

Standardization of Laboratory Tests - How to do it

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Outline

- What is standardization
- Why is it important
- How is it accomplished
- How are challenges being addressed

What is standardization

Equivalent results, within clinically meaningful limits, among different measurement procedures for the same laboratory test

Terminology

- **Standardization**: achieving equivalent results by having calibration traceable to a JCTLM listed reference system component
- **Harmonization**: achieving equivalent results among different measurement procedures
 - ❖ Usually implies there is no JCTLM listed reference measurement procedure or certified reference material

Why is it important

- **Patients will get the correct treatment**
 - ❖ **Many medical decisions are informed by laboratory results**
 - ❖ **Many clinical guidelines use a fixed laboratory test value for treatment decisions**

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

ISO Standards

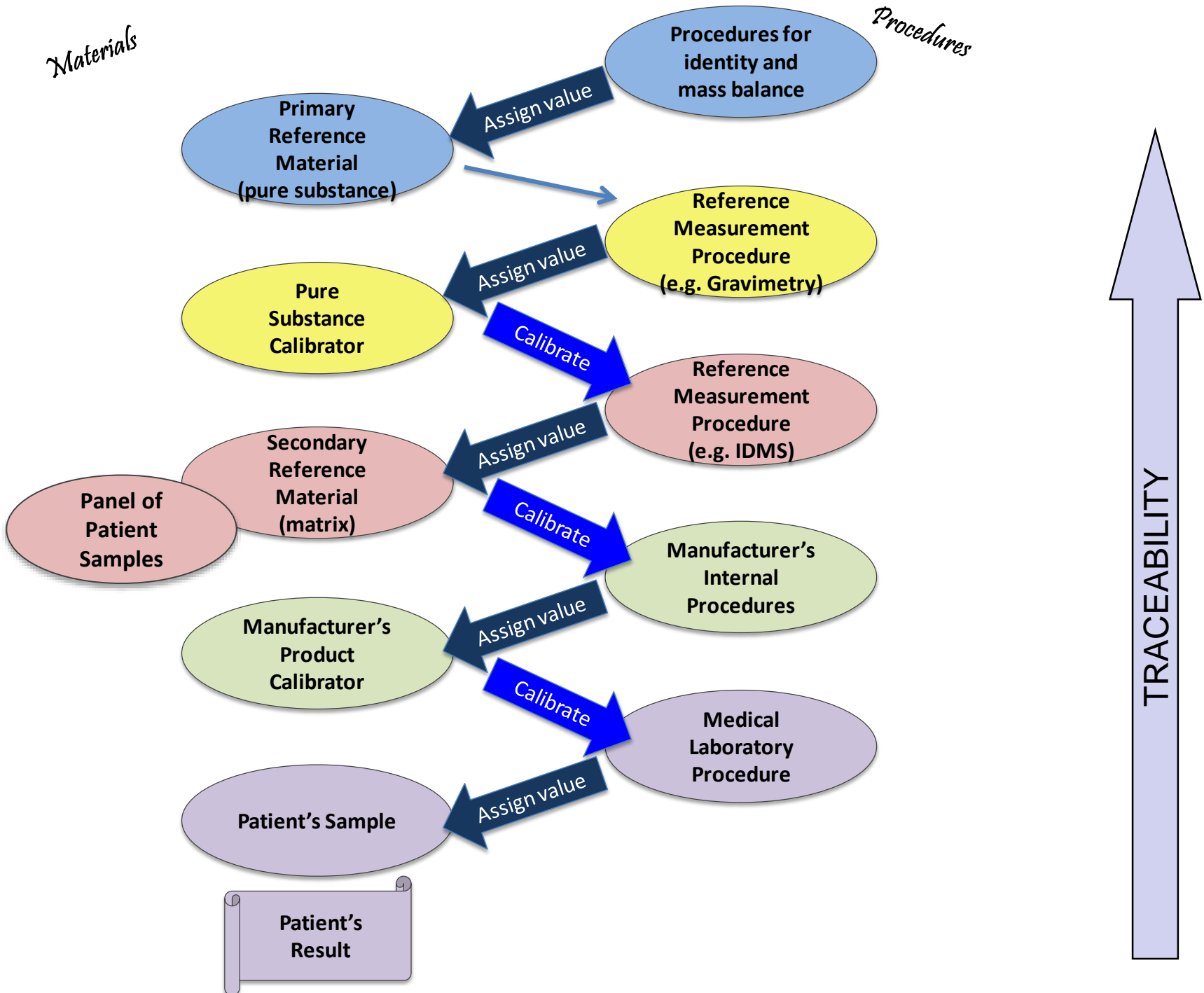
- ❖ 17511:2003, Calibration Traceability
- ❖ 18153:2003, Traceability for Enzymes
- ❖ 15193:2009, Reference Measurement Procedures
- ❖ 15194:2009, Certified Reference Materials
- ❖ 15195:2003, Reference Measurement Laboratories

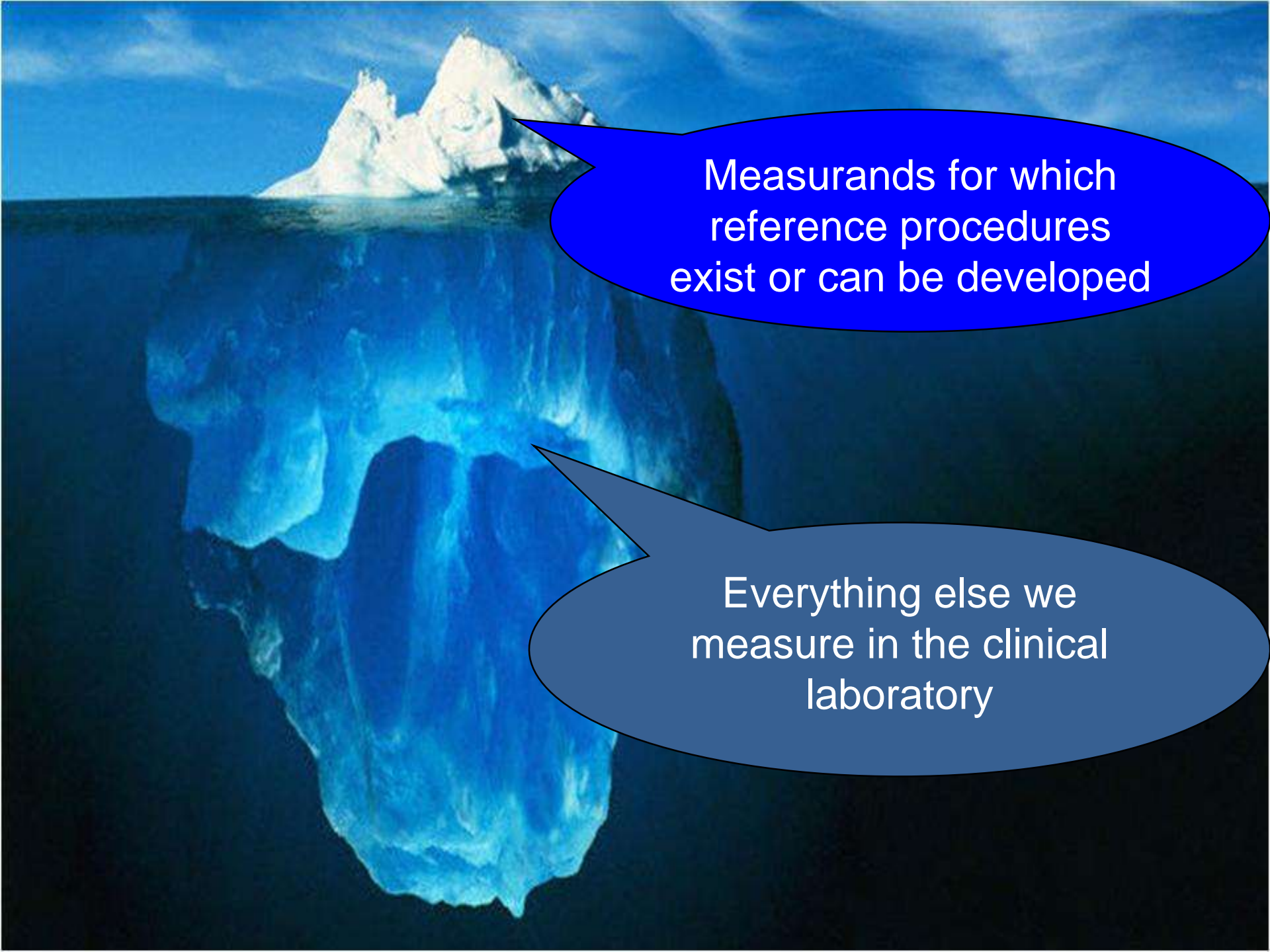
Joint Committee for Traceability in Laboratory Medicine

Lists reference materials, reference measurement procedures and reference laboratories that conform to the ISO Standards

Materials

Procedures



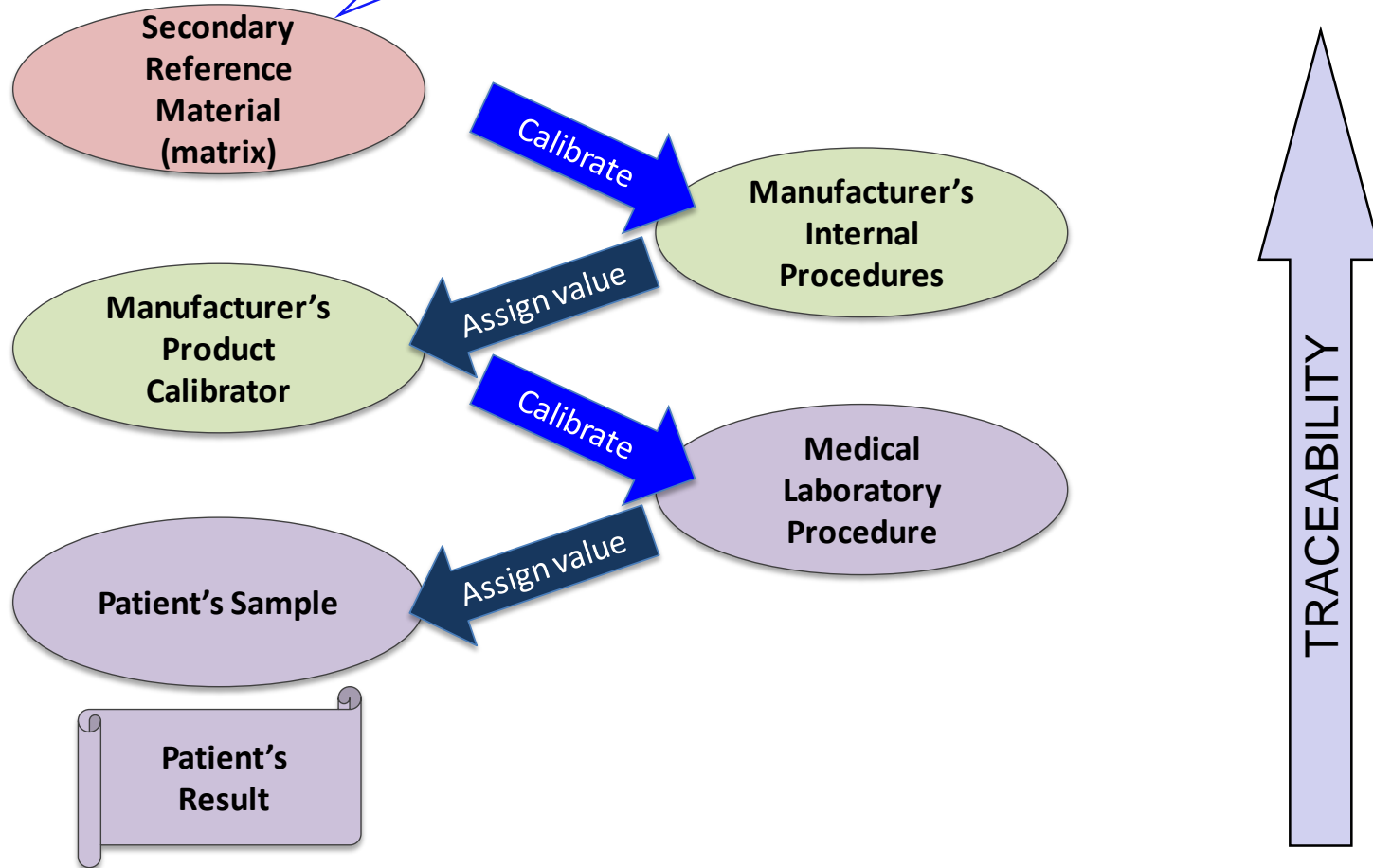
An iceberg floating in the ocean. The small tip above the water surface is white and jagged. The much larger part of the iceberg is submerged and appears as a dark blue, textured mass. Two speech bubbles are overlaid on the image. The top one is blue with white text and points to the tip of the iceberg. The bottom one is a darker blue with white text and points to the submerged part of the iceberg.

