Future challenges in EQA, with special emphasis on harmonization and commutability

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Baebies: consultant

BioRad Laboratories: speaking honorarium

NIST: research contract

Siemens Healthineers: speaking honorarium and travel support

Learning objectives

- Why commutability matters
- What is a harmonization protocol
- How EQA supports harmonization
- What are our next steps

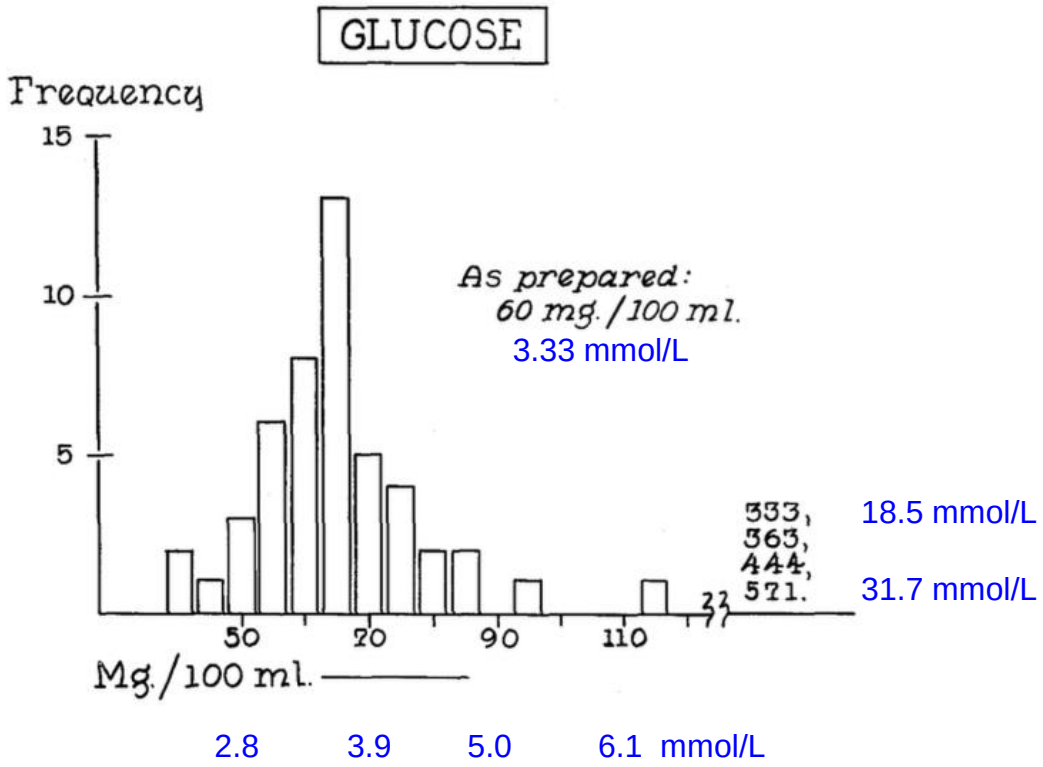
Conclusions

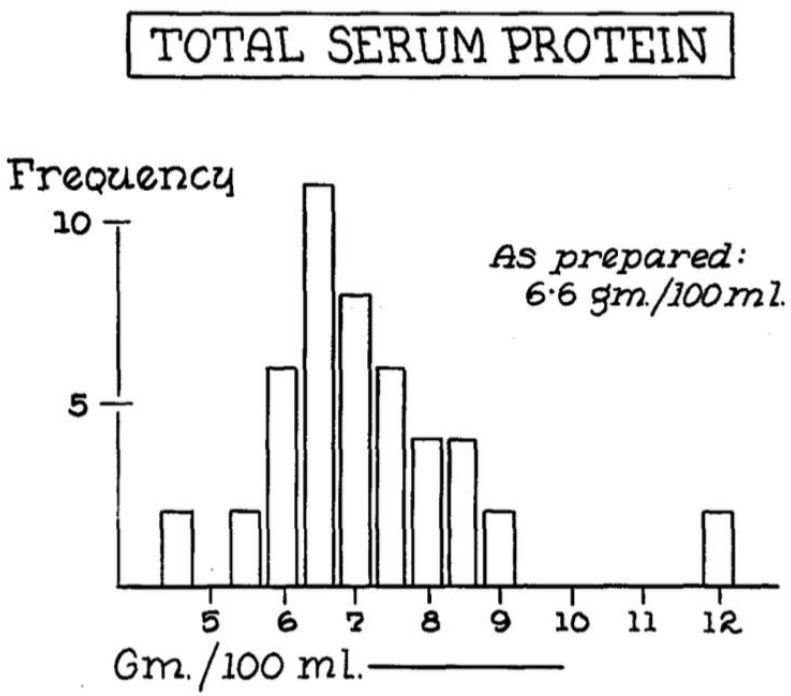
- **Harmonization of results is important to reduce medical errors**
- **EQA with commutable samples has an essential role in the process**
- **Global cooperation is needed to support harmonization**

EQA #1

Belk, Sunderman. A survey of the accuracy of chemical analyses in clinical laboratories. Am J Clin Pathol 1947;17:853-61.

- 59 Hospitals in Philadelphia, USA
- All tests were lab developed





Belk, Sunderman. Am J Clin Pathol 1947;17:853-61.

Standardization / Harmonization Timeline

1947 – first EQA; results need harmonization

1953-1972 – AACC publishes 7 volumes of *Standard Methods of Clinical Chemistry*

1954 – Coulter Counter introduced

1958 – Technicon AutoAnalyzer introduced

1967 – Radin. *What is a Standard?* Clin Chem 1967; 13: 55-76

EQA with "patient matrix" samples (not commutable)

1976 – First IFCC reference method: AST

1978 – CDC/FDA/NBS conference on reference systems; spawns NRSCL (USA) and other countries

EQA with RMP values for non-commutable samples – 1980s

CDC Cholesterol Reference Method Laboratory Network - 1989

CAP conference on "matrix effects" and EQA with commutable samples – 1992

EQALM founded 1989 – 1996

2018

Standardization / Harmonization Timeline

1998 – Dutch Calibration 2000

1998 – EU Directive (2017 EU Regulation)

2003 – ISO 17511 metrological traceability and JCTLM

Standardization to higher order CRMs and RMPs

Thienpont et al. … EQA … time to care about the quality of the samples.
Scand J Clin Lab Invest 2003; 63: 195-201

