Update from the IFCC Working Group on Commutability

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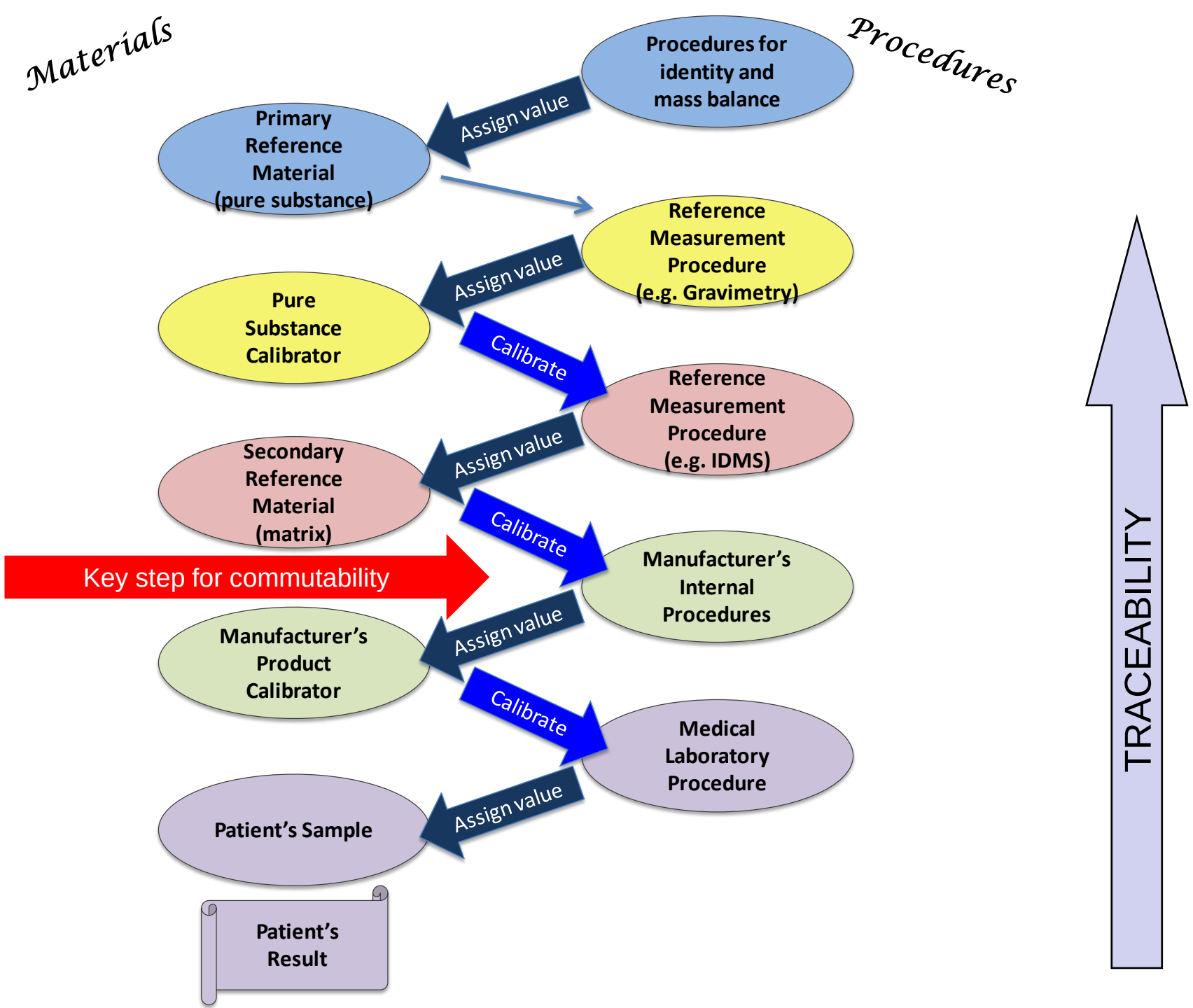
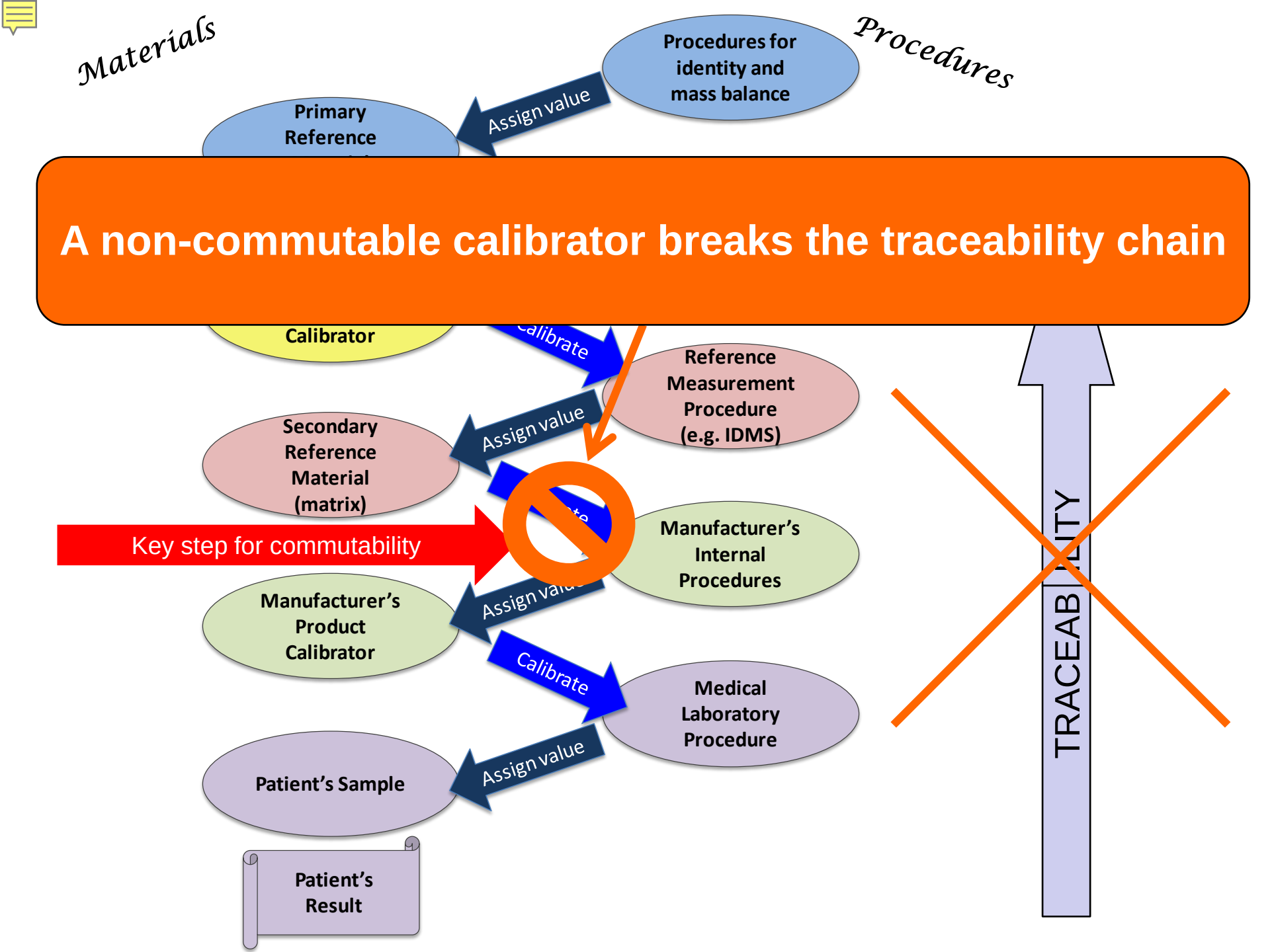
Outline

- Why commutability matters
- What is commutability
- How is commutability assessed
- What improvements are coming for commutability assessment


Materials
Procedures
Procedures for identity and mass balance
Assign value
Primary Reference Material (pure substance)
Reference Measurement Procedure (e.g. Gravimetry)
Assign value
Pure Substance Calibrator
Calibrate
Reference Measurement Procedure (e.g. IDMS)
Assign value
Secondary Reference Material (matrix)
Calibrate
Key step for commutability
Manufacturer's Internal Procedures
Assign value
Manufacturer's Product Calibrator
Calibrate
Medical Laboratory Procedure
Assign value
Patient's Sample
Patient's Result
TRACEABILITY


Materials
Procedures
Procedures for identity and mass balance
Assign value
Primary Reference
A non-commutable calibrator breaks the traceability chain
Calibrator
Calibrate
Reference Measurement Procedure (e.g. IDMS)
Assign value
Secondary Reference Material (matrix)
Key step for commutability
Manufacturer's Internal Procedures
Manufacturer's Product Calibrator
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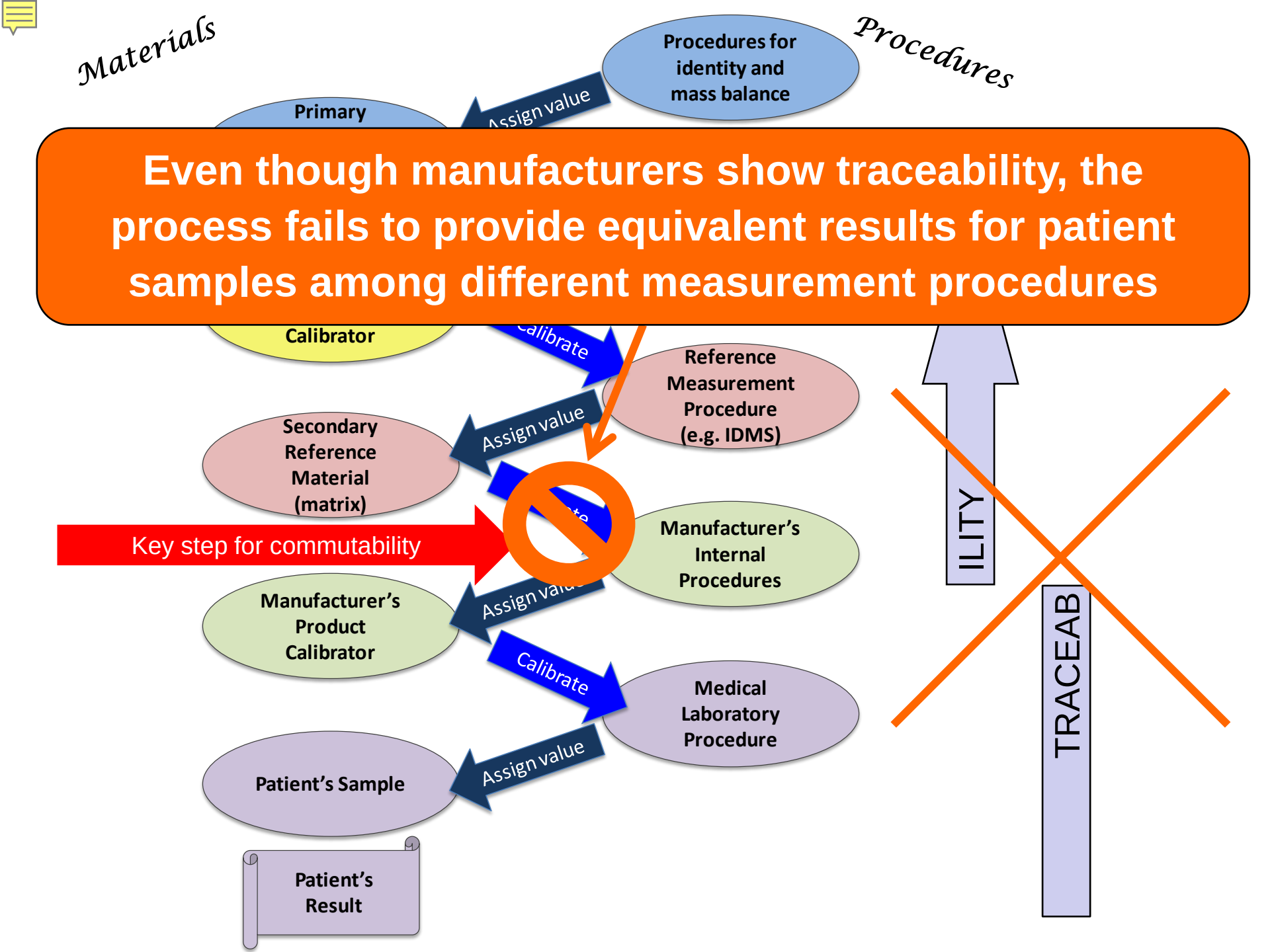
TRACEABILITY