Measurands for which
reference procedures
exist or can be developed

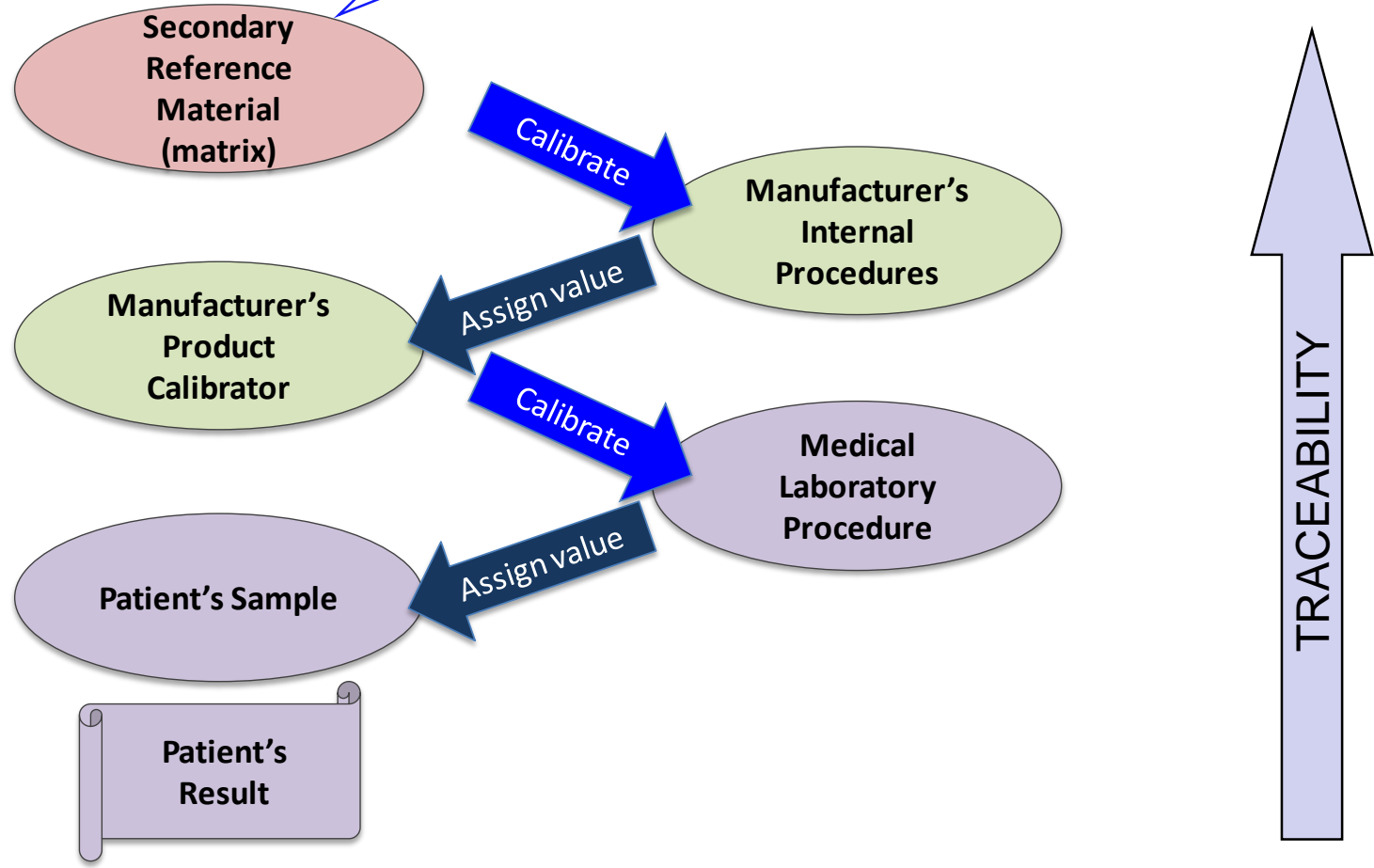
Everything else we
measure in the clinical
laboratory

What happens when there is no
reference measurement procedure

Traceability is established to a reference material



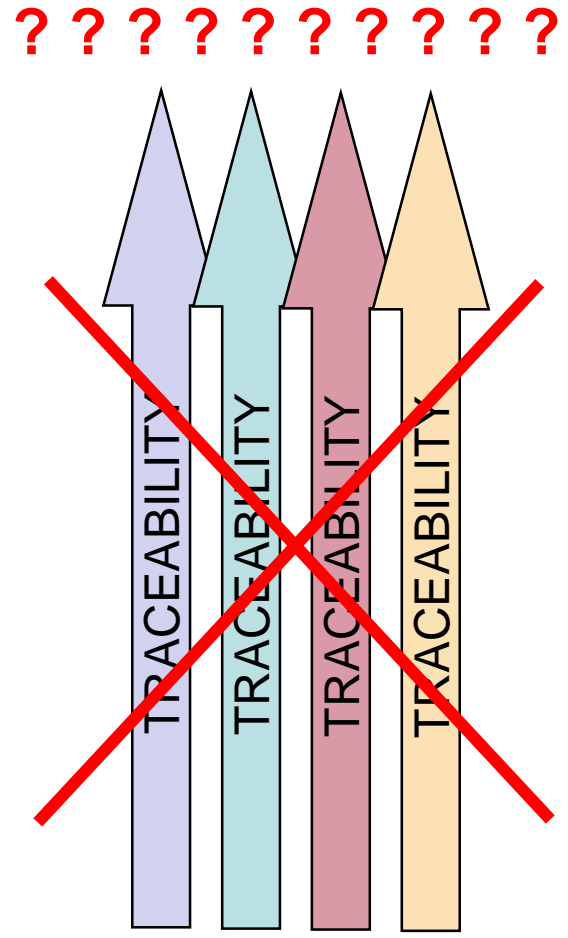
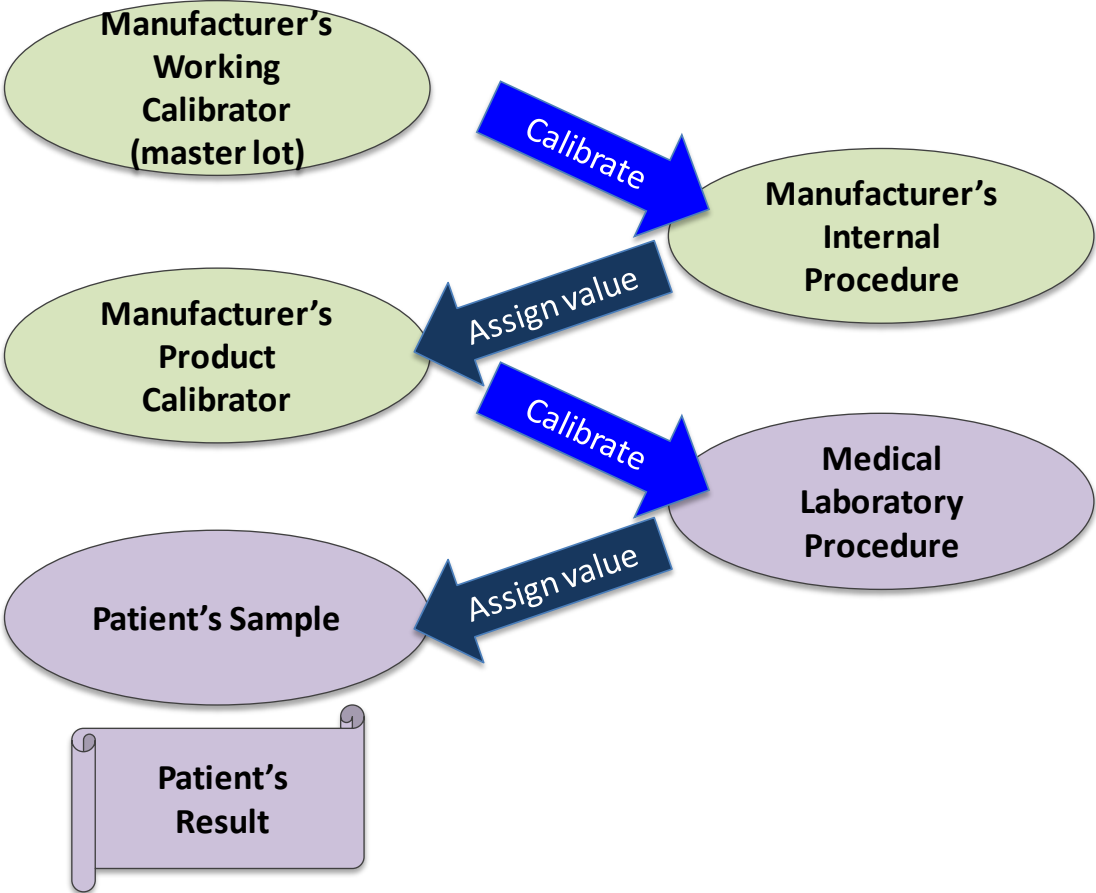
❖ Value assignment
❖ Commutability



What happens when there is both:

- no reference measurement procedure
- no reference material

Traceability is established to to a material selected for a measurement procedure
No coordination among producers (IVD or LDT)



