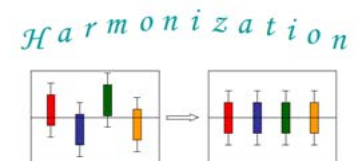


From Chaos to Order: The Role of Harmonization

Gary L. Myers, PhD, FACB

AACC

Washington, DC, USA

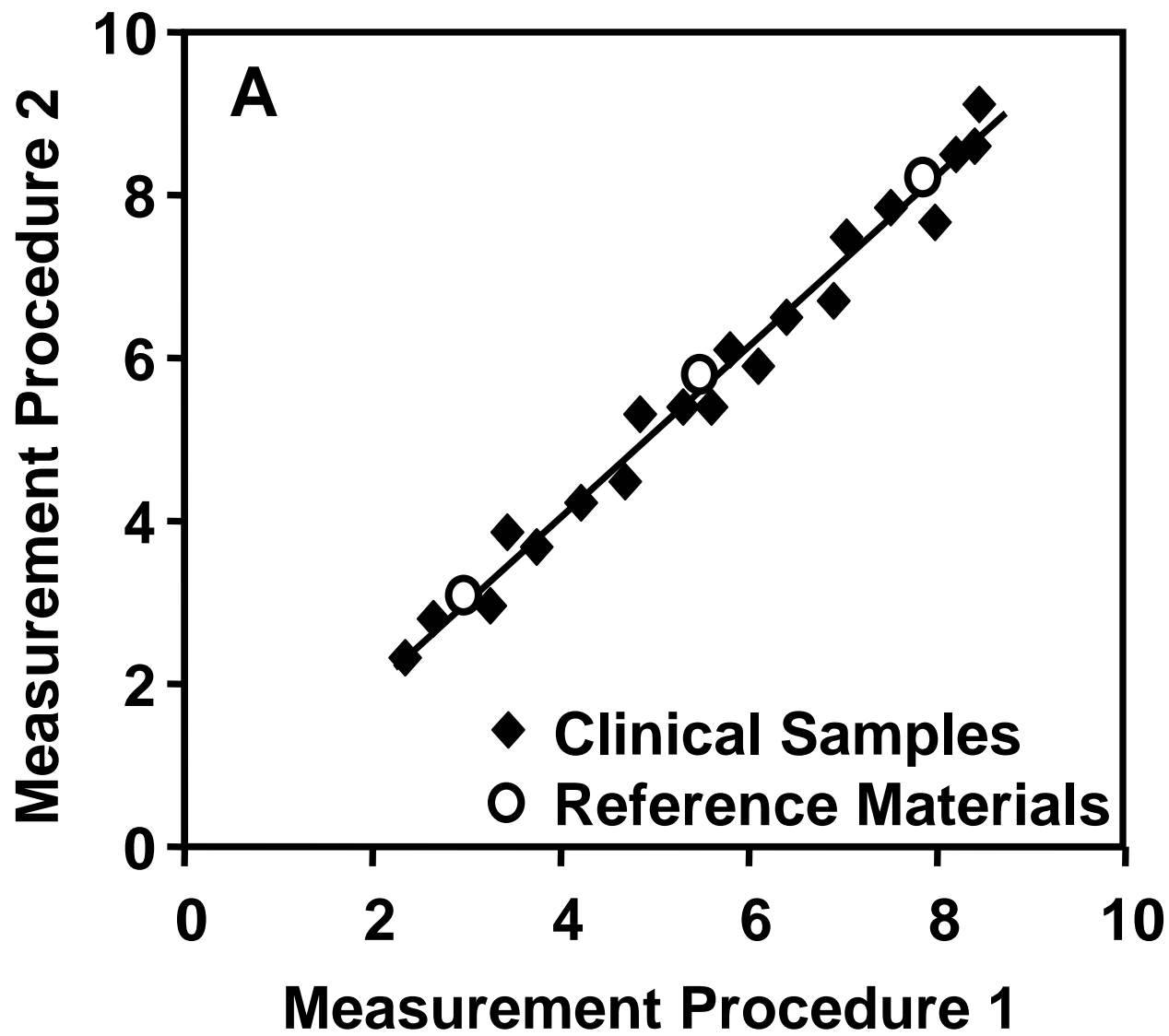


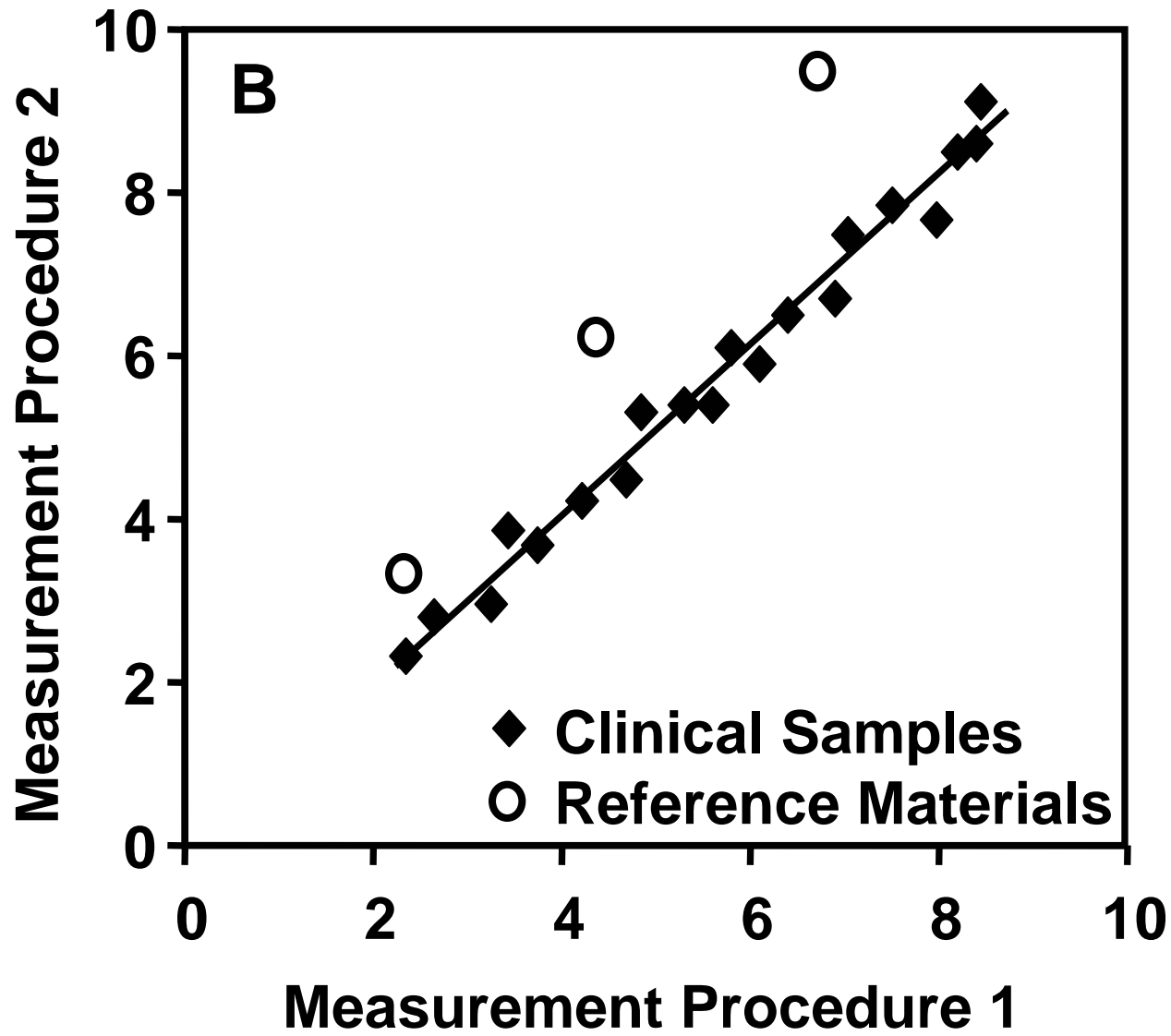
Primary reasons for testing

- To develop epidemiologic data from which to establish public health strategies for disease management
- To identify individuals at increased risk of disease and/or monitor disease management

Requirements to meet testing goals

- Precise and accurate assays
- Results must be comparable: independent of where and when test performed and assay used
- To accomplish this requires established standards for use in assay calibration
- Specifically such measurement standards of higher order include:
 - Reference measurement procedure(s) (RMP)
 - Reference laboratories that provide RMPs
 - Reference material(s) that are commutable
- Process or program to establish and maintain traceability to established standards





A National Understanding for the Development of Reference Materials and Methods for Clinical Chemistry