Materials
Procedures
Procedures for identity and mass balance
Assign value
Primary
Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures
Calibrator
Calibrate
Reference Measurement Procedure (e.g. IDMS)
Assign value
Secondary Reference Material (matrix)
Key step for commutability
Manufacturer's Internal Procedures
Manufacturer's Product Calibrator
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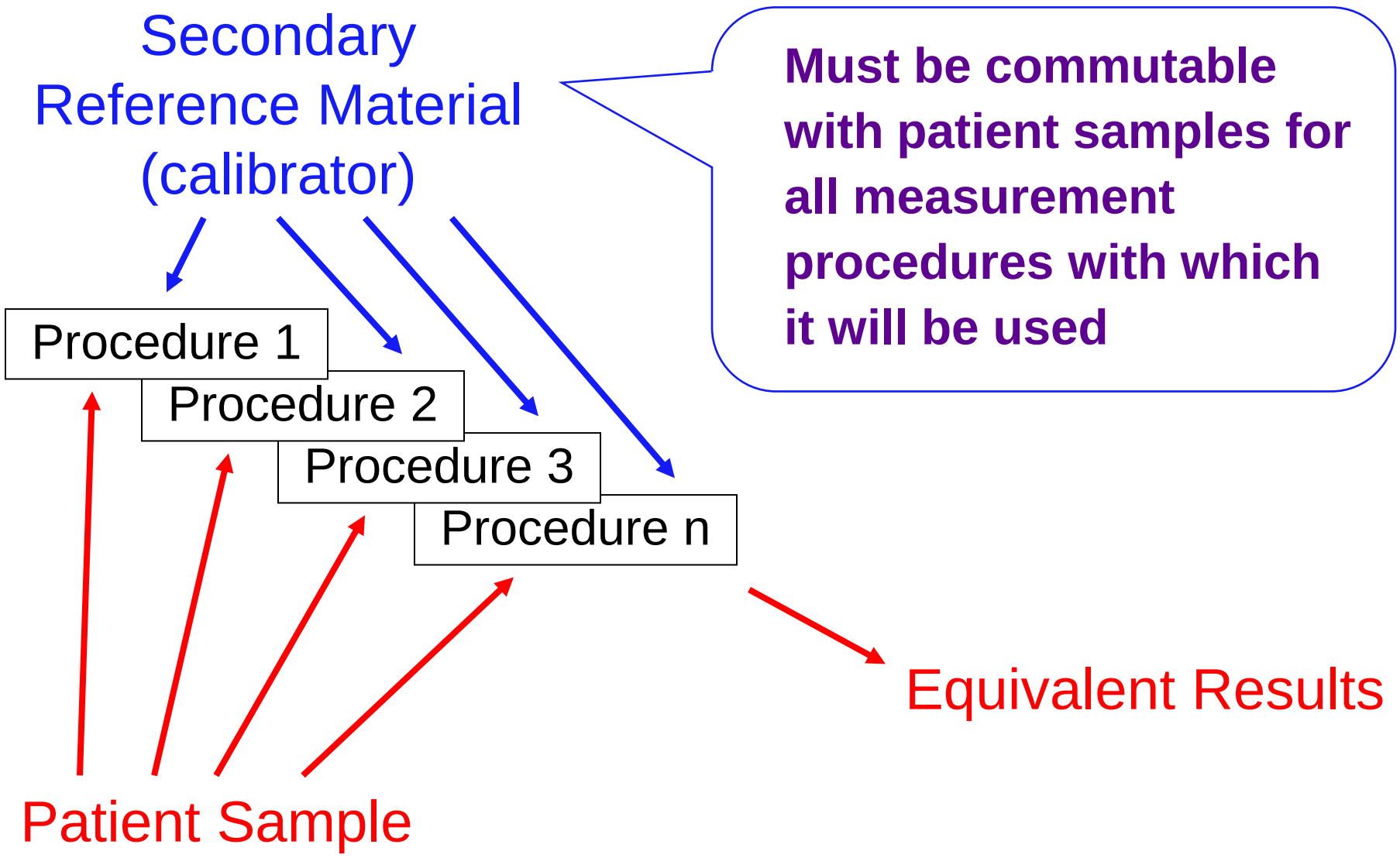
TRACEAB


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
Equivalent Results
Patient Sample

Use of a non-commutable material for calibration traceability will cause:

- Incorrect value assignment for a medical laboratory measurement procedure calibrator
- **Incorrect results for patient samples**

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

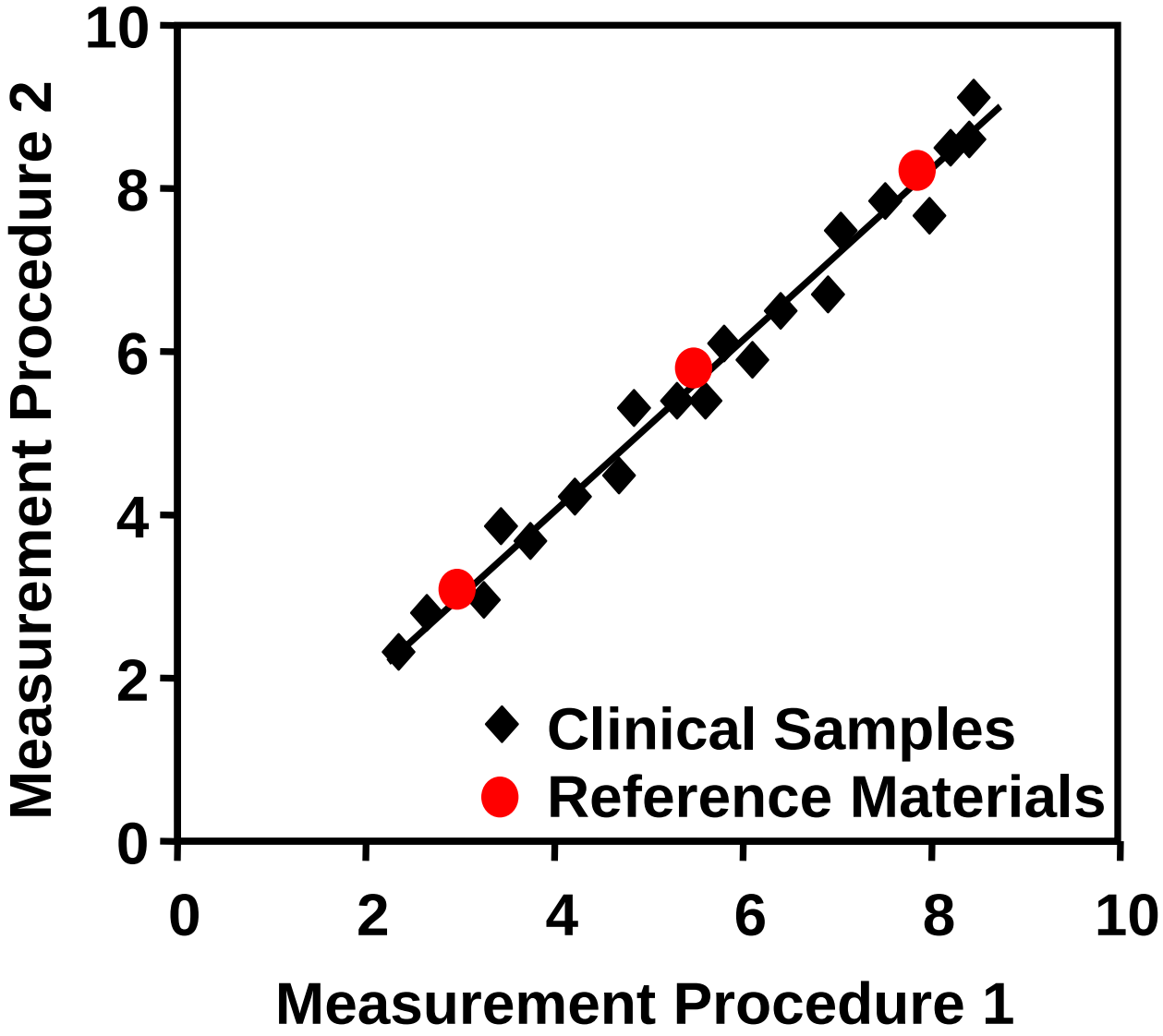
Commutability (Commutable)