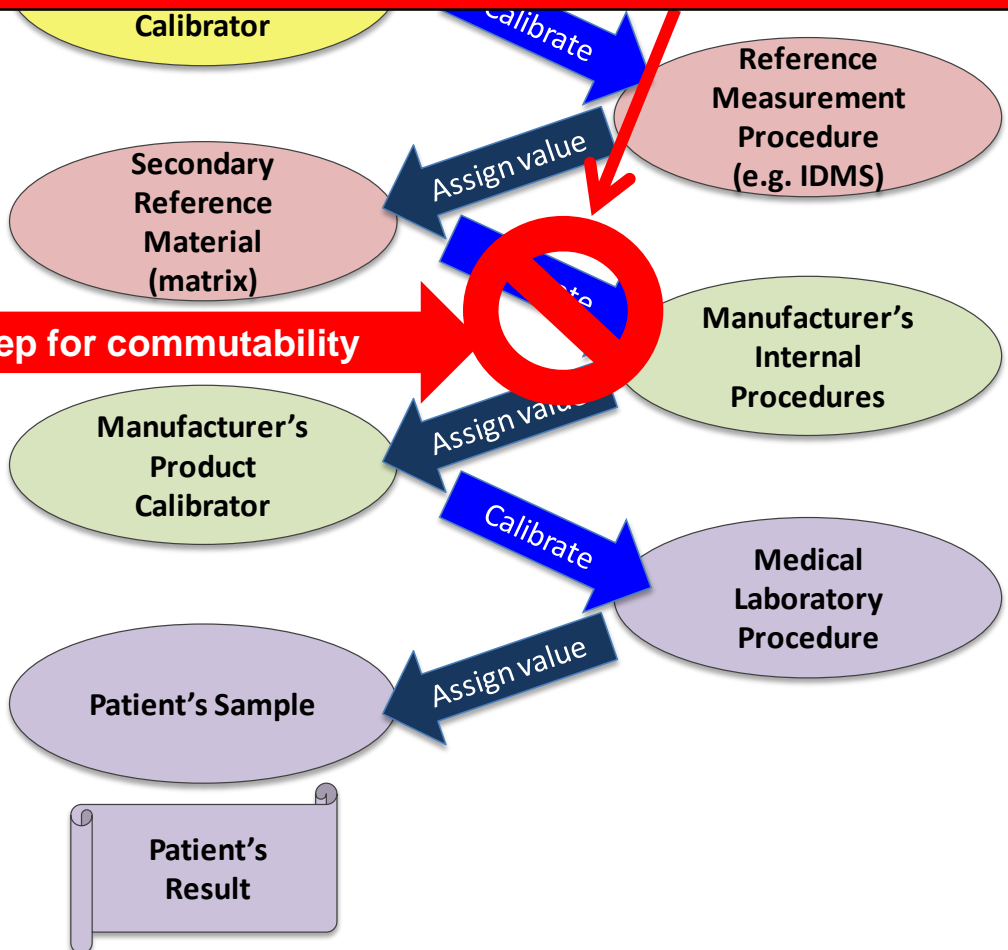
The commutability challenge

Materials

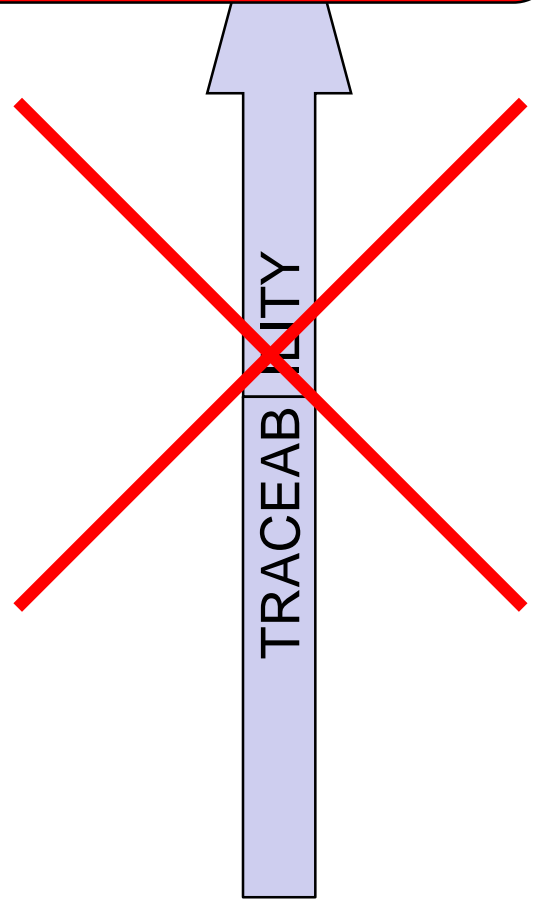
Procedures



A non-commutable calibrator breaks the traceability chain



Key step for commutability

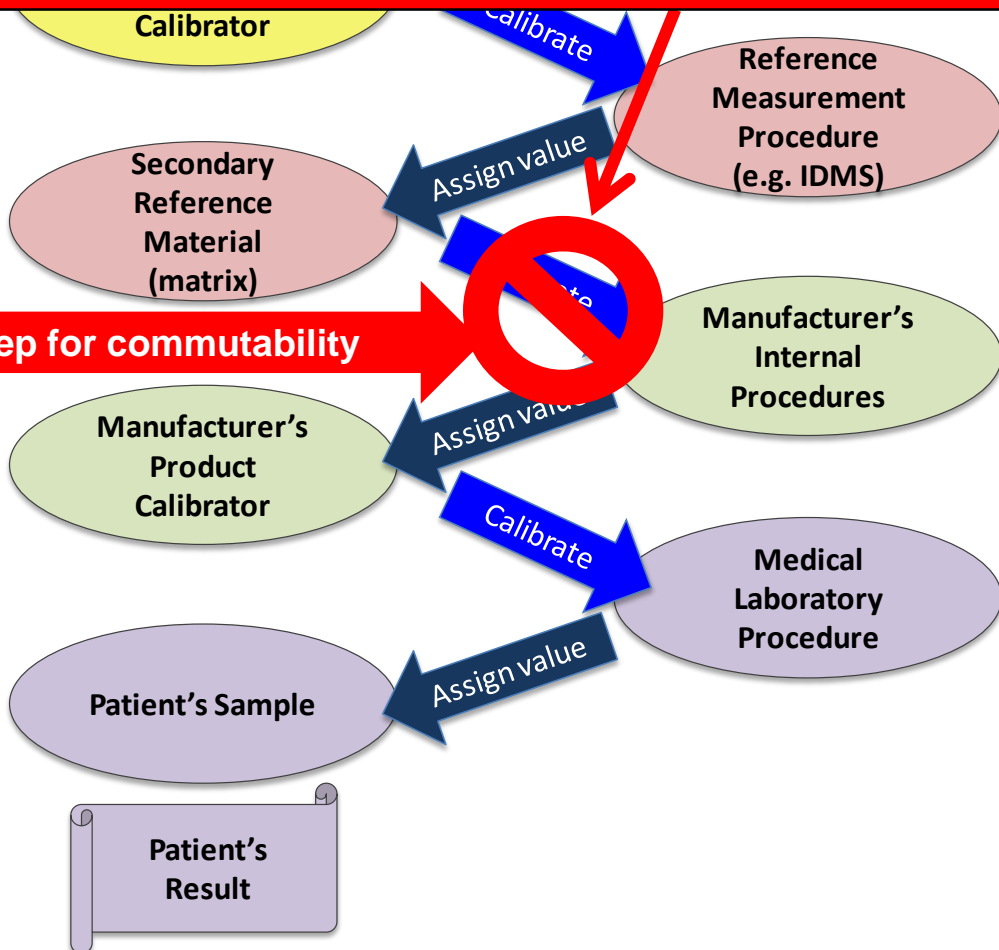


Materials

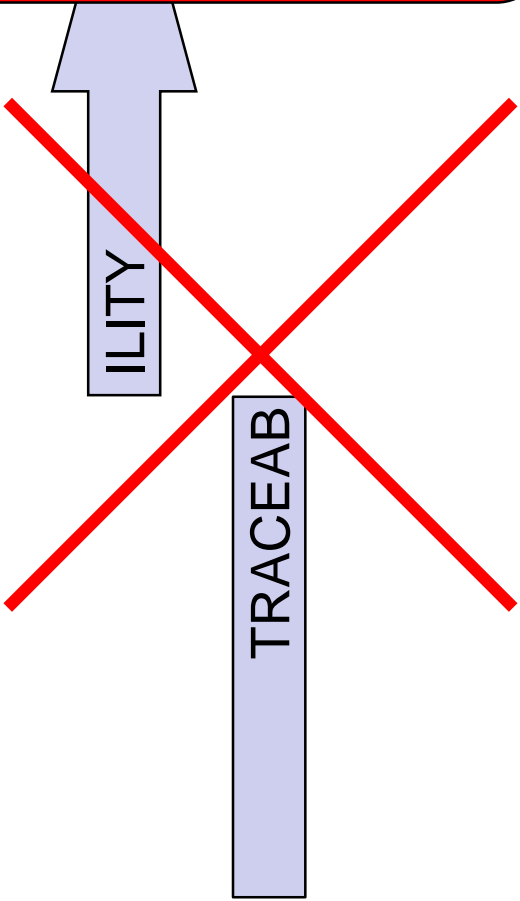
Procedures



Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures



Key step for commutability



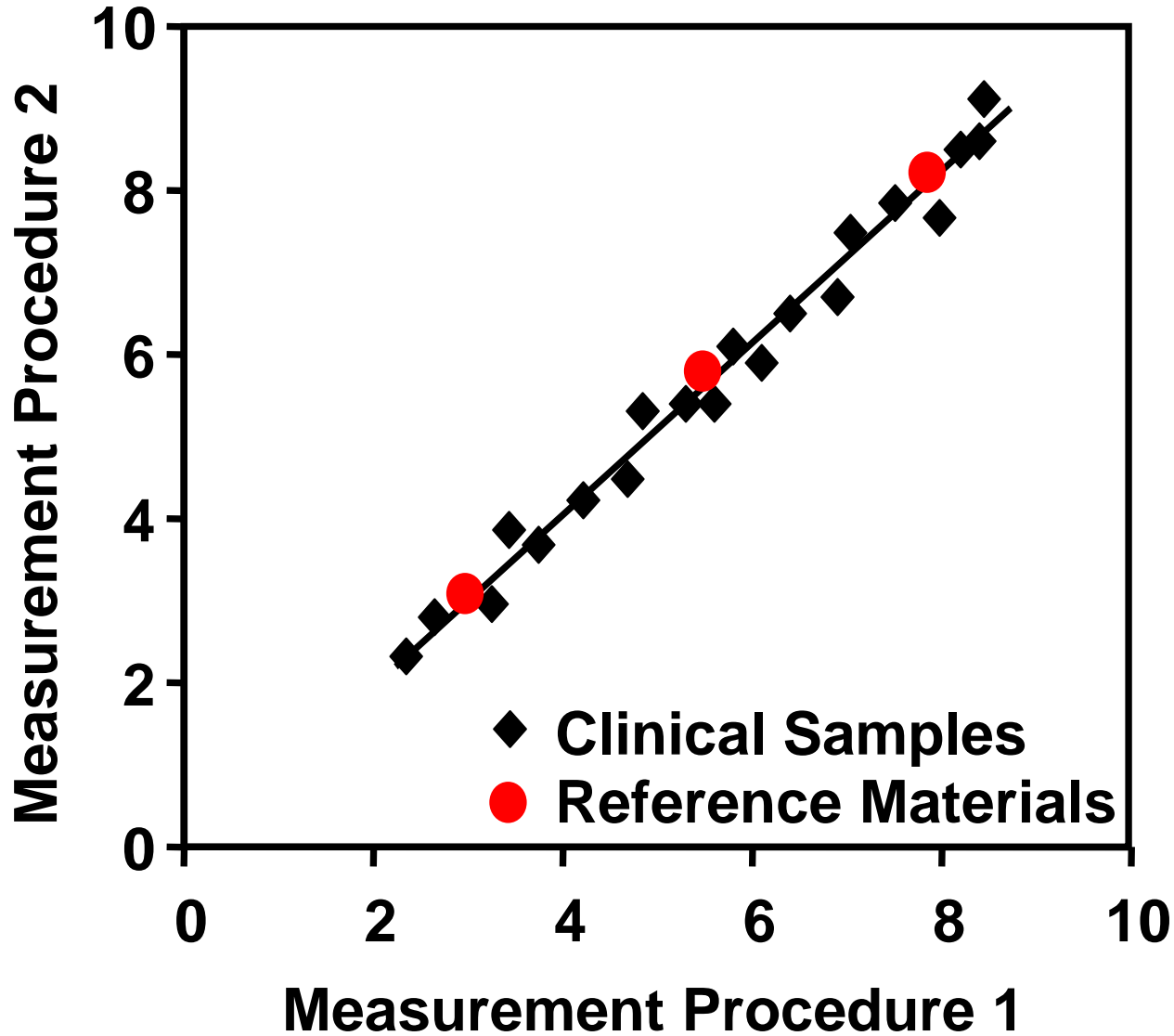
Commutability (Commutable)

Property of a reference material demonstrated by the closeness of agreement

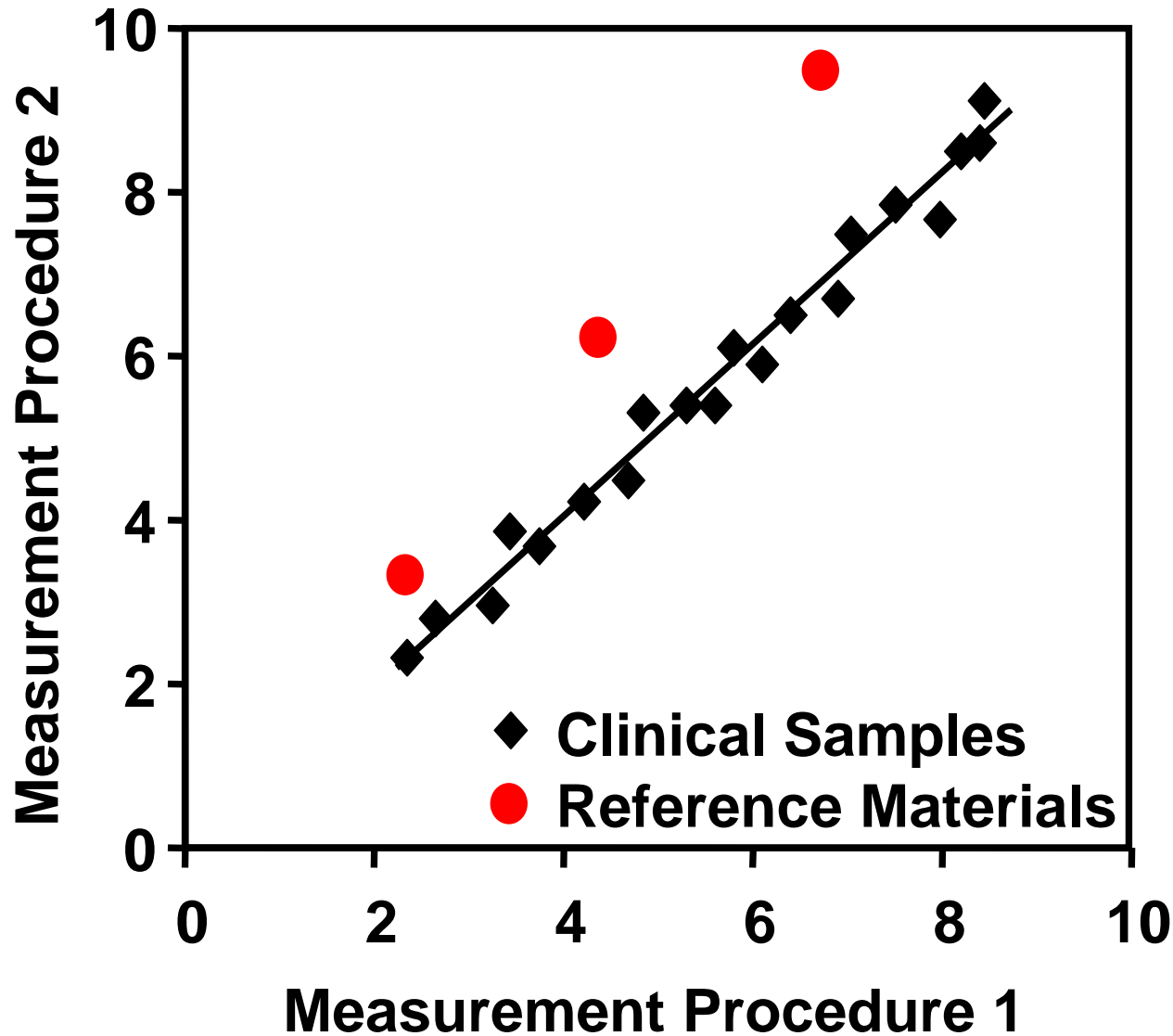
- between the relation among results for a reference material obtained from two measurement procedures
- and the relation among results for clinical samples from the same two measurement procedures

(Rephrased from VIM 3: 2008)

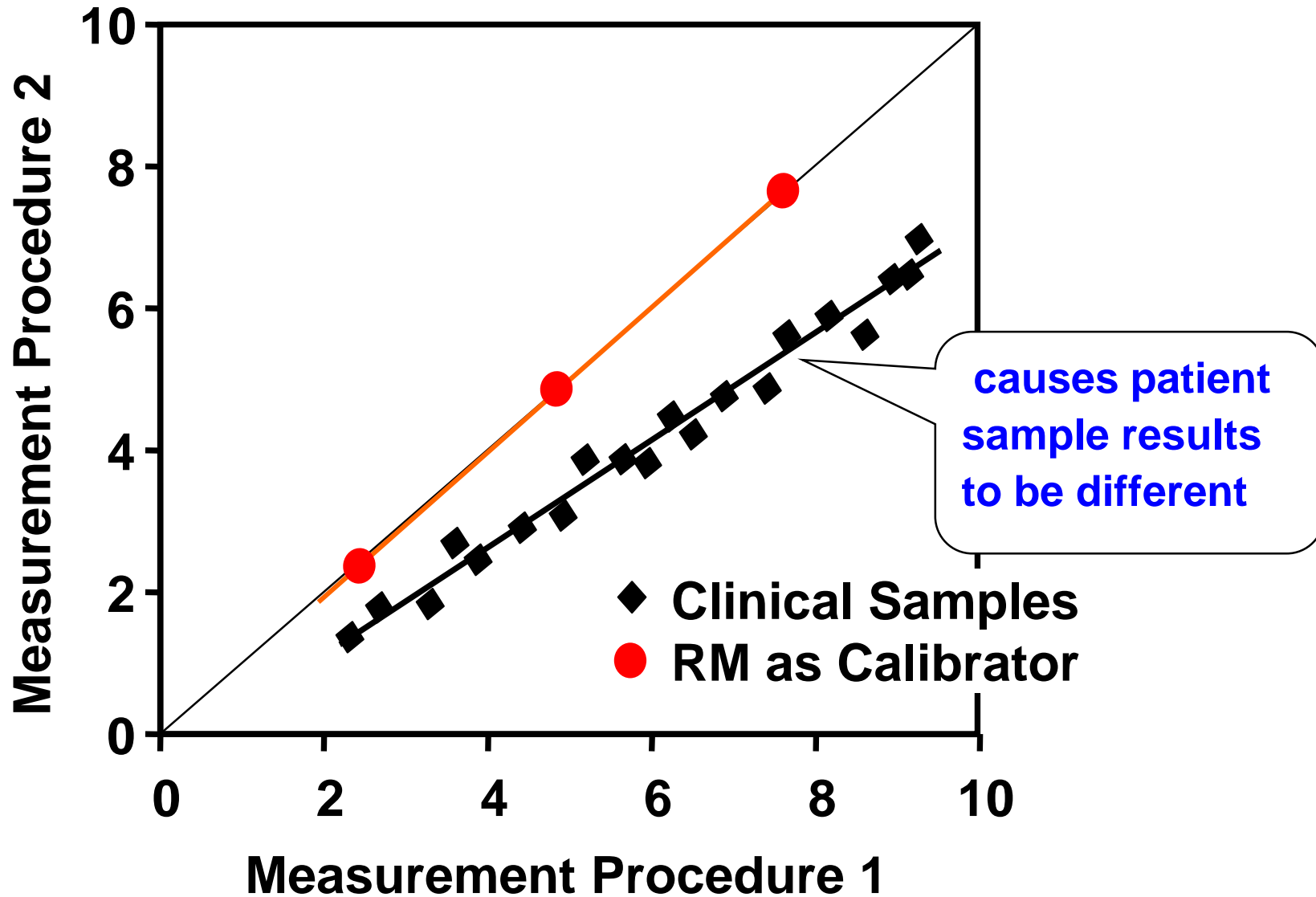
Commutable: same relationship for clinical samples and reference materials