- November, 1977
- CDC, Atlanta, GA

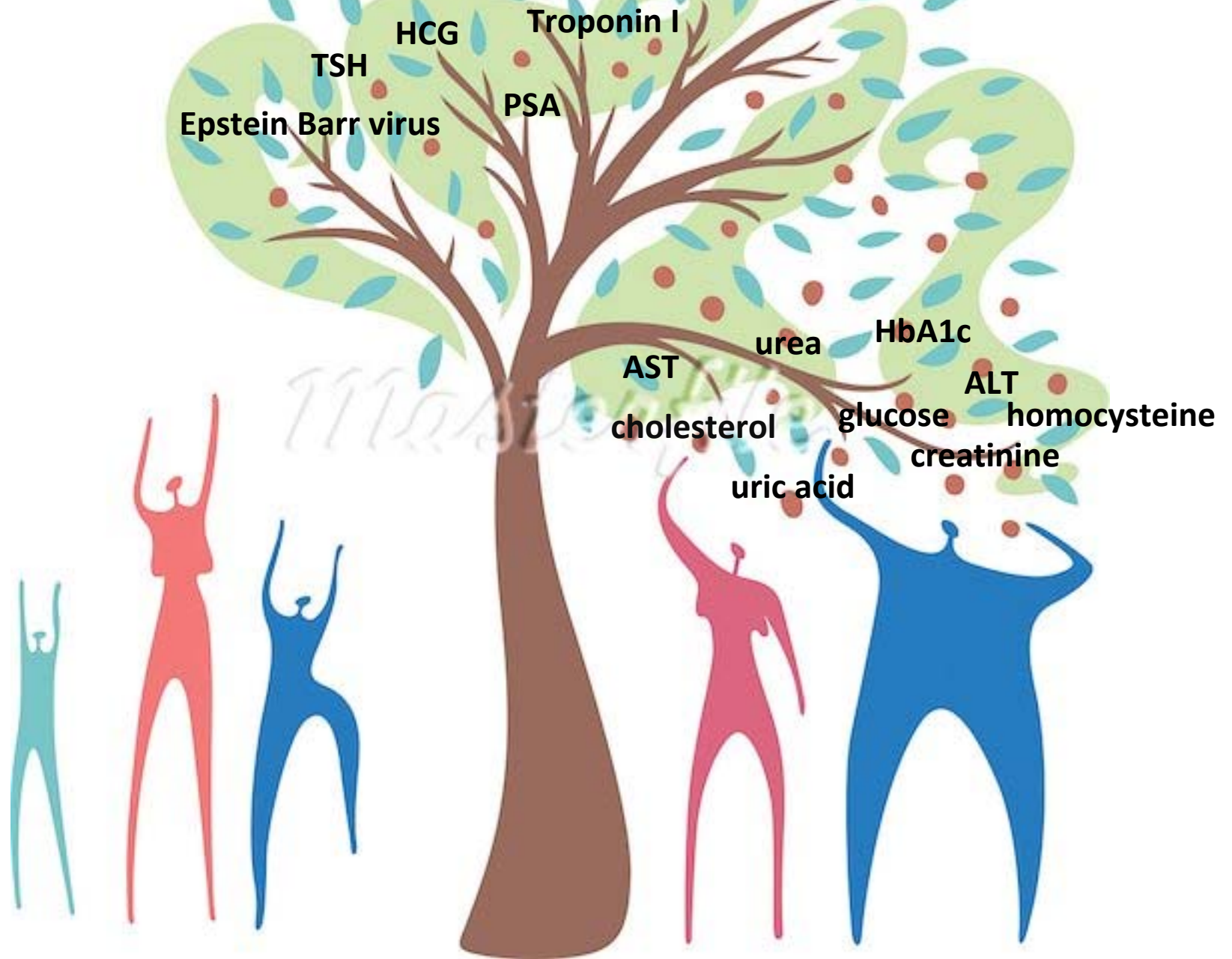
Participating Organizations

- American Association for Clinical Chemistry
- American Society of Clinical Pathologists
- College of American Pathology
- Center for Disease Control
- Food and Drug Administration
- Industry
- National Bureau of Standards
- National Committee for Clinical Laboratory Standards

Progress has been made!

- AACC
- CDC
- Clinical and Laboratory Standards Institute
- College of American Pathologists
- Industry
- Institute for Reference Materials and Measurements
- International Federation of Clinical Chemistry
- International Organization for Standardization
- International EQAS programs
- Joint Committee on Traceability in Laboratory Medicine
- National Glycohemoglobin Standardization Program
- NIST
- WHO

Picking the low-hanging fruit !





CLSI

CAP

IRMM

JCTLM

NGSP

NIST

Industry

IFCC

CDC

ISO

What do we do?



AACC Leadership Forum

Improving Clinical Laboratory Testing through Harmonization: An International Forum

October 26-27, 2010

Hosted by: The National Institute for Standards and Technology

AACC Harmonization Conference

Conference Goal:

To strengthen the quality of laboratory measurements and improve patient care by developing consensus on technical and organizational **processes** to achieve harmonization for clinical laboratory procedures for which no reference measurement procedure, and in many cases no suitable reference materials exist or are likely to be developed.

AACC Harmonization Conference

The conference addressed the following process topics:

- prioritizing measurands for harmonization
- conducting a situational analysis (gap analysis) to determine what is needed for harmonization
- developing a technical process to achieve harmonization for a measurand
- assessing successful harmonization for a measurand

AACC Harmonization Conference

Primary desired conference outcomes:

- Development of consensus procedures for how to accomplish harmonization
- Formation of working groups with specific tasks to ensure implementation of the conference recommendations
- Identification of organizations willing to accept responsibility for implementing one or more of the recommendations agreed upon
- A report published in *Clinical Chemistry* on the findings and recommendations from the conference

Traceability of Laboratory Results

Standardization and harmonization are based on traceability principles described in ISO standard 17511. Differences between standardization and harmonization

- Standardization: all measurement procedures get the same result for a sample and the result is traceable to SI with a reference measurement procedure
- Harmonization: all measurement procedures get the same result for a sample when there is no reference measurement procedure

Traceability of Laboratory Results

The standard includes 5 categories of reference systems. There are well established procedures to address standardization of measurands in categories 1, 2 and 3. Category 4 includes measurands for which reference materials are available for calibration, but there is no RMP. Category 5 includes measurands for which neither RMPs nor reference materials for calibration are available.

Category	Reference measurement procedure	Primary reference material (pure substance)	Secondary reference material (value assigned)	Examples
1	Yes	Yes	Possible	Electrolytes, glucose, cortisol
2	Yes	No	Possible	Enzymes
3	Yes	No	No	Hemostatic factors
4	No	No	Yes	Proteins, tumor markers, HIV ^a
5	No	No	No	EBV ^b , VZV ^c