Property of a reference material demonstrated by the closeness of agreement

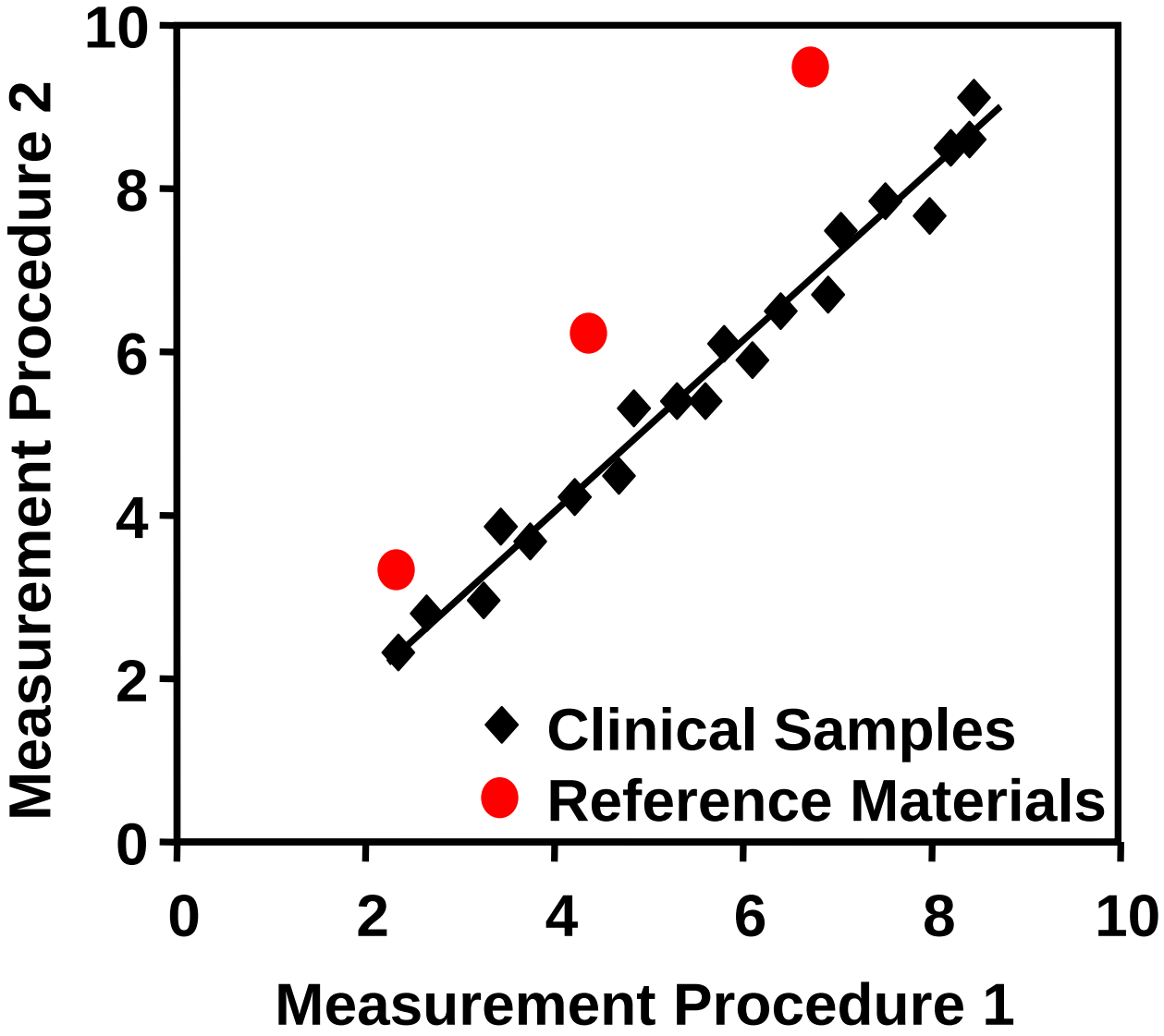
- between the relation among results for a reference material obtained from two measurement procedures
- and the relation among results for clinical samples from the same two measurement procedures

(Rephrased from VIM 3: 2008)

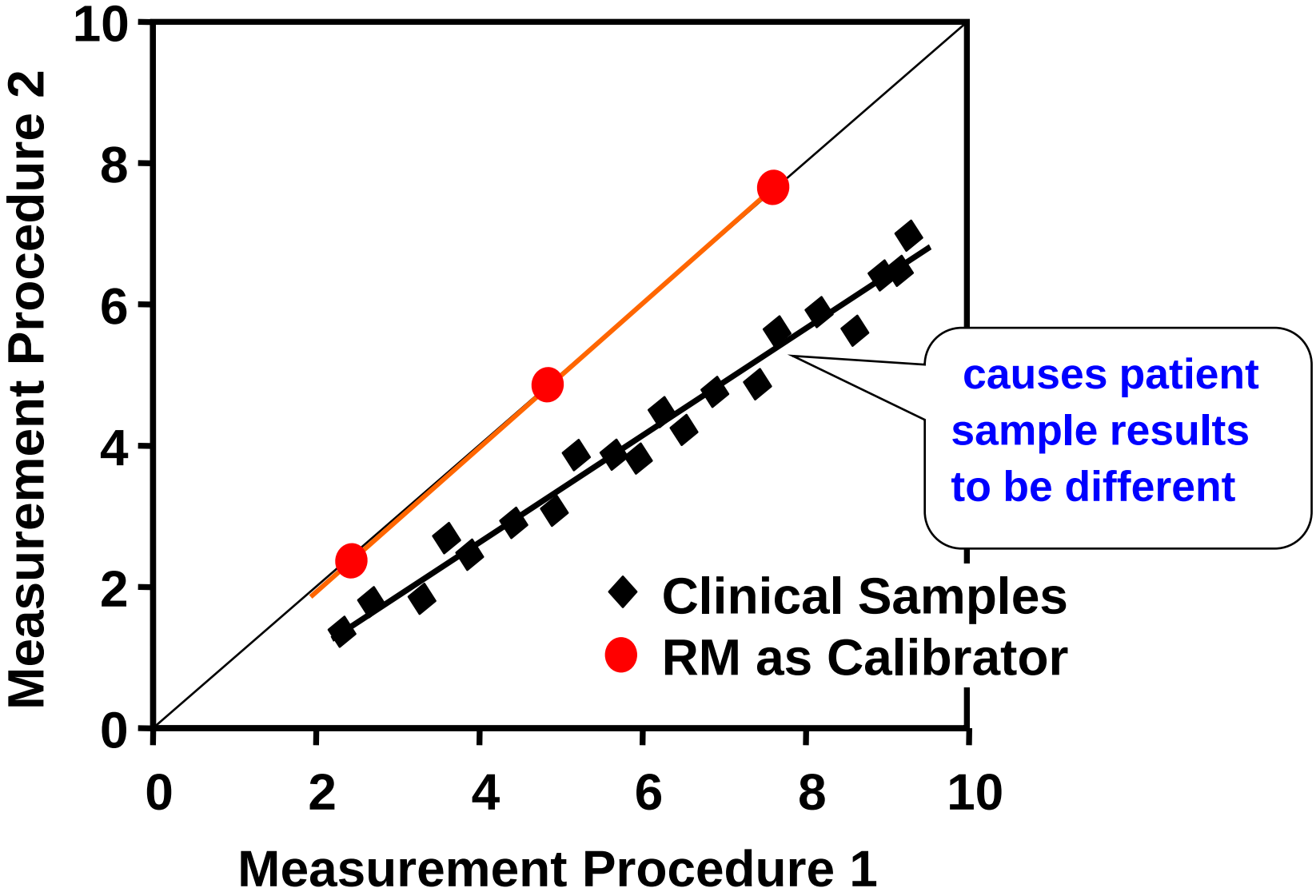
Commutable: same relationship for clinical samples and reference materials



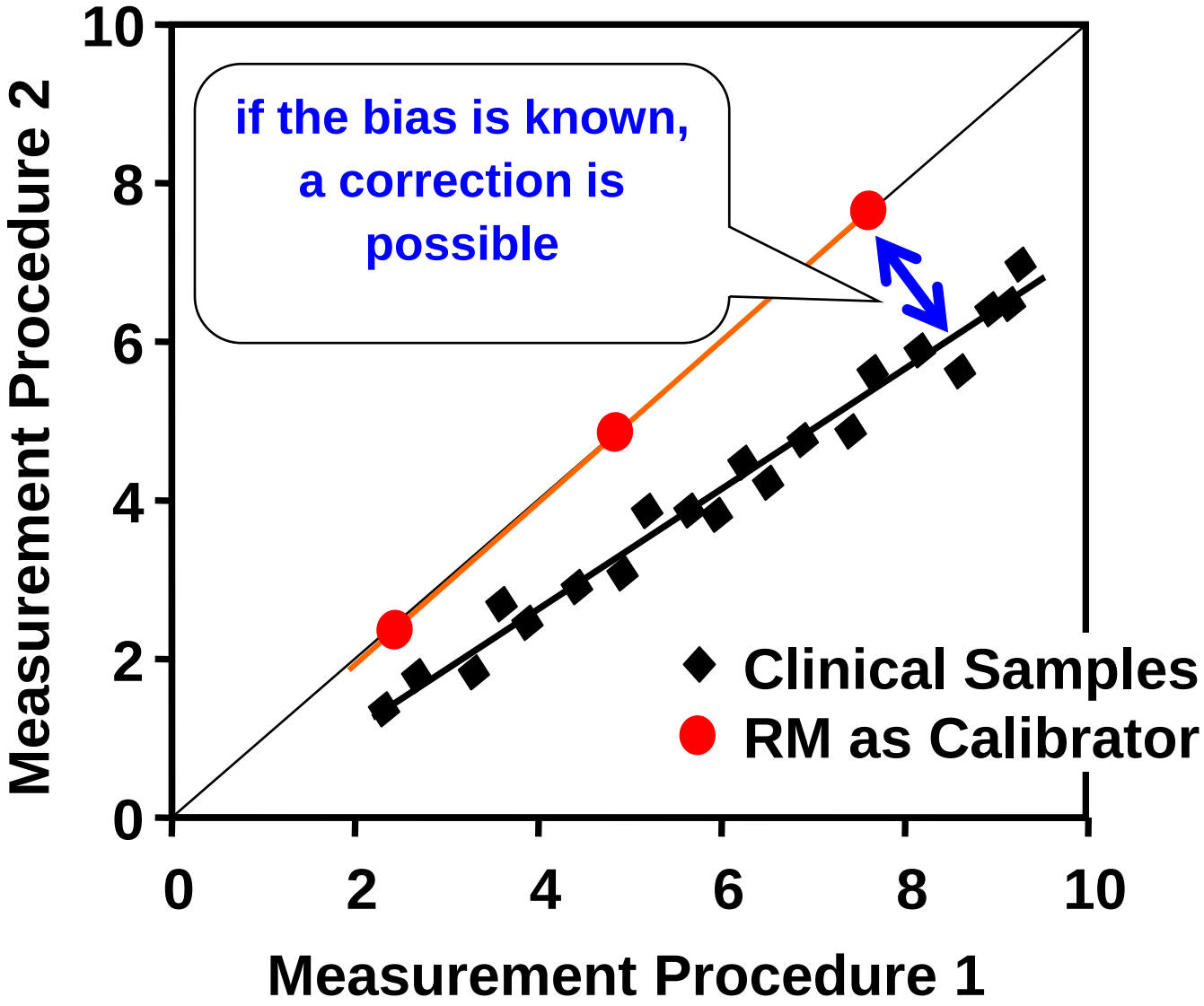
Non-commutable: different relationship for clinical samples and reference materials



