Measurement Uncertainty - How to Calculate It In The Medical Laboratory

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Introduction

Disclaimers

Procedure that I will be describing is not an approved OLA method but the contents are based largely on the information in the 2 OLA documents published in QMP-LS News, as well as on other peer reviewed publications.

My PowerPoint Presentation "Lacks Power & has no Point!!

Objectives

- Brief Introduction on UM concepts
- Overview of available methodology
- Description of the method/procedure used at GDML
- Some examples from GDML, Ottawa & Brampton Labs and Dr Lynn Allen's
- Questions/Discussion as time permits

Definitions of Uncertainties

- **UM: A parameter, associated with the result of measurement, which characterized the dispersion of the values that could <u>reasonably be attributed</u> to the measurand (the quantity intended to be measured)**

- **U (uncertainty): Parameter obtained from measurements, which serves, together with the measurement result, to characterize a range of values for the <u>true value</u> of the measurand**

- **Uncertainty of the Result: Estimated quantity intended to characterize a range of values which contains the <u>reference value</u>, where the latter may be either the <u>true value or the expectation</u>, depending on definition or agreement**

Ref EuroLab Technical Report 2006: Guide to Evaluation of Measurement Uncertainty for Quantitative test Results.

UM concepts

- Consists of Several Components
- Methods for Determining it Consists of Several Steps
- One or More and/or Combination of Approaches are Acceptable
- Applicable to a Measurement Procedure (Test or Analyte Procedure)
- Not to a Series of Replicate Measurements
- Steps include
  - *Specifying the measurand and the measurement procedure*
  - *Defining input quantities and identifying uncertainty sources*
  - *Determining & quantifying significant uncertainty sources*
  - *Assessing whether correlation exists between contributing sources of uncertainty*
  - *Calculating the combined standard uncertainty & defining the coverage factor*

UM concepts

- **Why should medical labs determine UM?**

- **A. Requirements for Accreditation (Regulatory)**
  - International standards requiring traceability of lab results/information to acceptable international reference (procedure or material)
  - JCTLM (IFCC, ILAC & CIPM)
  - Manufacturers/Vendors – COA (certificates of analyses) must state concentration and uncertainty of standards/calibrators.
- **B. Quality**
  - Laboratory services are essential to patient care (ISO 15189:2003); level of performance required for intended use; UM is another measure of quality

UM concepts

- ***NPAAC's (Australia) Summarizes…*** " *MU is one of the major potential contributors to the uncertainty of results interpretation, and laboratories should have such data available for clinical users"(* www.health.gov.au *)*

- **APLAC's** *(Asian-Pacific Lab Accreditation Cooperation) TC 010 (2009)…. "Many important business decisions are based on the results obtained from quantitative testing. It is important that an indication of the quality of reported numerical test results is available to you" (www.aplac.org).*

Overview of Methodology

….. not a single standardized method; different approaches are acceptable as long as GUM are observed….

1. **Modeling (equation or algorithm, modeling the analyte/test as a function of relevant inputs**

2. **Within or Single Lab Validation QC Data**

3. **Between or Inter-laboratory Comparison Data**

4. **Proficiency Testing Data (between lab comparison with estimate of bias relative to reference (i.e. Reference value; AMM; AMTM)**

5. **Combined (2 &4); 3 – 5 Top-Down Alternatives**

Bottom-up Mathematical Modeling Approach of GUM

- **Function of various inputs**

- **Mathematically complex equations**

- **Uncertainty budgets**

- **Correlations and co-Variances**

- **Not Suitable for routine use**

Within/Single Laboratory Validation and QC Data

- Within-Lab reproducibility (imprecision) and accuracy using suitable reference and QC materials

- Compare lab's results with those from a reference procedure run in parallel

$$\text{Bias} = (\text{mean}_{obs} - \text{ref})$$

$$\text{Imprecision} = SD_r$$

$$= \text{SQRT of Sum } (obs - \text{mean}_{obs})$$

$$\text{squared divided by } (n_{obs} - 1)$$

Inter-laboratory Comparison Data

- **Reproducibility SD for labs involved (SD_R)**

- **Test performance conform to standards**

- **Testing conditions are same in the labs and/or associated with suitable reference procedure**