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

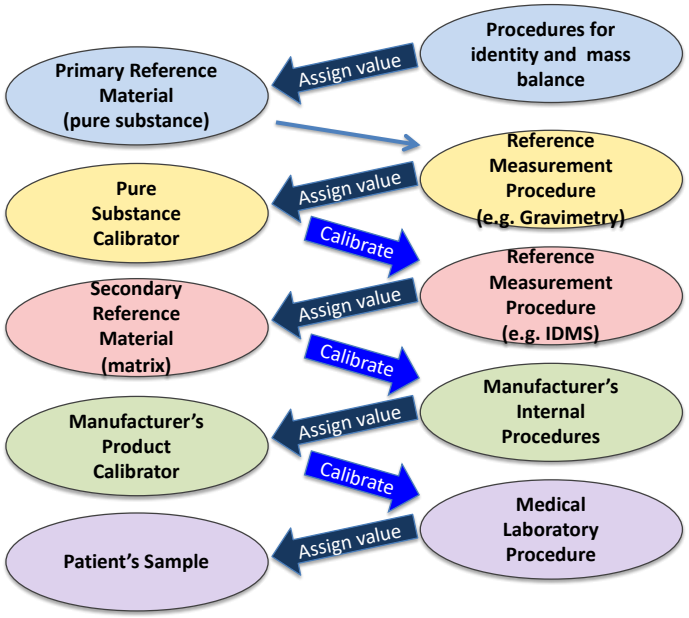
Miller et al. Roadmap for harmonization of clinical laboratory measurement procedures.
Clin Chem 2011;57:1108-17

Harmonization protocol when no CRM or RMP exists

2018

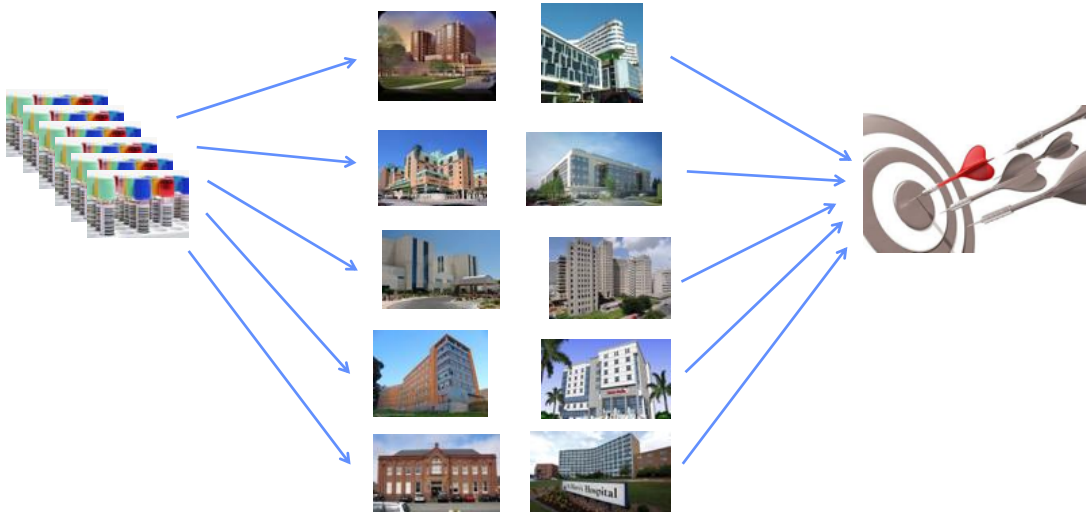
STANDARDIZATION / HARMONIZATION

METROLOGICAL TRACEABILITY



ASSESSMENT

EQA



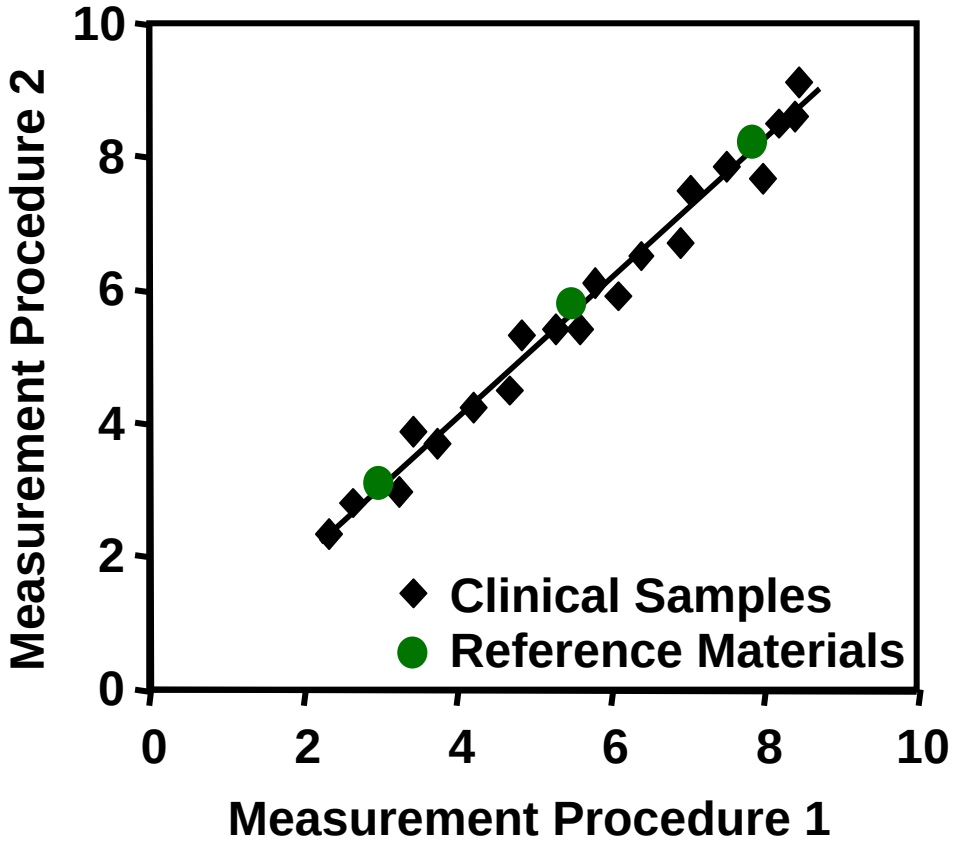
EQA Scheme Design

Sample Characteristics

	Value Assign by RMP or CRM	Accuracy of Lab			Harmonization of Measurement Procedures	
		vs. RS	vs. All	vs. Peer Grp	vs. RS	vs. All
Commutable	X	X	X	X	X	X
Commutable	◌	◌	X	X	◌	X
Non-Commutable				X		