Standardization

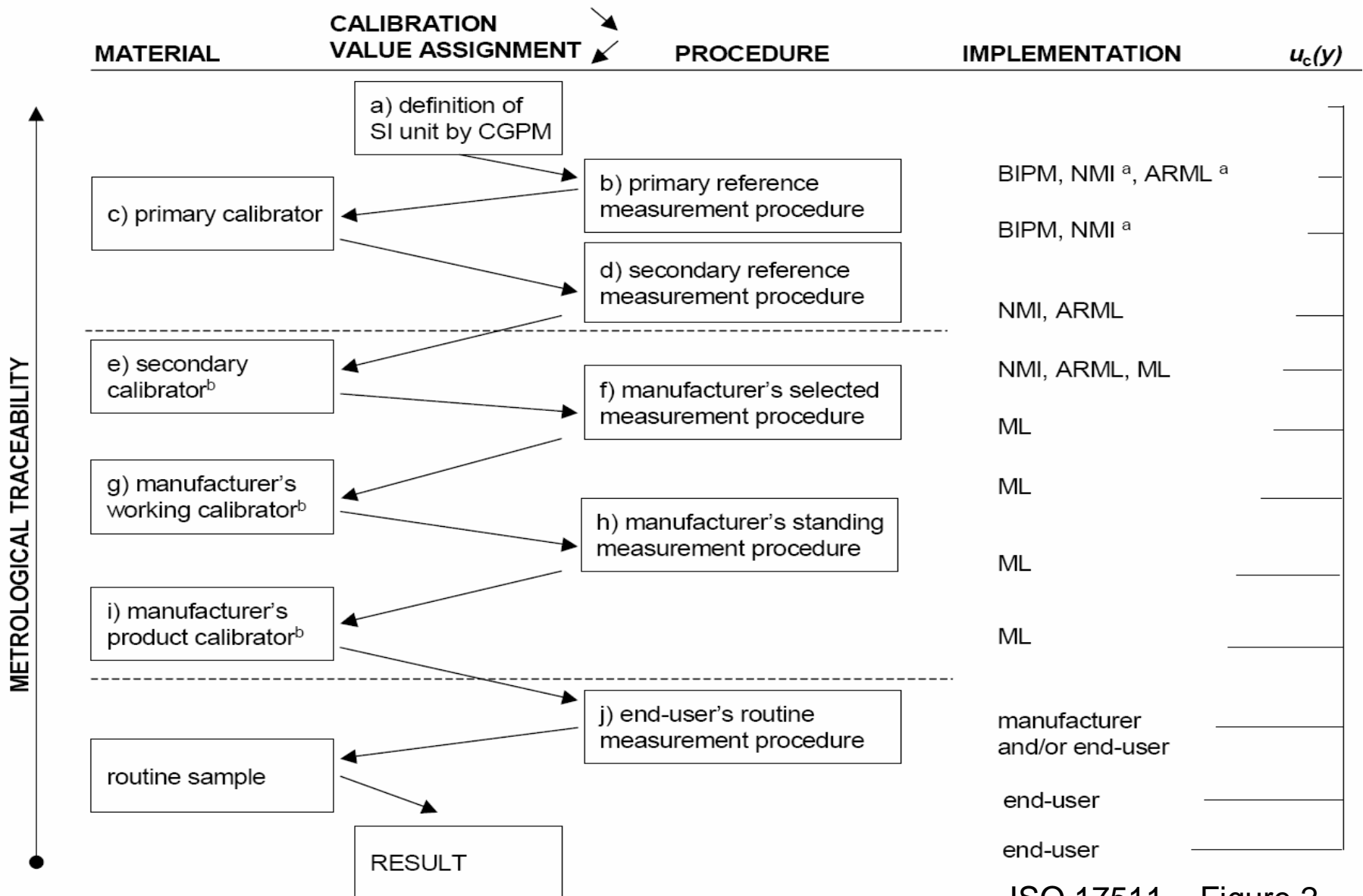
Harmonization

^a Human Immunodeficiency virus

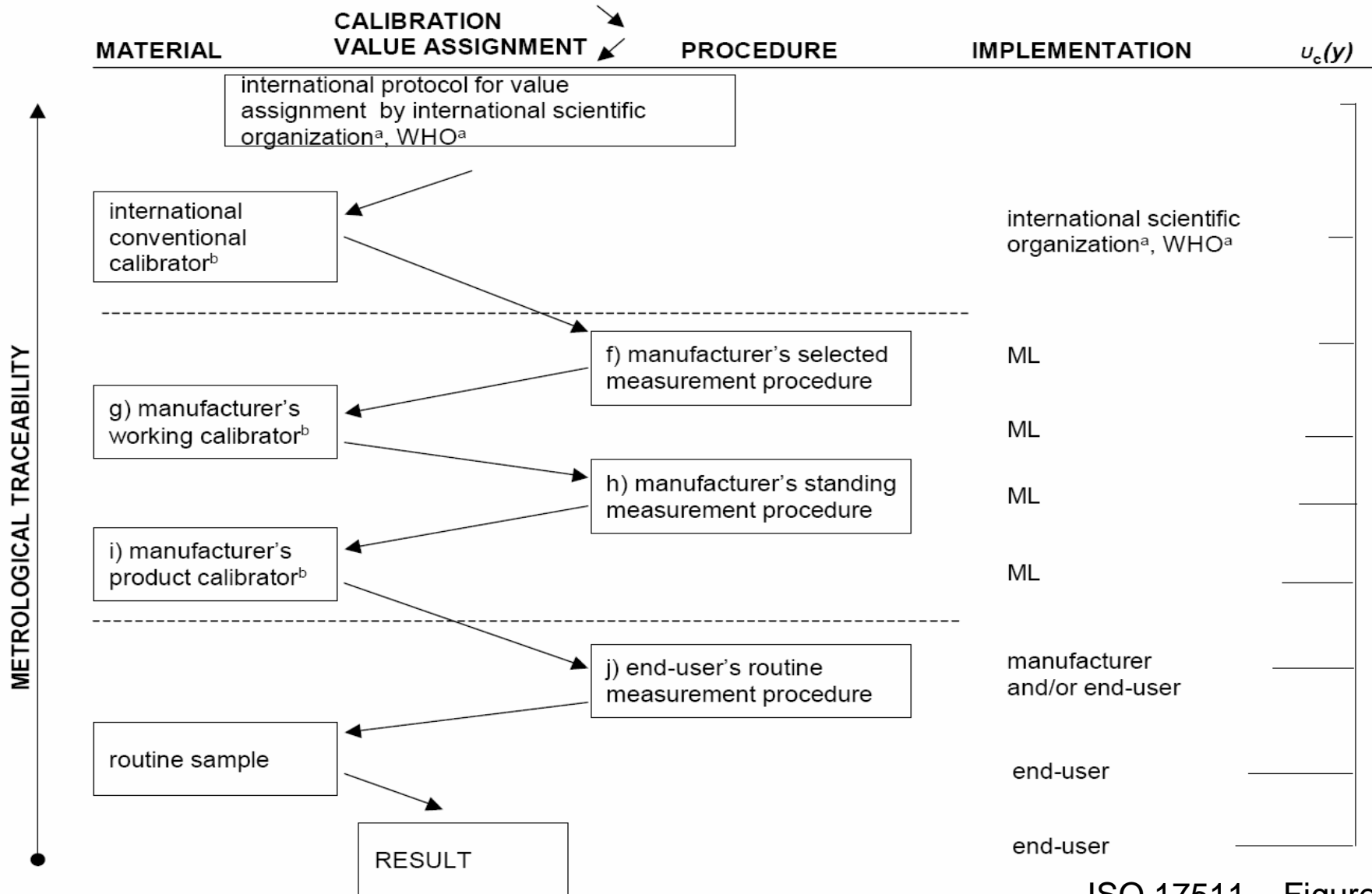
^b Epstein Barr virus

^c Varicella zoster virus

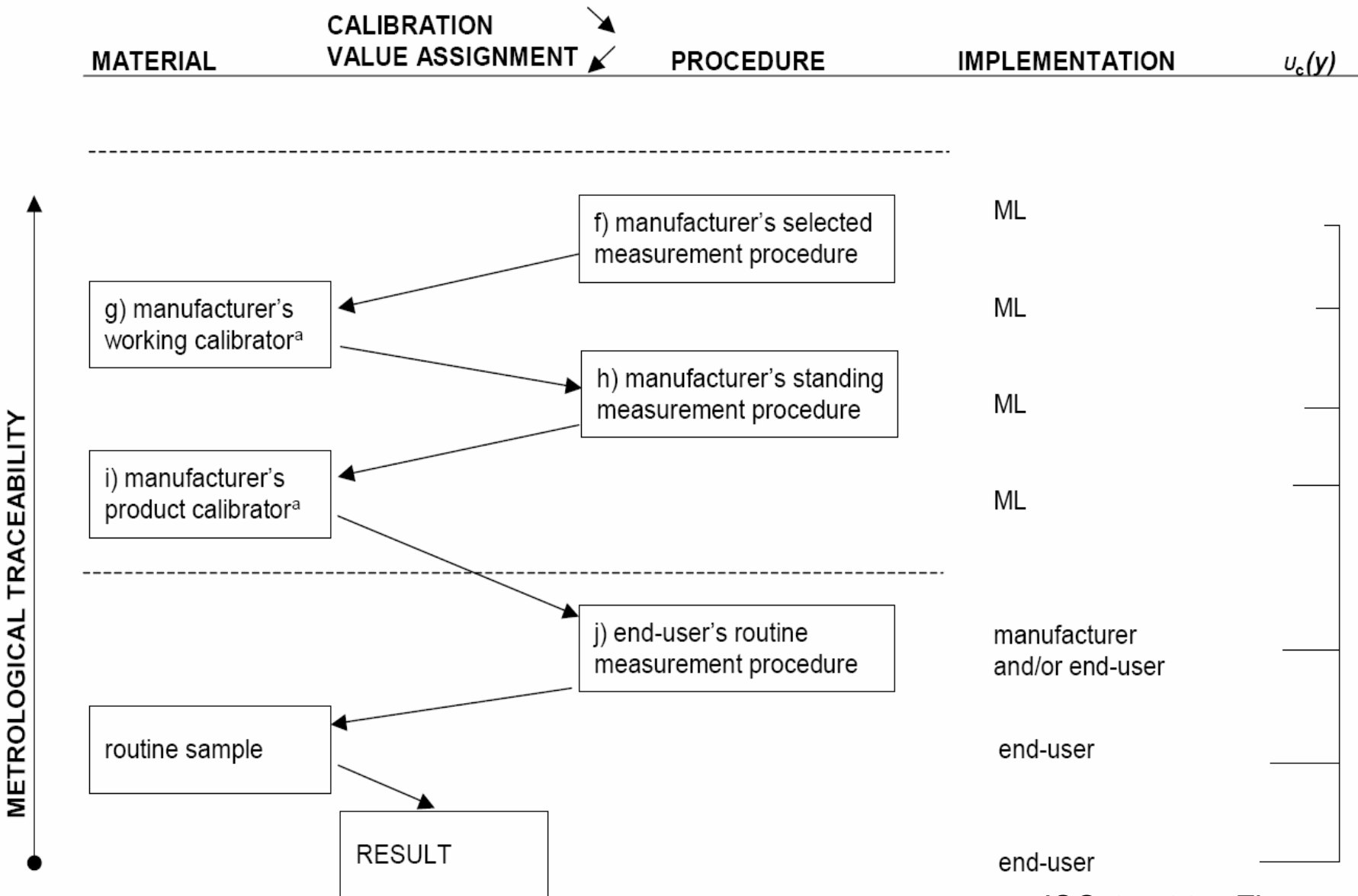
Traceability to Système International



Traceability to International Conventional Reference Material



Traceability to Manufacturer's Reference Measurement Procedure



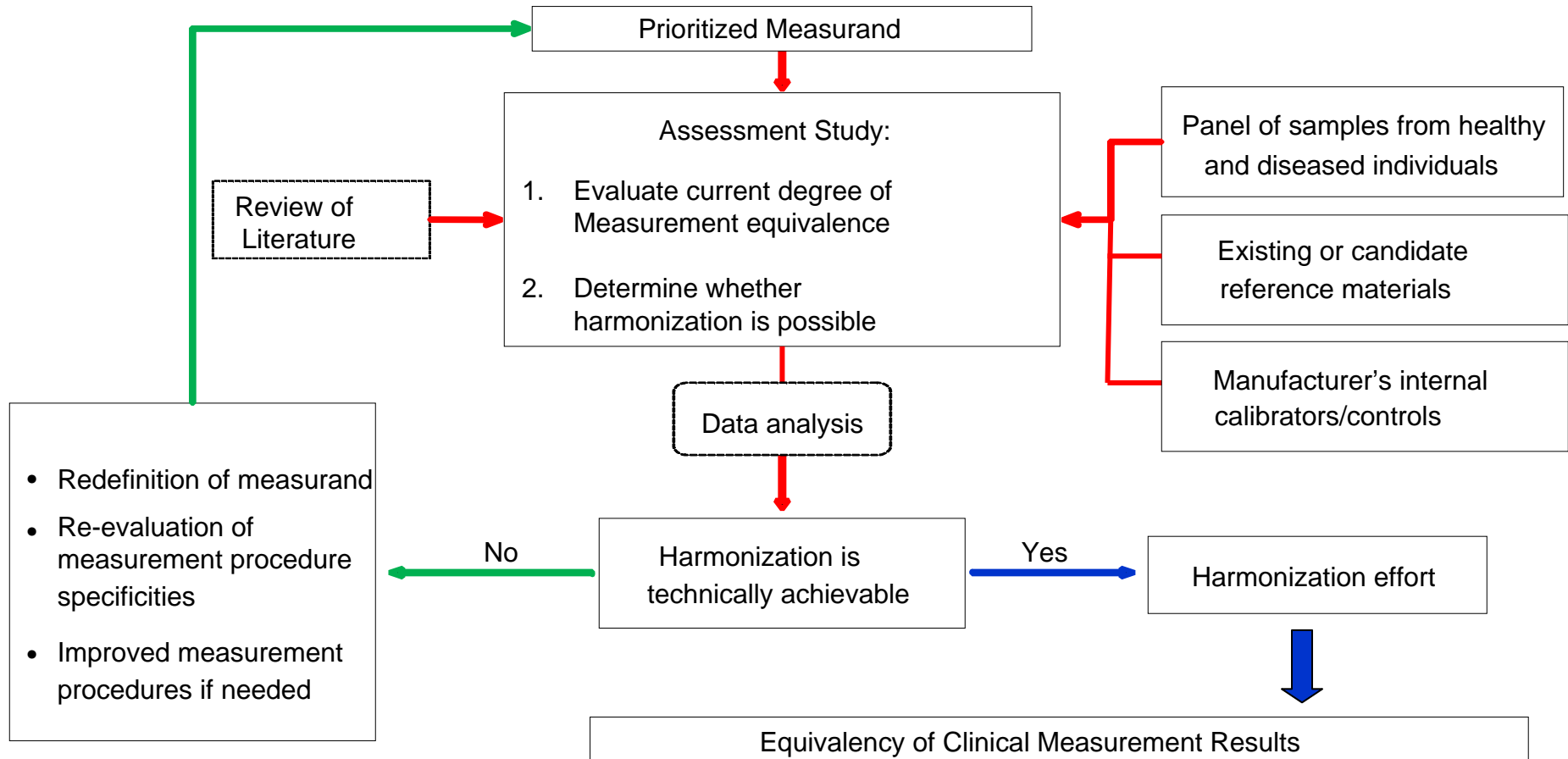
ISO 17511 – Figure 6

Barriers to Harmonization

- Lack of a systematic process to identify and prioritize measurands
- Lack of commutable reference materials
