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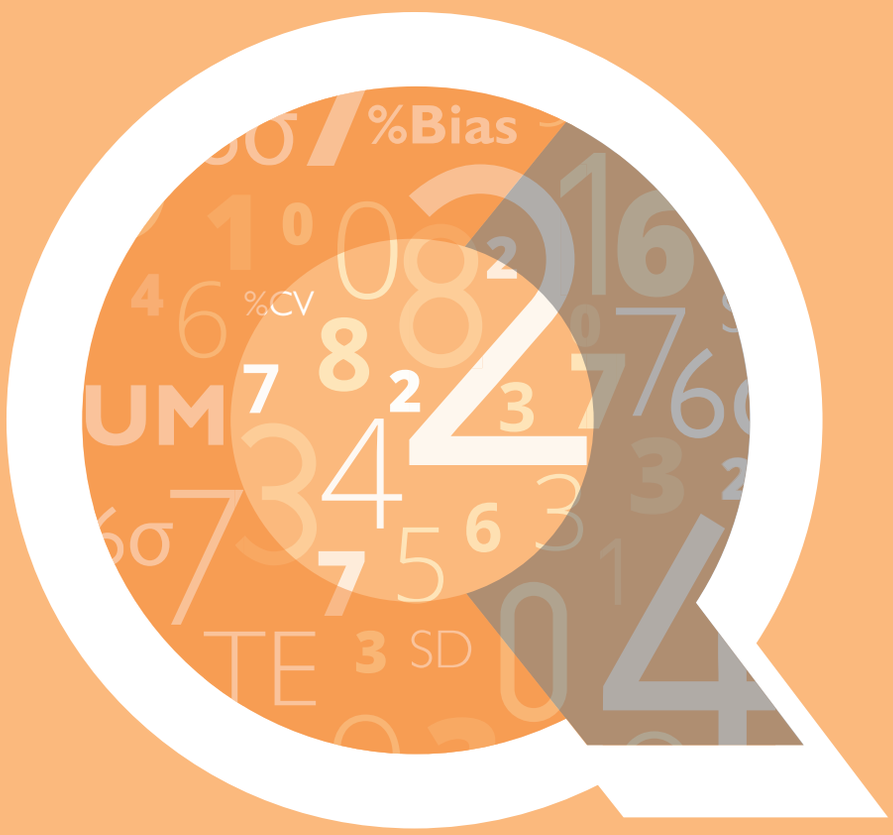
QUALITY CONTROL

Meeting ISO 15189:2012 Requirements for Measurement Uncertainty in the Clinical Laboratory



ACUSERA 24•7

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

Meeting ISO 15189:2012 Requirements for Measurement Uncertainty in the Clinical Laboratory

Background

Measurement Uncertainty (MU) 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'.

Since there is always a margin of doubt for any measurement, the clinical lab needs to ascertain the width of the margin and the significance of the doubt. Two values are needed in order to quantify uncertainty; the width of the margin or interval, and the confidence level, which states how sure we are that the 'true value' is within that margin.

Example: *If a piece of string measures 20cm, plus or minus 1cm at the 95% confidence interval, we say that we are 95% sure that the string is between 19cm and 21cm long.*

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

Regulatory Requirements for MU

ISO 15189:2012 states that: *"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 of uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty"*

Measuring Uncertainty using Quality Control Data

When using Quality Control (QC) data to calculate Uncertainty, we make several assumptions:

- The test system is under control
- The patient samples are treated in the same manner as QC
- Gross outliers are removed

It is also important to ensure the QC test system mimics that of the patient test system as closely as possible. For this reason, it is important to use high quality QC material.

High Quality QC Material

When evaluating the overall quality of QC material, ISO 15189:2012 recommends that two main aspects should be taken into consideration; a commutable sample matrix, and whether clinically relevant ranges are covered.

Commutable Sample Matrix: *The QC sample matrix should be as close as possible to that of the patient sample. A QC material which is made with 100% human source material should be used; ensuring a test system which closely resembles the patient sample*

Clinically Relevant Ranges: *Assayed QC material should cover clinically relevant ranges, as to confirm assay performance at the most vital points in the assay range – the points at which clinicians will determine whether, based on clinical results, interventions are necessary.*

Sources of Uncertainty

Calculating uncertainty can be difficult due to the large amount of potential sources of uncertainty. These can range from sample collection, reagent storage/preparation, instrument maintenance / calibration, personnel changes etc. Fortunately, the Standard Deviation (SD) encompasses all potential sources of uncertainty. If the SD is deemed to be high, then it stands to reason that there are multiple sources of uncertainty, or that some sources of uncertainty are particularly significant.

