Clinical Laboratory Test Harmonization

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ISLH, Chicago, May 21, 2015
Financial disclosures

1. Research grant from Abbott Diagnostics (2013-2014)

2. Travel expenses and honorarium from Roche Molecular Diagnostics
Outline

- What is harmonization
- Why is it important
- How is it accomplished
- What are the challenges
What is harmonization

- Equivalent results among different measurement procedures for the same laboratory test
  - Nomenclature
  - Patient preparation
  - Specimen collection and handling
  - **Result value**
  - Reporting units
  - Interpretive information

*Today's topic*
What is the problem

Many different laboratory measurement procedures that claim to measure the same measurand give different results for the same specimen.
What is the problem

Many different laboratory measurement procedures that claim to measure the same measurand give different results for the same specimen.

Measurand: the quantity (analyte, substance, property) intended to be measured.
Why does it matter

- Patients may get the wrong treatment
  - Many clinical decisions are informed by laboratory results
  - Many clinical guidelines use a fixed laboratory test value for treatment decisions
PTH concentration (pmol/L) in a single patient.

Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.

INR: Better than PT, but…

Error grid analysis of point of care (CC) vs. laboratory (LAB) prothrombin time (INR) before and after cardiopulmonary bypass (CPB).

Why else does it matter

- Clinical studies may use a central lab with a single method
  - Guidelines from the study cannot be implemented until all other methods are harmonized to the central lab

- Clinical studies may use different methods
  - Data cannot be aggregated to develop guidelines until the results are harmonized
Infrastructure

- ISO: International Organization for Standardization
  - 17511:2003, Calibration Traceability
  - 15194:2009, Certified Reference Materials
  - 15195:2003, Reference Measurement Laboratories
  - PWI, Harmonization Protocols
Infrastructure

- **JCTLM**: Joint Committee for Traceability in Laboratory Medicine
  - Reviews and approves reference system components for conformance to the ISO requirements
**Terminology**

- **Harmonization**: achieving equivalent results among different measurement procedures
  - Usually implies there is no JCTLM listed reference measurement procedure or certified reference material

- **Standardization**: achieving equivalent results by having calibration traceable to a JCTLM listed reference system component
How to achieve equivalent results

1. Calibration of all measurement procedures is traceable to a common reference system
   - ISO 17511:2003 (under revision)

2. All measurement procedures measure the same quantity (the same molecular form)
   - Analytical selectivity for the measurand
Traceability (based on ISO 17511)

- Pure Substance Reference Material
- Pure Substance Calibrator
- Reference Material (matrix)
- Secondary Reference Material
- Manufacturer’s Product Calibrator
- Manufacturer’s Internal Procedure
- Clinical Lab Method
- Patient’s Sample
- Patient’s Result

- Gravimetry
- Assign value
- Calibrate
- Assign value
- Calibrate
- Assign value
- Calibrate
- Assign value
- Calibrate

- Patient’s result is equivalent to that from the reference procedure
Measurands for which no reference procedures exist nor are likely to be developed
What happens when there is no reference measurement procedure
Traceability (based on ISO 17511)

- Value assignment
- Commutability

Secondary Reference Material (matrix) → Calibrate → Manufacturer’s Product Calibrator → Assign value → Clinical Lab Method → Calibrate → Clinical Lab Procedure → Assign value → Patient’s Sample → Calibrate → Manufacturer’s Internal Procedure → Assign value → Patient’s Result → Calibrate → Secondary Reference Material (matrix)
Approaches to value assignment

⇒ Arbitrary units, e.g. U/L

⇒ A nominal concentration based on a pure substance (e.g. purified or recombinant protein)
  • may not be the same as the clinical measurand
  • may contain reactive impurities or aggregated forms

⇒ By a designated comparison procedure, or mean of a group of measurement procedures
Value assignment by a consensus process is adequate