Non-commutable: different relationship for clinical samples and reference materials

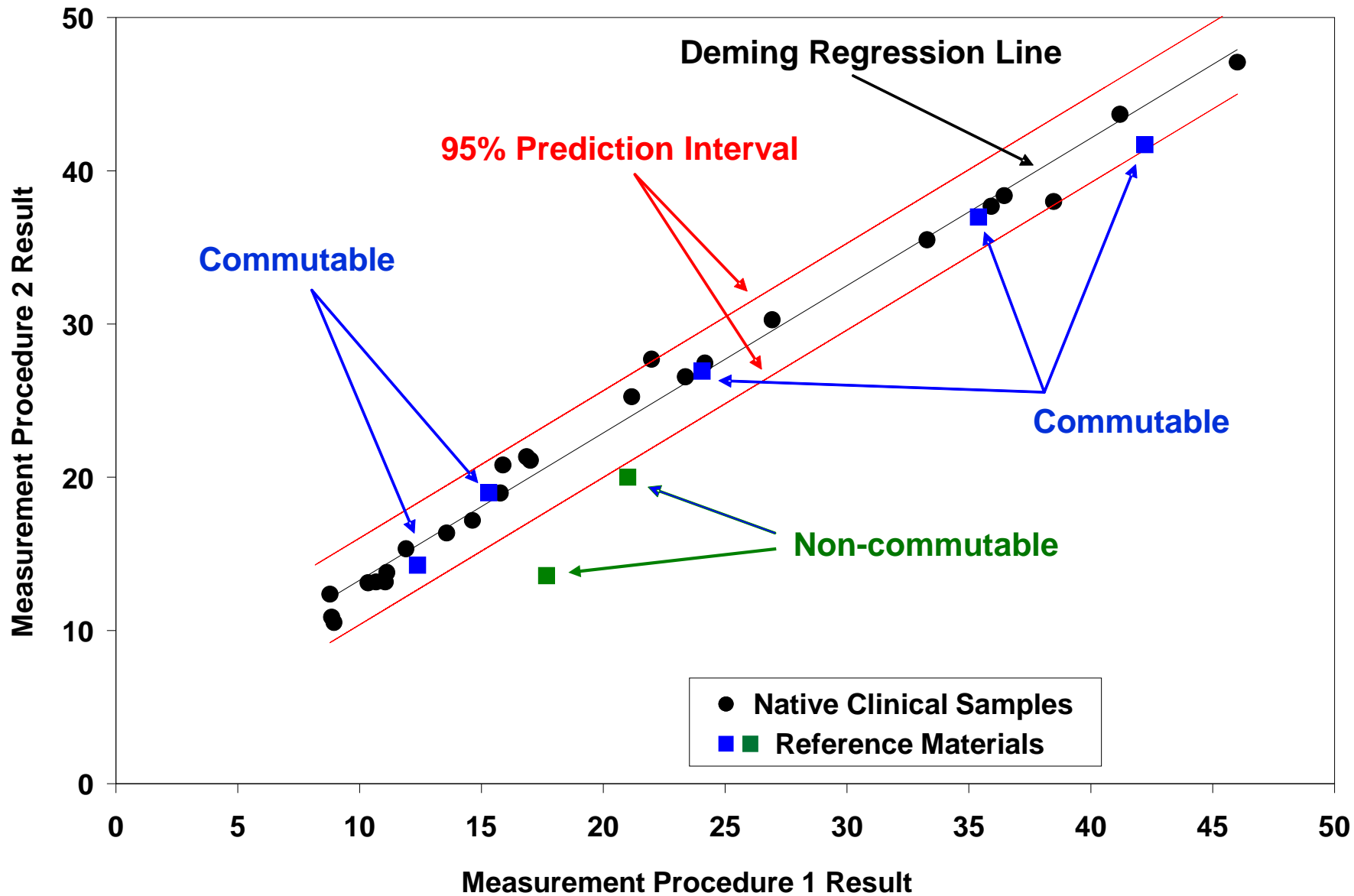


Calibration with non-commutable materials

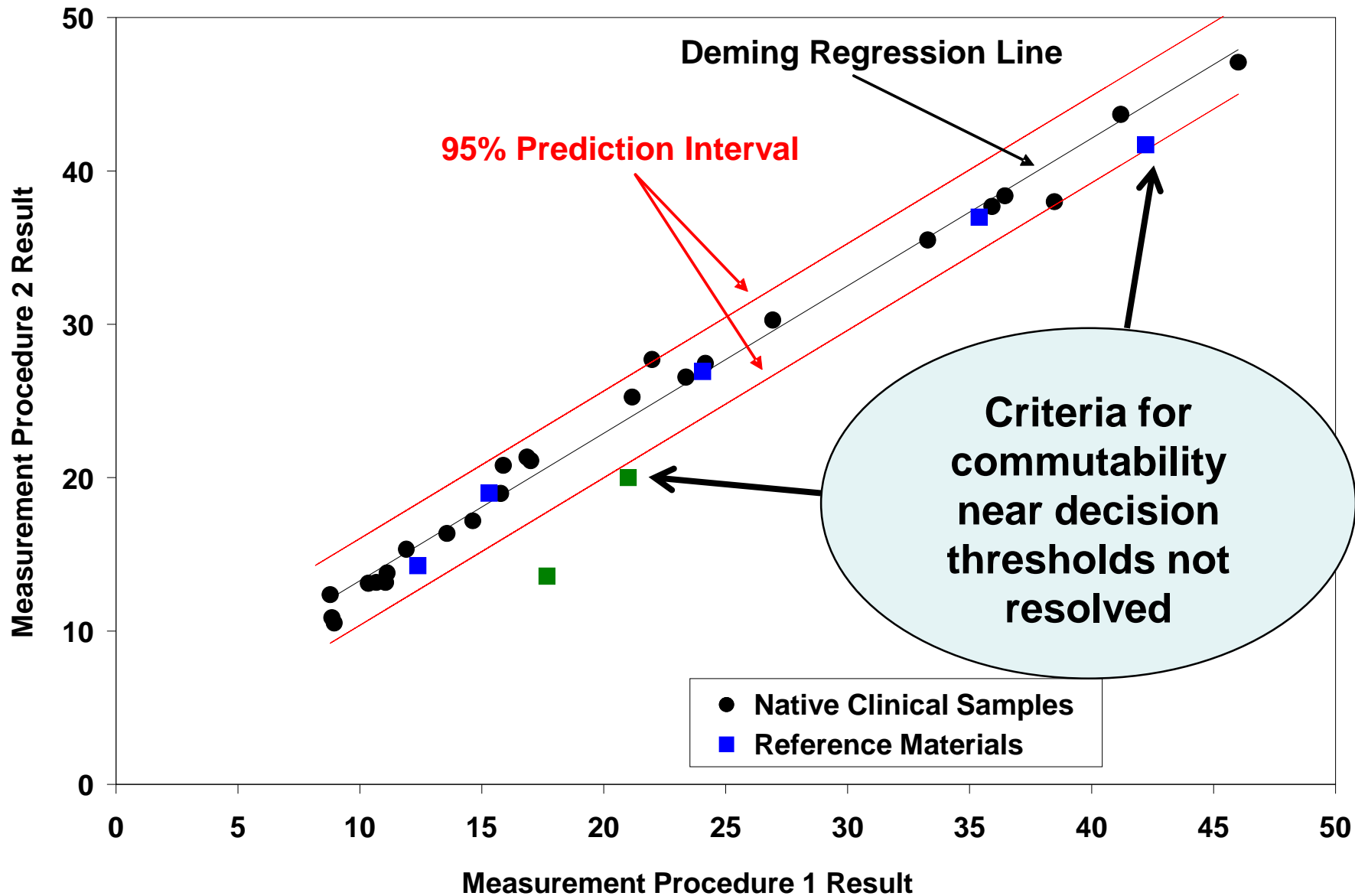


Guidelines are available from CLSI:

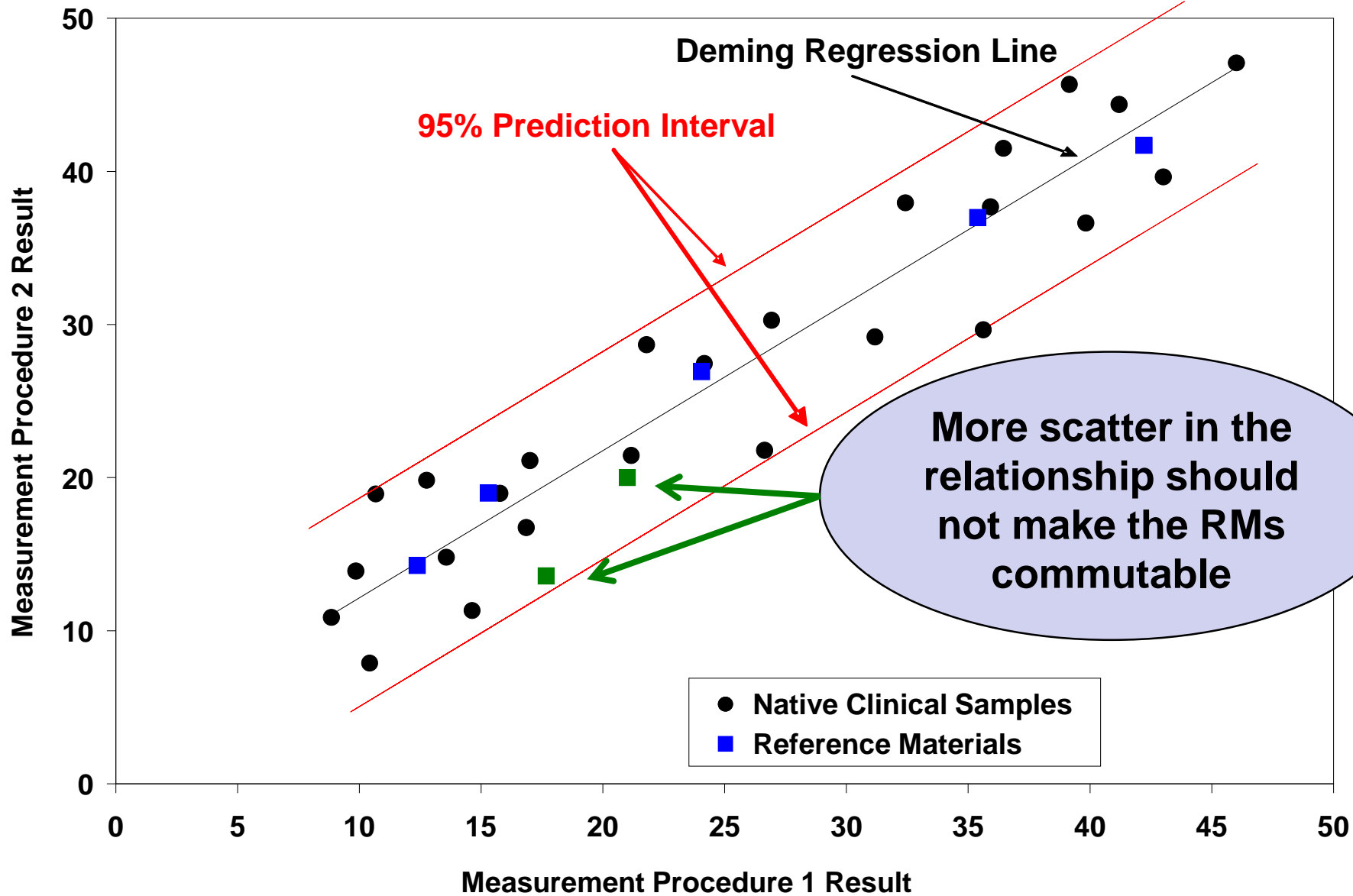
- EP30-A Characterization and qualification of commutable reference materials for laboratory medicine (2010 as C53-A)
- EP14-A3 Evaluation of commutability of processed samples (2014)



Adapted from CLSI EP30-A (used with permission)



Adapted from CLSI EP30-A (used with permission)



Modified from CLSI EP30-A (used with permission)

