Laboratory Standardization: Bringing Order to Chaos

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Clinical and Laboratory Standards Institute®

Laboratory Standardization

Two areas of standardization in the clinical laboratory:

- How testing is done (the procedures that are followed)
- Test methods used (obtaining comparable results regardless of the testing laboratory or method used)

Standardization of How Testing Is Done

CLSI is known worldwide for its documents that standardize how things are done in the clinical laboratory!

CLSI Background

- Established in 1968
- Nonprofit organization based in the United States
- American National Standards Institute (ANSI)–accredited standards-development organization
- Volunteer driven through its governance structure and technical operations
- An organization of organizations
- Publishes more than 200 standards and guidelines

CLSI's Vision

To be the leader in clinical and laboratory standards to improve the quality of medical care.

CLSI's Mission

To develop best practices in clinical and laboratory testing and promote their use throughout the world, using a consensus-driven process that balances the viewpoints of industry, government, and the health care professions.

CLSI Standards and Guidelines

Provide standardized procedures to accomplish many tasks in the laboratory in these areas:

- Automation and Informatics
- Clinical Chemistry and Toxicology
- Hematology
- Microbiology
- Molecular Methods
- Point-of-Care Testing
- Quality Systems and Laboratory Practices

Method Result Standardization

Good laboratory medicine requires

- Total error of measurement is small enough that a result reflects a patient's biological condition.
- Comparable results that are independent of:
  - Where and when a test was performed
  - The measurement procedure used

Total Error

- Calibration bias to an accepted reference (includes calibrator lot-to-lot variability)
- Imprecision in a measurement procedure
- Sample specific influences
  - non-specificity for the measurand
  - interfering substances

Why We Need Comparable Results

If different measurements give different results for the same patient sample:

- Clinical practice guidelines become less useful.
- Patients may receive incorrect treatment.

How To Achieve Comparable Results

- Calibration of all measurement procedures is traceable to a common reference system.
- Performance is monitored and maintained by surveillance using proficiency testing (PT), external quality assessment (EQA), or a certification program.

ISO 17511

In vitro diagnostic medical devices - Measurement of quantities in biological samples - **Metrological traceability of values assigned to calibrators and control materials**

Traceability Categories From ISO 17511

Standardization

Category	Reference measurement procedure	Primary (pure substance) reference material	Secondary (value assigned) reference material	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
5	No	No	No	Proteins, EBV, VZV

Harmonization

Terminology

- **Standardization:** results are uniform among measurement procedures
  - Traceability is established to SI using a reference measurement procedure.
- **Harmonization:** results are uniform among measurement procedures
  - NO reference measurement procedure and no “pure substance” reference material exists.

Traceability (based on ISO 17511)

A Reference System (ideal)

SI unit

Primary Reference Material
(pure substance)

Primary Reference Measurement Procedure
(e.g, gravimetry)

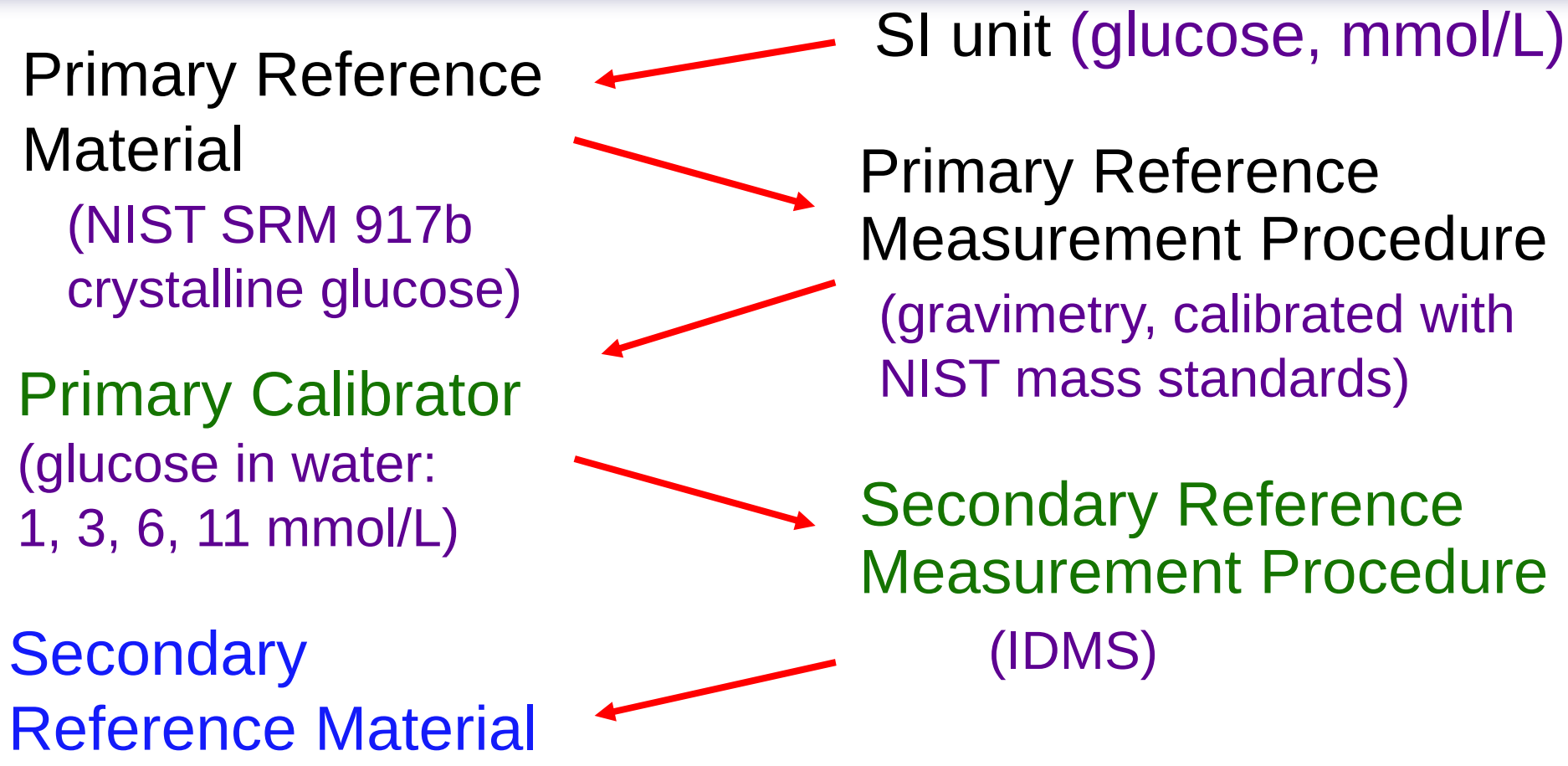
Primary Calibrator

Secondary Reference Measurement Procedure
(e.g, IDMS)