- Materials labeled as “reference materials” that have not been validated to be commutable
- Inadequate definition of the measurand
- Inadequate analytical specificity for the measurand
- Lack of systematic procedures to implement harmonization when there is no reference measurement procedure

Harmonization of a Measurand

The specifics of any harmonization effort will vary for different measurands. However, general strategies provide a framework for development of measurand specific protocols.



Harmonization Conference Recommendations

Create an infrastructure to manage harmonization of measurands without RMPs

Clinical
Laboratory
IVD ma

The Harmonization Oversight Group will coordinate all activity, will solicit and receive input from stakeholders, will

If work
refer

The Specialty Work Group comprised of experts in clinical use and laboratory measurement of the measurand will be created to evaluate the clinical importance of a measurand, evaluate the gap between clinical requirements and current practice, and using a checklist assess the technical feasibility to harmonize the measurand.

Create a Harmonization Implementation Group

- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

Domains and Elements of a Measurand Harmonization Checklist

- What is the clinical need for measurand measurement?

- **What disease(s) is relevant for measurand measurement?**
- **What are the outcomes associated with the disease(s)?**
- **What is the economic impact of the disease(s)?**
- **How is the measurand used clinically?**
- **Is use of this measurand considered “standard of care”?**

Harmonization Conference Recommendations

Create an infrastructure to manage harmonization of measurands without RMPs

Clinical practice groups
Laboratory practice groups
IVD manufacturers

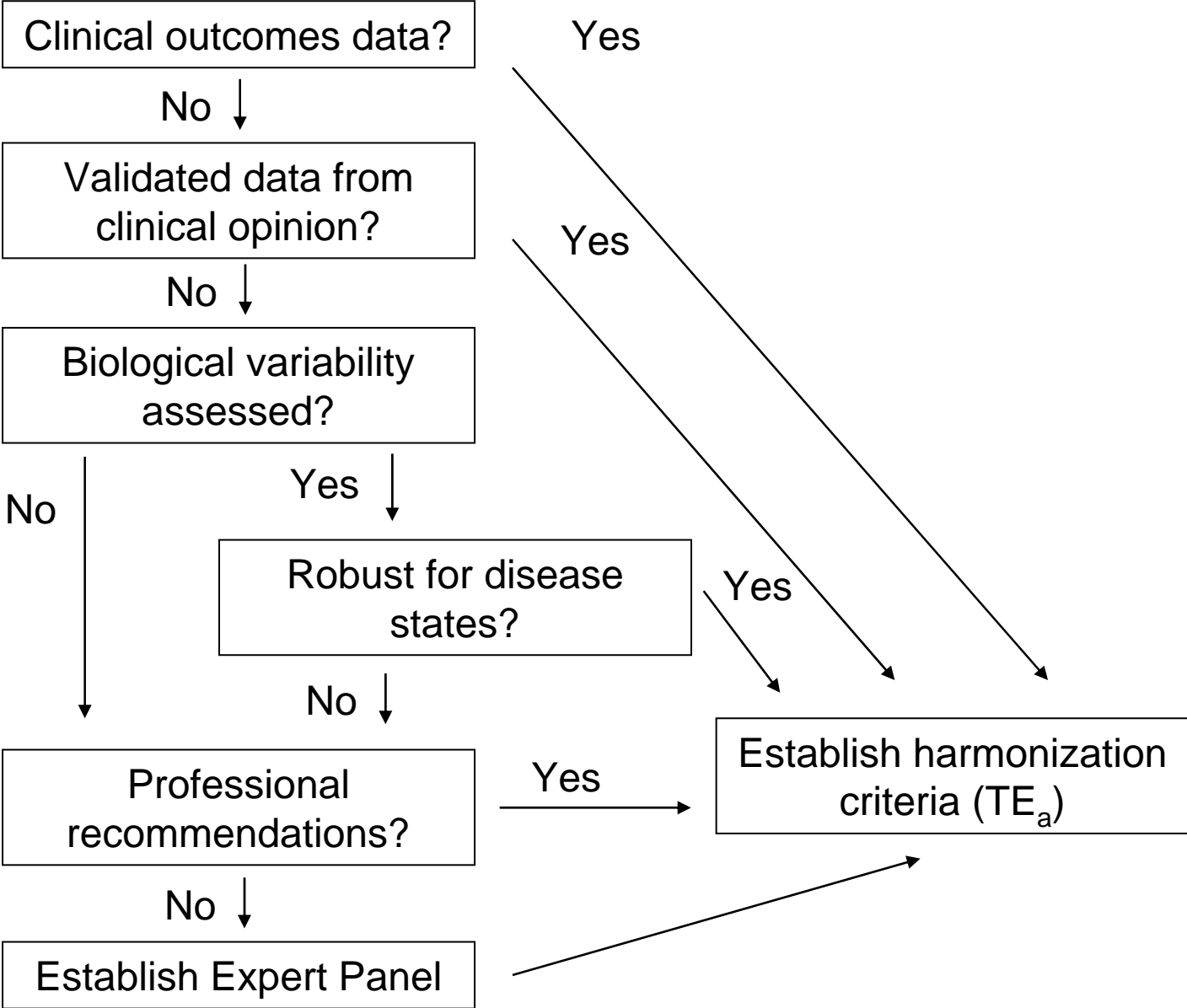
Metrology institutes
Standards organizations
Regulatory organizations