Calibration with non-commutable materials



Correction is possible



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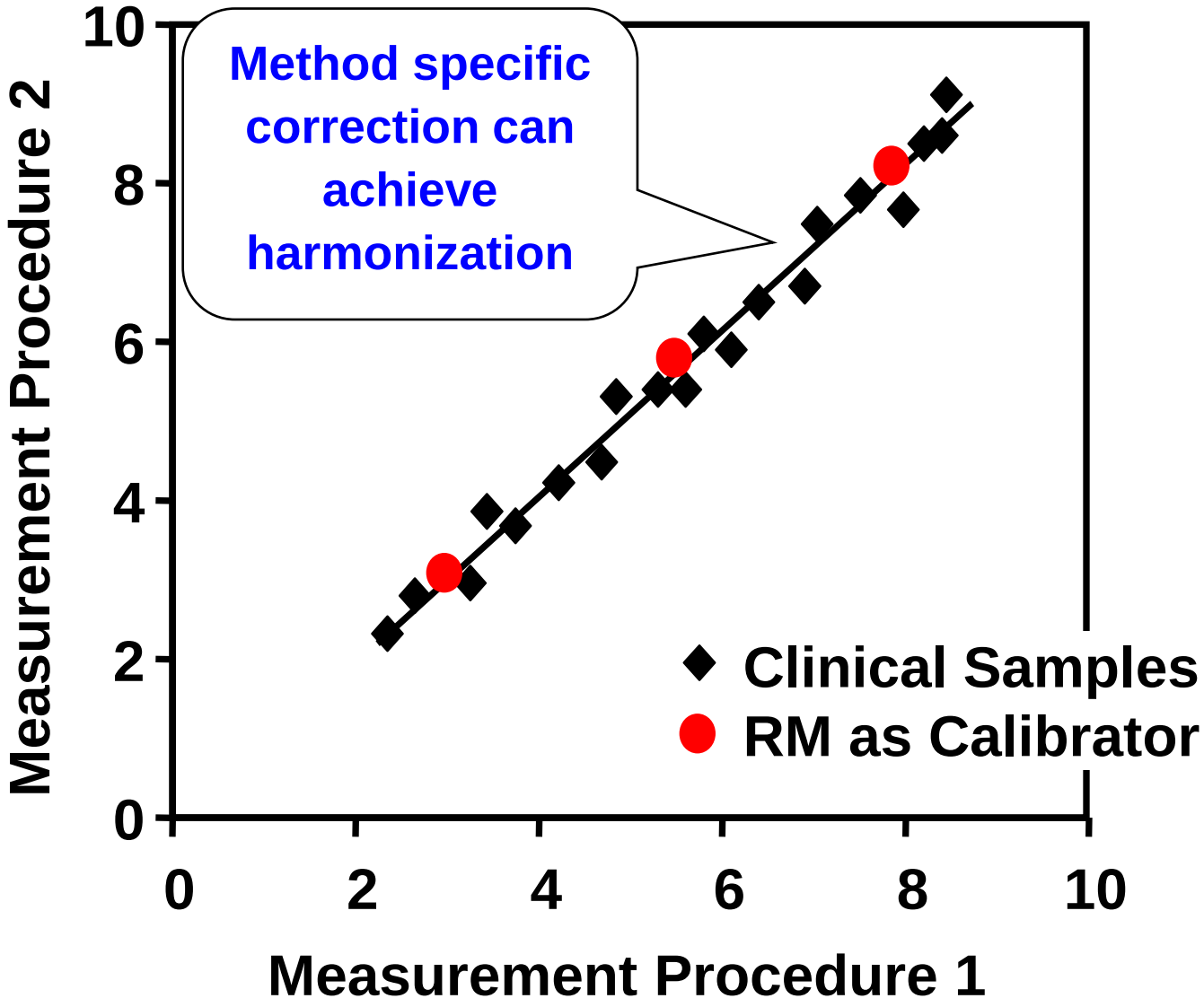


Must require commutability validation for reference materials intended for use with:

- Manufacturer's internal procedures
- Routine clinical laboratory procedures

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)

Validating commutability

1. Representative clinical samples

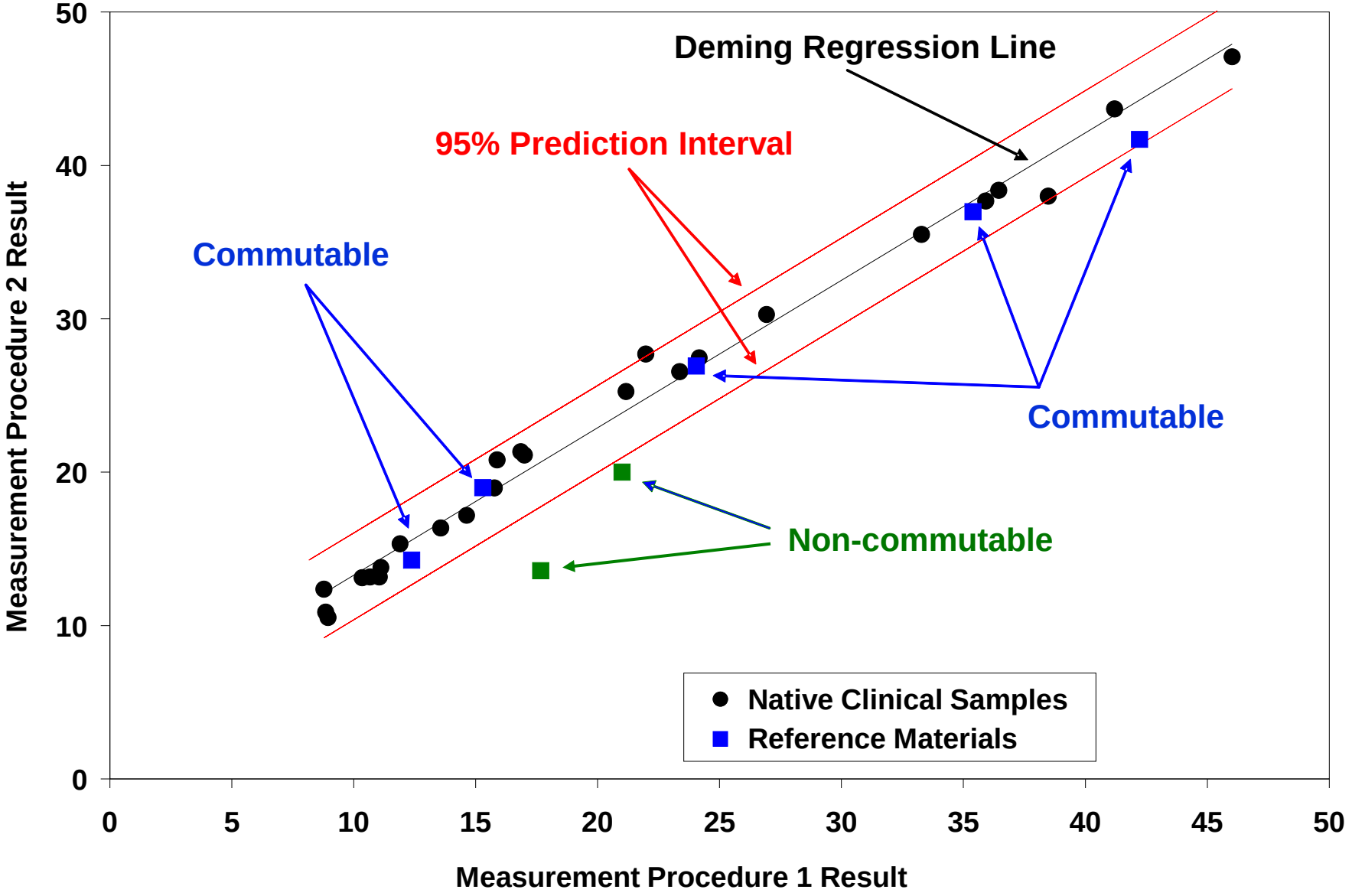
2. Candidate reference material(s)

3. Measure clinical samples and reference material(s) with all measurement procedures for a measurand

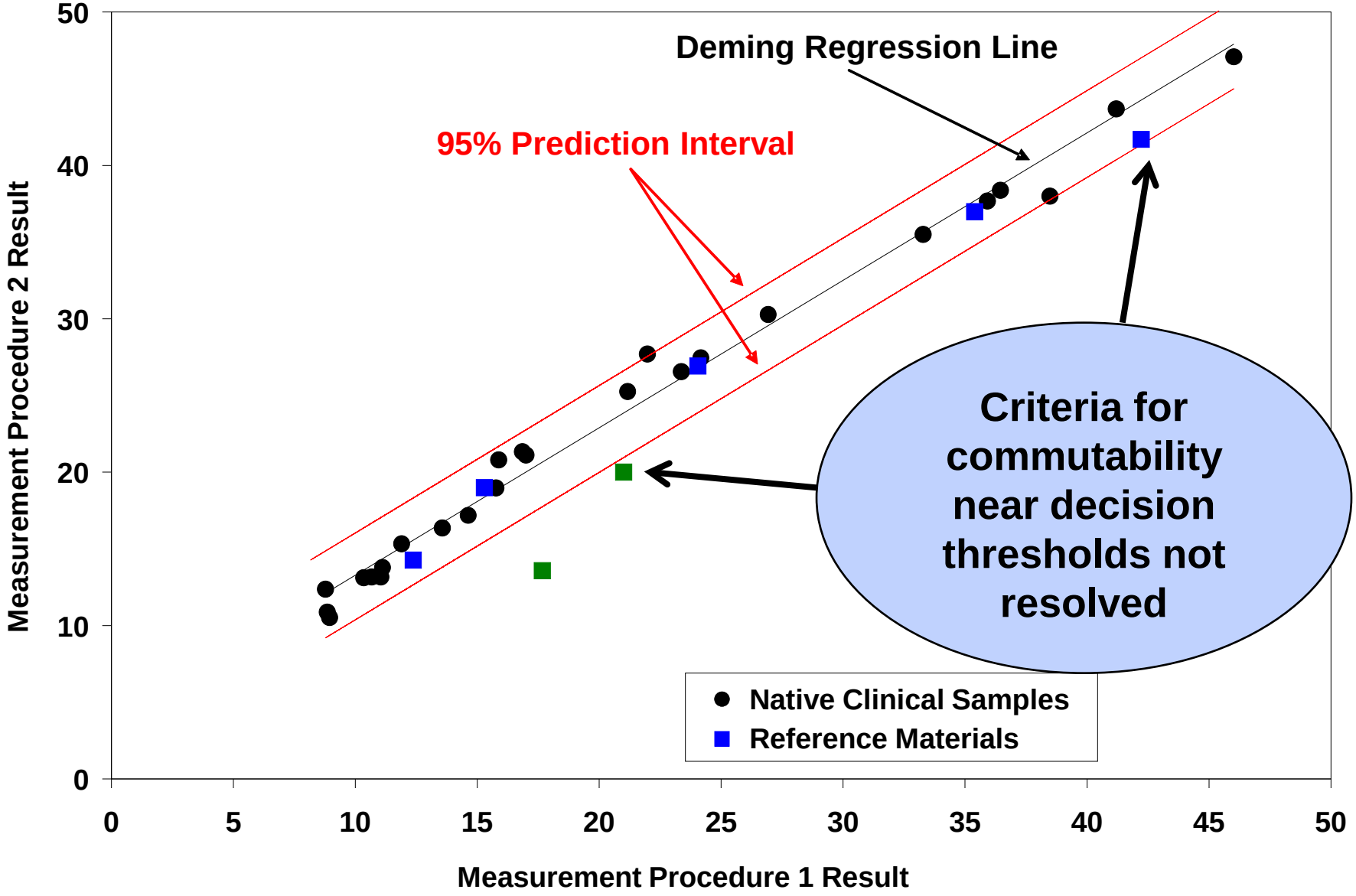
Validating commutability

4. Determine the relationships between the measurement procedures for the clinical samples

5. Determine if the relationships for a RM are close enough to those for the clinical samples for the intended use of the RM



Adapted from CLSI EP30-A (used with permission)