- The actual quantity value (e.g. concentration) may not be known
- Harmonization can be achieved
- Clinical guidelines can be implemented
Value assignment must be sustainable

- Replacement batches must be consistent
  - Quantity values
  - Other reactive characteristics
    - Measurand molecular form
    - Commutability
Traceability to a Reference Material

Secondary Reference Material (calibrator)

Must be commutable with patient samples for all measurement procedures with which it will be used

Procedure 1

Procedure 2

Procedure 3

Procedure n

Patient Samples

Results 1

Results 2

Results 3

Results n
Commutability (Commutable)

Property of a reference material demonstrated by the closeness of agreement

- between the relation among results for a reference material obtained from two measurement procedures
- and the relation among results for clinical samples from the same two measurement procedures

(Rephrased from VIM 3: 2008)
Commutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Calibration with non-commutable materials

Measurement Procedure 1 vs. Measurement Procedure 2

- **Clinical Samples**
- **RM as Calibrator**

The graph shows a linear relationship between the two measurement procedures. Using RM as a calibrator causes patient sample results to be different.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- Historically, commutability of reference materials was not validated for use with routine clinical laboratory measurement procedures.
Why commutability matters

The manufacturer’s procedure used for value assignment may be the same as the clinical lab method.
Why commutability matters

The manufacturer’s procedure used for value assignment may be the same as the clinical lab method.

A non-commutable calibrator breaks the traceability chain.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples when different measurement procedures are used.
TSH methods
All traceable to IS 94/674 (WHO)

Mean ±95% CI for 40 euthyroid patient samples; 0.5-6.6 mIU/L

Δ = 0.7
35%

Calibration traceability does not ensure accuracy for an individual patient’s sample

- Imprecision may be too large

- Measurement procedure may not be specific for the measurand
  - Interfering substances may influence the result

- Measurand may not be well defined
  - Molecular form(s) of clinical interest may not be understood
Challenges for harmonization

- Materials are labeled as “reference materials” that have not been validated to be commutable for the intended measurement procedures.

- Inadequate understanding of the measurand – the quantity intended to be measured.

- Inadequate analytical specificity for the measurand.
What happens when there is both:

- no reference measurement procedure
- no reference material
A measurement procedure producer establishes traceability to a selected material – no coordination among producers (IVD or LDT).

Patient’s result is not traceable to any international reference.
How will we harmonize without reference materials

Reference materials have challenges

Reference methods are gold
International Forum organized by AACC in October, 2010

90 participants from 12 countries

Representing 62 organizations & manufacturers
Challenges for harmonization

- Lack of a systematic process to identify and prioritize measurands in need of harmonization

- Lack of systematic procedures to implement harmonization, in particular:
  - when there is no reference measurement procedure
  - when there is no reference material
Challenges for harmonization

- Despite many organizations in many countries working to improve harmonization:
  - The work is not coordinated to prevent:
    - Duplication of effort
    - Different approaches by different groups
  - People do not know what others are doing
Challenges for harmonization

- Regulatory requirements
  - Changing calibration requires regulatory approval
  - Does the clinical benefit justify the cost to meet regulatory requirements?
  - Can regulatory guidance be modified to lower the cost?
The Roadmap

Develop an infrastructure to coordinate harmonization activities world wide:

1. Prioritize measurands by medical importance
2. Coordinate the work of different organizations
3. Develop technical processes to achieve harmonization when there is no reference measurement procedure or no reference material
4. Promote surveillance of the success of harmonization
AN INFRASTRUCTURE FOR HARMONIZATION

International Consortium for Harmonization of Clinical Laboratory Results

- Strategic Partners Group
- Council
- Harmonization Oversight Group
- Harmonization Implementation Groups
- Special Working Groups