Harmonization
Oversight Group

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graph TD; A["Clinical practice groups<br/>Laboratory practice groups<br/>IVD manufacturers"] --> C["Harmonization Oversight Group"]; B["Metrology institutes<br/>Standards organizations<br/>Regulatory organizations"] --> C; C --- D["A Harmonization Implementation Group will be formed to manage the technical implementation of a harmonization process for a specific measurand. This group will develop the criteria for acceptable agreement among clinical laboratory measurement procedures, the technical plan for harmonization, any needed reference materials, implement procedures to achieve harmonization, and ensure a process to assess the success of harmonization."];
```

A Harmonization Implementation Group will be formed to manage the technical implementation of a harmonization process for a specific measurand. This group will develop the criteria for acceptable agreement among clinical laboratory measurement procedures, the technical plan for harmonization, any needed reference materials, implement procedures to achieve harmonization, and ensure a process to assess the success of harmonization.

Proposed scheme for developing method harmonization criteria



Path Forward

- Conference report and recommendations: Roadmap for harmonization of clinical laboratory measurement procedures. *Clinical Chemistry* 2011; accepted.
- Task forces will be convened to develop the processes needed to refine and implement the scheme for harmonization.
- AACCC is committed to organizational support to develop the infrastructure needed for implementation.
- AACCC will launch a web site (URL: harmonization.net) to communicate with stakeholders and provide updates on progress of the harmonization effort.
- AACCC seeks collaboration and cooperation with other organizations to achieve a successful harmonization process.

Steering Committee

Primary Tasks

- Implement the organizational infrastructure
- Develop a website for posting harmonization activities/information
- Coordinate communication and foster collaboration with interested stakeholders
- Develop a business model and mechanisms for funding the infrastructure
- Find a “home” for the harmonization process (Harmonization Oversight Group)

Steering Committee Members (Member selection based on experience and expertise in laboratory standardization. Business affiliation provided.)

- Greg Miller - Co-Chair – Virginia Commonwealth Univ., USA
- Gary Myers – Co-Chair – AACC, USA
- Mary Lou Gantzer – Siemens Healthcare Diagnostics, USA
- Steve Kahn – Loyola Univ. Health System, USA
- Ralf Schönbrunner – Life Technologies, USA
- Linda Thienpont – Ghent Univ., BE
- Graham Beastall – Glasgow Royal Infirmary, UK
- Rob Christenson – Task Force Chair – Univ. of Maryland, USA
- Cas Weykamp – Task Force Chair – Queen Beatrix Hospital, NL

Task Force for Planning the Harmonization Oversight Group

Primary Tasks

- Develop a proposal for the organizational infrastructure
- Develop a process to solicit input from interested stakeholders
- Develop a process to create and manage Specialty Work Groups and Harmonization Implementation Groups to address specific measurands
- Develop a plan to communicate with the IVD industry on planned harmonization activities to insure coordination and provide lead time to plan and budget for participation