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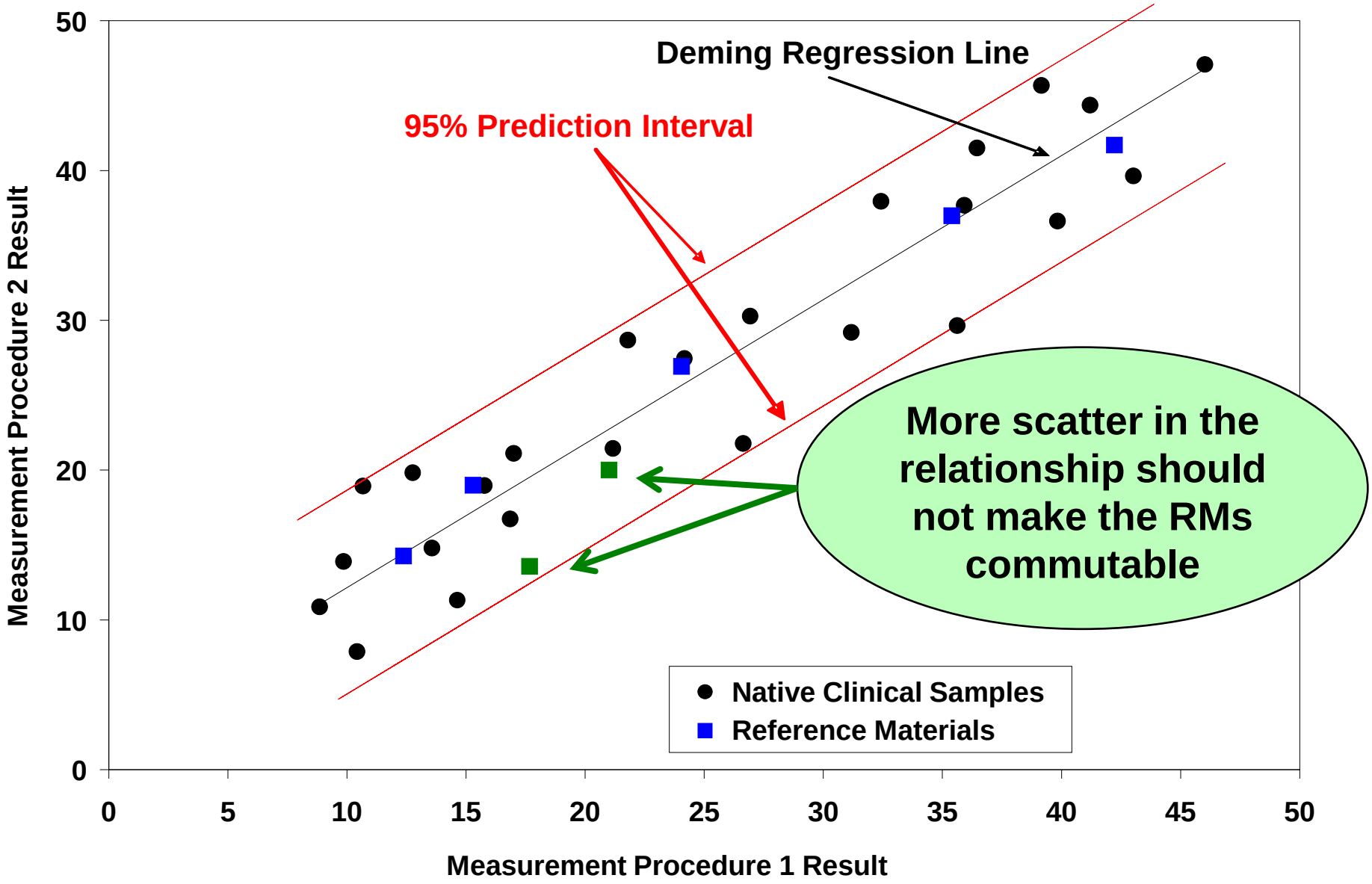


Modified from CLSI EP30-A (used with permission)

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 and the medical use of measurement procedure results
- Standard terminology to describe commutability characteristics
- Information to be provided regarding commutability
- Education of manufacturers, laboratories, end users

Assessment of commutability

- Evaluating a property of a reference material
- **NOT** evaluating the performance of the measurement procedures
- Assessment of closeness of agreement is influenced by the performance of the measurement procedures

Qualification of measurement procedures

1. Adequate specificity for the measurand
   - Good correlation between measurement procedures for clinical samples
   - Small error component from sample specific effects
2. Adequate precision

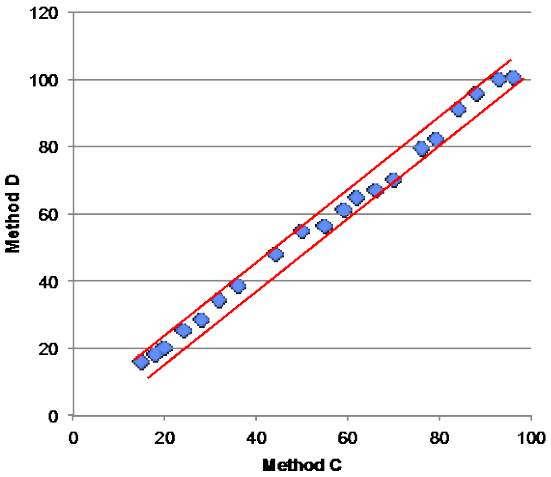
➡ **Measurement procedure improvement may be a prerequisite for inclusion in a commutability assessment**

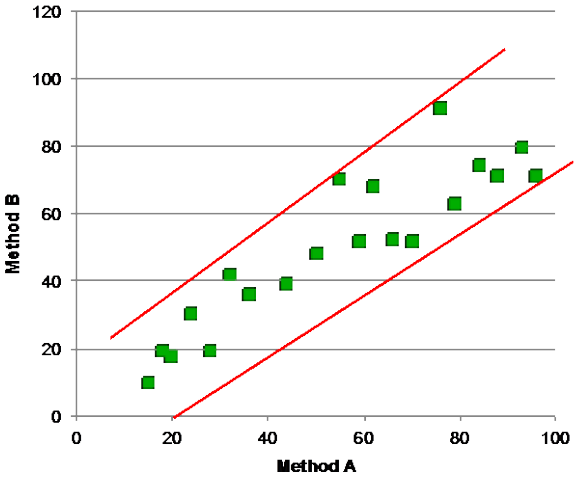
Qualification of clinical samples

1. Should not contain unusual interfering substances or analyte forms that will influence the measurement procedures
2. Must cover the concentrations of the RM(s)
3. Individual samples are preferred
4. Pooled samples may be needed to meet volume requirements – pooling must be validated
5. Preparation and storage conditions must be validated

Criteria for commutability

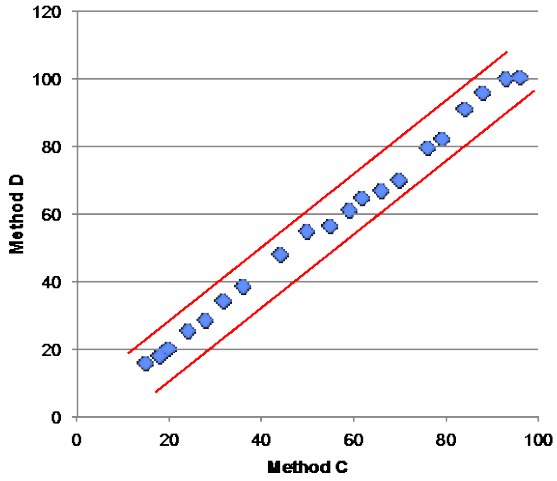
1. Criteria based on statistical distribution of results for patient samples are difficult to apply consistently
   - o Criteria change among measurement procedures with different performance characteristics
   - o Criteria may not relate to intended use

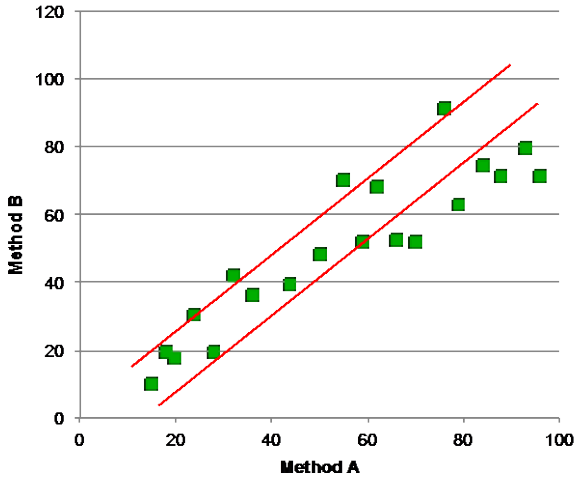




Criteria for commutability

2. Fixed criteria based on the medical requirements for using patient results are preferred





How to establish criteria based on medical use requirements

- CCLM 2015;53(6) Special Issue: 1st EFLM Strategic Conference “Defining analytical performance goals − 15 years after the Stockholm Conference”

- Fraction of the uncertainty required for a RM’s use in a calibration traceability hierarchy

- Fraction of the uncertainty required for assessment using EQA

Criteria for commutability

3. A RM should be suitable for use by a large fraction of measurement procedures

   - A large fraction is challenging to specify
     - ✧ Number of measurement procedures
     - ✧ Number of clinical results reported
   - Labelling should declare for which measurement procedures a RM was evaluated and for which its commutability is or is not suitable for use

Statistical models

1. Assess closeness of agreement for the difference in bias between two measurement procedures for RM compared to clinical samples

2. Assess harmonization effectiveness of a RM used for calibration traceability by a group of measurement procedures

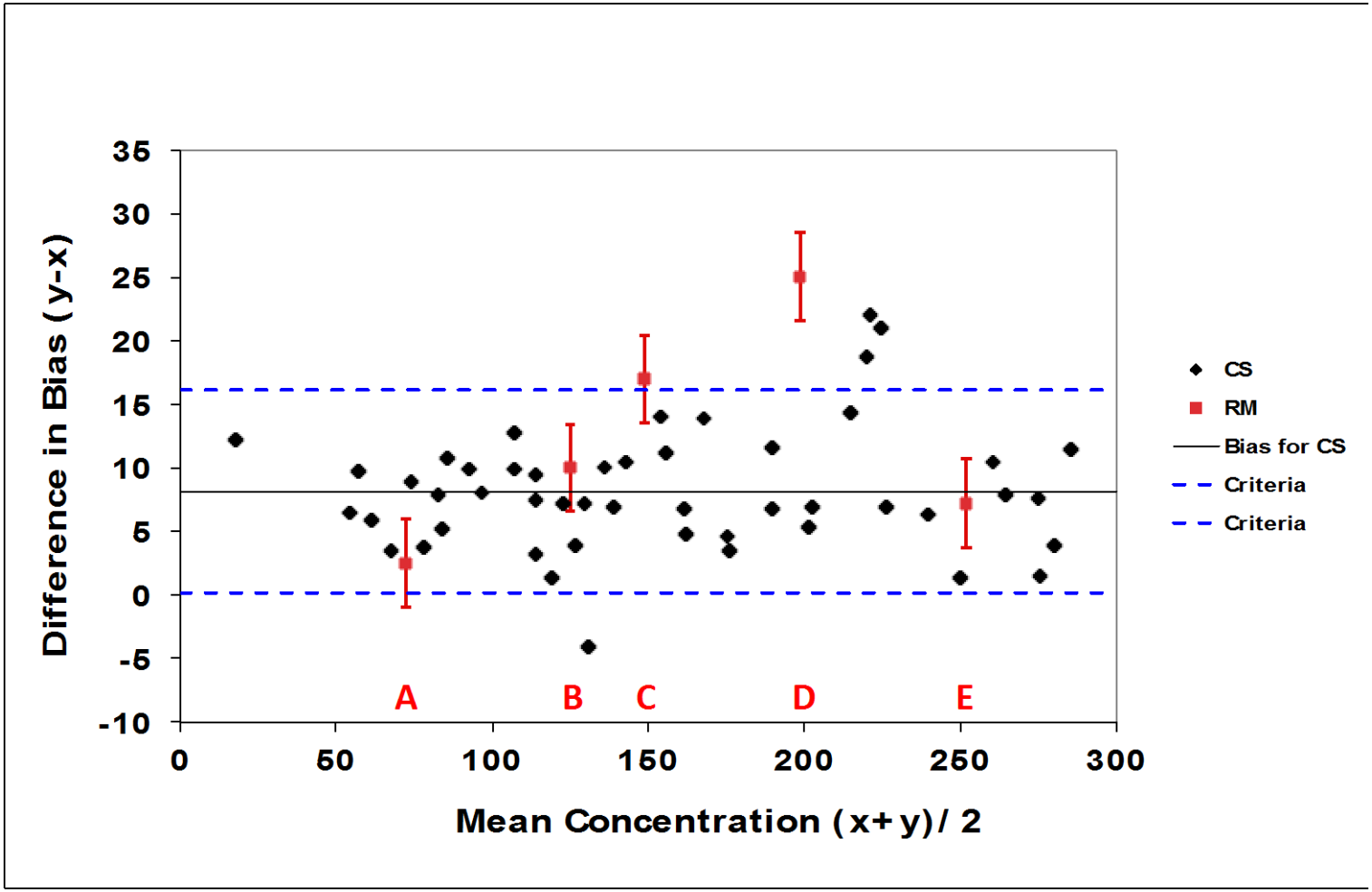
Closeness of agreement model

- Assess closeness of agreement vs. a fit-for-purpose fixed criterion
- NOT assessing the equivalence of the relationship