Data Collection

Patient sample testing and comparison with a reference value is carried out over time. With this in mind, it is logical that the QC data used to carry out Uncertainty calculation is gathered in a similar fashion - over time. The Australian Association of Clinical Biochemists recommends that at least 6 months of QC data should be used to calculate Uncertainty. In addition to this, Westgard QC maintains that over 100 data points should be used to generate a representative Gaussian distribution of the test system. If 100 repeat measurements were taken in one day by an individual laboratory professional, the sources of Uncertainty would be greatly reduced, thereby limiting the accuracy of the Uncertainty estimation.

Optimum data collection would involve using more than 100 data points, generated over at least a 6 month period. This opens the data and test system up to more common sources of uncertainty, and as a result, increases the accuracy of the final Uncertainty calculation.

Calculating Uncertainty

The first step in calculating Uncertainty is to look at Intra-assay precision and the Inter-assay precision. Intra-assay precision refers to measurement precision within a run. It is normally measured by running 20 or more replicates of the same sample at the same time. This process helps to identify any random uncertainties within a test system (instrument sampling errors, bubbles in pipettes etc.). Inter-assay 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. run one replicate every day for 20 days. This process will identify any systematic uncertainties within the test system.

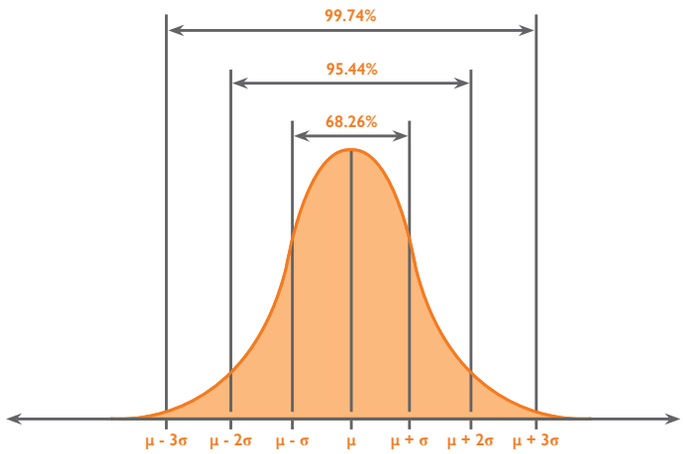
Calculation

To measure Uncertainty (u), the lab must first calculate the Standard Error of the Mean (SEM) of the Intra-assay 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):

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

As Uncertainty is calculated as SD, and 1SD 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).

$$U = 2 \times u$$



Benefits of Calculating Uncertainty

In addition to helping meet ISO 15189:2012 requirements, Measurement Uncertainty has a range of added benefits for the laboratory:

- It provides quantitative evidence that measurement results adhere to the clinical requirements for reliability.
- It provides labs with an indication of potential sources of Uncertainty. Efforts can then be taken to reduce or eliminate these sources, thereby improving overall efficiency.
- It allows labs to accurately compare results with reference values using the same measurement procedure.
- It is an essential component for achieving standardized and harmonized measurement results through metrological traceability.

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

Automatic Calculation of Uncertainty with Acusera 24•7 Live Online

Calculating Measurement Uncertainty for each individual assay, as required by **ISO 15189:2012**, can be a cumbersome and time-consuming task. Acusera 24•7 Live Online is a global QC peer group reporting program which includes automatic calculation of **Sigma Scores, Measurement Uncertainty** and other advanced statistical analyses. Acusera 24•7 calculates the Inter-assay precision for each individual test **automatically**. Once users enter the Intra-assay precision for a test, Uncertainty and Expanded Uncertainty are automatically calculated; drastically reducing the overall time and labor input into Uncertainty calculation. With access to peer group statistics updated live in real-time, the cloud based platform will also help to speed up troubleshooting procedures, making it easy to identify if a QC failure is unique to your lab or a widespread problem amongst your peers. In addition the software will generate a range of comprehensive charts enabling instant identification of any trends or bias in the test system.

%Bias is also automatically calculated for each assay compared to the **Reference Value** and the **Peer Group Mean**. Users can identify any significant Bias and make attempts to reduce or eliminate this as per recommendations.

For more information on Acusera 24•7 Live Online please visit *http://www.randox.com/acusera-247-interlaboratory-data-management/.*

Conclusion

Measurement Uncertainty is a useful tool, and can help labs identify deficiencies in their testing systems. The potential sources of Uncertainty are vast, and encompass the entirety of the Analytical Testing System; Pre-Analytical, Analytical and Post-Analytical.

Measurement Uncertainty allows for a quantitative analysis of overall performance, and is therefore a valuable asset in increasing overall efficiency in the laboratory. As an ISO 15189:2012 requirement, all accredited labs should implement Measurement Uncertainty calculations, and with Acusera 24•7 Live Online the process has never been easier.

If you would like further information please contact:

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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 informative yet user-friendly reports.

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