TECHNOPATH
CLINICAL DIAGNOSTICS

Uncertainty of Measurement

QUALITY CONTROLS FOR OPTIMAL PATIENT CARE

Contents

Uncertainty of measurement

Uncertainty of measurement is defined by ISO 15189 as "a parameter associated with the result of a measurement that characterises the dispersion of values"

With the adoption of the International Organization for Standardization (ISO) laboratory standard Medical Laboratories – Particular Requirements for Quality and Competence (ISO 15189), clinical pathology laboratories have been required to provide estimates of measurement uncertainty for all quantitative test results.

Uncertainty of measurement (UM, also referred to as measurement uncertainty, MU), traceability and numerical significance are inter-related concepts that affect both the format and the information conveyed by a quantitative result. As every measurement is prone to error, it is often stated that a measurement result is complete only when accompanied by a quantitative statement of its uncertainty. This uncertainty assessment is required in order to decide if the result is adequate for its intended purpose (fit for purpose) and to ascertain if it is consistent with other similar or previous results. The development of strategies for setting quality goals in laboratory medicine and procedures for assessing fitness for purpose have been well covered in the clinical biochemistry literature. In particular, quality specifications based on biological variation have been discussed in detail. The accuracy, precision and fitness for purpose of medical laboratory results rely on the basic metrological concepts of a common system of units, traceability of measured values, and uncertainty of measurement and commutability of results within a calibration hierarchy.

"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
Section 5.6.2

Uncertainty of Measurement and Measurement Error

The result of any quantitative measurement has two essential components:

- A numerical value (expressed in SI units as required by ISO 15189) which gives the best estimate of the quantity being measured (the measurand). This estimate may well be a single measurement or the mean value of a series of measurements.

- A measure of the uncertainty associated with this estimated value. In clinical biochemistry this may well be the variability or dispersion of a series of similar measurements (for example, a series of quality control specimens) expressed as a standard uncertainty (standard deviation) or combined standard uncertainty.

By definition, the term error (or measurement error) is the difference between the true value and the measured value. The most likely or 'true' value may thus be considered as the measured value including a statement of uncertainty which characterises the dispersion of possible measured values. As the measured value and its uncertainty component are at best only estimates, it follows that the true value is indeterminate. Uncertainty is caused by the interplay of errors which create dispersion around the estimated value of the measurand; the smaller the dispersion, the smaller the uncertainty.

Even if the terms error and uncertainty are used somewhat interchangeably in everyday descriptions, they actually have different meanings. They should not be used as synonyms. The ± (plus or minus) symbol that often follows the reported value of a measurand and the numerical quantity that follows this symbol, indicate the uncertainty associated with the particular measurand and not the error.

If repeated measurements are made of the same quantity, statistical procedures can be used to determine the uncertainties in the measurement process. This type of statistical analysis provides uncertainties which are determined from the data themselves without requiring further estimates. The important variables in such analyses are the mean, the standard deviation and the standard uncertainty of the mean (also referred to as the standard deviation of the mean or the standard error of the mean).

Measuring Uncertainty

Measurement of uncertainty in the clinical pathology laboratory can be determined by 'Type A evaluation '(of uncertainty): any method for evaluating uncertainty using statistical analysis of a series of observations. Using Internal Quality Control material is a common practice when certain assumptions are made.

- The Internal Control Material represents a similar sample matrix to clinical samples
- Analyte concentrations are representative of levels found routinely in clinical samples
- Both controls and clinical samples share a common analysis pathway and are treated in an identical manner
- The method of analysis is stable and remains consistently under control.
- Current guidelines suggest at least 6 months data is recommended when calculating uncertainty

For clinical pathology laboratories to measure uncertainty, certain basic statistical analysis of Internal Control material must first be completed. To begin with Intra assay precision within a run must be determined. This is normally calculated by running repeated replicates of the same sample at the same time to determine the precision within a run and will identify any random uncertainties. Inter assay precision calculation on the same material refers to precision over a number of different runs, it is normally measured by running replicates of the sample over several days e.g. one replicate every day for 30 days. This process will identify any systematic uncertainties. To measure uncertainty (u) the clinical pathology laboratory must first calculate the standard error of mean (SEM) of the intra assay precision (A) and the SD of the inter assay precision (B).