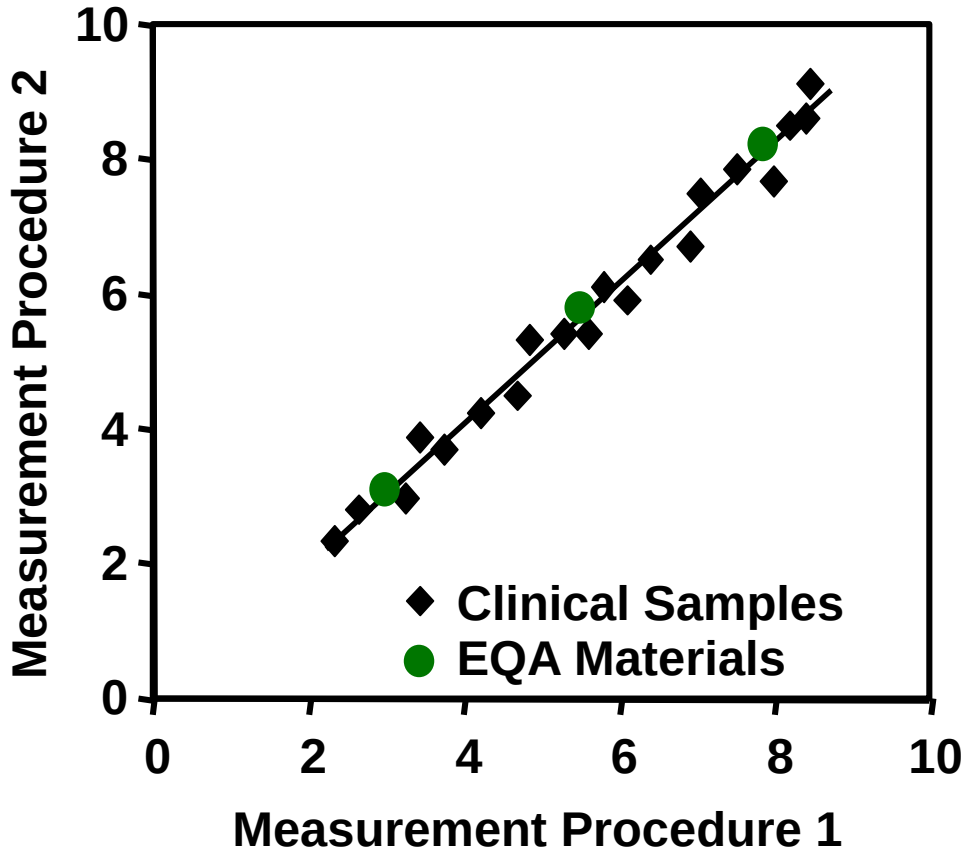
Adapted from Miller et al. Clin Chem 2011;57:1670-80

Commutable



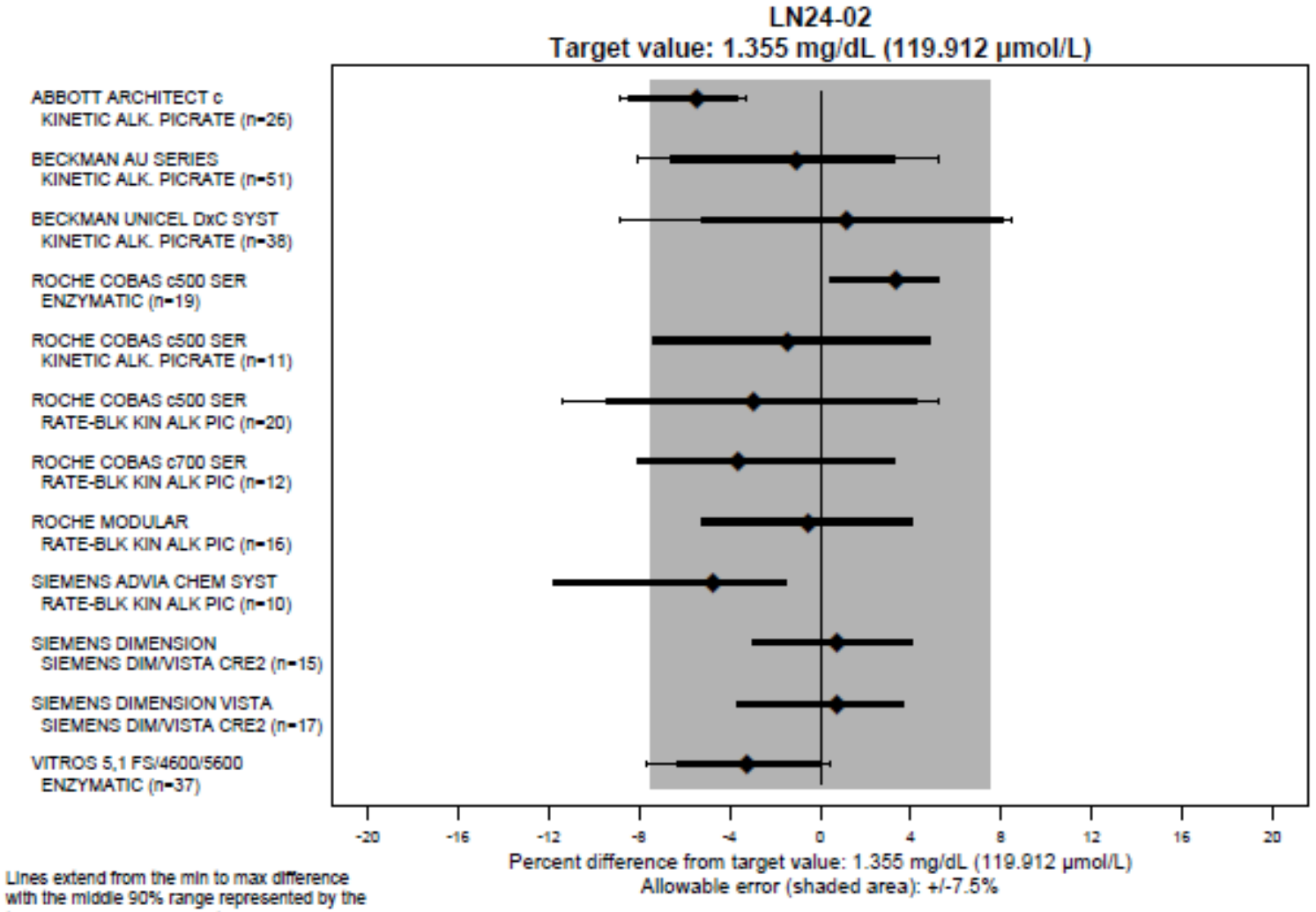
RM and CS results have the same relationship between measurement procedures