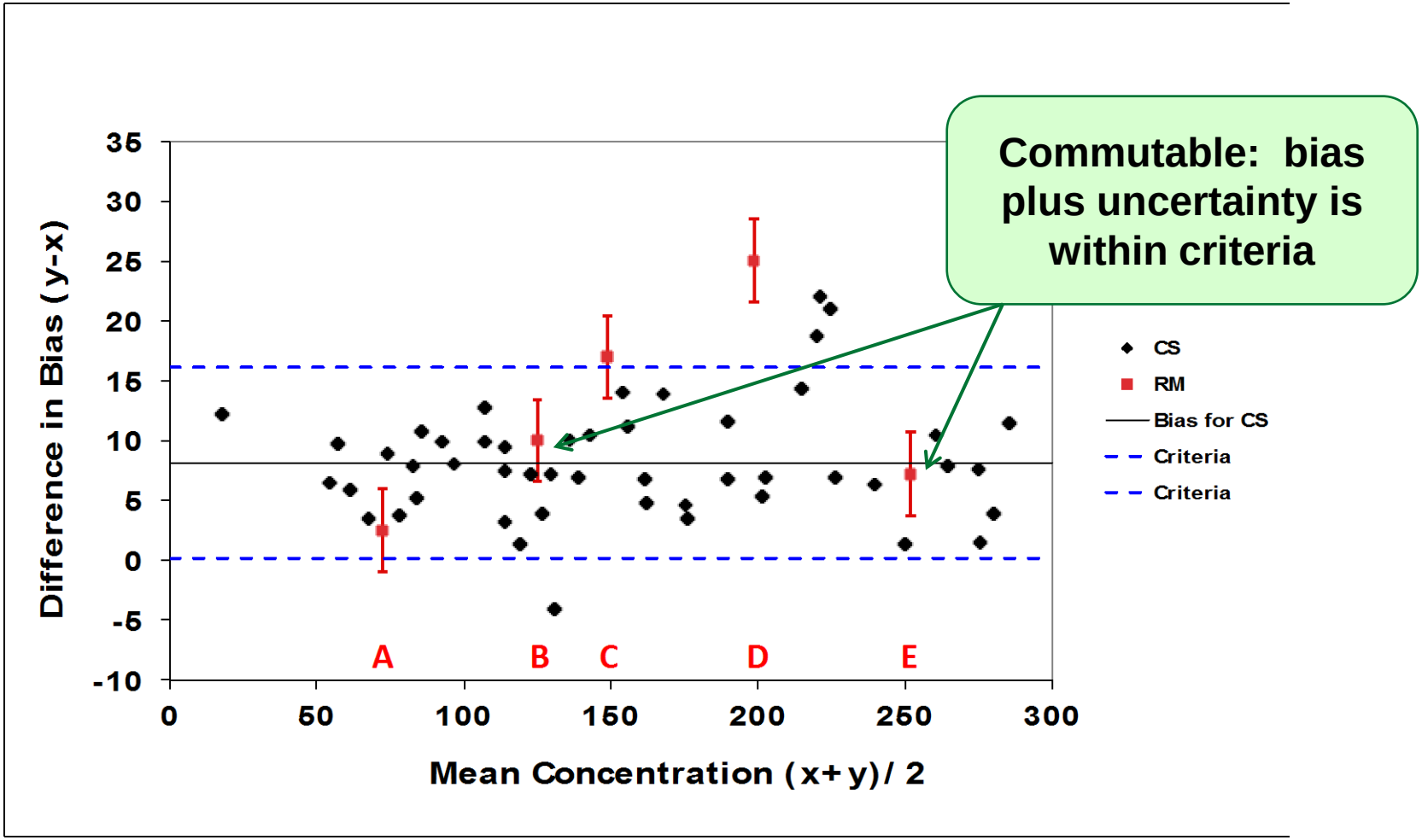
Closeness of agreement model

1. Estimate the bias between 2 measurement procedures for the patient samples and for the reference material(s)
2. Estimate the precision 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



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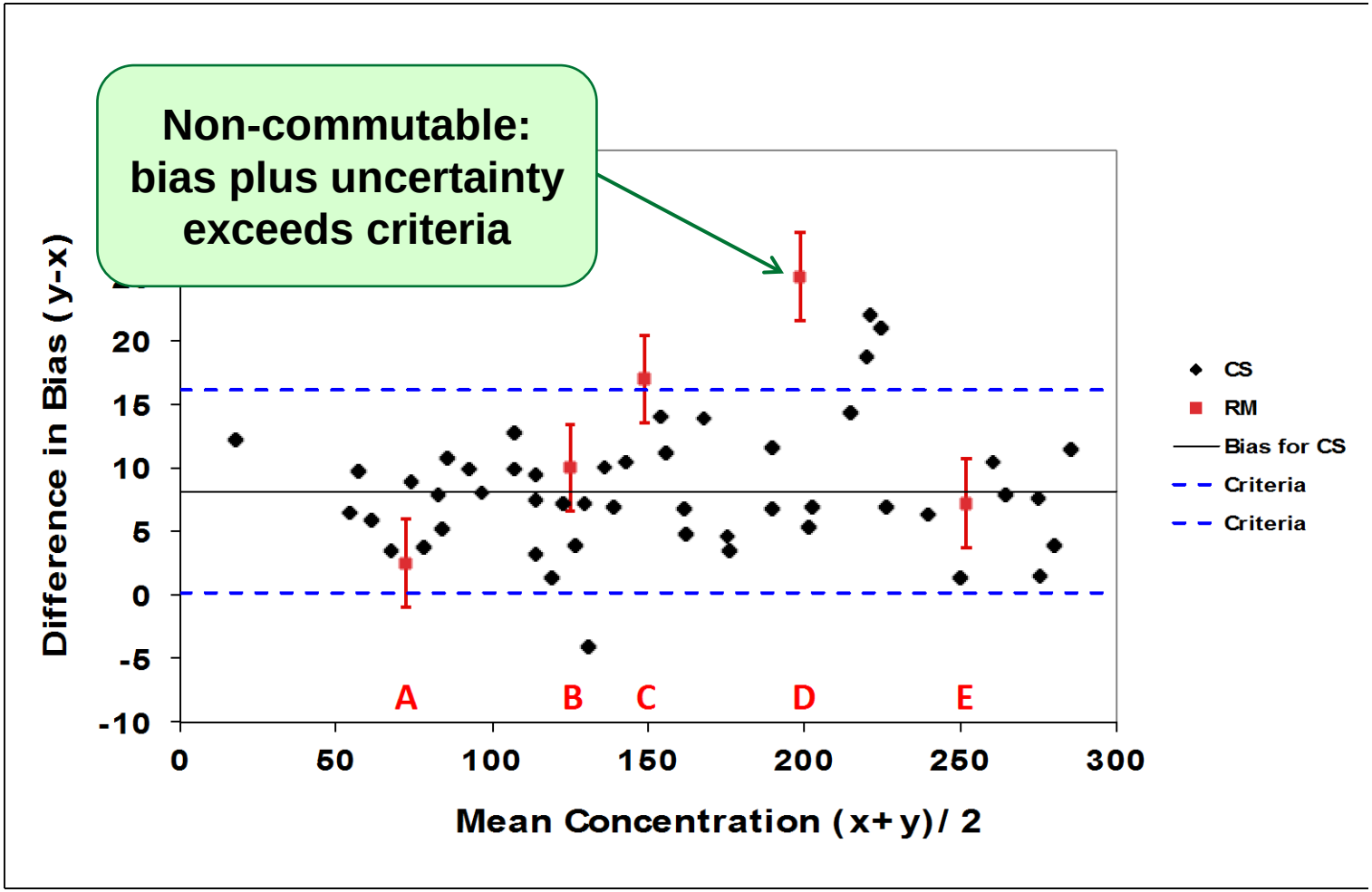
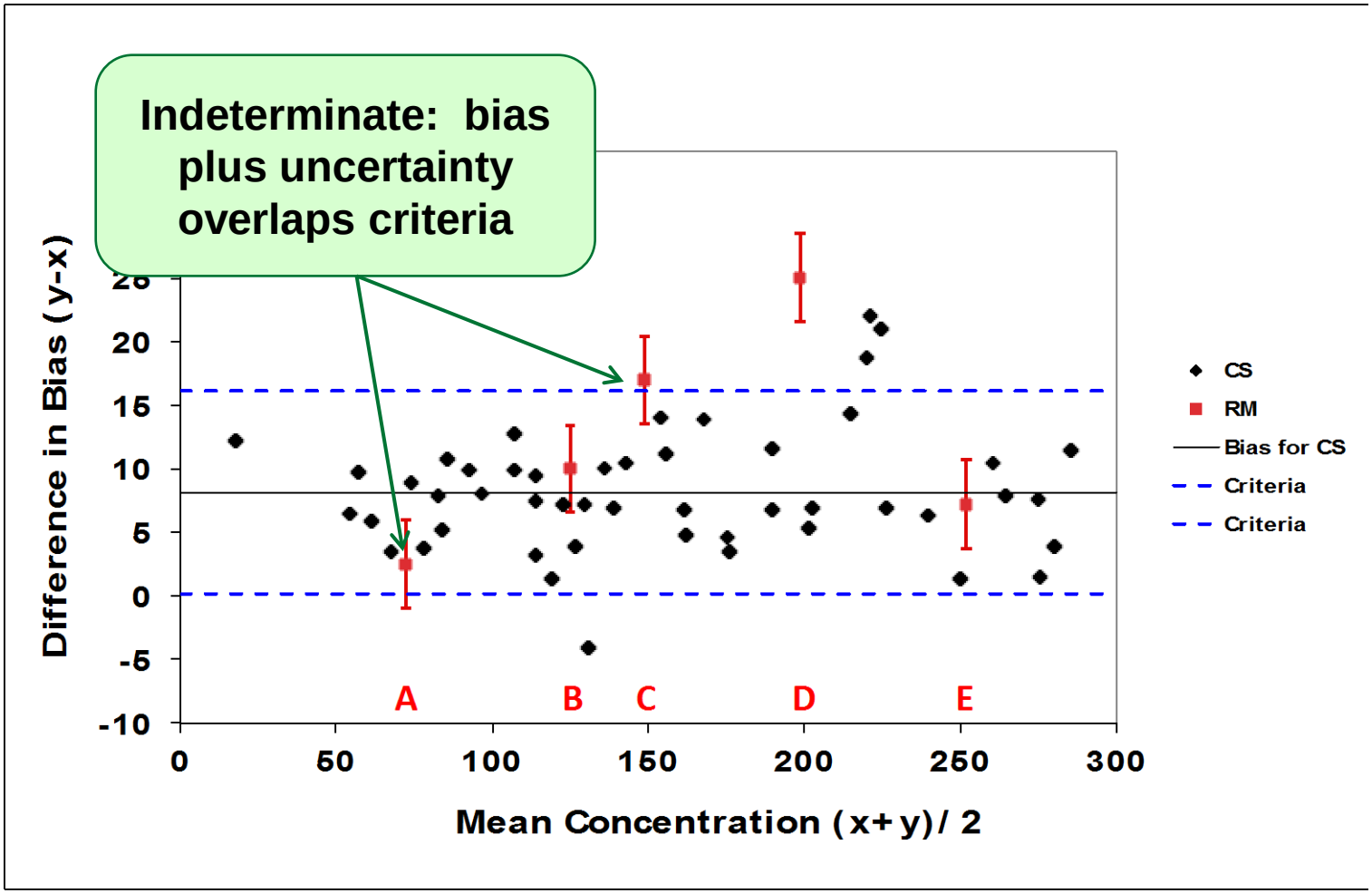