Once calculated, both A and B now need to be squared, add together and then a final calculation of the square root (see below).

$$u = \sqrt{A2 + B2}$$

Coverage factor k

Once clinical pathology laboratories have determined the uncertainty they may then want to re-scale the result. The standard uncertainty may be thought of as equivalent to 'one standard deviation', but we may wish to have an overall uncertainty stated at another level of confidence, e.g. 95 percent. This re-scaling can be done using a *coverage factor, k*. Multiplying the *standard uncertainty, u* , by a *coverage factor* gives a result which is called the *expanded uncertainty*, usually shown by the symbol *U*.

A particular value of coverage factor gives a particular confidence level for the expanded uncertainty. Most commonly, we scale the overall uncertainty by using the coverage factor k = 2, to give a level of confidence of approximately 95 percent. (k = 2 is correct if the combined standard uncertainty is normally distributed).

Some other coverage factors (for a normal distribution) are:
k = 1 for a confidence level of approximately 68 percent
k = 2.58 for a confidence level of 99 percent
k = 3 for a confidence level of 99.7 percent

Factors Affecting Uncertainty

When calculating uncertainty for laboratory assays it is important that we consider bias. Bias must be measured and, if it is significant, removed or minimised when calculating uncertainty. If we do not remove it the uncertainty of the bias, correction must be calculated and included in the overall uncertainty measurement. To calculate this we must first determine the uRef, uncertainty of the analyte value assigned to the reference material / EQA, and uRep, uncertainty of the analyte value in the reference material / EQA when measured in replicate in the Clinical Laboratory. The uncertainty bias is then calculated using the following formula: **uBias = √ Ref2 + uRep2**

Clinical Laboratories can investigate the bias of assays by measuring them against the following:

- An assayed QC material
- Unassayed QC material alongside a peer group reporting programme
- External Quality Assessment or Proficiency Testing scheme
- Calibration or reference materials

Sources of Uncertainty

Sources of uncertainty can be due to analytical error, according to J. Hammerling (2012) there are three phases during the analytical process when error can occur; pre-analytical, analytical and post- analytical.

Pre-analytical Errors

Results can be affected before the patient sample reaches the laboratory. Sample collection, storage and transportation, as well as the patient's state can all affect testing. Examples of pre-analytical error include; incorrect tests ordered, samples labelled incorrectly, in proper sample collection and incorrect sample storage. According to Hammerling (2012) this is the stage at which most errors occur.

Post-analytical Errors

This is the final stage of the analytical process. When Clinical laboratories release results to the clinician the interpretation of the results provided will affect how they move forward with patient care, therefore your report format and LIS/Middleware should be considered. In order to detect and minimise these sources of error in the analytical process there should be procedures in place to govern every stage.

Analytical Errors

"The analytical phase begins when the patient specimen is prepared, and ends when the test result is interpreted and verified by the technologist in the laboratory" (Hammerling, 2012:43). Whilst the pre-analytical stage is completely out of the Clinical Laboratory hands, any errors that occur at this stage will occur in the Clinical laboratory. This can be due to how the reagents are stored and prepared, the performance of your instruments, operator performance and calibration of the instruments.

Because QC already manages all these areas of uncertainty in the Clinical laboratory's analytical processes, we can use it to calculate the measurement uncertainty

Additional Factors

Note: When calculating combined uncertainties for analytes that are calculated using addition or subtraction, e.g. Anion gap, the SD or 'u' value can be used. On the other hand when calculating combined uncertainties for analytes that are calculated using division and multiplication, e.g. creatinine clearance, the SD or 'u' must first be converted to CV.

Conclusion

Uncertainty of a measurement refers to the doubt, which exists for the result of any measurement within the laboratory. There are a number of factors which must be considered when calculating uncertainty, including the chosen method, Bias, analytical errors and so on. If uncertainty is quantified it is no longer uncertainty but the confidence interval within which the results fall. Uncertainty should be assessed regularly and attempts made to improve the value.

References

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