Commutable EQA



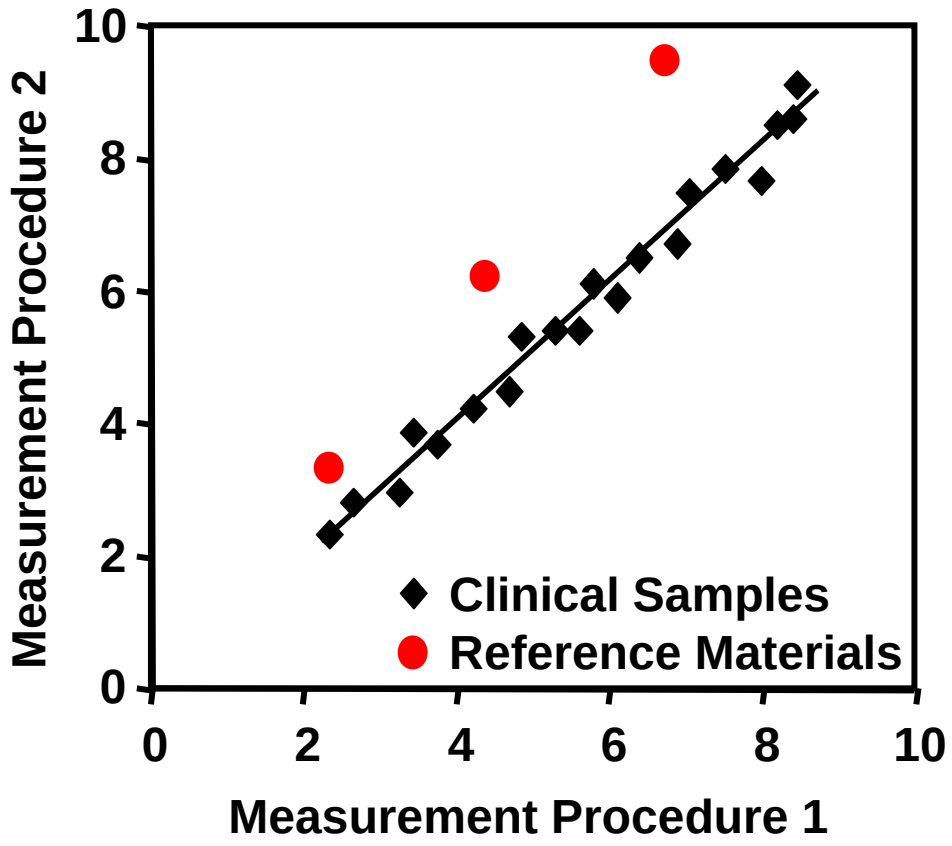
EQA results reflect status of clinical sample results

CAP Accuracy Based Creatinine Survey



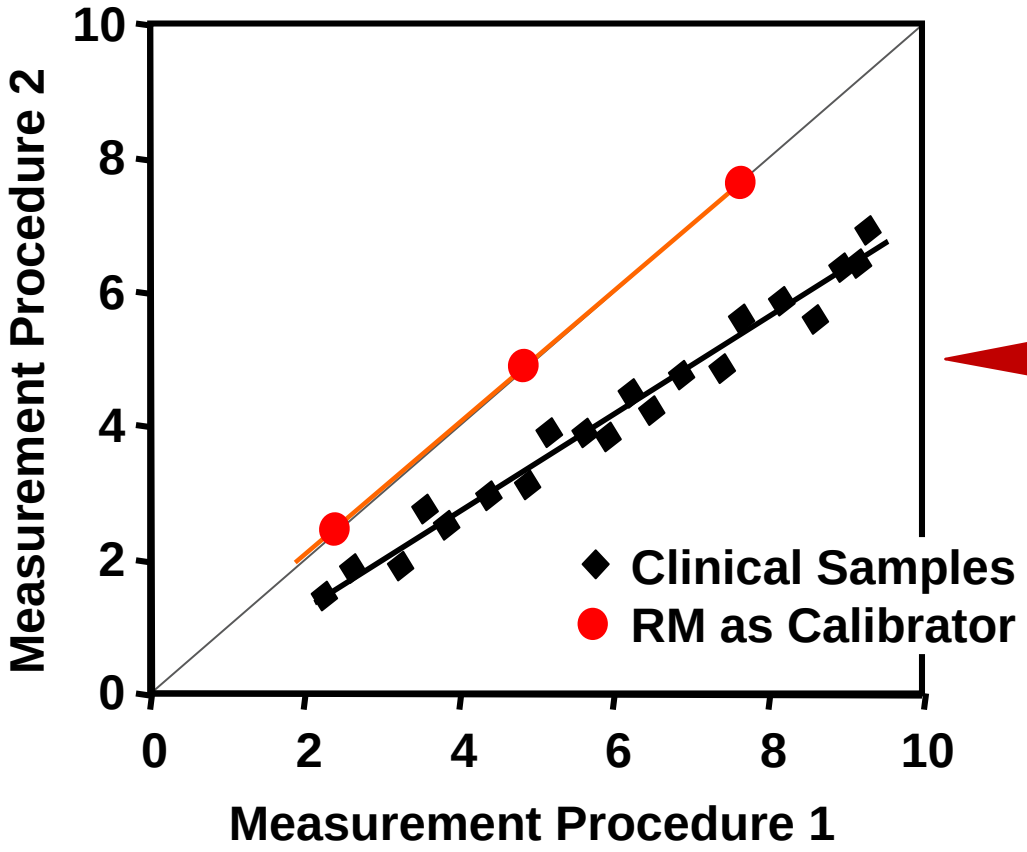
Lines extend from the min to max difference with the middle 90% range represented by the thicker line. The median is the solid diamond. Outliers were excluded from this analysis.