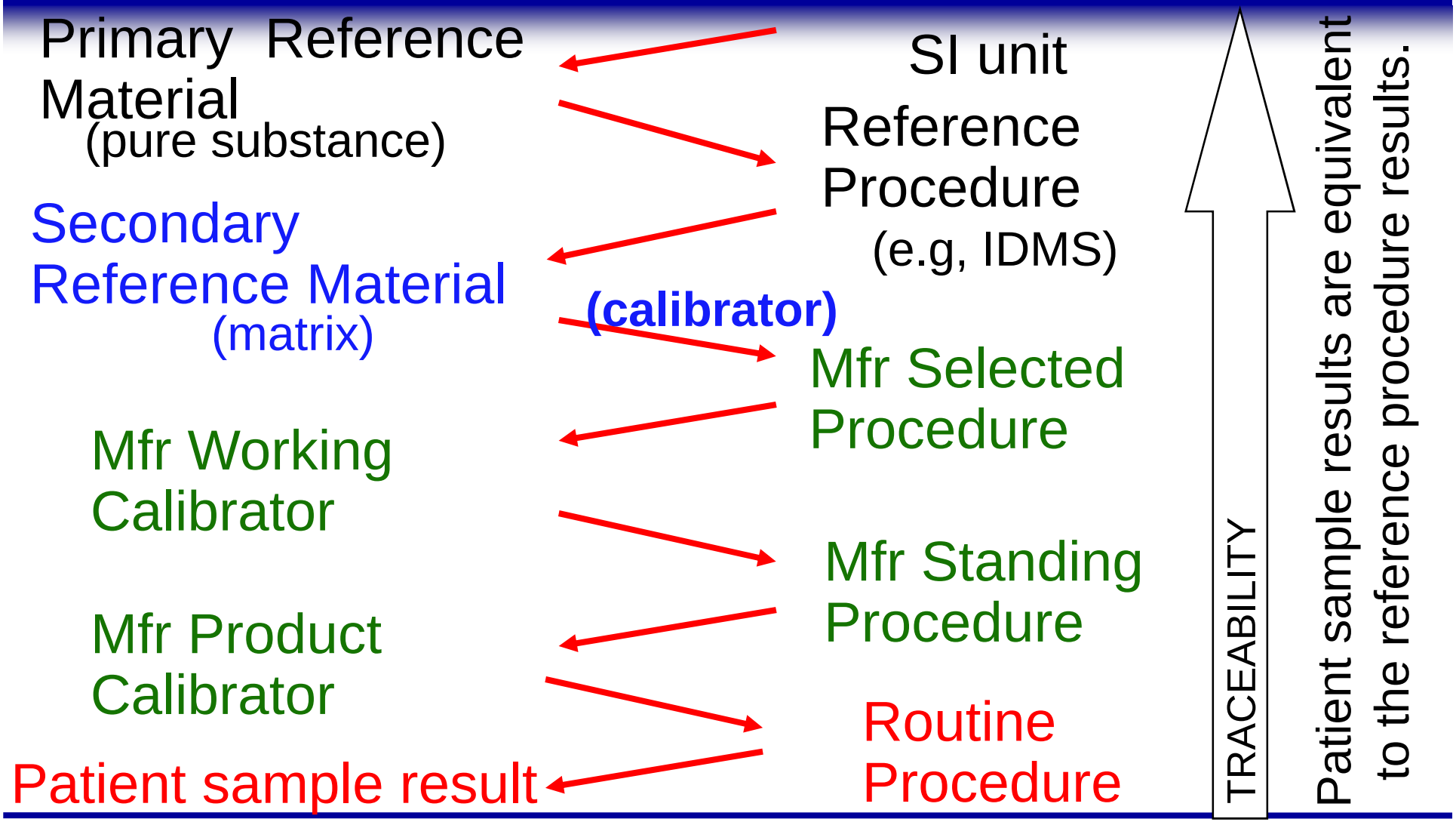
Secondary Reference Material
(matrix)

Traceability (based on ISO 17511)

A Reference System for Glucose



Traceability (based on ISO 17511)



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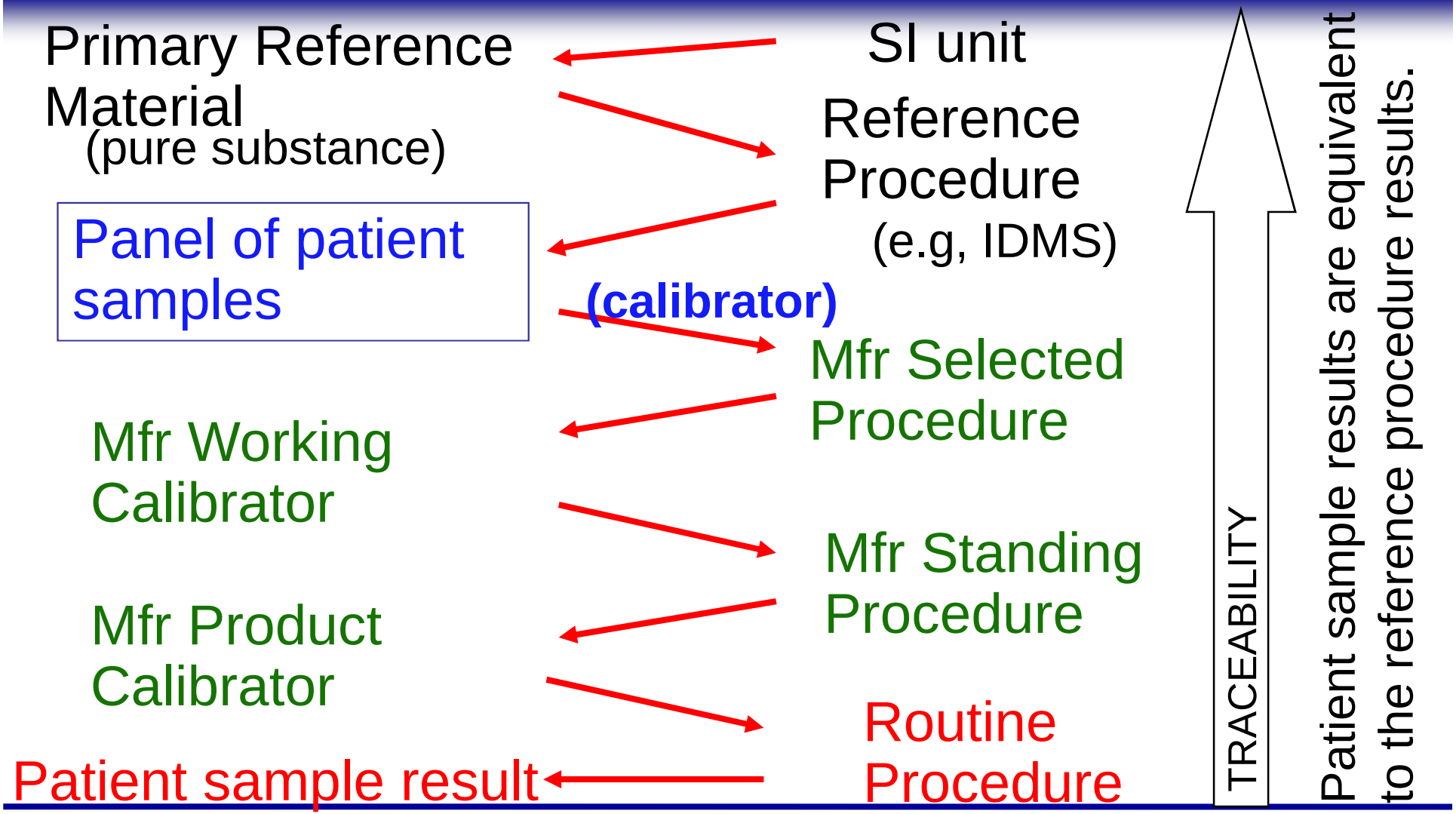
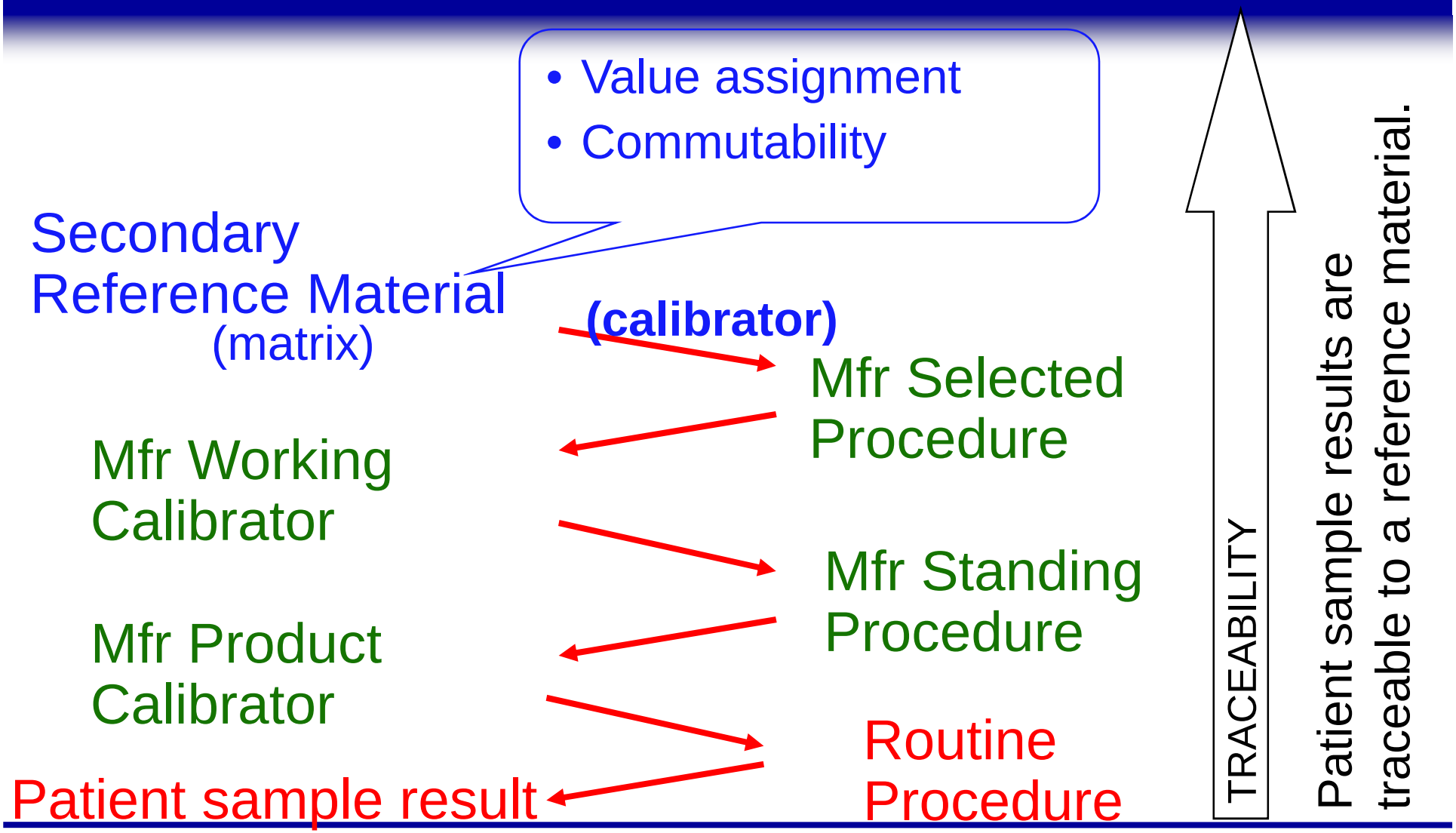


