels of confidence for a normal distribution.

Coverage Probability	Coverage Factor (K)
90%	1.64
95.45%	2.00
99%	2.58
99.73%	3.00

Other factors affecting Uncertainty

It is important to consider bias when calculating uncertainty. Bias must be measured and if it is significant removed or minimised. If bias is not removed the uncertainty of the bias correction must be calculated and included in the overall uncertainty measurement.

To calculate the uncertainty of bias we must first determine uRef and uRep

uRef – Uncertainty value of the analyte assigned to the reference material/EQA. This can be obtained from the reference material or EQA report.

uRep – Uncertainty value of the analyte in the reference material/EQA when measured in replicate in your lab.

The uncertainty of the bias is then calculated by combining the two uncertainties, *(see formula below)*.

$$uBias = \sqrt{uRef^2 + uRep^2}$$

Bias can be investigated by measuring it against:

- Assayed QC material
- Unassayed QC material alongside a peer group reporting program
- EQA/PT
- Calibration material or reference materials

Sources of Uncertainty

Sources of uncertainty fall into three main categories; pre-analytical, analytical and post analytical.

Pre-analytical	Analytical	Post Analytical
Sample collection	Reagent storage/preparation	Interpretation of results
Sample storage/transportation	Instrument performance	Report format
Patient state	Operator performance	LIS/Middleware
	Calibration	

(Procedures should be put in place to detect and minimise these sources)

Additional factors to consider

When calculating combined uncertainties for parameters that are calculated using addition and subtraction e.g. Anion gap, the SD or 'u' value can be used.

Similarly when calculating combined uncertainties for parameters that are calculated using division and multiplication e.g. creatinine clearance, the SD or 'u' must first be converted to CV.

Conclusion

The uncertainty of a measurement relates to the doubt that exists for the result of any measurement. If uncertainty is measured it is no longer uncertainty, but the confidence interval within which the result falls. Uncertainty should be assessed regularly and attempts made to improve the value.

Glossary

Error - The difference between the measured value and the true value.

Uncertainty - A quantification of the doubt relating to a measured value.

Standard Deviation (SD) - A measure of how spread out a set of numbers are. Approximately two thirds of all readings will fall between ± one SD of the average and around 95% of all readings will fall within 2SD.

$$SD = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$$

Coefficient of Variation (CV) - The CV is a dimensionless number defined as the standard deviation of a set of measurements divided by the mean. It is used to express the precision or repeatability of a set of results.

Standard Error of Mean (SEM) - Is the standard deviation of a sample or using the sample mean as a method of estimating the population mean.

$$SEM = \sqrt{\frac{SD}{n}}$$

ACUSERA

Randox is a world leading provider of multi-analyte, third party controls designed to help streamline QC in even the most demanding laboratories. Our unique combination of analytes enables complete test menu consolidation and will ultimately reduce costs without compromising on quality or performance.

Helping to facilitate ISO 15189 accreditation, our complete range of true third party controls will enable unbiased performance assessment with any instrument or method.

Why choose Randox as your third party QC provider?

• **Consolidation:** Delivering unrivalled consolidation and covering clinical decision levels the Acusera range will significantly reduce costs and preparation time without compromising on quality.

• **Value Assignment:** Our unique value assignment process not only ensures the availability of accurate target values for multiple instruments and methods but reduces the time spent assigning controls.

• **Third Party Controls:** Our controls are independently manufactured enabling unbiased performance assessment with any instrument or method.

• **High Quality Material:** As the most commutable controls on the market a matrix that reacts to the test system in the same manner as the patient sample is guaranteed.

• **Choice:** Our comprehensive product portfolio includes liquid ready-to-use, liquid frozen and lyophilised controls to meet all laboratory preferences and requirements.

• **Stability:** Designed to ensure continuity of lot supply our lyophilised controls have a shelf life of up to 4 years while our liquid controls are stable for up to 2 years from the date of manufacture. Furthermore the extended working stability of our controls will minimise waste and reduce costs.

Acusera portfolio:

Antioxidants
Blood Gas
Cardiac Markers
Clinical Chemistry
Coagulation
Diabetes
Haematology
Immunoassay
Lipids
Proteins
Therapeutic Drugs
Toxicology
Urine

ACUSERA 24•7

Acusera 24•7 Live Online is an interlaboratory data management and peer group reporting package designed to complement the **Acusera** range of third party controls. Using **Acusera 24•7** will help medical laboratories to improve error detection, reduce false rejections and ensure accurate patient test results.

Why run a peer group reporting program?

- Quickly identify trends, system errors and reagent issues, minimising expensive repeat tests
- Bridges the gap between daily quality control and external quality assessment
- Improve EQA performance by eliminating any undetected bias
- Facilitate regulatory compliance
- Reduce false rejections through the use of QC multi-rules
- Increase confidence in assigned QC target values
- Rapid and effective troubleshooting therefore shorter delays in reporting

With Acusera 24•7, peer group data is uniquely updated every 24 hours, giving you access to the most up-to-date information available. Access to relevant peer group data enables rapid and effective troubleshooting, it may even help to identify errors earlier.

Key Features

- Online access anytime, anywhere

- Unique dashboard displaying poor performing QC tests at-a-glance

- Interactive Levey-Jennings & Histogram charts capable of combining multiple parameters, lots and instruments on a single chart

- Peer group data uniquely updated every 24 hours

- Acusera Advisor automatically recommends QC multi-rules and optimal QC frequency

- Connects directly to LIMs facilitating automated data entry

- Audit trails documenting all actions relating to the creation, modification or deletion of a record
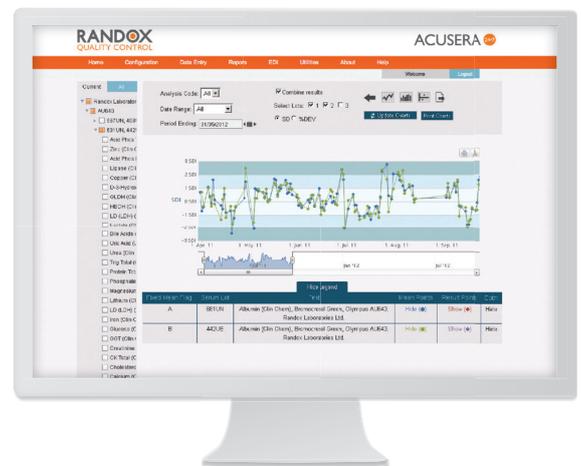
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True third party controls offering complete test menu consolidation

Uniquely combining more than 100 analytes conveniently in a single control, laboratories can significantly reduce costs and consolidate without compromising on quality. As true third party controls, unbiased performance assessment with any instrument or method is guaranteed.

ACUSERA 24•7

Online QC software with real-time peer group statistics

Compatible for use with the Acusera range of third party controls, the Acusera 24•7 software is designed to help laboratories monitor and interpret their QC data. Access to an impressive range of features including interactive charts and real time peer group data generated from our extensive database of laboratory participants, ensures Acusera 24•7 is the most comprehensive package available.
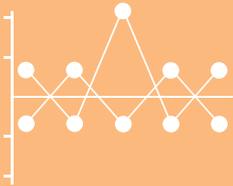
RIQAS 🌍

The largest global EQA scheme with over 35,000 lab participants

Comprising over 360 routine and esoteric parameters in 32 comprehensive and flexible EQA programmes, RIQAS is designed to cover all areas of clinical testing. Each programme benefits from a wide range of concentrations, frequent reporting and comprehensive yet user-friendly reports.

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