Measurement Uncertainty
Emma Stevenson
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What is measurement uncertainty?

UKAS: “MU is a parameter, associated with the result of a measurement… that defines the range of the values that could reasonably be attributed to the measured quantity.”
What causes MU?
Why bother?

• The International Standard defines the specific requirements for competence and quality that a medical laboratory should meet in order to produce technically valid results.

• Previously: “the laboratory should determine the uncertainty of results, where relevant and possible.”
Why bother?

ISO 15189:2012:

“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.”
How to calculate MU

**Type A** (bottom-up) – complex mathematical model

**Type B** (top-down) – IQC under intermediate precision conditions
How to calculate MU

ISO 15189 gives some guidance.

1. The relevant uncertainty components are those associated with the actual measurement process, commencing with the presentation of the sample to the measurement procedure and ending with the output of the measured value.

2. Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure, e.g., changes of reagent and calibrator batches, different operators, scheduled instrument maintenance.
How to calculate MU

- MU = long term CV%
- Expressed as ±1.96 CV% (95% confidence limit)
How to calculate MU: example

Creatinine

- Biochem: four analysers over both sites.
- Measured six months’ IQC:

<table>
<thead>
<tr>
<th>Low QC</th>
<th>CV%</th>
<th>High QC</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRH Line 1</td>
<td>2.4</td>
<td>GRH Line 1</td>
<td>2.0</td>
</tr>
<tr>
<td>GRH Line 2</td>
<td>2.4</td>
<td>GRH Line 2</td>
<td>1.8</td>
</tr>
<tr>
<td>CGH 6000</td>
<td>3.2</td>
<td>CGH 6000</td>
<td>1.8</td>
</tr>
<tr>
<td>CGH 311</td>
<td>3.1</td>
<td>CGH 311</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>2.8</strong></td>
<td><strong>Average</strong></td>
<td><strong>1.8</strong></td>
</tr>
</tbody>
</table>

- Average overall = 2.3%
- Reported MU (± 1.96 CV%) = 4.5%
- e.g. creatinine result of 64 µmol/L could actually be anything between 60 and 67 µmol/L.
How does MU benefit patients?

Reference change values (RCVs)

- Determines whether the difference between two results is negligible due to uncertainty or significant due to a genuine change in the condition of the patient.
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Reference change values (RCVs)

- Determines whether the difference between two results is negligible due to uncertainty or significant due to a genuine change in the condition of the patient.

- Uses analytical variation ($CV_A$), aka MU, and biological variation ($CV_I$) data. Biological variation database available at: http://www.westgard.com/biodatabase1.htm

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Number of papers</th>
<th>Biological Variation</th>
<th>Desirable specification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CV&lt;sub&gt;W&lt;/sub&gt;</td>
<td>CV&lt;sub&gt;G&lt;/sub&gt;</td>
</tr>
<tr>
<td>S- Albumin</td>
<td>24</td>
<td>3.2</td>
<td>4.75</td>
</tr>
<tr>
<td>U- Albumin, concentration, first morning</td>
<td>3</td>
<td>36.0</td>
<td>65.0</td>
</tr>
<tr>
<td>U- Albumin, output, night urine</td>
<td>3</td>
<td>29.5</td>
<td>58.0</td>
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<tr>
<td>S- Albumin, glycated</td>
<td>1</td>
<td>5.2</td>
<td>10.3</td>
</tr>
<tr>
<td>S- Aldosterone</td>
<td>2</td>
<td>49.4</td>
<td>40.1</td>
</tr>
<tr>
<td>U- Aldosterone</td>
<td>1</td>
<td>39.4</td>
<td>40.1</td>
</tr>
<tr>
<td>S- Alkaline phosphatase</td>
<td>22</td>
<td>6.45</td>
<td>28.1</td>
</tr>
</tbody>
</table>
How does MU benefit patients?

Reference change values (RCVs)

- Analytical variation ($CV_A$), aka MU, and biological variation ($CV_I$) allow the laboratory to state (with 95% confidence) whether a result produced on a patient differs significantly from a previous result from a sample on that same patient.

$$RCV = 2.77 \times \sqrt{(CV_A^2 + CV_I^2)}$$
How does MU benefit patients?

Reference change values (RCVs)

Creatinine:

<table>
<thead>
<tr>
<th></th>
<th>QC1</th>
<th>QC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological variation</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Analytical variation (MU)</td>
<td>2.8</td>
<td>1.8</td>
</tr>
<tr>
<td>RCV = 2.77 x √(CV_A^2 + CV_I^2)</td>
<td>18.2</td>
<td>17.3</td>
</tr>
<tr>
<td>Average</td>
<td>17.7</td>
<td></td>
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If a patient had a result of 64 µmol/L, the second result would have to be at least 75 µmol/L for there to be 95% confidence that it was both analytically and biologically different.
What next?

- ISO 15189: “upon request, the laboratory should make its estimates of measurement uncertainty available to laboratory users.”
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- Pathology web pages.

http://www.pch-pathlab.com/cms/?q=node/10
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• ISO 15189: “upon request, the laboratory should make its estimates of measurement uncertainty available to laboratory users.”
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• Regularly review.
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• Pathology web pages.
• Regularly review.
• Delta checks?
Conclusions

• Measurement uncertainty is here to stay and we will be being assessed on our adherence to ISO 15189.
• It is useful for both the laboratory in assessing quality and to the clinician who is establishing whether the patient’s condition has changed.
• This all benefits the patient!
References

- ISO 15189:2012 Medical laboratories - requirements for quality and competence.
- Desirable Biological Variation Database specifications http://www.westgard.com/biodatabase1.htm
- Peterborough & Stamford Hospitals Pathology website http://www.pch-pathlab.com/cms/
Thank you!

“We demand rigidly defined areas of doubt and uncertainty!”

Douglas Adams, *The Hitchhiker's Guide to the Galaxy*