Difference in bias vs. fixed criteria



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

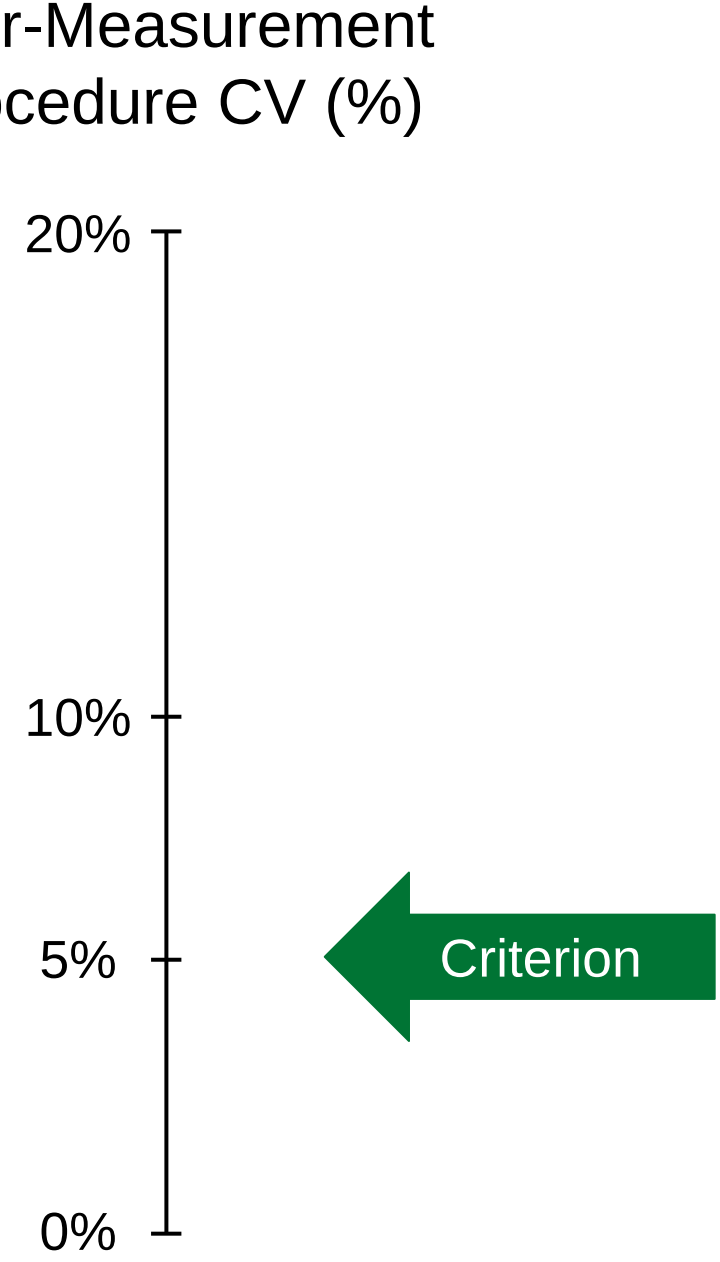
3. Compare the pooled CV plus uncertainty to a fixed fit-for-purpose criterion

4. Use the RM for calibration traceability and repeat steps 1-2-3

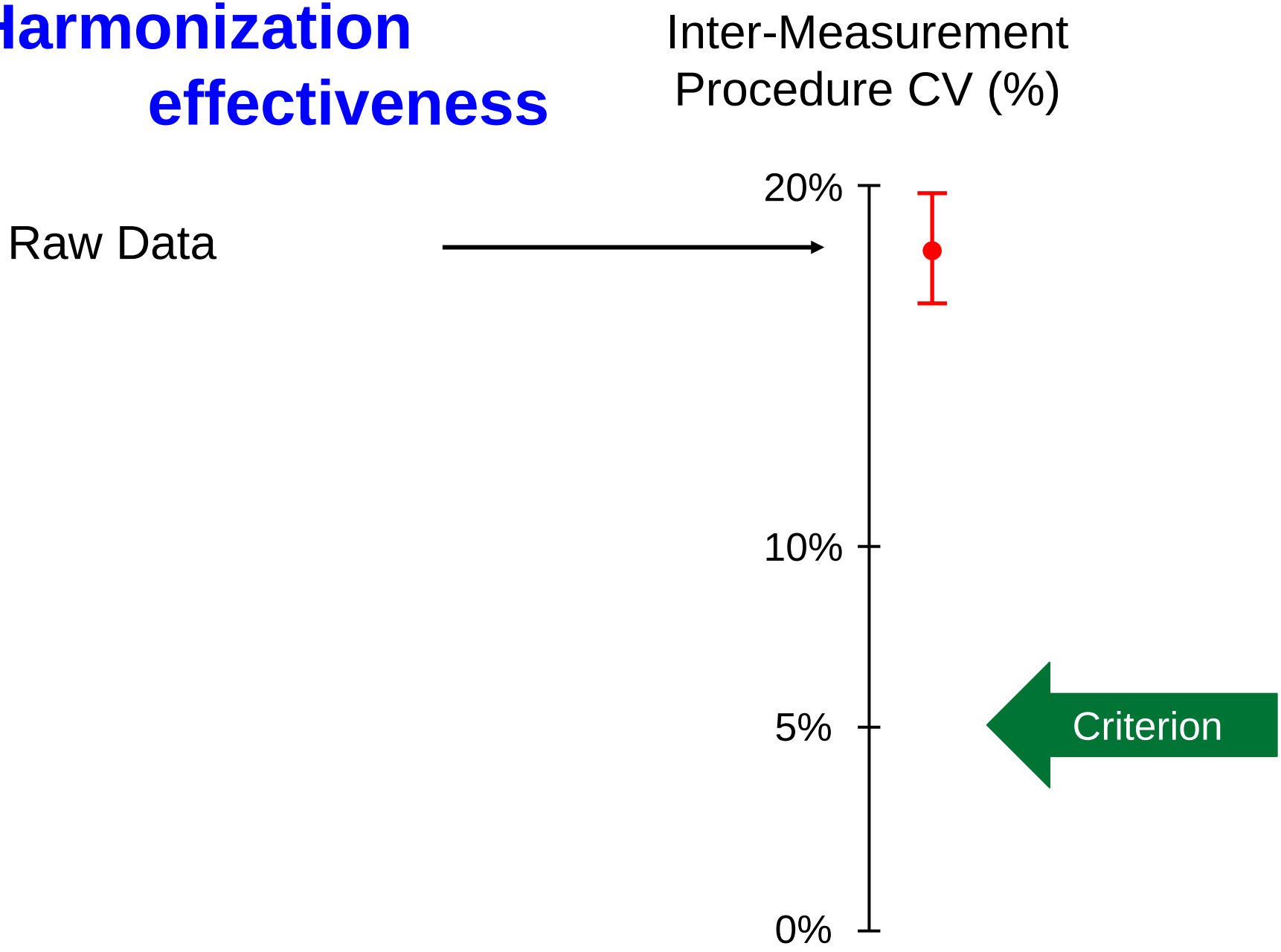
    - Can be a mathematical recalibration

