Traceability in laboratory medicine: why is it important?

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On behalf of the Joint Committee for Traceability in Laboratory Medicine
Outline

• Background
• Traceability in laboratory medicine
• JCTLM
• Example
• Relevance to EQALM
Everyday examples of traceable measurements

Weight (mass)

Length

Time

Temperature
Traceable results are comparable

“The Kilogram”
BIPM, Paris

G Jones
Athens 2017
Local weights and measures: Falkirk, Scotland
Système Internationale (SI) units

Mass
Length
Time
Electric current
Temperature
Amount of substance
Luminosity

kilogram
metre
second
Ampere
Kelvin
mole
candela

kg
m
s
A
K
mol
cd

SI units underpin our scientific, manufacturing & technological civilisation
So what about laboratory medicine?

Patients assume and expect that all methods will give the same result for a single test!
HbA2 and clinical practice guidelines

Many clinical practice guidelines exist for thalassaemia that link diagnosis to target HbA2 levels.

For example UK NHS sickle cell and thalassaemia screening programme:

“A national recommended cut-off for HbA2 of 3.5% has been set as the action point in the diagnosis of carriers of beta thalassaemia.”
Current HbA2 EQA performance

Figure from UK NEQAS with permission
Why should different methods to give the same result?

Adapted from Plebani, *Clin Chem Lab Med* 2013; 51: 741-51
What can we standardise / harmonise in laboratory medicine?

Standardise / Harmonise

Laboratory Protocols
- Test requesting
- Sample handling
- Reporting
- Local

Laboratory Parameters
- Test names and units
- Reference intervals
- Critical values
- Local / National

Laboratory Methods
- Technology
- Traceability
- Commutability
- Local / International

Adapted from Plebani, Clin Chem Lab Med 2013; 51: 741-51
Reducing between method variability

Comparable results

**Monitoring**
- Consistent performance maintained via PT, EQA etc

**Design**
- Calibration and traceability to a common reference system
- Standardisation Harmonisation
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What is traceability in laboratory medicine?

- Metrological traceability is the property of a measurement result, which can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.
- Traceability requires both (certified) reference materials and the reference measurement procedures (methods) in which they are used.
- For structurally simple measurands (analytes) it is possible to get pure substance primary reference materials. For more complex measurands pure substance may not be available.
- Primary reference measurement procedures are based on physical methods (e.g. ID-MS).

**Reference materials (calibrators)**
- Primary reference material (pure substance)
- Primary calibrator (SI traceable)
- Secondary calibrator
- Product calibrator

**Reference measurement procedures**
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected procedure
- Routine laboratory procedure
The metrological traceability chain

Definition of measurand: Concentration in SI units

- Primary reference material
- Primary calibrator
- Secondary calibrator
- Manufacturer master calibrator
- Product calibrator
- Patient result
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected measurement procedure
- Manufacturer standing measurement procedure
- Routine laboratory method
- Metrology institute / Reference lab
- IVD method manufacturer
- Routine lab

Adapted from EN ISO 17511 2003
‘Higher order’ materials and procedures

Higher order

1. Primary reference material
   - Primary RMP
     - Primary calibrator (SI traceable)
       - Secondary RMP
         - Secondary calibrator

Metrological traceability

Lower order

2. International CC (non-SI)
3. International conventional RMP
4. International CC (non-SI)
5. Manufacturer’s selected method

Adapted from White GH Ann Clin Biochem 2011; 48: 393-408
Requirements for traceability in laboratory medicine

European Union In-Vitro Diagnostic Directive (IVDD): 98/79/EC

“The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.”

EU In-Vitro Diagnostic Device Regulation (IVDR): EU/2017/746

“9.3. Where the performance of devices depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order.”
Who are the stakeholders in achieving traceability?

- Select methods based on quality performance
- Use commutable materials to monitor method performance
- Produce methods that are traceable to a reference system, when available
- Raise analytical and clinical quality targets
- Lists available materials and methods. Promotes traceability
- Provide reference materials and higher-order reference methods
- Define clinical decision values and analytical requirements

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Joint Committee for Traceability in Laboratory Medicine

Formed in 2002 to enable a global response to the IVD Directive

- Intergovernmental treaty organisation for measurement standards
- International NGO for professionals in laboratory medicine
- International NGO for accreditation bodies

Now has 49 members from 19 countries
 NMIs, EQA providers, professional bodies, IVD manufacturers
What does JCTLM do?