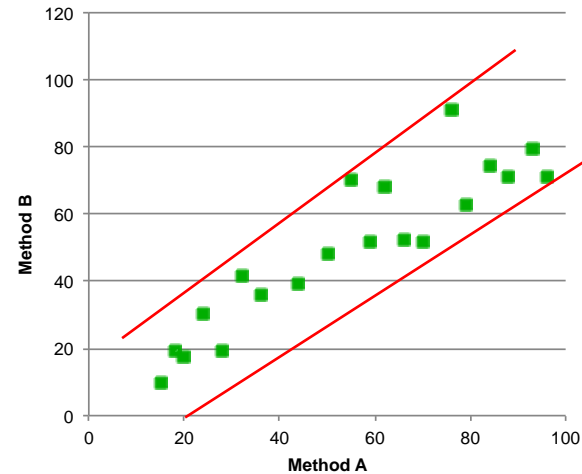
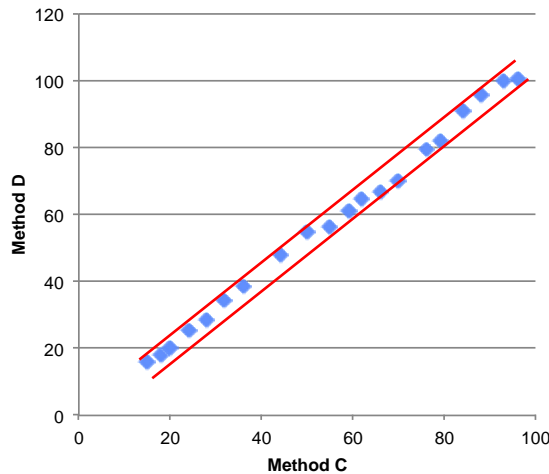
IFCC Working Group on Commutability

(established March 2013)

- Operating procedures for the formal assessment of commutability
- Criteria for commutability taking into account the intended use of a reference material

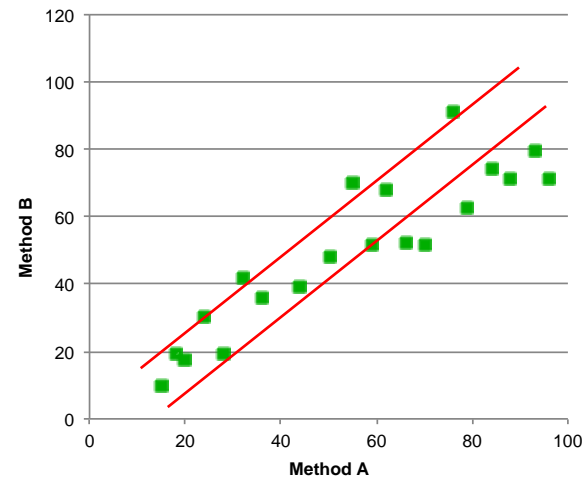
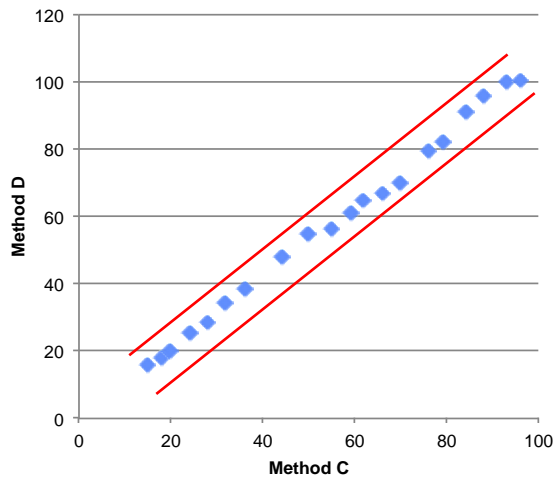
Criteria for commutability

1. Criteria based on statistical distribution of results for patient samples do not relate to the intended use of a RM
 - Criteria change among measurement procedures with different performance characteristics



Criteria for commutability

2. Recommend fixed criteria based on the intended use of the reference material



Intended use refers to the allowable total error (TE_a) for a medical decision

- ✧ Fraction of the uncertainty required for a RM's use in a calibration traceability hierarchy
- ✧ Fraction of the uncertainty required for assessment of performance using EQA

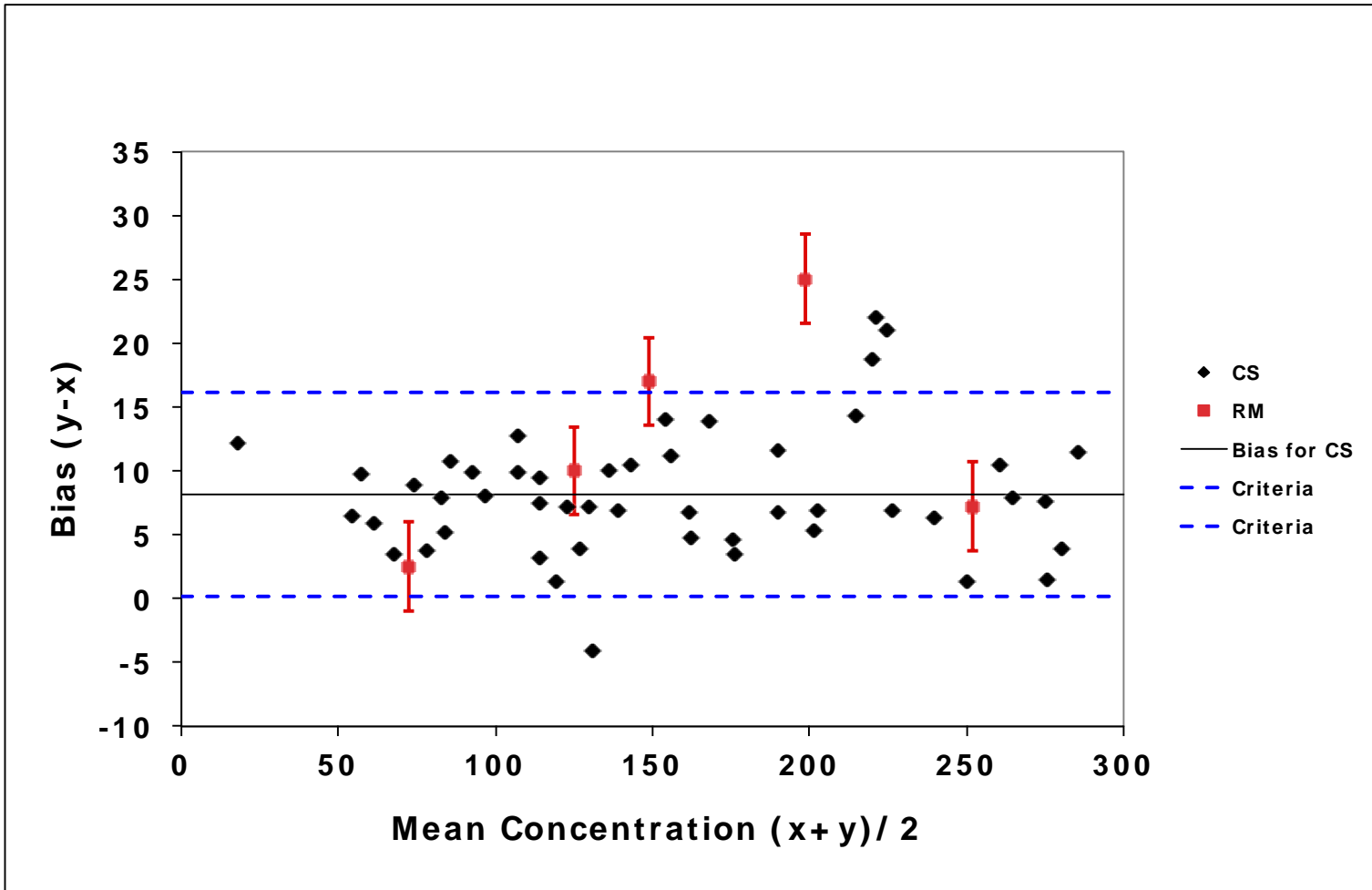
Statistical models

1. Assess the closeness of agreement for the **difference in bias** for RM compared to clinical samples between measurement procedures
2. Assess **harmonization effectiveness** of a RM used for calibration traceability by a group of measurement procedures

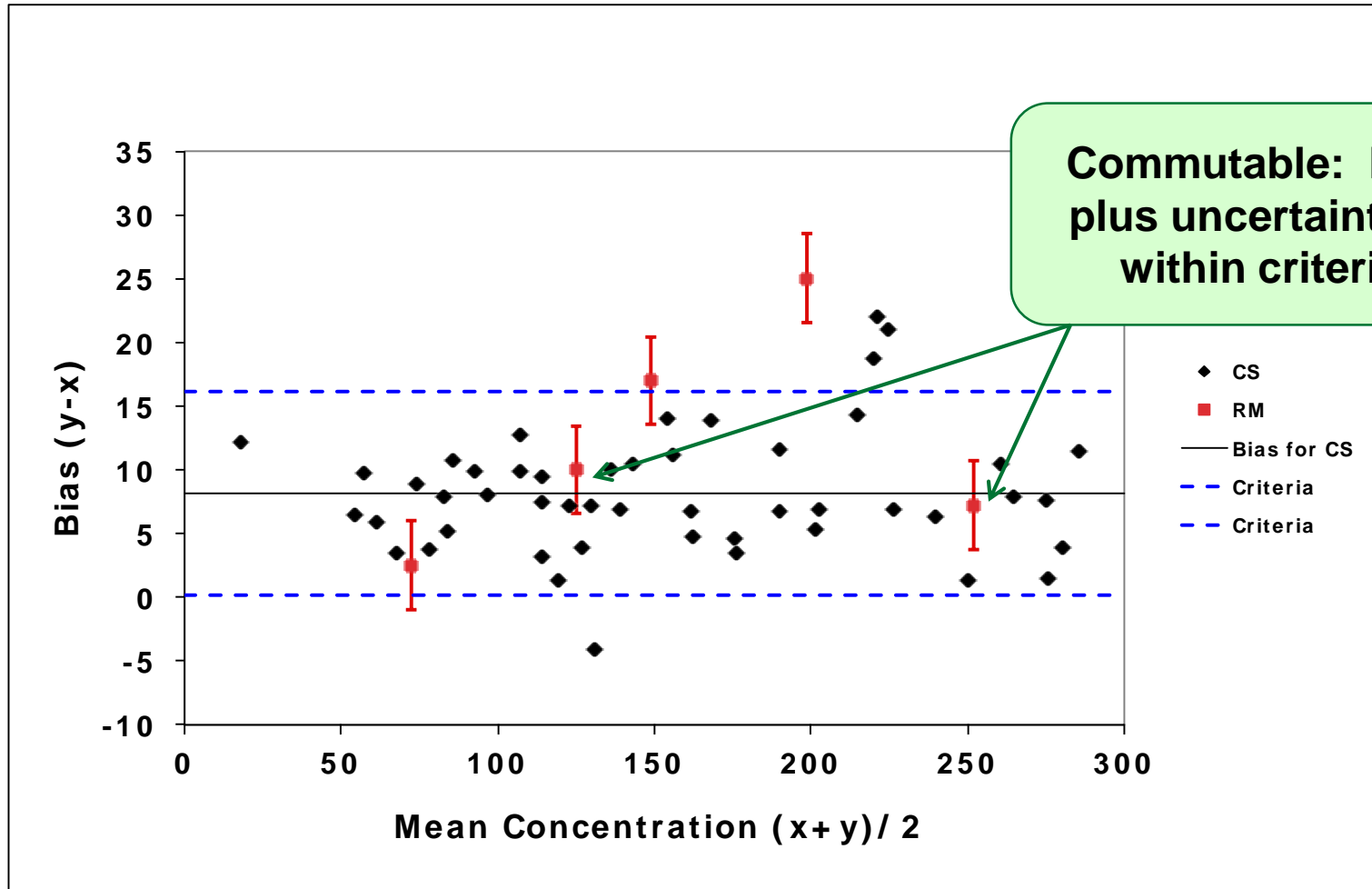
Difference in bias model

1. Estimate the bias between 2 measurement procedures for the patient samples and for the reference material(s)
2. Estimate the random error components including sample specific effects
3. Calculate the difference in bias for reference material(s) vs. patient samples
4. Estimate the uncertainty of the difference in bias
5. Commutable if the difference in bias plus uncertainty are within a criterion that is suitable for the intended use of the reference material