What happens when there is no reference measurement procedure?

Traceability (based on ISO 17511)



Value Assignment When There Is No Reference Measurement Procedure

International conventional calibrator (reference material)

- Arbitrary, eg, U/L
- Bioassay for hormone activity
- An arbitrary designated comparison procedure

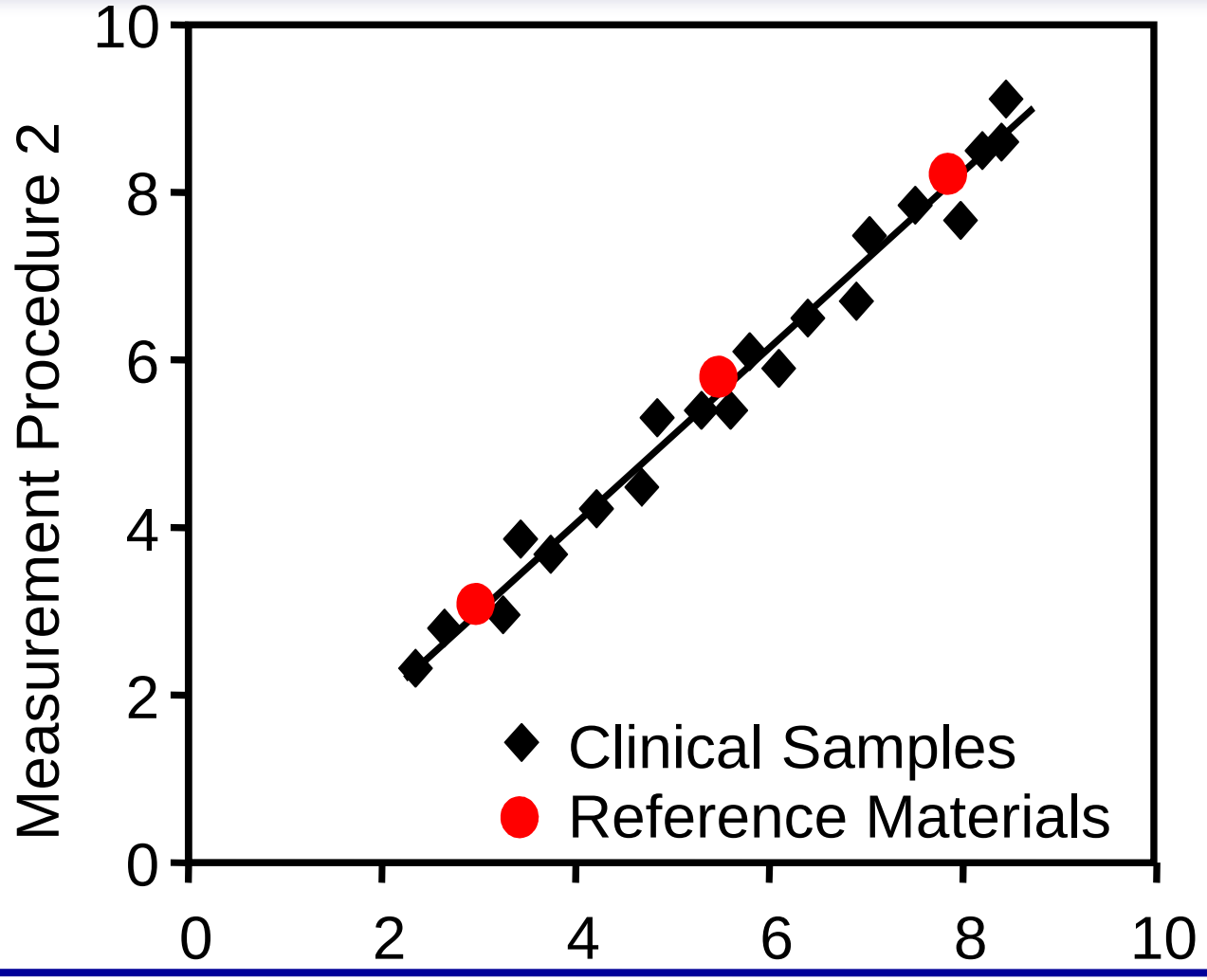
Traceable to an International Conventional Reference Material

- The true value is not known.
- Since the goal of harmonization is comparable results irrespective of the measurement procedure used:
  - Clinical guidelines can still be implemented.