Non-Commutable



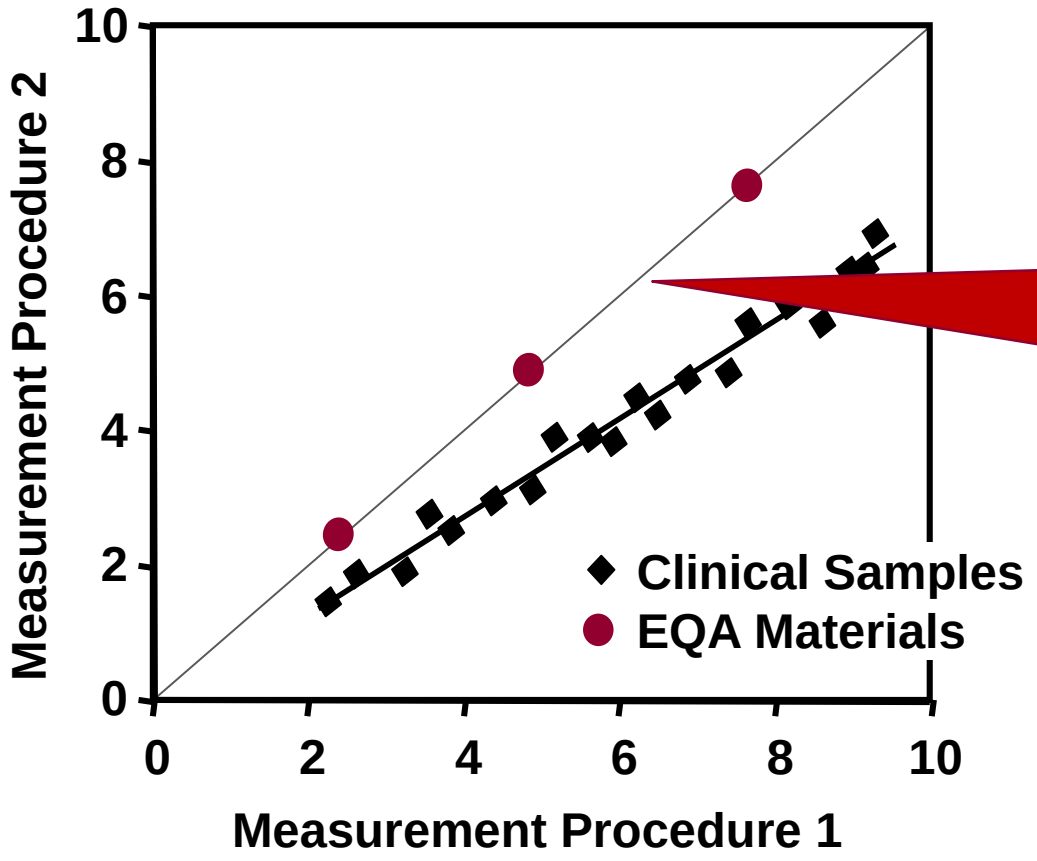
RM and CS results have a different relationship between measurement procedures

Non-Commutable Calibrator



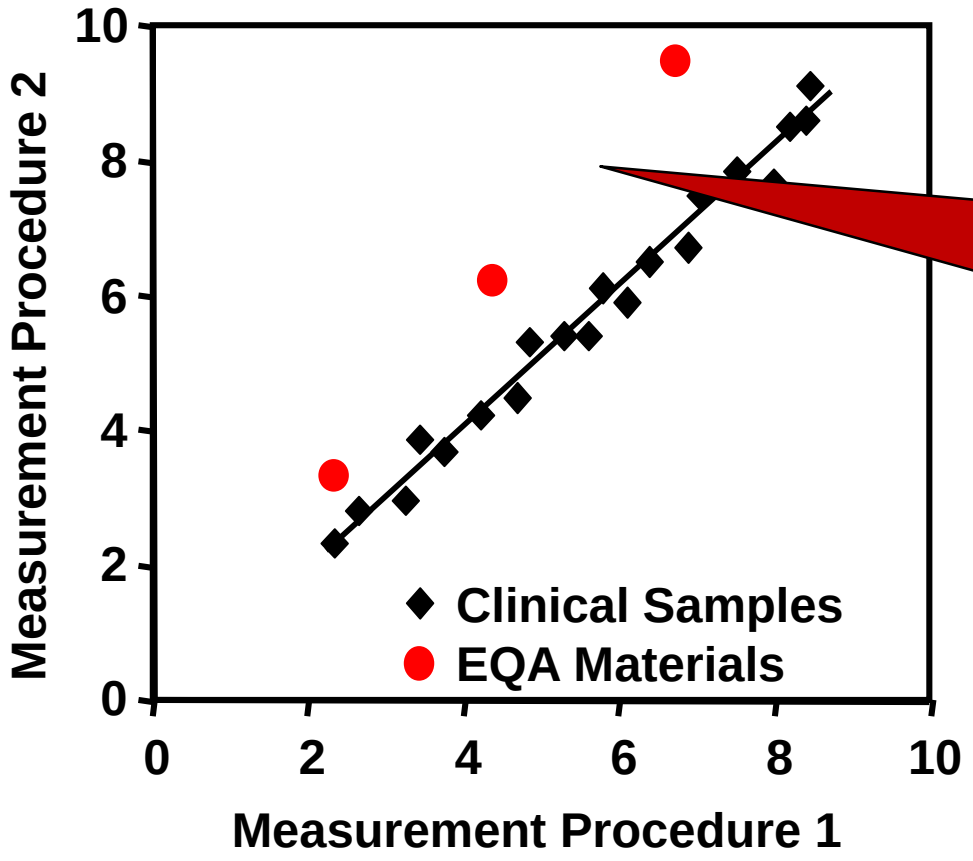
causes CS results to be different

Non-Commutable EQA



Apparent agreement for EQA results means patient results DO NOT AGREE

Non-Commutable EQA



Lack of agreement for EQA results does **NOT** mean patient results are different