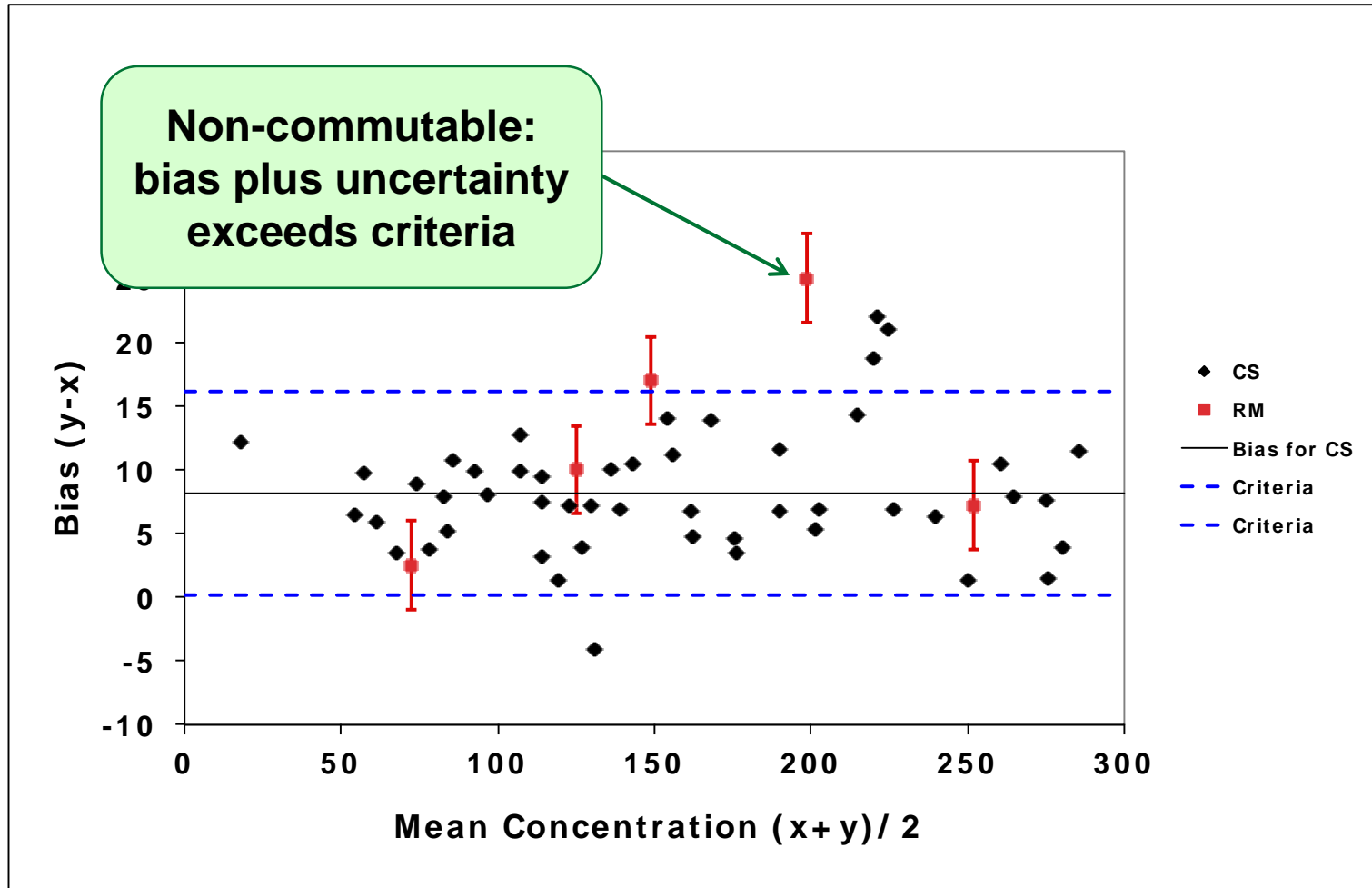
Difference in bias vs. fixed criteria



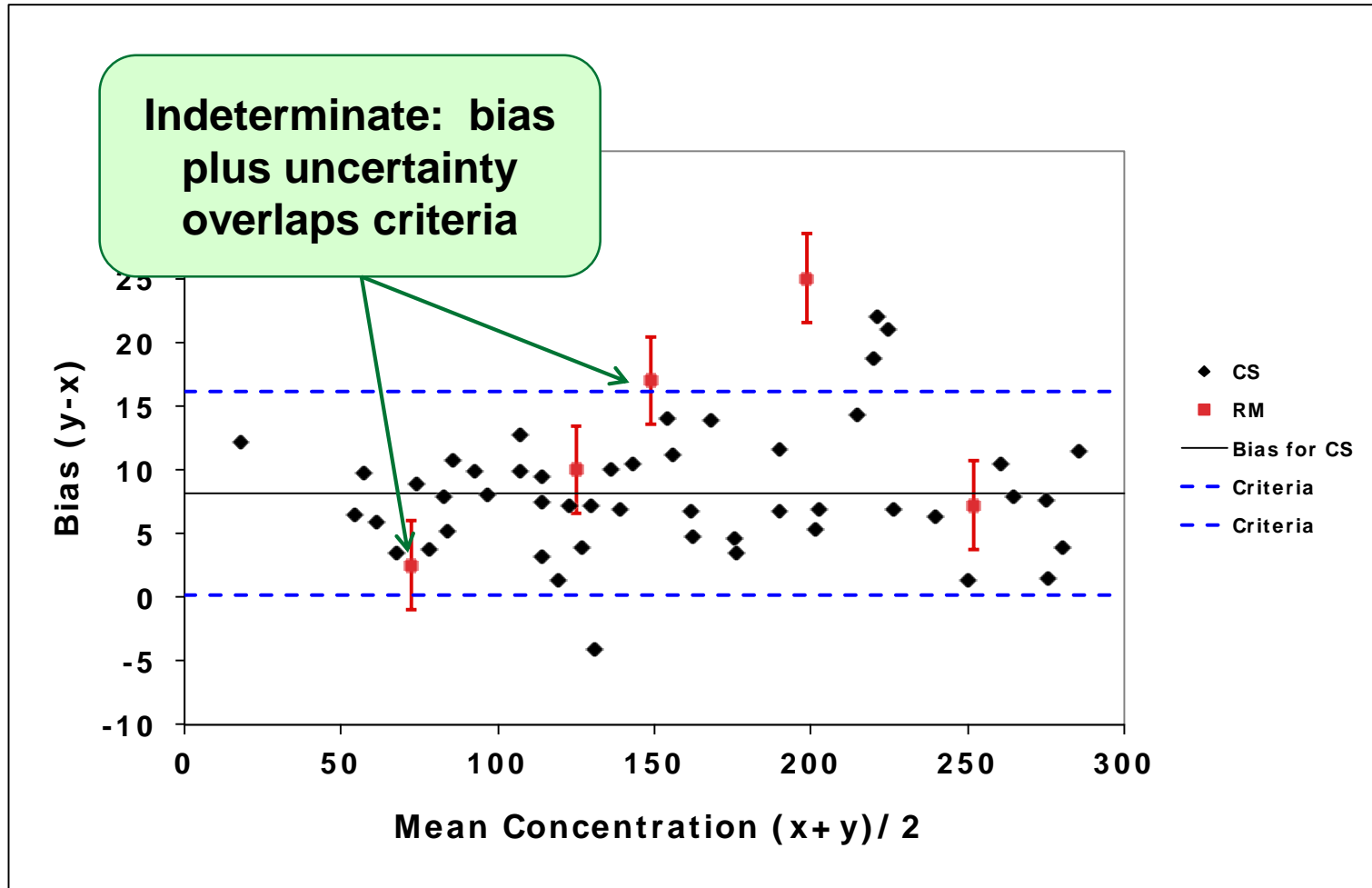
Difference in bias vs. fixed criteria



Difference in bias vs. fixed criteria



Difference in bias vs. fixed criteria



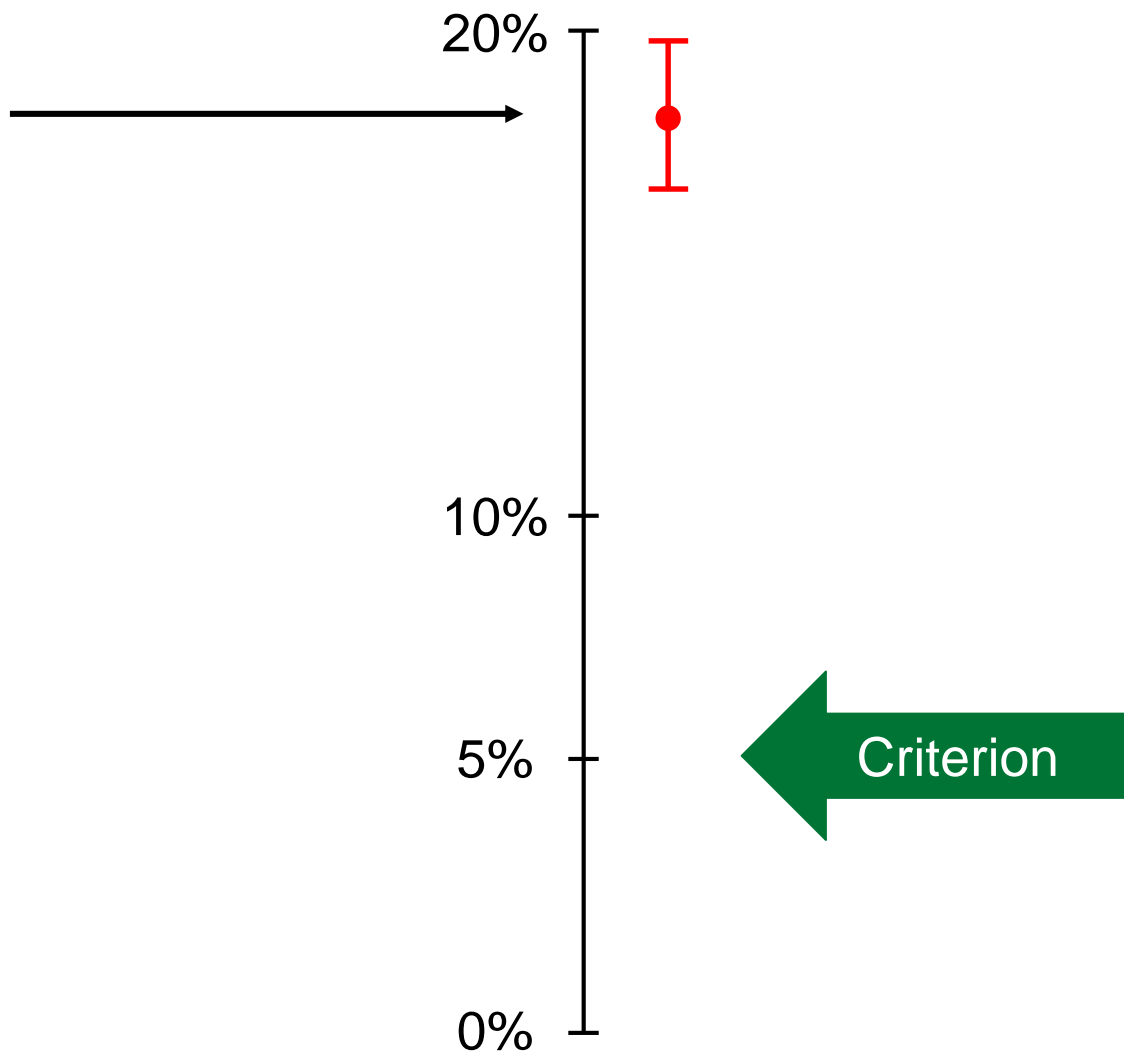
Harmonization effectiveness model

1. Estimate the inter-measurement procedure CV for each clinical sample's results
2. Calculate an overall pooled inter-measurement procedure CV and its uncertainty for all clinical samples
3. Compare the pooled CV plus uncertainty to a fixed criterion that is suitable for the intended use of the reference material
4. Use the RM for calibration traceability and repeat steps 1-2-3

Harmonization effectiveness

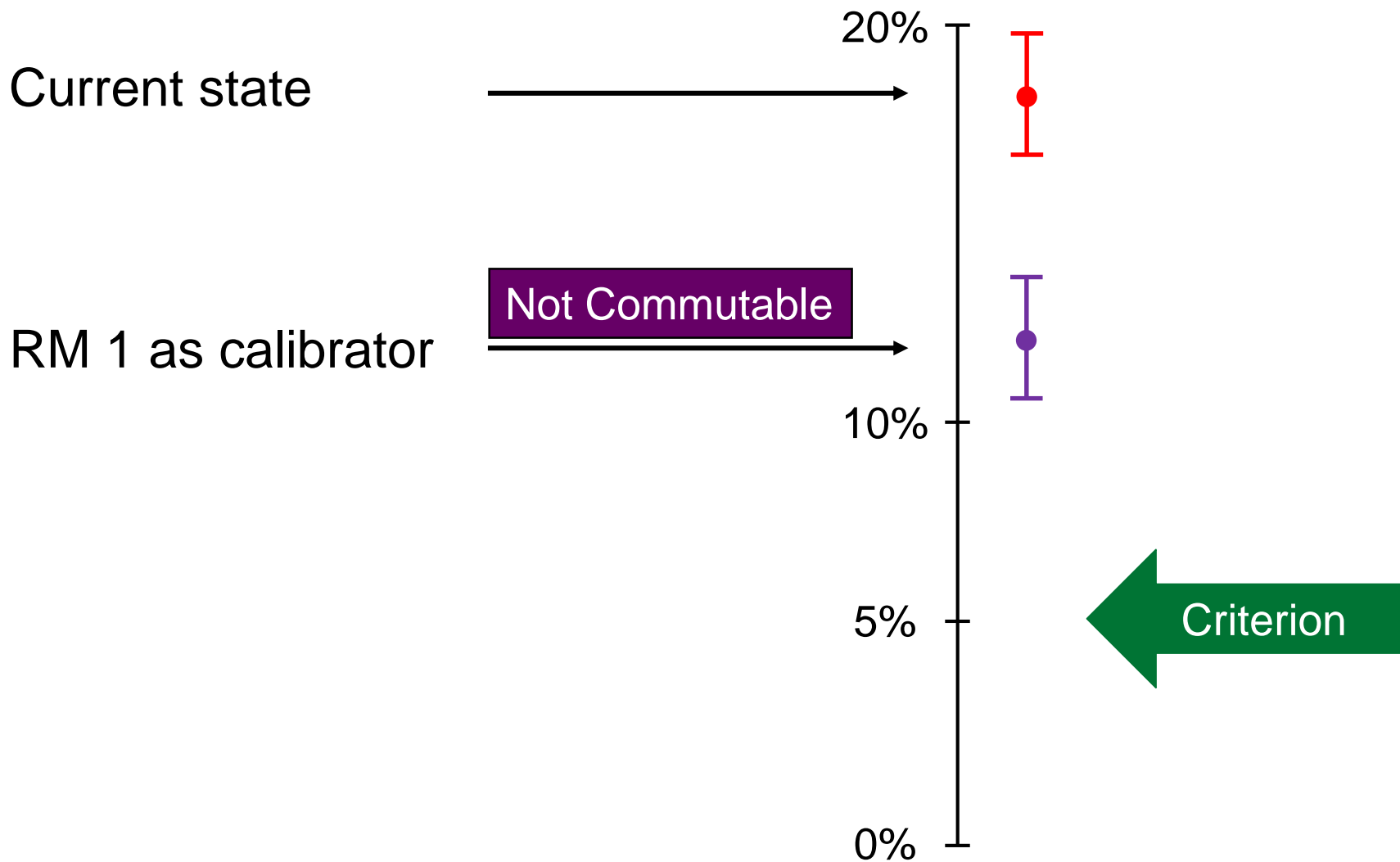
Inter-Measurement Procedure CV (%)