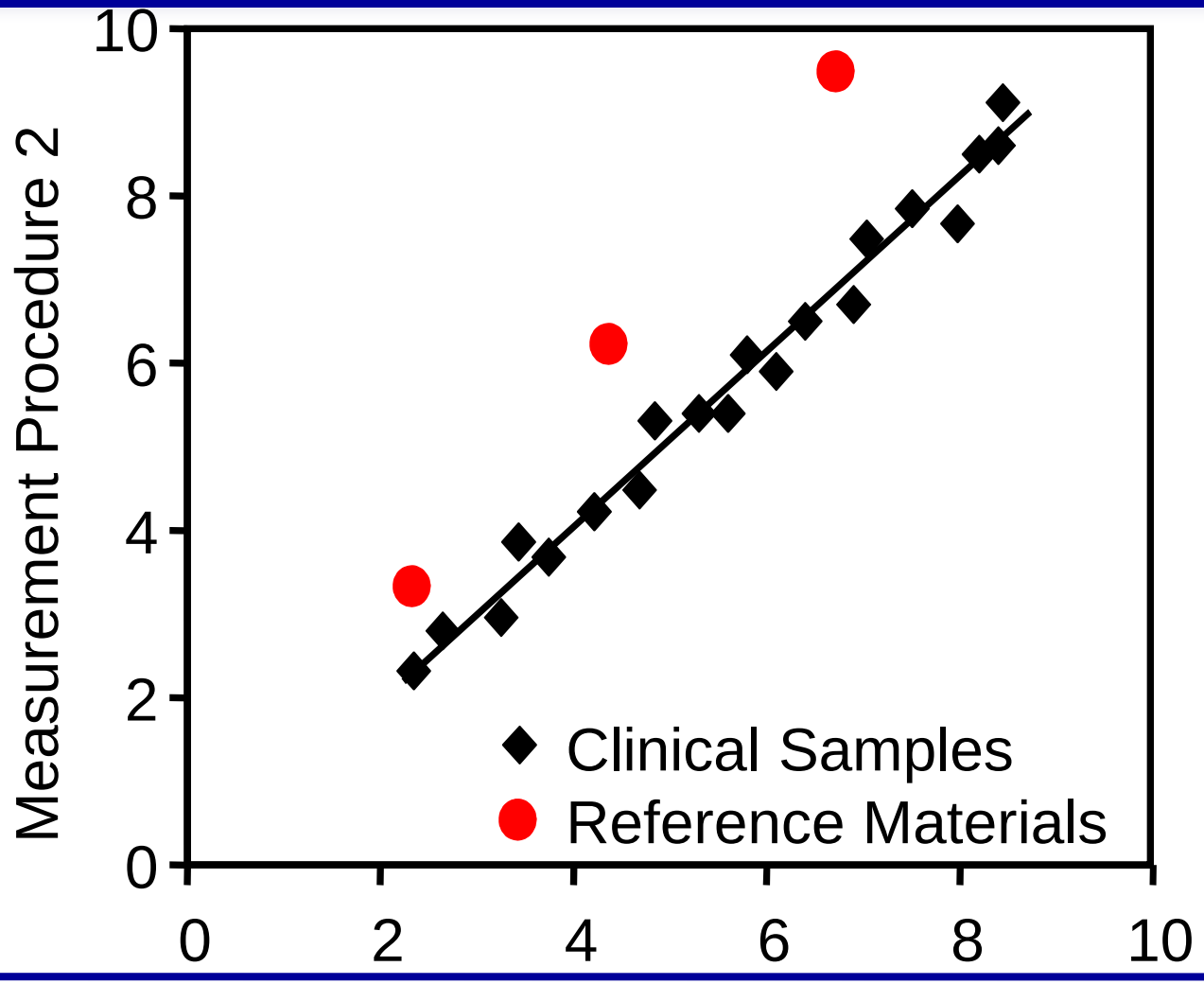
Traceability Requires Commutable Calibration Materials

Commutable means that values measured for a calibration material and for native clinical samples have the same relationship among two, or more, measurement procedures for the same measurand.

Commutable: Same Relationship for Clinical Samples and Reference Materials



Non-commutable: Different Relationship for Clinical Samples and Reference Materials



ML78 See comment on previous slide regarding text in this area.
Megan Larrisey, 2012/08/15

Use of a Non-commutable Material for Calibration Traceability Will Cause:

- Incorrect value assignment for a routine (field) measurement procedure calibrator
- Incorrect results for patient samples

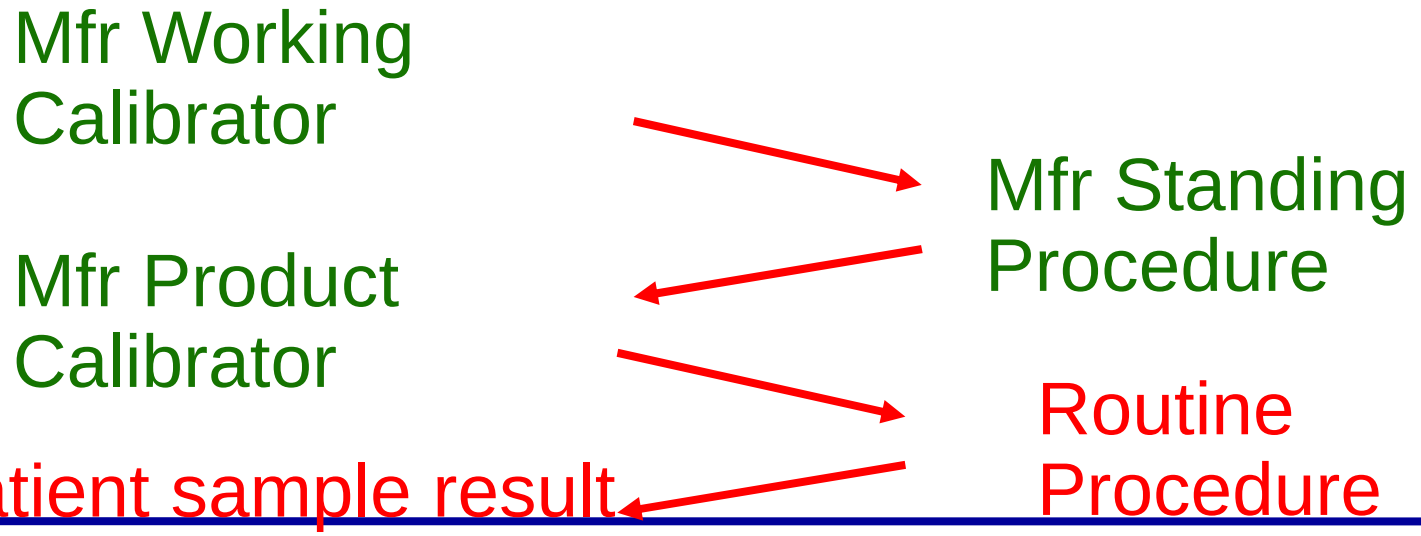
Miller, Myers, Rej. Why commutability matters. Clin Chem 2006; 52: 553-4 .

What Happens When There is Both:

- No reference measurement procedure
- No reference material

Traceability (based on ISO 17511)

- There is no coordination among manufacturers.
- Method-specific reference intervals or decision values are used.