Influence of reagent lot on peer group mean

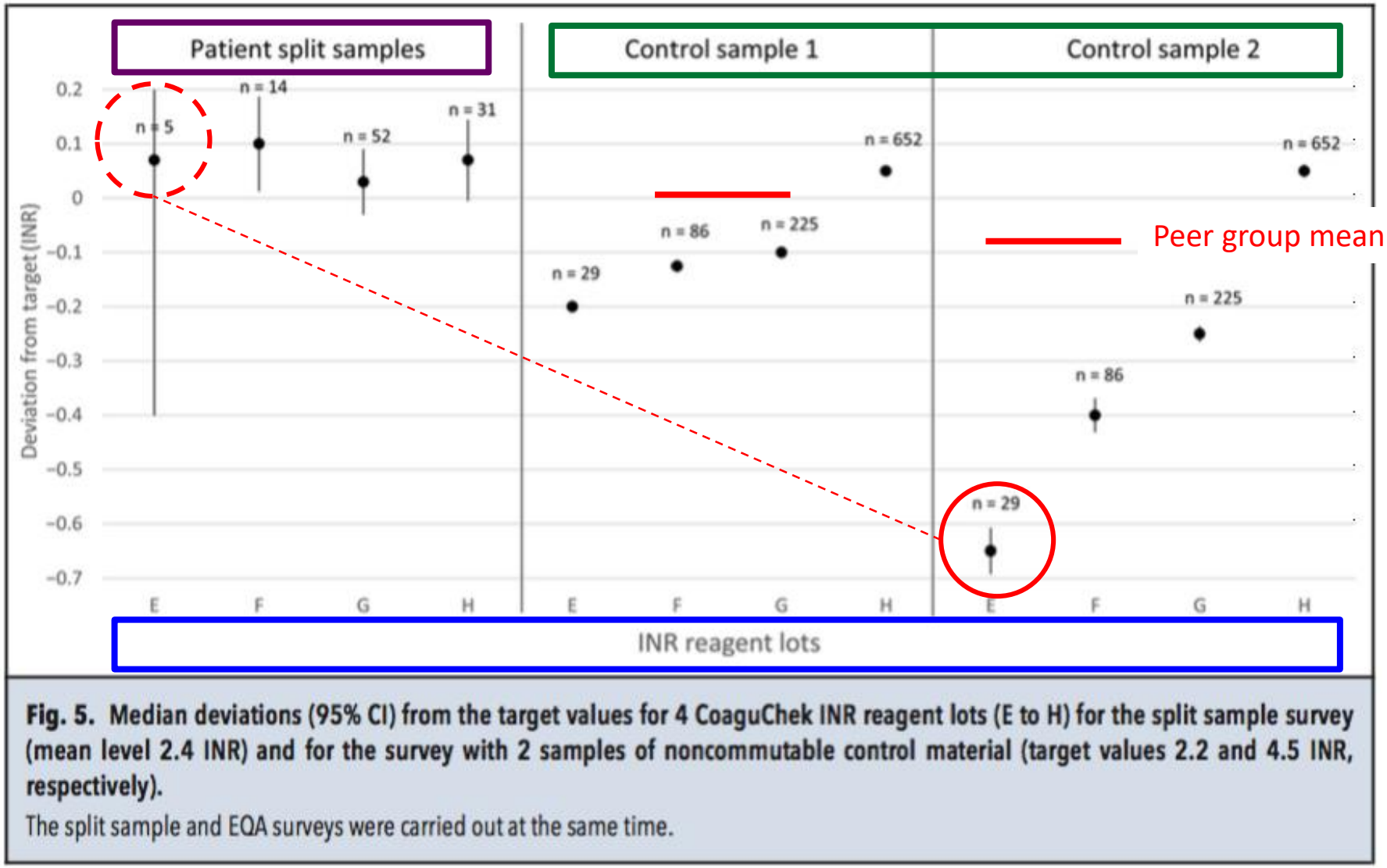
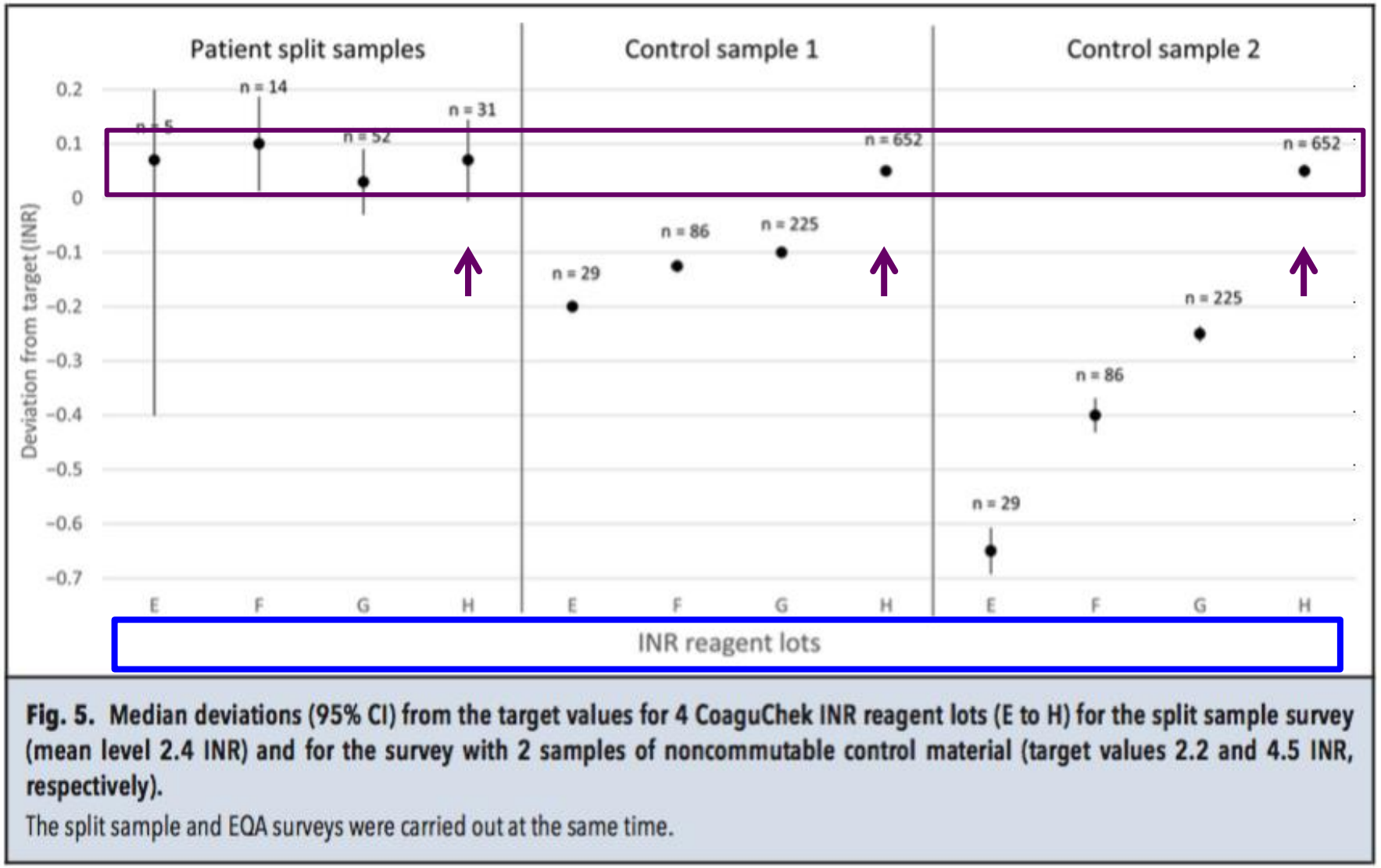