    - Or a physical recalibration

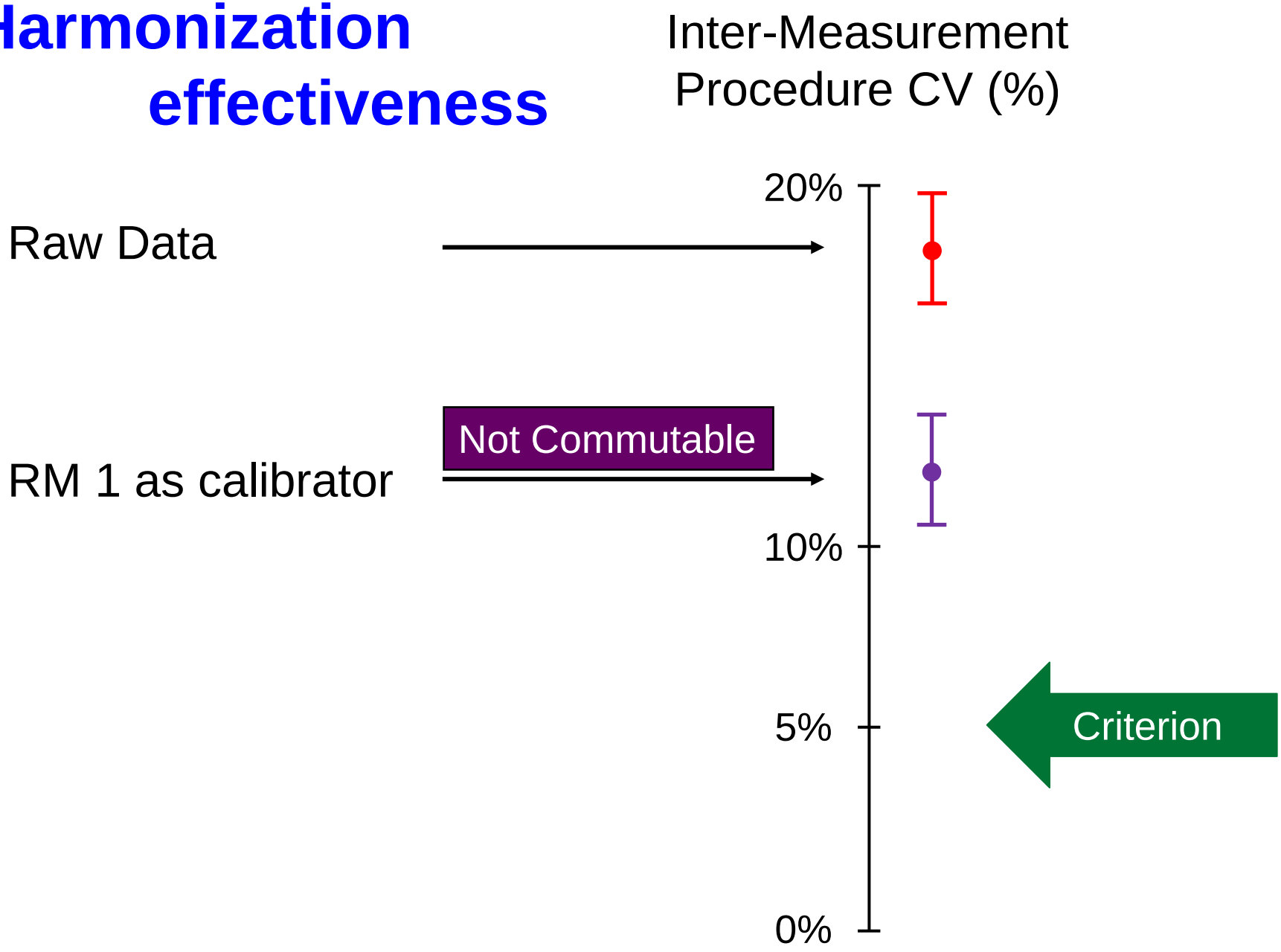
Harmonization effectiveness



Harmonization effectiveness



Harmonization effectiveness



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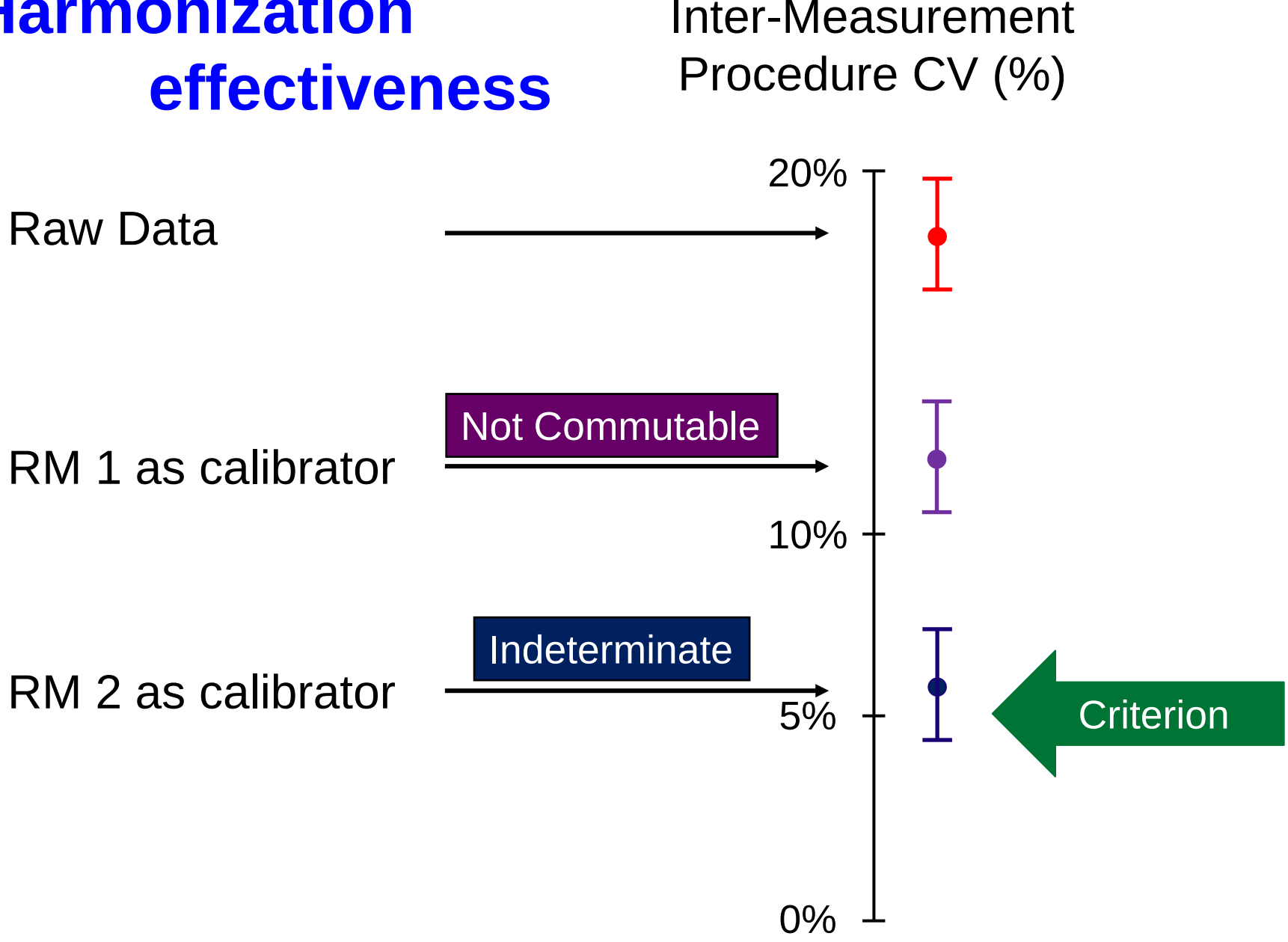
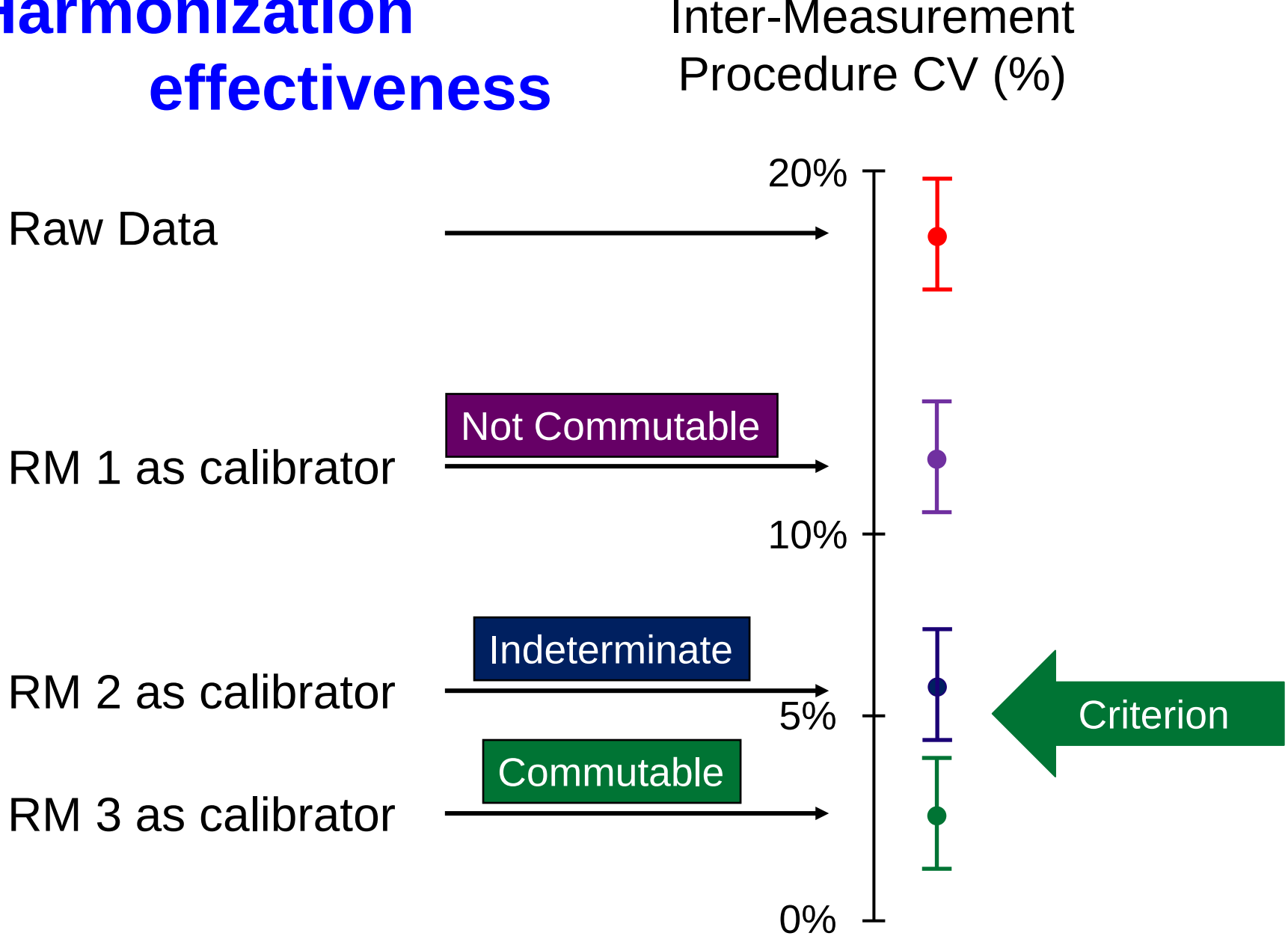


Harmonization effectiveness



Commutability decision applies at a point in time

1. Applies to the RM and measurement procedures included in the commutability assessment

2. Influences such as new reagent lot or other changes in measurement conditions may alter commutability

3. The commutability of a RM may change on storage

Assumptions

- The commutability of a RM does not change over time
  - RM is stable on storage
  - Insignificant influence of changes in measurement conditions such as new reagent lots or maintenance items over time

- The difference in bias between RM and clinical samples is the same over time irrespective of changes in measurement conditions or RM storage

Correction for non-commutability

A correction for non-commutability can be applied to the quantity value of a RM to make it useful for a measurement procedure for which it otherwise would not be suitable for use

- A correction for non-commutability can improve harmonization of patient results
- and is better than calibration with a non-commutable RM

Correction for non-commutability

- Closeness of agreement model allows the magnitude of non-commutability (difference in bias) to be quantitated

- Harmonization effectiveness model allows a correction to be applied to a RM value and the subsequent improvement in inter-measurement procedure CV to be assessed

Correction for non-commutability

3. Requires the correction to be consistent over time and not influenced by changes in measurement conditions or changes in the RM

   - ❖ The same assumptions are made for a commutable RM
   - ❖ The magnitude of the difference in bias that caused a non-commutability decision is larger

Correction for non-commutability

- Can we have confidence in consistent performance when the influence quantities that caused non-commutability are unknown – is the confidence related to the magnitude of a difference in bias

- Key influence quantities
  - Clinical samples – molecular forms, interferences
  - RM formulation – source of matrix, supplements, artifacts
  - Reagent formulation – reactive components, impurities

Correction for non-commutability

4. Requires the uncertainty of a correction to be small enough for the intended use of a RM

5. The correction is determined by the user of a RM based on additional experimental data beyond what was used for the commutability assessment

Commutability for a new lot of RM

- New lots of RM may not require a new full commutability assessment if prepared to the same specifications
  - A challenging task when using biological materials
  - The specifications must be complete
- A validation scheme is being investigated

Validation approach

- Measure commutable RM and new RM in the same run by measurement procedures in the original commutability assessment
- Calculate the ratio of results
- Ratios that are the same mean the new and old lots have the same commutability
- Should a small number of clinical samples also be included

Commutability: who is responsible

- **Reference material producer**
  - Cannot know all procedures in use
  - Should make a material likely to be commutable
  - Should validate for commonly used procedures
- **Measurement procedure producer**
  - Must confirm commutability for an intended use
  - Responsible for new procedures introduced

Questions / Comments