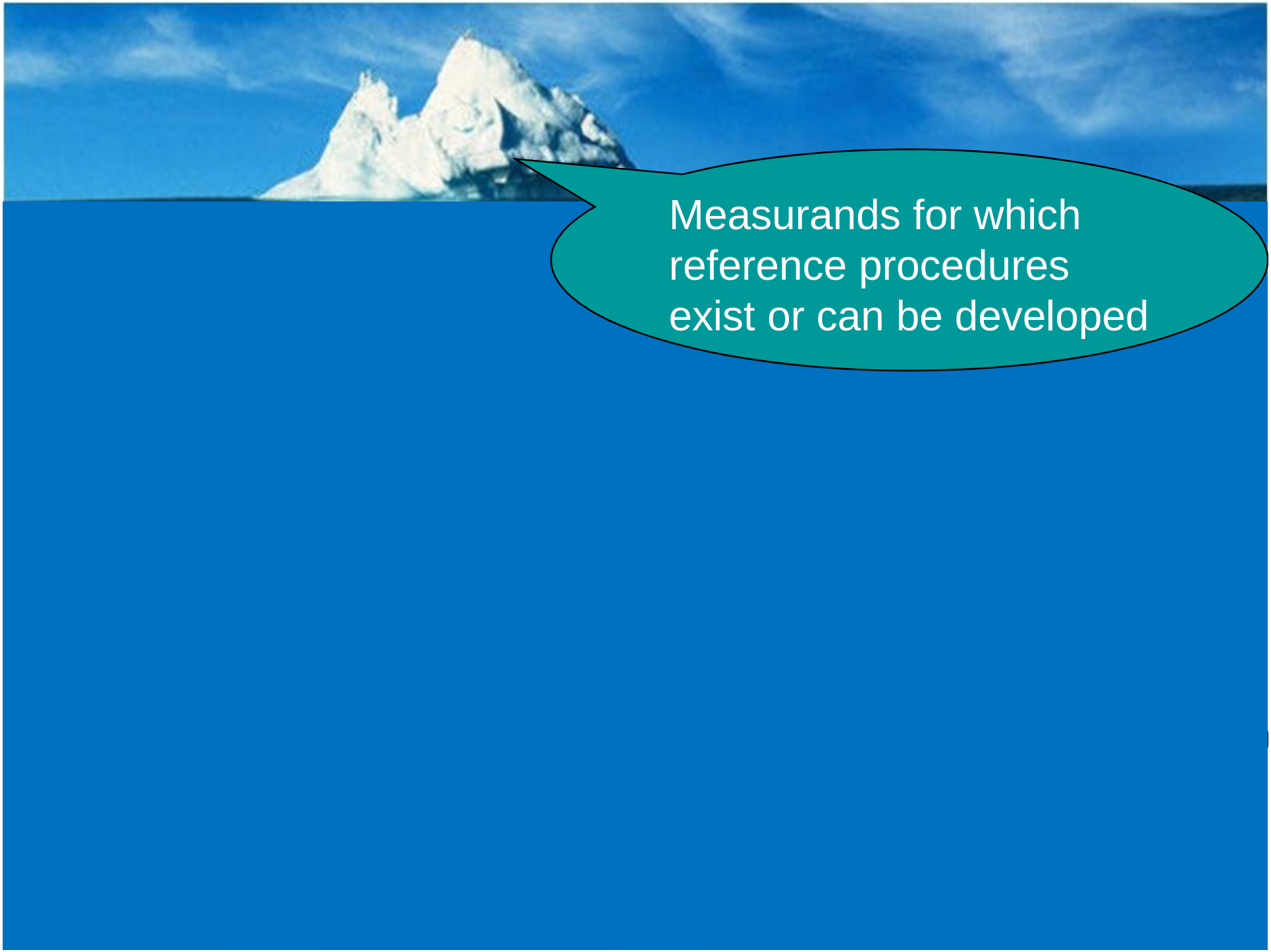
TRACEABILITY

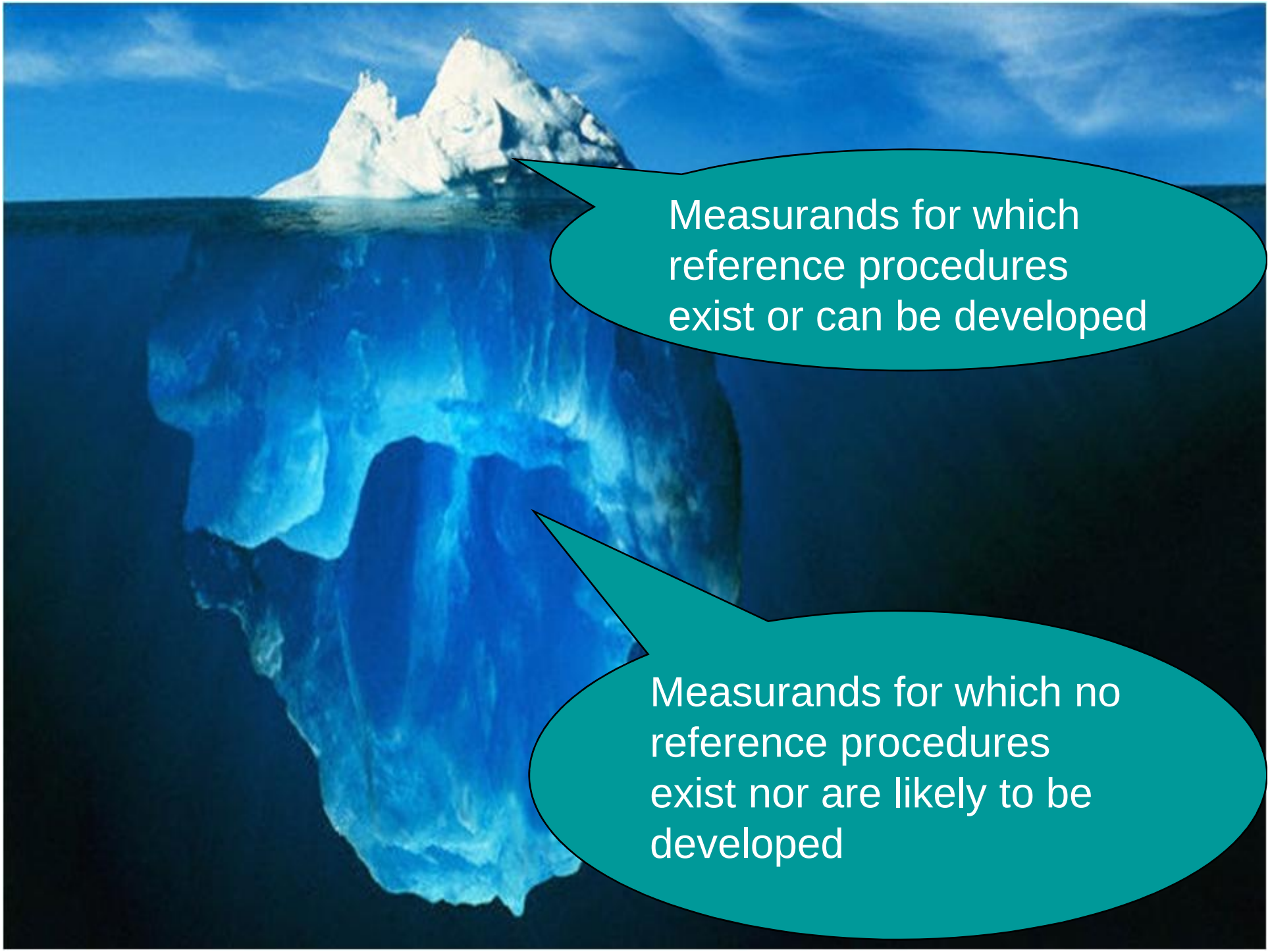
Patient sample results are not traceable to any international reference.

ISO 17511 Category 5 Needs Practical Procedures to Achieve Harmonization

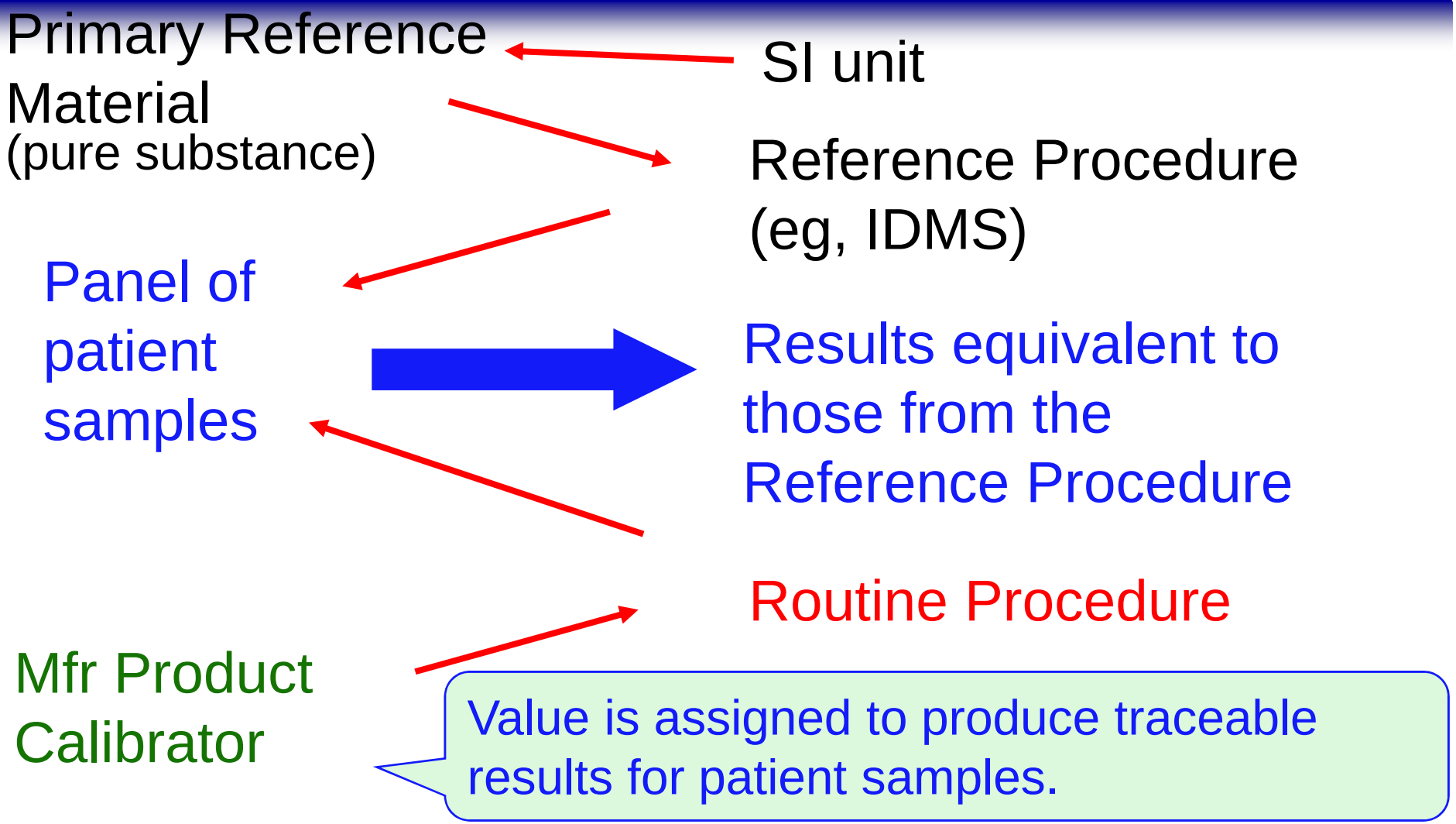
Possibilities for consideration:

- Traceable to an all methods mean (outliers removed) of a panel of patient samples
- Traceable to a designated measurement procedure (arbitrary, but which has good correlation with clinical outcome)

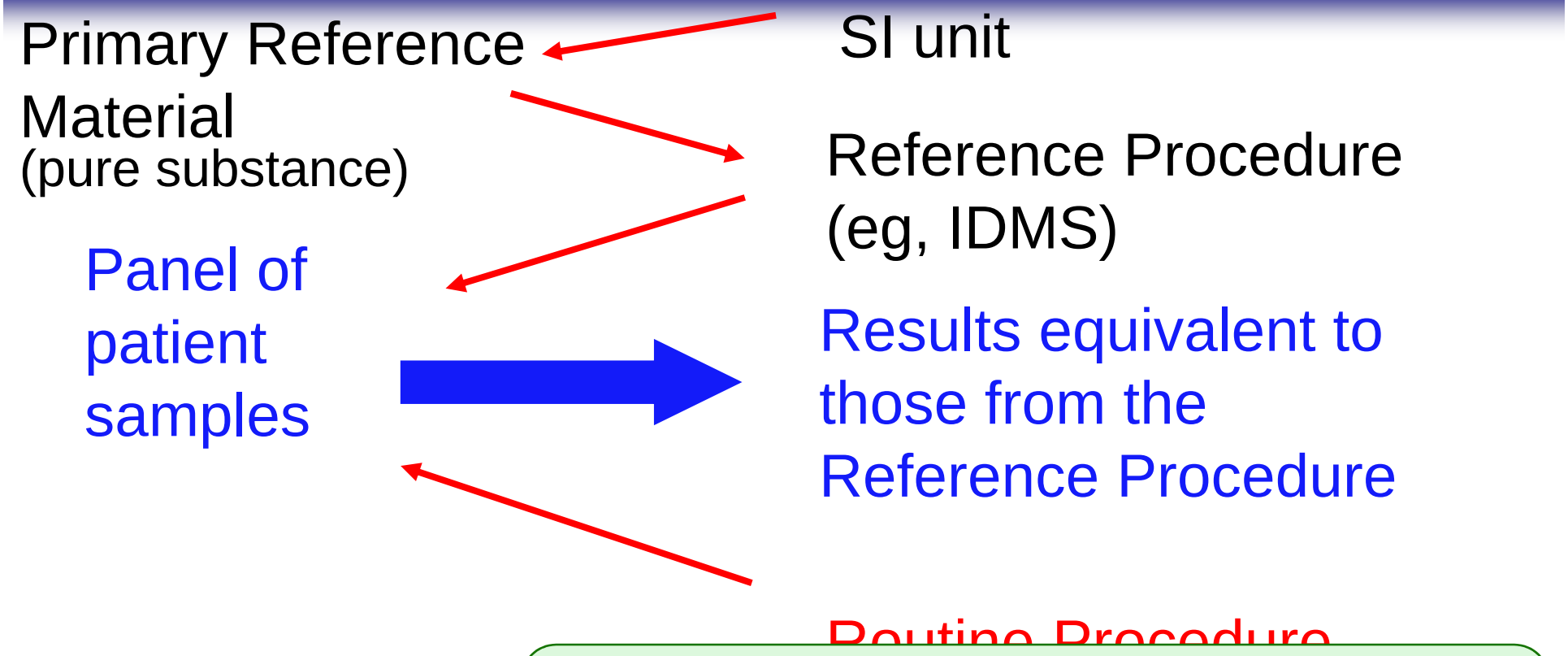

Measurands for which
reference procedures
exist or can be developed


Measurands for which reference procedures exist or can be developed
Measurands for which no reference procedures exist nor are likely to be developed

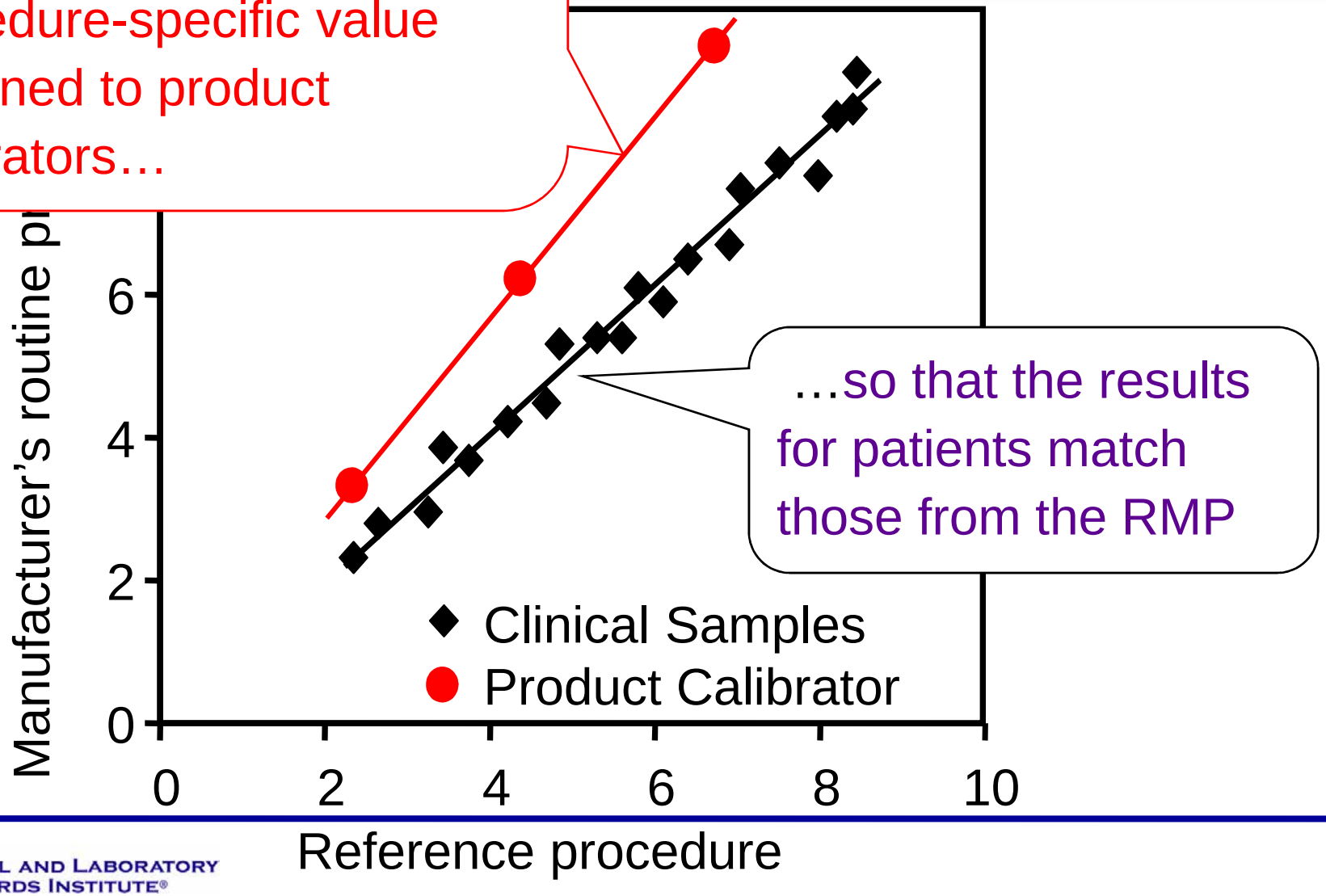
Traceability (an application)