Inter-Laboratory Comparison for Proficiency Testing

- **Successful Participation in Inter-Lab Proficiency Testing Program**

- **Useful in Assessing Bias and Associated UM**

  - $u_{bias} = (RMS_{your\ lab}^2 + u_{ref}^2)\text{^}0.5$ **..ref value given**

  - $u_{bias} = (RMS_{your\ lab}^2 + S_R^2/n)\text{^}0.5$ **..ref value not given**

- **Combined standard uncertainty**
  - $u_c = [SD_m^2 + u_{bias}^2]\text{^}0.5$

Combined Alternative Approach

- **Top-down alternative approach with internal QC and PT Results**

- **6-step approach; PT results from EQA (QMP-LS) and DigitalPT**

- **MS Excel (1 worksheet each Test selection, Method SD determination; Bias estimation; UM calculation)**

- **Method SD from internal QC; multiple analyzers/modules over six months**

- **Bias and Z-value (SDI, bias/method SD ratio); minimum of 3 surveys with 2 or more levels per survey**

- **Combined and expanded uncertainty of measurement calculated as absolute and relative (%) values Details about this topic**

Calculating Method/Procedure SD

- **Average or Pool (Type A or B) – Internal QC Data; Min. 6 months**

- **Type A (Averaged) - per QC or per Analyzer**

  - $\{[(SD^2)_{L1} + (SD^2)_{L2}] / 2\}^{1/2}$

- **Type A (Pooled) – per all QC's and Analyzers**

  - $[(n_1 SD_1^2 + n_2 SD_2^2 + \ldots n_n SD_n^2) / (n_1 + n_2 + \ldots n_n)]^{1/2}$

- **Type B (other)**

  - **(HIGH – LOW) / (12)^0.5**

  - **(HIGH – LOW) / (24)^0.5**
  - **Typical – semi-quants. with known cut-offs, lower and higher detection/measuring ranges (uncertainty known at both ends and need to calculate combined standard uncertainty)**

Calculating Uncertainty Associated with Bias

PT Data

- **Uncertainty & Reference / Assigned Value Stated or known**

  $$- u_B = [(RMS_{yourLab}{}^2) + (uC_{ref}{}^2)]^{1/2}$$

- **All Method Mean Provided as Target or Reference Value**

  $$u_B = [(RMS_{yourLab}{}^2) + (S_R{}^2/n)]^{1/2}$$

  S_R is all method reproducibility

  n is the number of labs

  RMS is Root Mean Square of Bias for your lab.

Calculating Combined Standard and Expanded UM

Combined Standard, u_c

$$u_c = [(uSD)^2 + (uB)^2]^{1/2}$$

$$= [(uSD)^2 + (SEM)^2 + (uC_{ref})^2]^{1/2}$$

$$= [(1/N \times SD^2) + (uC_{ref})^2]^{1/2}$$

Expanded Uncertainty, U

$$U = Uc \times 1.96 \; (\sim 2);$$

u_B: SEM requires CRM's; Use RMS (root mean square) from PT results or assigned reference value for material tested by an internationally accepted reference method.
RMS = est SD at bias = 0 (both the actual bias and the variation of bias are considered)

Top-down Alternative Approach – Steps

- Select/Define the test/analyte/examination (Measurand)

- 2. Determine method SD or CV; at least 2 levels; minimum of six months period.