Maintains a global database of:
• Reference materials
• Reference methods
• Reference laboratories
www.bipm.org/jctlm

Co-ordinates the nomination and review process for database entries
www.bipm.org/jctlm

Contributes to ISO Working Groups on reference systems, which are responsible for global standards

Provides news and freely available resources on traceability in laboratory medicine:
• Webinars; publication lists
www.jctlm.org

Hosts a biennial scientific meeting
JCTLM Database: Laboratory medicine and *in vitro* diagnostics

**Analyte keyword search for reference materials, measurement methods/procedures and services**

Type an analyte name in part or full, e.g. cholesterol

- **Refine search by analyte category**
  - All

- **Refine search by matrix category**
  - All

Please select your requirement:

- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

[Reset] [Search]
### JCTLM Database Entries: October 2018

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<tr>
<th>Category</th>
<th>Materials</th>
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<th>Services</th>
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Number of entries in 2018
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Zagreb October 2018
Case study: haemoglobin A$_{1c}$ (HbA$_{1c}$)

Established from major clinical trials as key analyte for long-term monitoring of diabetes

Method improvement following IFCC standardisation [Ref 1]

IFCC reference laboratory network established [Ref 2]

Many laboratory and POCT methods available

2. IFCC network laboratories for HbA1c www.ifcchba1c.net
Why is HbA$_{1c}$ so important?

DCCT* showed that HbA$_{1c}$ is the best long-term marker of diabetes control.

Better control of HbA$_{1c}$ leads to better outcomes in people with diabetes.

- Deaths related to diabetes: 21%
- Microvascular complications: 37%
- Myocardial infarction: 14%

* DCCT = Diabetes Control and Complications Trial

HbA1c: typical current EQA

<table>
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<tr>
<th>Specimen: 370B</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>CV(%)</th>
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</table>

![Graph showing between-laboratory agreement by concentration for HbA1c [IFCC]](image)

**Your result:** 52

**Target value (ALTM):** 48.1

- **%bias:** +8.2
- **transformed bias:** +160
- **Accuracy Index:** 160

- **Secondary IFCC value:** 47.8
- **DCCT comp. value:** 6.52
- **ALTM:** 48.07

**UK NEQAS**
HbA1c as a diagnostic test for diabetes

- Many clinical practice guidelines exist that link monitoring of diabetic control to target HbA1c levels.
- WHO guidelines for HbA1c in diagnosis of diabetes

**WHO Guideline 2011**

“HbA1c can be used as a diagnostic test for diabetes **providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to international values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 48mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes. A value of <48mmol/mol does not exclude diabetes diagnosed using glucose tests.”
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Facing the challenge

The world population of 7.7 billion people is entitled to believe that all methods will give the same result on their specimen.
What can EQA achieve?

- EQA is an essential and effective tool to reduce between method variability
- In addition to its proficiency testing role EQA has an important educational role with users and IVD method manufacturers
- Wherever possible EQA specimens should perform like fresh patient specimens (commutable EQA)
- However, EQA alone may not be sufficient to harmonise patient results from different methods:
  - Different measurands
  - Different reference materials
  - Different measurement procedures (e.g. antibodies)
- EQA organisers have a vital role in highlighting analytes with high between method variability that may benefit from an international standardisation / harmonisation initiative
Possible roles for EQALM

**Possible Projects**

**Project 1**
Review clinically important analytes where EQA performance is poor and identify candidates for method harmonisation ([www.harmonization.net](http://www.harmonization.net))

**Project 2**
- Lead / support a project to explore relationship of EQA performance to method traceability
- **Outcome**
  - Review article
  - Presentation at international meeting
  - Freely available webinar

**Publicity and Promotion**

Working with JCTLM
- Encourage EQA organisers to include a session on TLM in their user group meetings
- Distribute news and educational material on traceability in laboratory medicine (TLM) to participants and manufacturers
- Highlight methods where performance is improving as a result of EQA leadership
- Promote [www.jctlm.org](http://www.jctlm.org) to participants and manufacturers