RANDOX

EDUCATIONAL GUIDE

How to Measure Uncertainty

QUALITY CONTROL

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?

Measurement Good Practice Guide No. 11

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.

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:

- Uncertainty estimates from repeated readings
- 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.

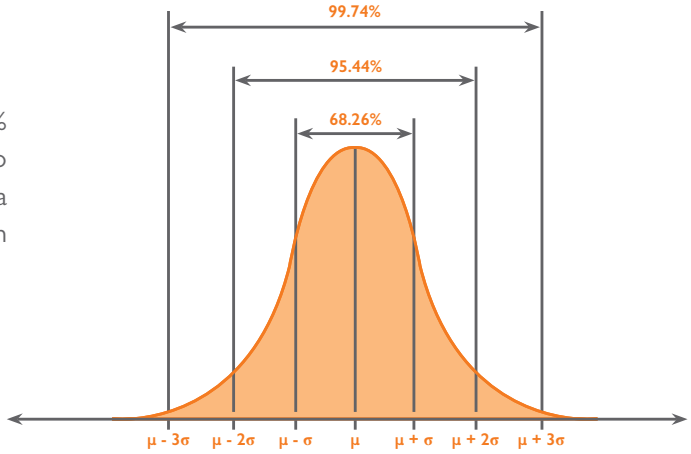
To measure uncertainty (u) the lab must first calculate the SEM of the intra precision (A) and the SD of the inter assay precision (B). Once we have calculated A and B we need to square them, add them and calculate the square root *(see formula below)*.

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

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



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.

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

If you would like further information please contact:

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ACUSERA True third party quality controls

As a world leading manufacturer of multi-analyte true third party controls, thousands of laboratories rely on Randox to accurately assess test system performance and ultimately empower them with the confidence required to release patient test results. With more than 390 analytes available, the number of individual controls required to cover your test menu is significantly reduced while simultaneously reducing costs, time and storage space. A choice of formats is available, including liquid or lyophilised, which ensures flexibility and suitability for laboratories of all sizes and budgets. Many features of the Acusera range can help you to meet ISO 15189:2012 requirements:

- Designed to react to the test system in the same manner as a patient sample, helping to reduce inconvenient shifts in QC results when reagent batch is changed and ultimately providing a true indication of laboratory performance.
- The presence of analytes at key decision levels ensures accurate instrument performance and eliminates the need for additional low/high controls at extra expense.
- Manufactured independently from any instrument, the Acusera range delivers unbiased performance assessment with any instrument or method, while eliminating the need for multiple instrument specific controls.

Product Portfolio

Antioxidants | Blood Gas | Cardiac Markers | Routine Chemistry | Coagulation | Haematology | Diabetes Immunoassay | Immunology | Lipids | POCT | Therapeutic Drugs | Toxicology | Urine Chemistry

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.

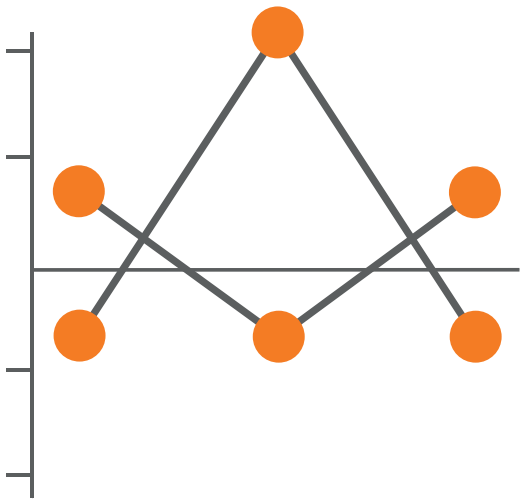
ACUSERA 24•7 Interlaboratory Data Management

Designed for use with the Acusera range of third party controls, the Acusera 24•7 software helps laboratories monitor and interpret their QC data. Access to an impressive range of features, including interactive charts, the automatic calculation of Measurement Uncertainty & Sigma Metrics and live peer group data generated from our extensive database of laboratory participants, ensures Acusera 24•7 is the most comprehensive package available.

- Advanced statistical analysis with automatic calculation of performance metrics including; Sigma, UM, TE & %Bias.
- Instantly discover how you compare to your peers with peer group statistics updated live in real-time reducing time and money spent troubleshooting.
- Interactive charts allowing you to add events and multiple data sets for quick and easy performance monitoring.
- Automated data import with bi-directional connection to LIMS (eliminating manual data entry).

Software Features

Dashboard | Result History | Interactive Levey-Jennings Charts | Interactive Histogram Charts
Performance Summary Charts | Statistical Analysis Report | Statistical Metrics Report
Uncertainty of Measurement Report | Exception Report | Peer Group Statistics | Acusera Advisor
Audit Trail Report



'The laboratory shall have a procedure to prevent the release of patient results in the event of quality control failure. When the quality controls rules are violated and indicate that examination results are likely to contain significant errors the results shall be rejected… Quality Control data shall be reviewed at regular intervals to detect trends in examination performance'.

ISO 15189:2012

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