Fig. 5. Median deviations (95% CI) from the target values for 4 CoaguChek INR reagent lots (E to H) for the split sample survey (mean level 2.4 INR) and for the survey with 2 samples of noncommutable control material (target values 2.2 and 4.5 INR, respectively).

The split sample and EQA surveys were carried out at the same time.

Stavelin et al. Clin Chem 2016;62:708-15.

EQA samples were commutable when reagent lot H was used



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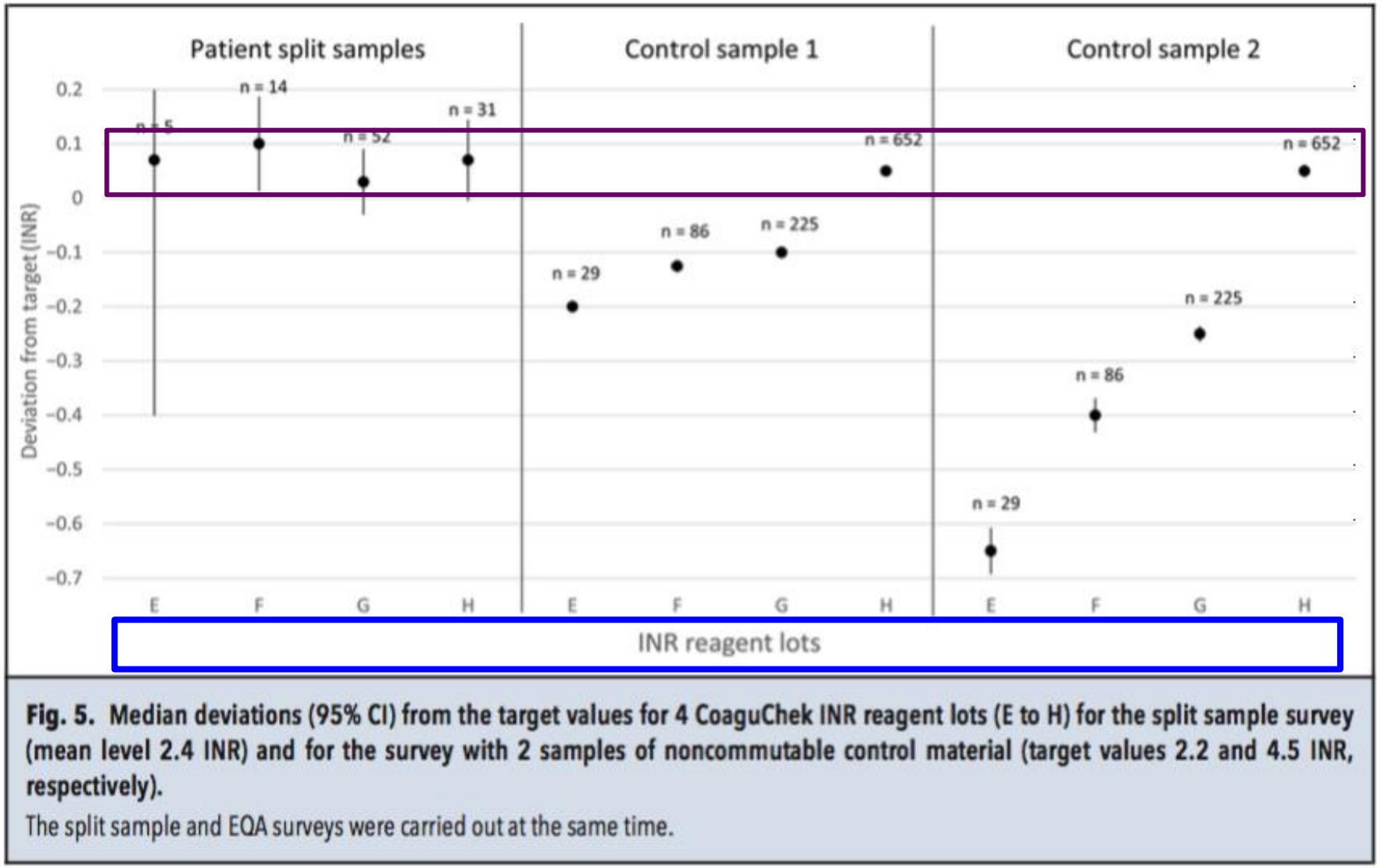
The split sample and EQA surveys were carried out at the same time.

Stavelin et al. Clin Chem 2016;62:708-15.

Commutability with the next reagent lot is unknown



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The split sample and EQA surveys were carried out at the same time.

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Stavelin et al. Clin Chem 2016;62:708-15.