Traceability (an application)



The known matrix-related bias can be offset in the procedure-specific value assigned to product calibrators…

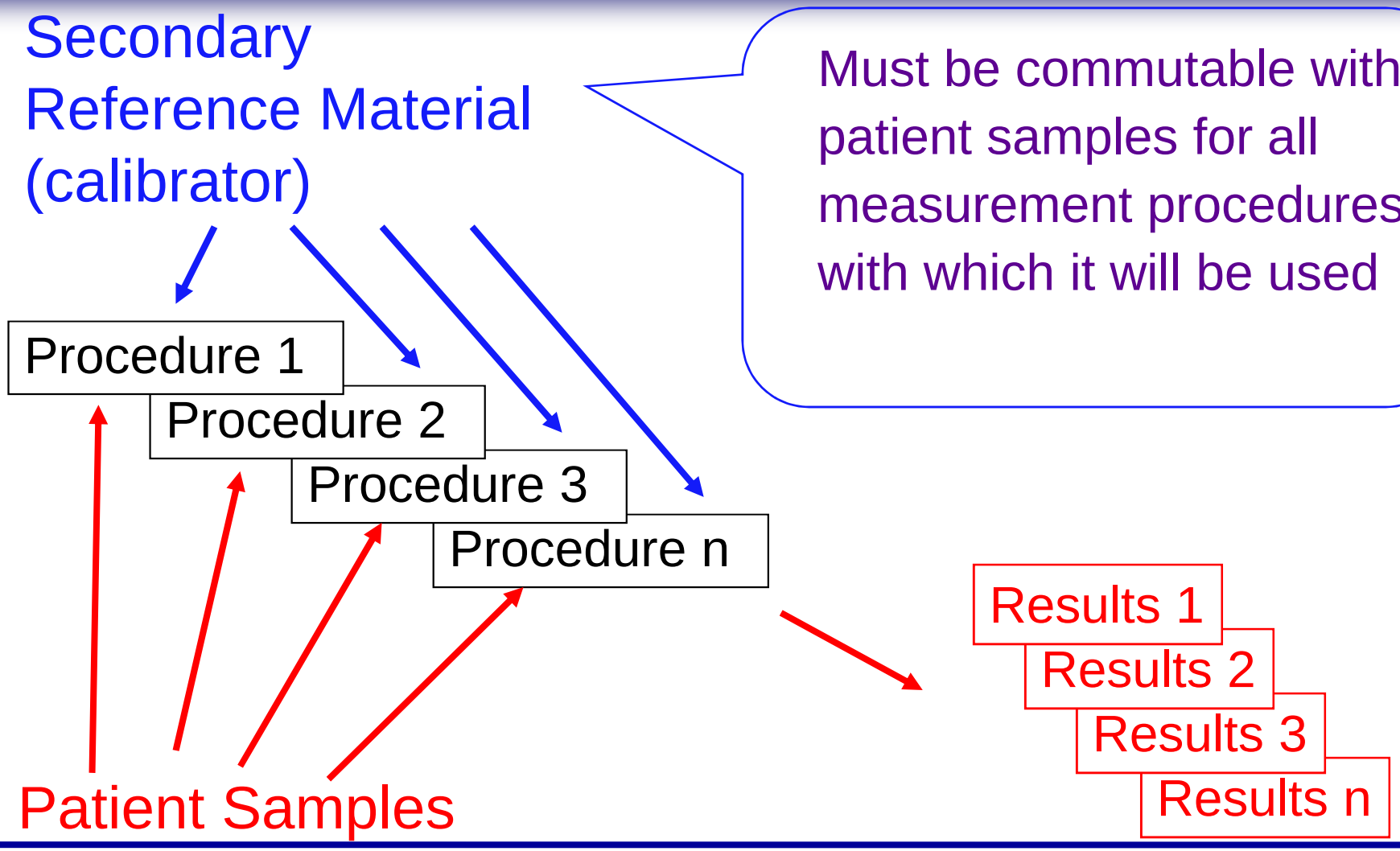


…so that the results for patients match those from the RMP

Important

- A manufacturer's product calibrator is intended for use with a specific measurement procedure.
- It cannot be used with a different manufacturer’s measurement procedure.

Traceability to a Reference Material



The Problem

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

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

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- A manufacturer's standing procedure is frequently the same as the clinical laboratory procedure but calibrated with a "master lot of calibrator" that may be traceable to a non-commutable reference material.

The Problem

Ma als are
not al
sa tory
procedures

A non-commutable calibration material breaks the traceability chain.

- A manufacturer's standing procedure equently the same as the clinical laboratory procedure but calibrated with a "master lot of calibrator" that may be traceable to a non-commutable reference material.

The Problem

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

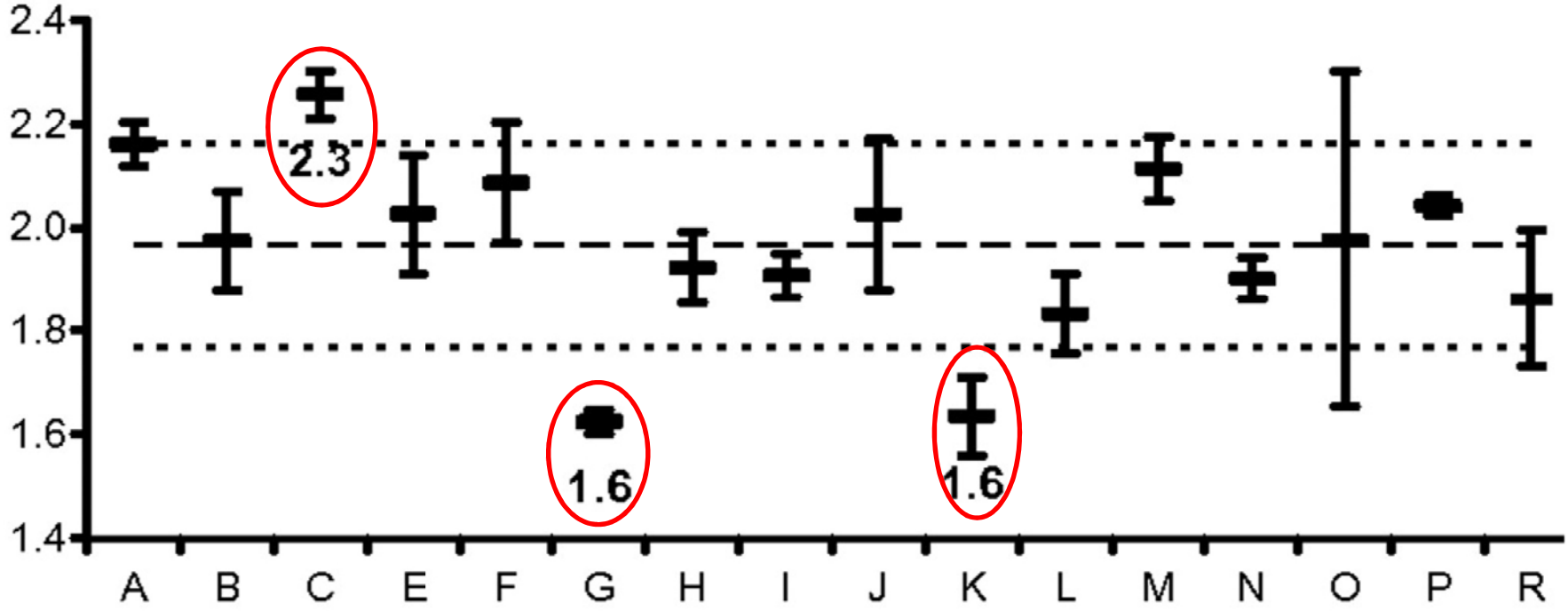
- Even though manufacturers claim traceability, the process fails to provide equivalent results for patient samples when different measurement procedures are used.