- Develop a plan to communicate with stakeholders for funding specific harmonization projects

Task Force Members (Member selection based on experience and expertise in laboratory standardization. Business affiliation provided.)

- Greg Miller-Co-Chair – Virginia Commonwealth Univ., USA
- Gary Myers – Co-Chair – AACC, USA
- Mary Lou Gantzer – Siemens Healthcare Diagnostics, USA
- Ralf Schönbrunner – Life Technologies, USA
- Ian Young – Queen’s University Belfast, UK
- William Rosner – Roosevelt Hospital, USA
- Julie Lin – Harvard Medical School, USA
- Wenxiang Chen – Beijing Hospital, China

Task Force for Developing Checklists

Primary Tasks

- Develop process for prioritizing measurands and the supporting checklists for use in the process
- Develop a process for conducting a gap analysis (current state vs. desired state for harmonization) and the supporting checklists
- Develop processes to define the measurand

Task Force Members (Member selection based on experience and expertise in laboratory standardization. Business affiliation provided.)

- Rob Christenson - Chair – Univ. of Maryland, USA
- Cathie Sturgeon – Royal Infirmary of Edinburg, UK
- Steve Kahn – Loyola Univ. Health System, USA
- Peter Meijer – ECAT Foundation, NL
- Jack Zakowski – Beckman Coulter, Inc., USA
- Christa Cobbaert – Leiden Univ. Medical Center, NL
- Chris Price – Univ. of Oxford, UK
- Alexandra Valsamakis, Johns Hopkins, USA

Task Force for Developing Technical Processes for Assessment and Harmonization of Measurands

Primary Tasks

- Develop generic processes for harmonization of a specific measurand. Processes may include experimental and mathematical components
- Achieve consensus for the processes developed
- Develop proposals to credential or approve the processes for harmonizing measurands
- Recommend surveillance schemes to sustain the success of harmonization and identify needed attributes of such schemes

Task Force Members (Member selection based on experience and expertise in laboratory standardization. Business affiliation provided.)

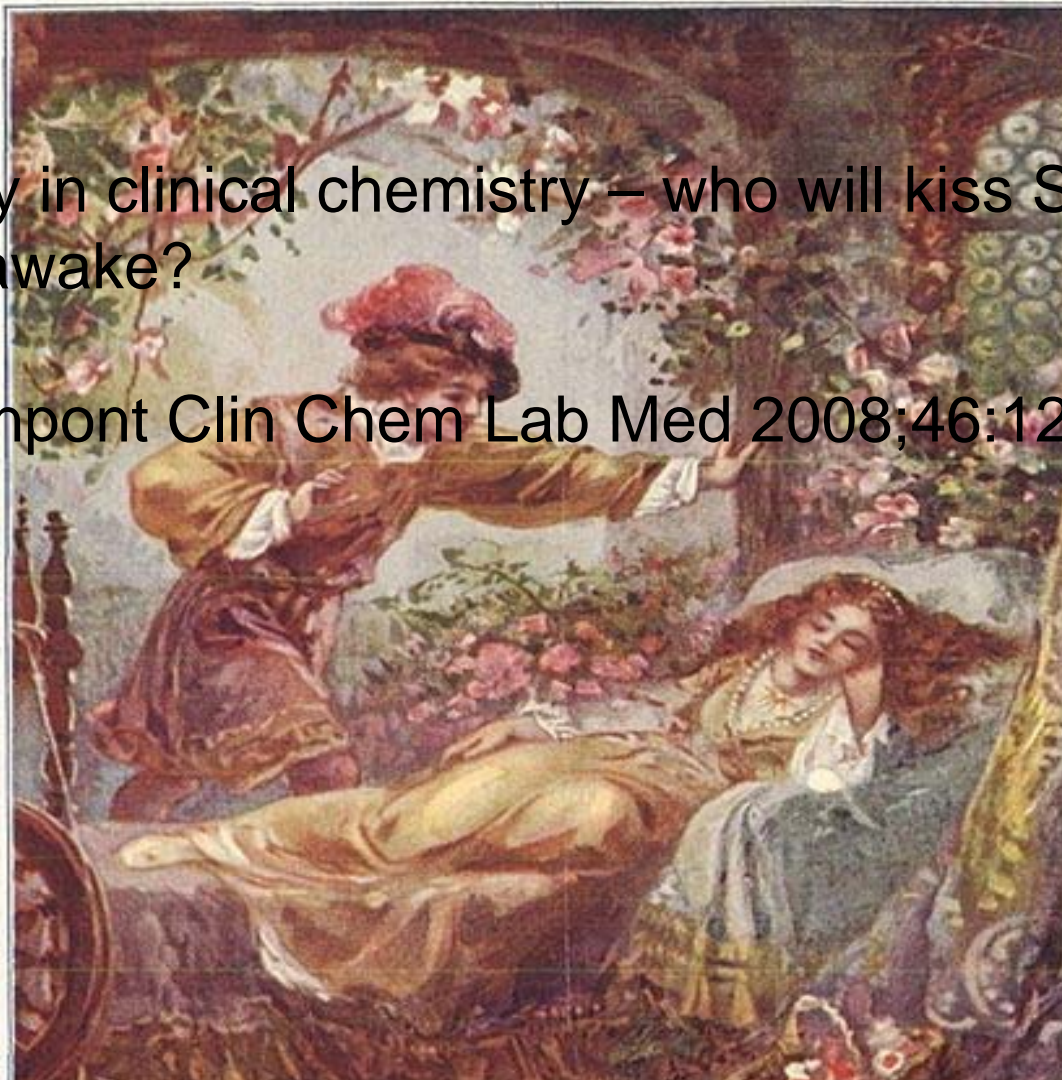
- Cas Weykamp - Chair – Queen Beatrix Hospital, NL
- John Eckfeldt – Univ. of Minnesota, USA
- Bill Roberts – ARUP Laboratories, USA
- Hubert Vesper – CDC, USA
- Angela Caliendo – Emory Univ., USA
- Tina Morris – US Pharmacopeia, USA
- Linda Thienpont – Ghent Univ., BE
- Chris Burns – NIBSC, UK
- Thomas Ciesiolka/Joseph Passarrelli – Roche Diagnostics, GE

Conclusions

- The goal for the Steering Committee and Task Forces is to have an operational harmonization process in place by the end of 2012.
- Implementation of the harmonization process will require the involvement of international clinical and medical organizations, IVD manufacturers, clinical laboratories, metrology institutes, standards setting organizations, and regulatory agencies.
- The Harmonization Oversight Group will ideally be convened and housed by a universally recognized organization.
- Long term success will depend on collaboration among stakeholders committed to improving patient care and providing financial resources required for implementation of harmonization processes.
- To receive information contact Jean Rhame: jrhame@aacc.org

Accuracy in clinical chemistry – who will kiss Sleeping Beauty awake?

LM Thienpont Clin Chem Lab Med 2008;46:1220-2



Prince Harmonization finds the Sleeping Beauty

Thank You!