Review and Recommend

Governance, Administration

Operations Management

Secretariat/Host - AACC

Strategic Partners Group

Council

Harmonization Oversight Group

Harmonization Implementation Groups

Special Working Groups

Work Groups
ICHCLR: Council members
Strategic Partners Group

Members of the Strategic Partners Group have the opportunity to support the program by submitting measurands in need of harmonization and to nominate experts for consideration to serve on the Harmonization Oversight Group. Members will receive project plans and milestone updates from Harmonization Implementation Groups for review and comment. Stakeholders who are committed to harmonization of clinical laboratory results (e.g. clinical laboratory and medical organizations, IVD manufacturers, metrology institutes, standard-setting organizations, public health organizations, regulatory agencies and individuals) may become members of the Strategic Partners Group. The annual membership fee for a Strategic Partners Group member is $500. Subscription to the Strategic Partners Group during 2014 will carry a Strategic Partner's membership status forward through December of 2015 to coincide with an annual membership period.

Click here for more information on the operation of the International Consortium for Harmonization of Clinical Laboratory Results.

Current Members
Strategic Partners Group

Alero Healthcare, Inc.
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This section provides information on the status of harmonization or standardization of measurands. Information on reference measurement procedures and reference materials under development is provided when such information is available as well as information on commutability of existing reference materials where information exists. Links to organizations actively addressing harmonization of particular measurands are provided for inquiry on additional information on those projects. For measurands not yet harmonized, information is provided on the priority and technical feasibility for harmonization determined by the Harmonization Oversight Group.

Submit a Measurand  Review my Submissions

Download the submission form data elements.
# Measurands

## Summary of Measurands

<table>
<thead>
<tr>
<th>Measurand</th>
<th>Matrix</th>
<th>Medical Importance</th>
<th>Technical Feasibility</th>
<th>Harmonization Status</th>
<th>Reference Material Commutability</th>
<th>Reference Material Reference</th>
<th>JCTLM Listed</th>
<th>Organization</th>
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<tbody>
<tr>
<td>IgG antibodies to myeloperoxidase</td>
<td>Serum</td>
<td></td>
<td></td>
<td>Active</td>
<td></td>
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<td>Active</td>
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<td>IFCC</td>
</tr>
</tbody>
</table>
We need your help

- Identify harmonization / standardization activity by organizations around the world to add to the web site

- Submit high priority measurands to add to the list
Other ICHCLR activities

1. Initiated a new work item to ISO TC212 for a harmonization protocol
2. Organized a forum with IVD industry and FDA to address regulatory approaches for recalibration of existing tests to achieve harmonized results
3. Developed a position statement with AACC on harmonization of clinical laboratory test results
4. Met with US congress to include language in the Continuing Resolution and Further Continuing Appropriations Act of 2015 that supports harmonizing clinical laboratory test results
Resources

Below are resources to support global harmonization of clinical laboratory measurement procedures.

- AACC Releases Position Statement on Harmonization of Clinical Laboratory Test Results
- International Consortium for Harmonization of Clinical Laboratory Results: Operating Procedures
- Meeting Summaries
- Strategic Partners Update Reports
- Measurand Checklist and Report Form for Special Working Group
- Toolbox of technical procedures to be considered when developing a process to achieve harmonization for a measurand
Toolbox

1) Integrated Harmonization Protocol

2) Step-up Design for Harmonization
   - Basis for an ISO TC212 preliminary work item for a harmonization protocol standard
   - Revision of ISO 17511 is considering traceability to a harmonization protocol as a recognized approach for standardization
Traceability to a harmonization protocol

- **Patient's Result** is traceable to a harmonization protocol.

- **Manufacturer’s Product Calibrator**
  - Assign value
  - Calibrate

- **Clinical Lab Method**
  - Calibrate

- **Manufacturer’s Internal Procedure**
  - Calibrate

- **Harmonization Protocol for Value Assignment**
  - May utilize a panel of patient samples or other suitable materials for value transfer to product calibrator(s)

- **Patient’s Sample**
  - Assign value

- **Patient’s Result**
International Consortium for Harmonization of Clinical Laboratory Results:
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