Secondary Reference Materials may not Be Commutable

- A reference material may not have been validated to be suitable for use as a calibrator for all routine measurement procedures.
- Limitation may apply to:
  - ⇨ National metrology institutes (eg: NIST, IRMM)
  - ⇨ Other providers of standards and calibrators such as: WHO, professional organizations, commercial providers

TSH Methods
All Traceable to IS 94/674 (WHO)

Mean ± 95% CI for 40 patient samples



Thienpont,et al. Clin Chem 2010; 56: 902-911.

Calibration Traceability Does Not Ensure Accuracy for an Individual Patient Sample

- Measurement procedure may not be specific for the measurand.
- Measurand may not be well defined.
  - ⇨ Molecular form(s) of clinical interest
- Interfering substances present in a patient's sample may influence the result.

Change in Practice Needed

Must change practice to require commutability validation for reference materials intended for use with:

- Manufacturer's standing procedures
- Routine clinical laboratory procedures

A guideline is available: CLSI C53-A-*Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine* (2010)

Progress Has Been Made!

A number of organizations are addressing standardization/harmonization around the world.

- ⇨ IFCC has been a key leader in developing science.
- ⇨ Many national and international groups are engaged.

However,

- The approach has been ad-hoc based on individual interests.
- There is no central organizing body to coordinate the work of different groups.
- Minimal work to address measurands with no RMP.

Joint Committee for Traceability in Laboratory Medicine

Composed of three organizations:

- International Committee of Weights and Measures
- International Federation of Clinical Chemistry and Laboratory Medicine
- International Laboratory Accreditation Cooperation

JCTLM has a credentialing function; maintains lists of reviewed and approved:

- Reference measurement procedures
- Reference laboratories
- Reference materials
  - Commutability requirements are being addressed.

Barriers to Harmonization

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

Clinical Chemistry 57:8
1108–1117 (2011)

Special Report

Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,[1*] Gary L. Myers,[2] Mary Lou Gantzer,[3] Stephen E. Kahn,[4] E. Ralf Schönbrunner,[5] Linda M. Thienpont,[6] David M. Bunk,[7] Robert H. Christenson,[8] John H. Eckfeldt,[9] Stanley F. Lo,[10] C. Micha Nübling,[11] and Catharine M. Sturgeon[12]

Report from an *AACC* conference, October 2010: Improving Clinical Laboratory Testing through Harmonization: An International Forum

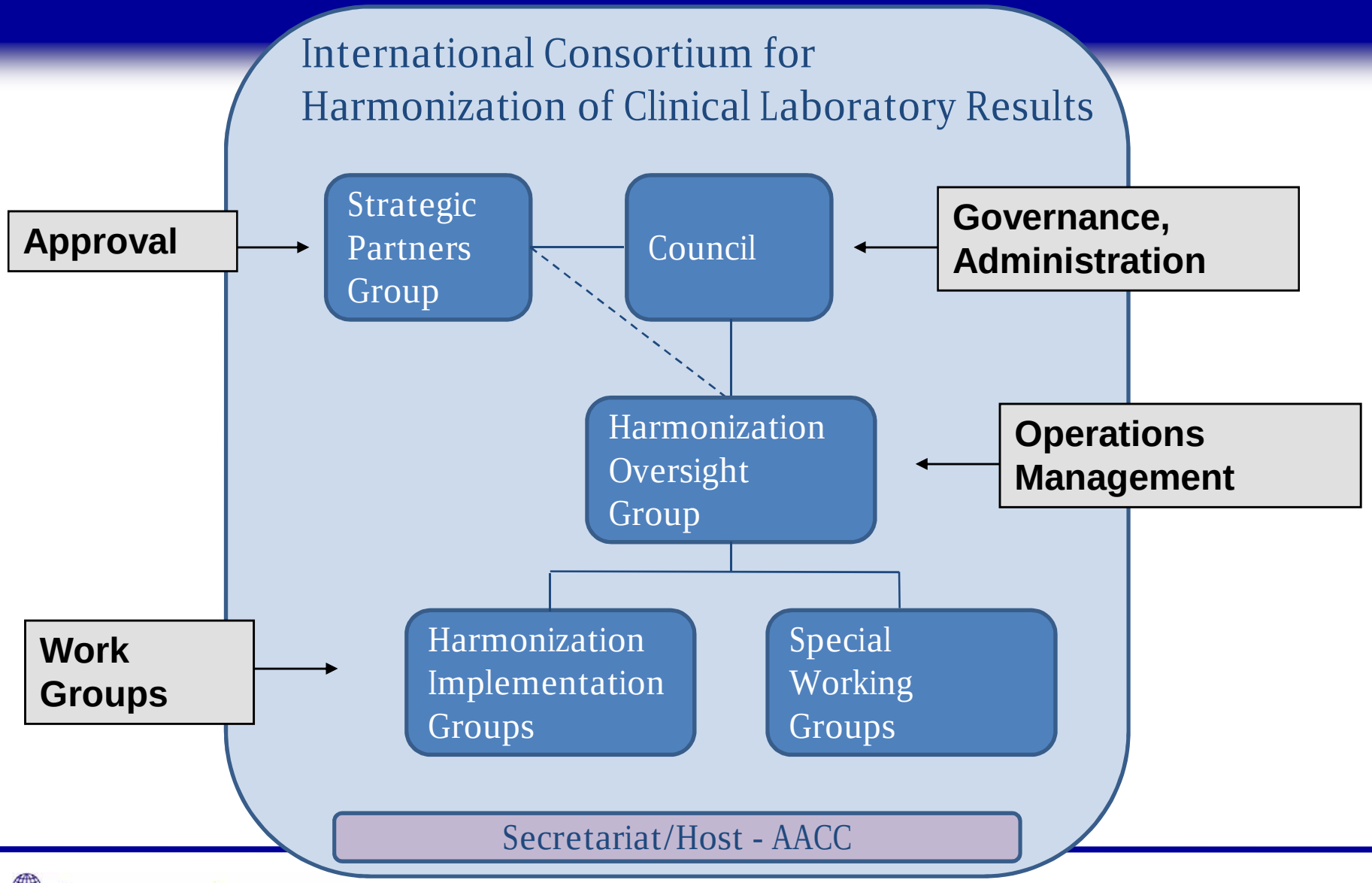
Cooperate

- Collaborate with other organizations already working to improve standardization/harmonization.
- Provide a communications portal and prioritization scheme among organizations to coordinate standardization/harmonization activities.
- Maintain an open and transparent process.

Focus Technical Work on Measurands for Which No Reference Measurement Procedure Exists

Measurands in ISO 17511 categories 4 and 5 have been technically more difficult to address, thus there have been few effective procedures implemented for harmonization in these categories.

An Infrastructure for Harmonization

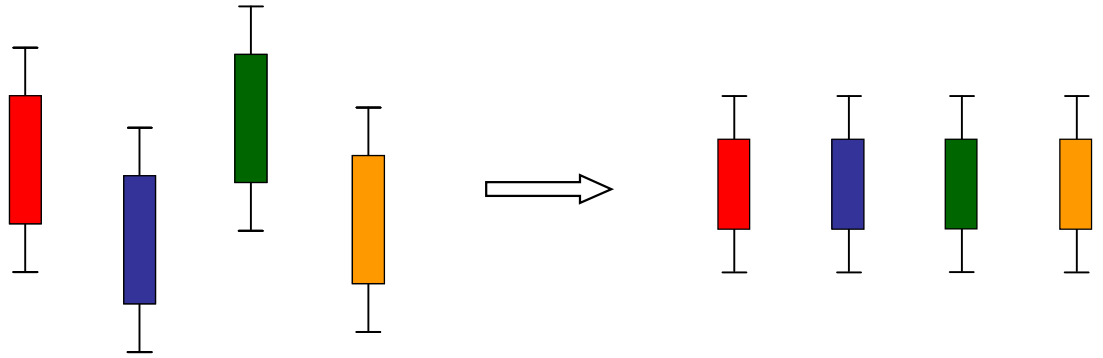


www.harmonization.net

- A general information portal for global standardization/harmonization activities
  - Communication with stakeholders
  - Status reports on measurands
  - Useful technical information
  - Information on global activities
  - Links to other organizations

Coming soon: International Consortium for Harmonization of Clinical Laboratory Results

Harmonization.net



Thank you!