- 3a. Estimate bias (absolute and/or relative) and SDI from PT (EQA, QMP-LS & DigitalPT, HealthMetrx; SDI = Abs bias relative method SD or CV)

- 3b. SDI < or = 2, uncertainty associated with bias is not included in the calculation of the combined uncertainty, uC

- 3c. SDI > 2, uncertainty associated with the bias is included in the calculation of the combined uncertainty, uC

- 4. Calculate uc, the combined uncertainty from the pooled or individual QC SD's (steps 2 or 3) and the uncertainty associated with bias

- 5. Calculate U, the expanded uncertainty by multiplying the uc by coverage factor, k (1.96 or 2; 95% CI)

- 6. U expressed as Abs or Relative (%) *[Test/Analyte = measured value +/- U units]*

Minimal UM Data Defining Test/Analyte

- **Quantity**
- Measurand
- Units
- Method
- Measurement Procedure
- Test limitations
- Clinically significant interferences
- Calibrator measurement uncertainty (uRef)
- Expressing UM - Analyte/Test: Result +/- U units
  - eg Plasma or serum glucose: 5.1 +/- 0.2 mmo/L

Summary Results of Calculated UM's for Some Chemistry and INR/PT Tests

- **Expanded Uncertainties for 26 routine chemistry tests at 2 or more levels**

- **Absolute and Relative (%) combined standard uncertainty**

- **5 of 26 had SDI > 2 (Alb, T Bili, Creat, Glu & K)**

- **Relative U ranged from 1.95 – 40.18 %**

- **Average Relative U, (INR) 19.39 & 19.51 % at 1.0 & 1.7**

GDML'S UM DATA FOR SOME ROUTINE CHEMISTRY TESTS

Analyte	RI	Units	Applicable Analyte Level	SDI (Rel Bias)	U Relative %	U Absolute
Albumin	Adult: 34 - 48	g/L	29.06	4.11	11..24	3.27
			44.13		10..93	4.82
Alk Phos	Adult: M: 40 -129 F: 35 - 122	U/L	77..28	1.14	5.66	4.37
			344.23		5.24	18.03
Cholesterol	Adult: < 5.20	mmol/L	2.66	0.77	4.38	0.12
			6.57		4.04	0.27
			8.57		4.11	0.35
Triglycerides	Adult: < 2.30	mmol/L	0.89	1.72	12..67	0.11
			2.15		12..23	0.26
			5.25		12..20	0.64
Creatinine	Adult: M: 60 -110 F: 50 - 100	umol/L	69	2.62	19.1	-
			513		18.4	-
Total Protein	Adult: 64 - 81	g/L	44.06	1.79	5.35	2.36
			67.71		5.26	3.57
Total Calcium	Adult: 2.20 – 2.65	mmol/L	2.04	1.44	6.46	0.13
			3.02		6.14	0.19

In Summary Medical Labs Need UM for….

- **Traceability**
  - **Accreditation/Regulatory Requirements**
  - **Commutability of Lab Results**
- **Fit-for-purpose (Quality Component)**
  Checking validation precision and accuracy data for new method/instrument
  - **Assessing appropriateness of commonly established goals (total allowable error; ref change value; clinical decision levels, etc)**
  - **Comparison with published values for same method or for reference method or with previous values.**
- **Metrology**
  - **Labs produce numbers & are required to know the uncertainty associated with these numbers**
  - **UM is used quantitatively as a measure of trueness (accuracy) of the measured value (cf. ISO/TS 21749 document "Measurement uncertainty for metrological applications repeated measurements and nested experiment"**
- **The combine top-down alternative method is preferred for routine medical laboratory practice**

References

General

- **Moses & Crawford. Traceability and uncertainty of measurement for medical laboratories. QMP-LS News Sep 2007 & Apr 2009.**

- **ISO TC 214/WG2 (N 173) & CEN TC 240/WG2 (N 244): Medical Laboratories – Calculation and expression of measurement uncertainty (2007) – Another key component to this doc is the "Terms & Definitions"**

- **EuroLab Technical Reports (2006 & 2007): Guide to the Evaluation of measurement uncertainty quantitative test results & Measurement uncertainty revisited: Alternative approaches to uncertainty evaluation (www.eurolab.org)**

- **Graham H. White. Basics of estimating measurement uncertainty (2008). Clin Biochem Rev 29:S1; S53 − S60**

   How to
- **Fisicaro et al (2008). Acced Qual Assur 13: 361 − 366**

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Thank You for your attention!!!!

Questions/ Comments??