Measurement Uncertainty and Reference Change Values

Distribution List:
Director
Quality Officer
Supervisor Clinical Chemistry & Hematology
Supervisor Microbiology
Supervisor Environmental Laboratory

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General Information

No part of this document shall be altered without the prior authorization of competent authority (either the department supervisor, Clinical Biochemist or Microbiologist). Any suggestions for change shall be written on a separate A-4 paper and submitted to their respective department supervisor and such suggestions for modifications can only be approved by the Clinical Biochemist / Medical Microbiologists.

The new version will then be transferred to the Quality Officer to adapt the SOP and generate a new version.
1 Subject
This procedure describes two tools for the laboratory and its users to properly assess the uses and limitations of (medical) laboratory tests and to also determine (for medical tests) when two consecutive laboratory test results constitute a medically significant change.

2 Definitions and common terms
MU: Measurement of Uncertainty
CVa: Analytical Variation
CVb: within-subject biologic variation
RCV: Reference Change Value
EQAS: External Quality Assurance System
SI: International System for units
CU: Conventional Units
NIST: National Institute of Standards and Technology
SRM: Standard Reference Method
K: a constant of the coverage interval with a stated probability

3 Procedure
3.1 Background
All tests that are performed within a laboratory carry a certain variation which leads to “measurement uncertainty (MU)”. While the following list is not exhaustive, MU has different components that make up the cumulative MU. This is also dependent on the type of test. Quantitative medical laboratory tests carry different components than for instance colony counting (colony forming units) within microbiological testing. Also, analytical chemistry tests to ascertain the quality of water (or effluent testing) for example depend on other components. Here are examples of steps/conditions/materials/circumstances that may influence test variability broken down by the various phases of the entire testing cycle:

Pre-analytical phase:
- Sampling time
- Sampling day
- Sampling arm (medical tests)
- Phlebotomist performing the venipuncture (medical test)
- Position of the patient (medical testing)
- Patient preparation (diet/exercise/fever etc) (medical test)
- Water Sample location (near a holding tank or at the end of the grid)
- Sample transport time (all types of testing)
• Variation of sample storage temperature
• Variation in sample to anticoagulant ratio (medical test)

Analytical Phase:
• Variation in pipette volumes
• Variation in pipette calibration
• Variation in pipette techniques
• Variation in calibration output of machines/tests
• MU of the used calibrator. This can be a liquid preparation but can also be a standardized weight
• Day to day variation of the analyzer (pipetting, mixing, measuring)
• Inter and Intra-operator variations
• Lot-to-lot variations for controls, reagents, etc
• Lot to-lot variations in culture media plates (pH, thickness, composition)
• Water filtering on filter paper (non-medical); e.g. volume filtered variance
• Percent transfer of bacteria colonies from filter paper to the culture media plate (non-medical)

Post-analytical:
• Variation in interpretation of the analytical test by the technologist
• Variation in interpretation of the analytical test by the physician

3.2 Biological variations as the basis for the analytical quality requirement of medical tests

The NEN-ISO 15189;2012 (section 5.5.1) states that “the laboratory shall use examination procedures …..which meets the need of the users…and are appropriate for the examination…."

The key word in the above sentence is “appropriate”. SLS NV has determined first and foremost that tests used within its premises are traceable to higher standards. Secondly, the analytical variation specifications for each medical test is invariably tied to the biological variation of the measurand within the individual. Various societies have defined analytical quality criteria for tests which depend on the analytical variation (CVa) or the intra-individual biological variation (CVb) (see references). Fraser has proposed, based on earlier studies and consensus papers, that to comply with desirable performance, for a measurand, the CVa < 0.5 x CVb. The reason for mentioning this is that the CVa is a major component to calculate the MU. Furthermore, MU are tied to maximum criteria because the CVa has to comply with desirable analytical quality requirements.

3.3 Calculation of MU

Several methods have been described to calculate the MU of a test/measurand. The Australasian Association of Clinical Biochemists (AACB) published a laboratory implementation guide for calculating MU using the CVa as a basis. CVa can be calculated from 1) long term internal QC data or 2) EQAS year reports. Other societies have included bias in the formula as a means to expand the MU calculation. SLS NV chooses not to use bias obtained from EQAS reports as a “calibration target” but rather to ascertain if the reported EQAS results fall within the total allowable error limits as set by the EQAS provider. Ultimately, our users require us to maintain within-laboratory variations to acceptable limits and not to introduce bias when changing methods, but rather to adjust reference/normal values when needed.
Example of calculating the MU in SLS NV:

- Determine the measurand. This includes describing the test, the reporting units (SI or CU), decimals of reporting and the traceability of the test
- Determine a medical decision level for that test: this can be based on international consensus or can be in consultation with your local requesting clients (e.g. doctors)
- Obtain the long-term CVa from internal quality control files. In this case, we have registered 30-60 QC data points
- Calculate the 95% confidence Interval by using the k factor set at 2.

Thus, for the following Sodium (Na) test (0 decimals for reporting):

- Measurand is Sodium (Na), method is Indirect-ISE, reporting unit is (mmol/l) and the test/calibration is traceable to NIST SRM 909
- Medical decision level (upper reference range): 145 mmol/l
- Long term QC expressed as CV% is 0.95%. This is multiplied by the coverage factor (k=2) and is 1.9 %
- The 95% confidence interval is thus: 145 mmol/l ± 1.9%, therefore (142 – 148).

Interpretation: if the laboratory reports “145 mmol/l”, it can say with 95% confidence that the value falls within 142 – 148 mmol/l.

4 Reference change values (RCV)

While a client (e.g. a doctor) is interested in knowing how “well” a laboratory test performs (the smaller the uncertainty, the better, he/she is really interested in knowing how this uncertainty (confidence interval) may/can affect the interpretation of serial measurements of the same test when the doctor is following the patient in time. Examples include the serial measurements (i.e. increases) of cardiac troponins to determine biochemically if an AMI is occurring or not.

In order to ascertain TRUE change between consecutive measurements, one needs to take into account two factors: CVb and CVa. For this, the reference change value formula (see reference C.G. Fraser) is used: 

\[ RCV = \sqrt{2} \times Z \times \sqrt{(CVa^2 + CVb^2)} \]

where by \( Z = 1.96 \) (rounded off to 2).

Example for the same Sodium test:

\[ RCV = \sqrt{2} \times 2 \times \sqrt{(0.9^2 + 0.6^2)} = 3.2\% \]

Interpretation: with 95% confidence, a relative change between two-successive measurements of Sodium within one patient > 3.2% signifies a significant change!

5 Responsibilities

The supervisor of the department is responsible for monitoring the long-term CV% and to alert the clinical chemist or microbiologist of any deviations from internal QC rules.

The technologist is responsible for the day to day management of the internal QC and to alert for any variations that deviate from internal QC rules.
The clinical chemist or microbiologist establishes analytical quality criteria and ascertains if a test is suitable for use.

6 Comments/Remarks/Limitations
For tests performed at the Environmental laboratory, local regulations establish maximum tolerance of imprecision and/or deviation from expected targets.

7 Accompanying documents/forms
- SLS.GEN.FOR.030 Measurement of Uncertainty table
- SLS.GEN.FOR.056 Analytical quality requirements

8 References
- C.G. Fraser. Biological Variation: from principles to practice
- www.westgard.com/biodatabase1
- P905 -A2LA Metrological traceability policy
- P903: Policy on estimating Measurement Uncertainty for ISO15189 testing laboratories (A2LA)