Current state



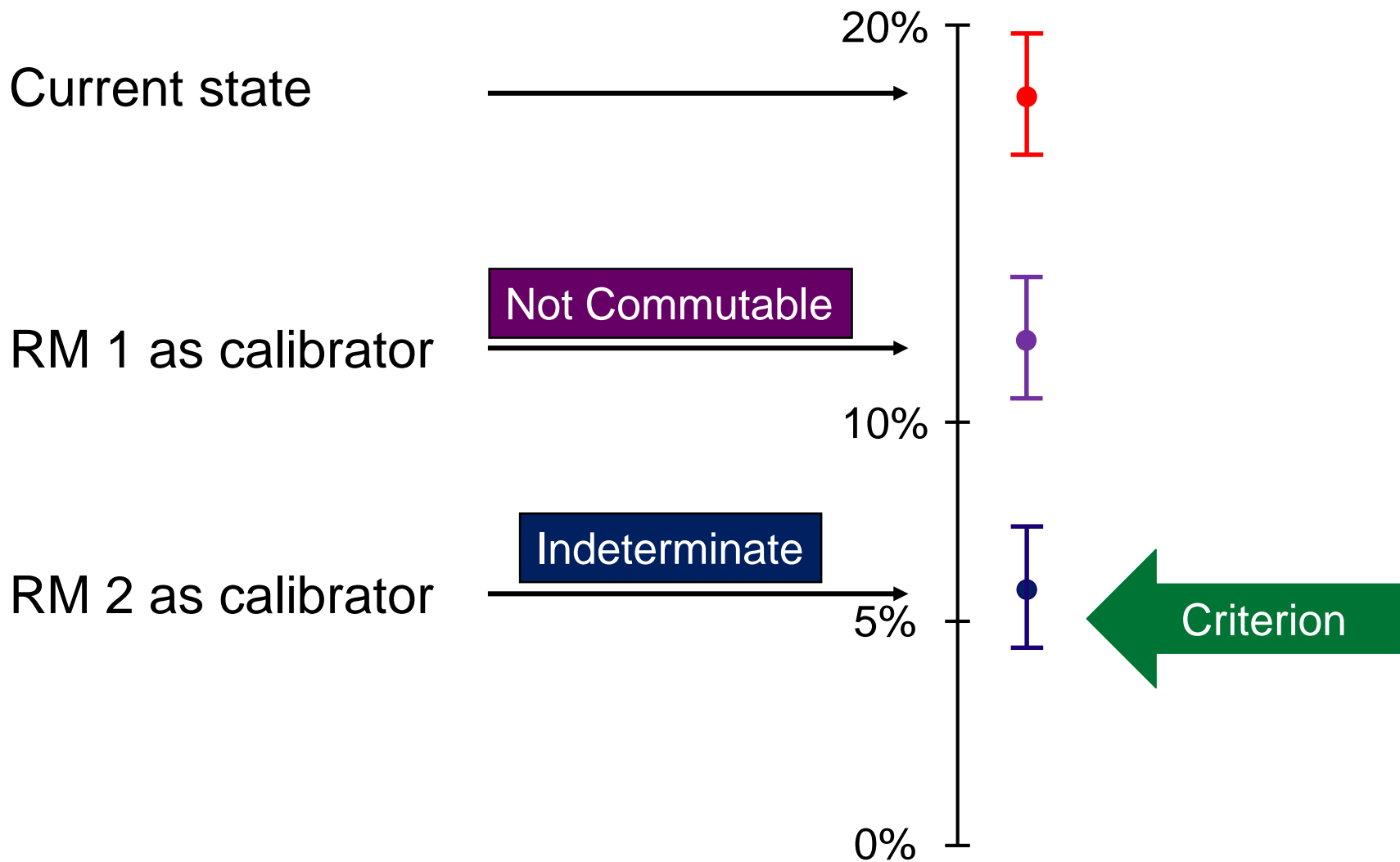
Harmonization effectiveness

Inter-Measurement Procedure CV (%)



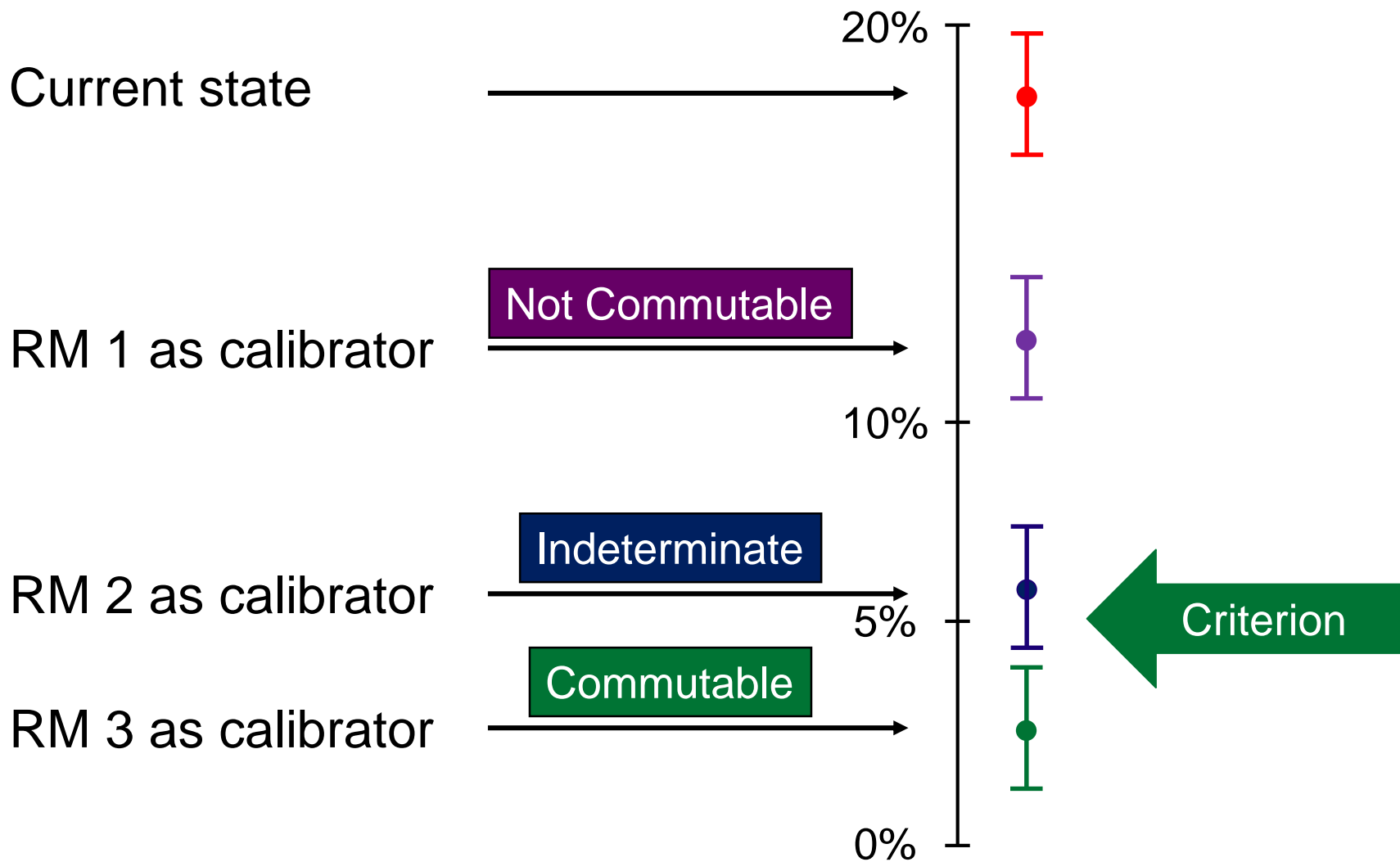
Harmonization effectiveness

Inter-Measurement Procedure CV (%)



Harmonization effectiveness

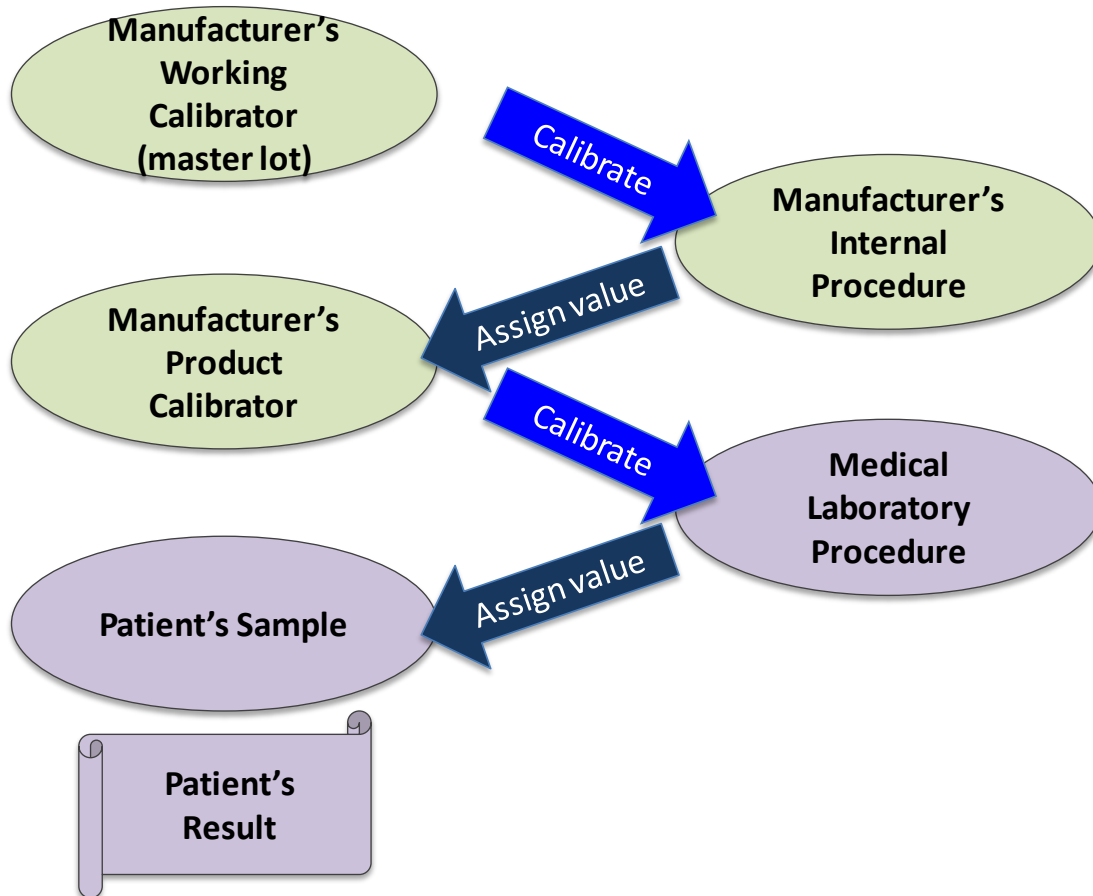
Inter-Measurement Procedure CV (%)



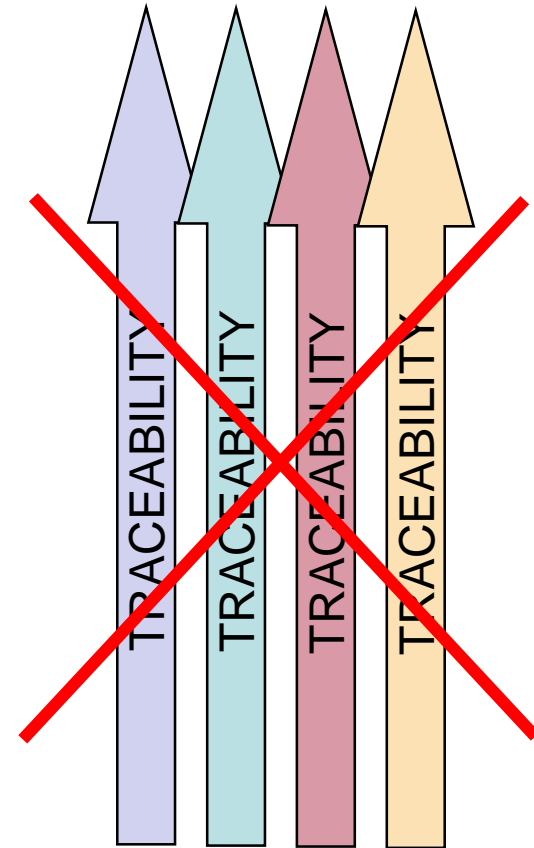
Other commutability topics

1. Qualify measurement procedures for inclusion
2. Individual samples vs. pools
3. Replacement of a RM with a new lot or batch
4. Correction to the assigned value of a non-commutable RM

The harmonization challenge



??????????



ISO TC 212 WG2

Revision of the traceability standard 17511 is expected to include traceability to a harmonization protocol as one type of calibration traceability hierarchy

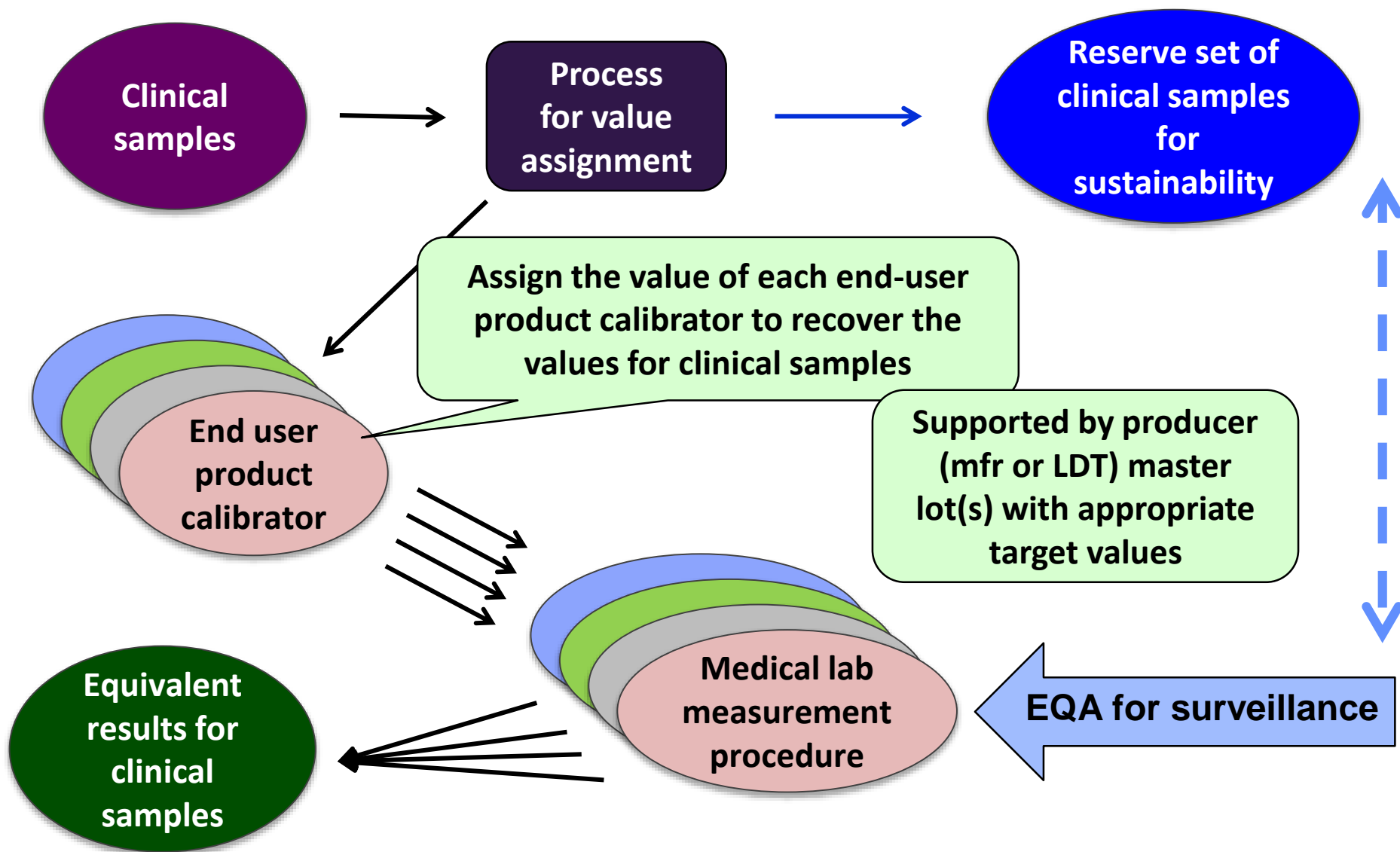
A new standard is in development to support JCTLM listing of a harmonization protocol.

ISO 20089: *Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and patient samples*

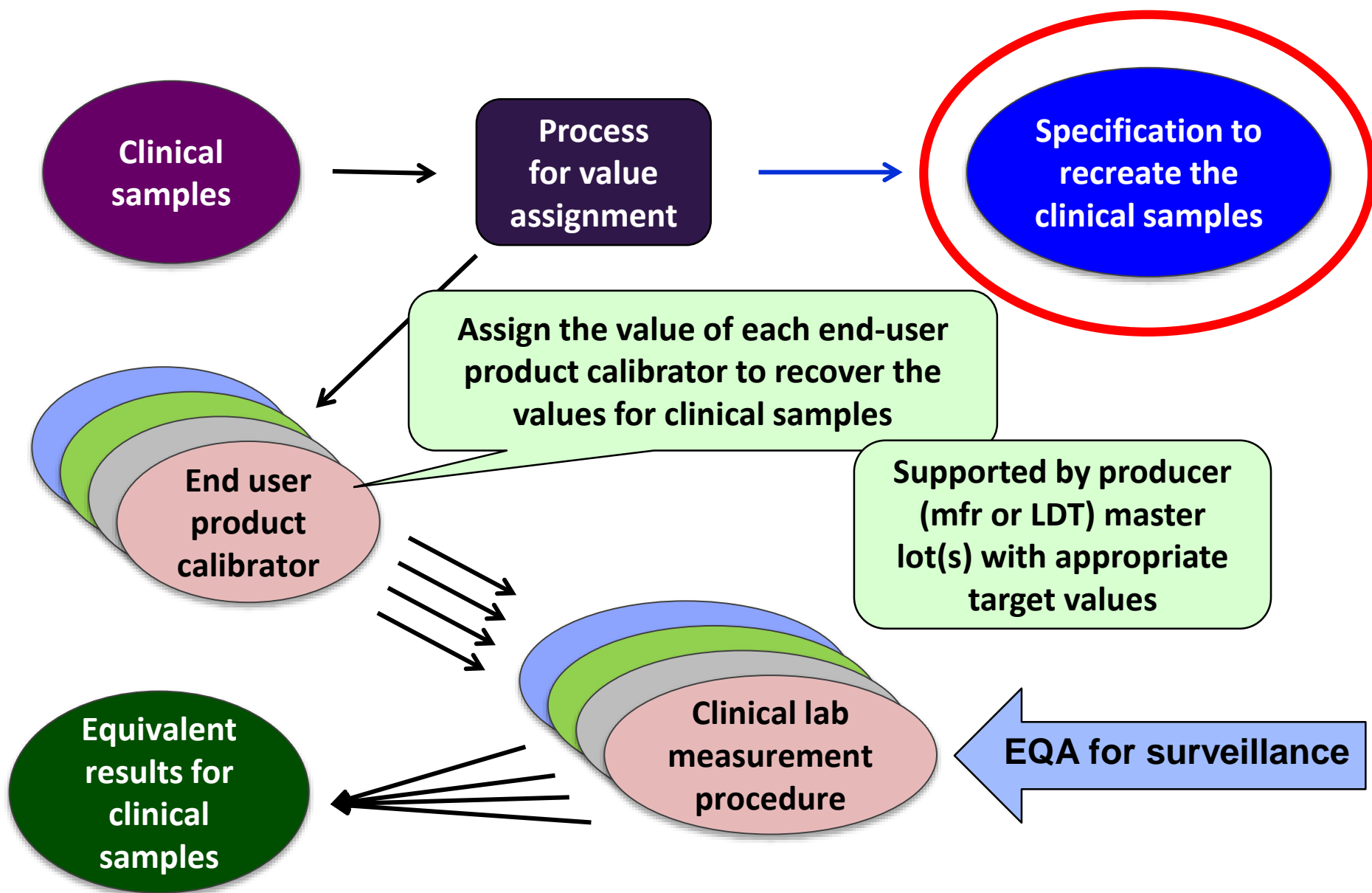
Critical components for harmonization

1. Calibration of all measurement procedures is traceable to a common reference protocol
2. All measurement procedures measure the same quantity (the same molecular form)
3. Traceability can be sustained over time and location

Example 1: harmonization protocol



Example 2: harmonization protocol



The prioritization and coordination challenge

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. Sturgeon¹²

- International Forum organized by **AACC** in October, 2010
- 90 participants from 12 countries
- Representing 62 organizations & manufacturers

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 reference material
4. Promote surveillance of the success of harmonization



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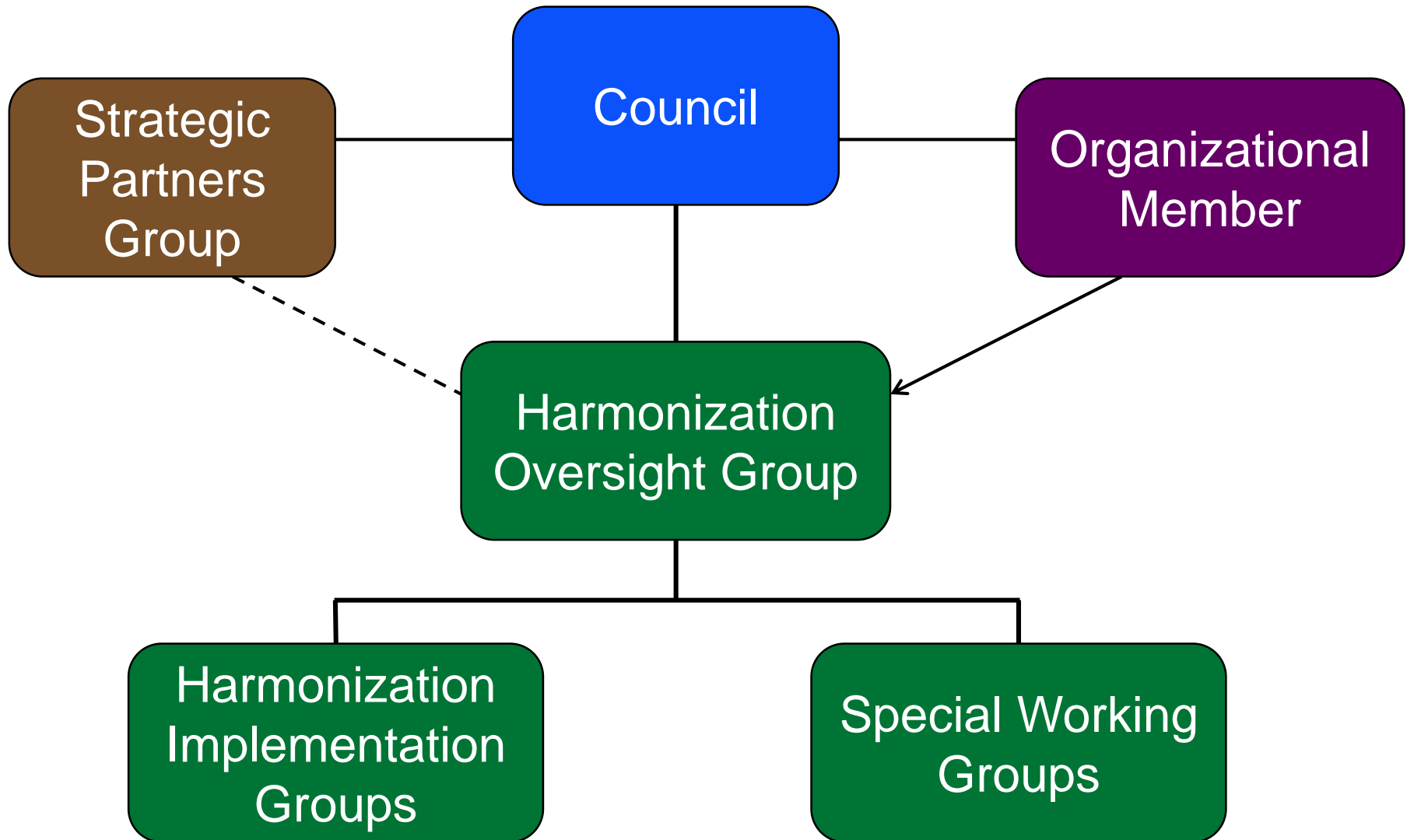


A Global Effort to Improve Patient Care

Our vision is that clinical laboratory test results will be comparable independent of the medical laboratory that produced the results.

Our mission is to provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results.

International Consortium for Harmonization of Clinical Laboratory Results



ICHCLR: Council members

AACC

*Better health through
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The Korean Society for
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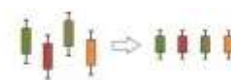
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Harmonization > Measurands

Measurands

Summary of Active Measurand Procedures

Measurand	Matrix	Medical Importance	Harmonization Status	JCTLM Listed	Organization
Bilirubin, conjugated	Serum	Medium	Inactive		
B-type Natriuretic Peptide (BNP)	Serum	High	Inactive		
Aspartate Aminotransferase (AST)	Serum	Medium	Active		IFCC
Amylase	Serum	High	Active		IFCC
Albumin	Serum	Medium	Inactive		
IgG antibodies to myeloperoxidase	Serum	Medium	Active		IFCC
Thyroid stimulating hormone (TSH)	Serum	High	Active		IFCC
Thyroxine, free (FT4)	Serum	High	Active		IFCC
Thyroxine (T4)	Serum	High	Active		IFCC
Alanine Aminotransferase (ALT)	Serum	Medium	Active		IFCC/IRMM
Creatine Kinase (CK)	Serum	High	Adequate		IFCC/IRMM
Lactate Dehydrogenase (LDH)	Serum	High	Active		IFCC/IRMM
Akaline Phosphatase (ALP)	Serum	High	Active		IFCC/IRMM
pancreatic lipase	Serum	High	Active		IFCC
CSF	CSF		Active		IFCC



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Resources

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

- **International Consortium for Harmonization of Clinical Laboratory Results-Current Status and Future Promise**

Greg Miller, Ph.D.

Chair, ICHCLR Harmonization Oversight Group

Professor of Pathology, Virginia Commonwealth University

International Consortium for Harmonization
of Clinical Laboratory Results
- current status and future promise

Greg Miller, PhD, ICHCLR
Virginia Commonwealth University
Richmond, VA, USA

ICHCLR Website: June 20, 2014. Internal. Only



- **AACC Releases Position Statement on Harmonization of Clinical Laboratory Test Results**
- **Roadmap for Harmonization of Clinical Laboratory Measurement Procedures** Clinical Chemistry 2011 v. 57, p. 1108-1117.
- **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**

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