Commutability is important for:

Matrix-based CRMs used as calibrators

EQA materials used to assess harmonization

IFCC Working Group on Commutability

Recommendations for assessing commutability:

Part 1: general experimental design; *Clin Chem* 2018;64:447-54

Part 2: using the difference in bias between a reference material and clinical samples; *Clin Chem* 2018;64:455-64

Part 3: using the calibration effectiveness of a reference material; *Clin Chem* 2018;64:465-74

Qualification of measurement procedures to include in a commutability assessment

1. **Adequate calibration model and selectivity for the measurand**
   - **Good correlation between measurement procedures for clinical samples**
   - **Small error component from sample specific influences**
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 most 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**

Criterion for commutability is based on medical use requirements

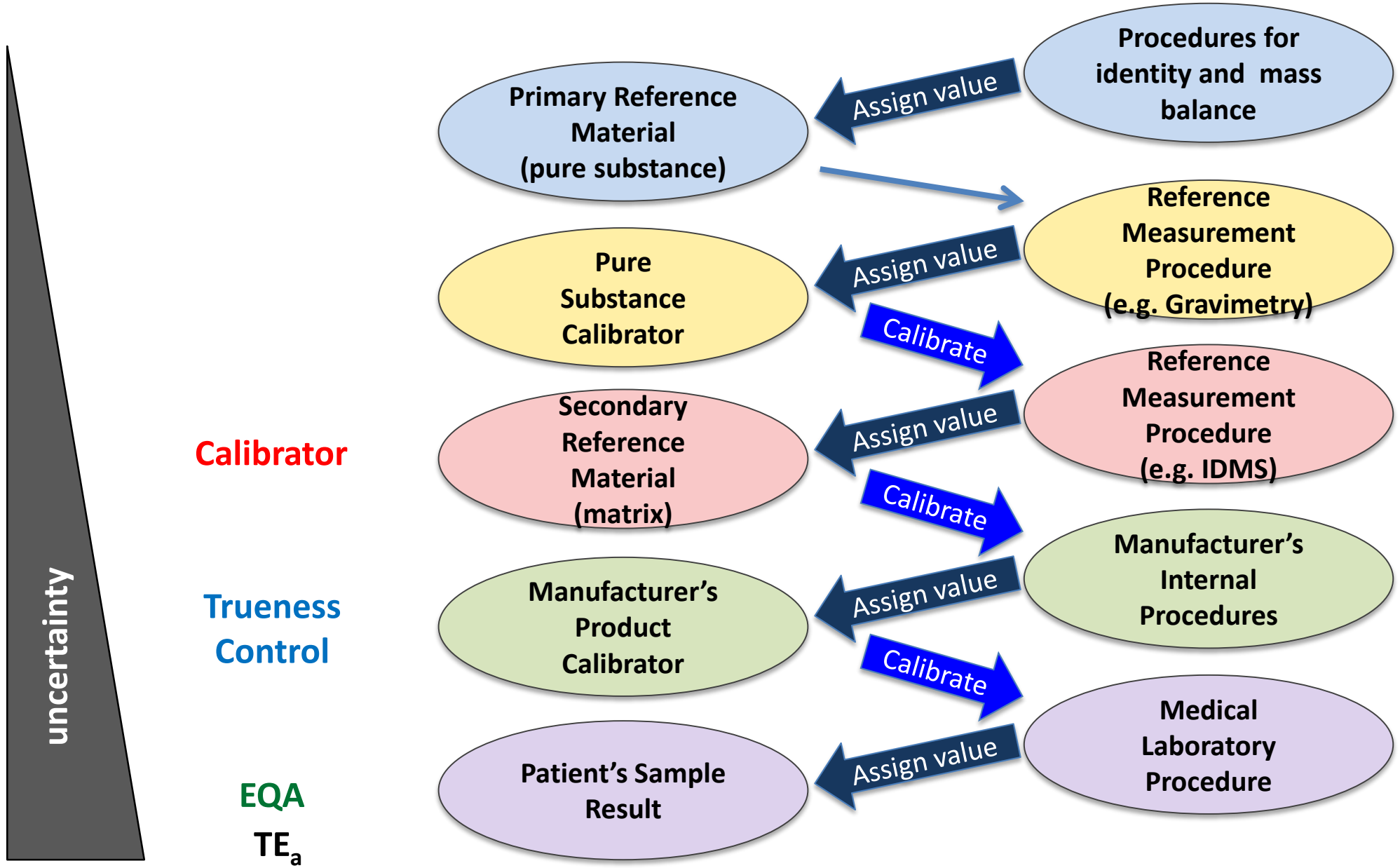
1. **Establish the analytical performance requirement for patient sample results**

Defining analytical performance goals – 15 years after the Stockholm Conference. CCLM 2015;53(6) Special Issue

- **Outcome**
- **Biological variation**
- **State of the art**

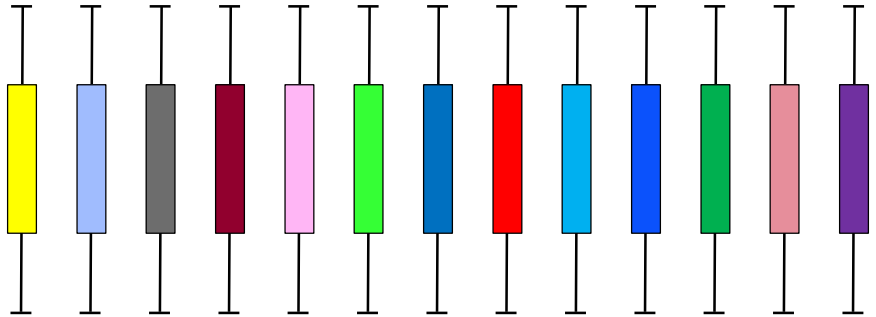
2. **Establish the criterion for commutability as a fraction of the uncertainty required for a reference material's intended use to meet the analytical performance requirement for patient sample results**

Criterion is the same for all measurement procedures in the commutability assessment


uncertainty
Calibrator
Trueness Control
EQA
TE$_a$
Primary Reference Material (pure substance)
Procedures for identity and mass balance
Assign value
Reference Measurement Procedure (e.g. Gravimetry)
Pure Substance Calibrator
Assign value
Calibrate
Reference Measurement Procedure (e.g. IDMS)
Secondary Reference Material (matrix)
Assign value
Calibrate
Manufacturer's Internal Procedures
Manufacturer's Product Calibrator
Assign value
Calibrate
Medical Laboratory Procedure
Patient's Sample Result
Assign value

What is harmonization

Equivalent results among different measurement procedures for the same laboratory test

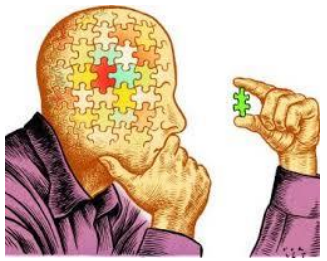


Standardization:

equivalent results are achieved by metrological traceability to a fit-for-purpose higher order reference system

Equivalent

- **Equivalent does not mean identical**
- **Equivalent means within a total allowable error consistent with an acceptable risk of harm from decisions based on a lab test result**

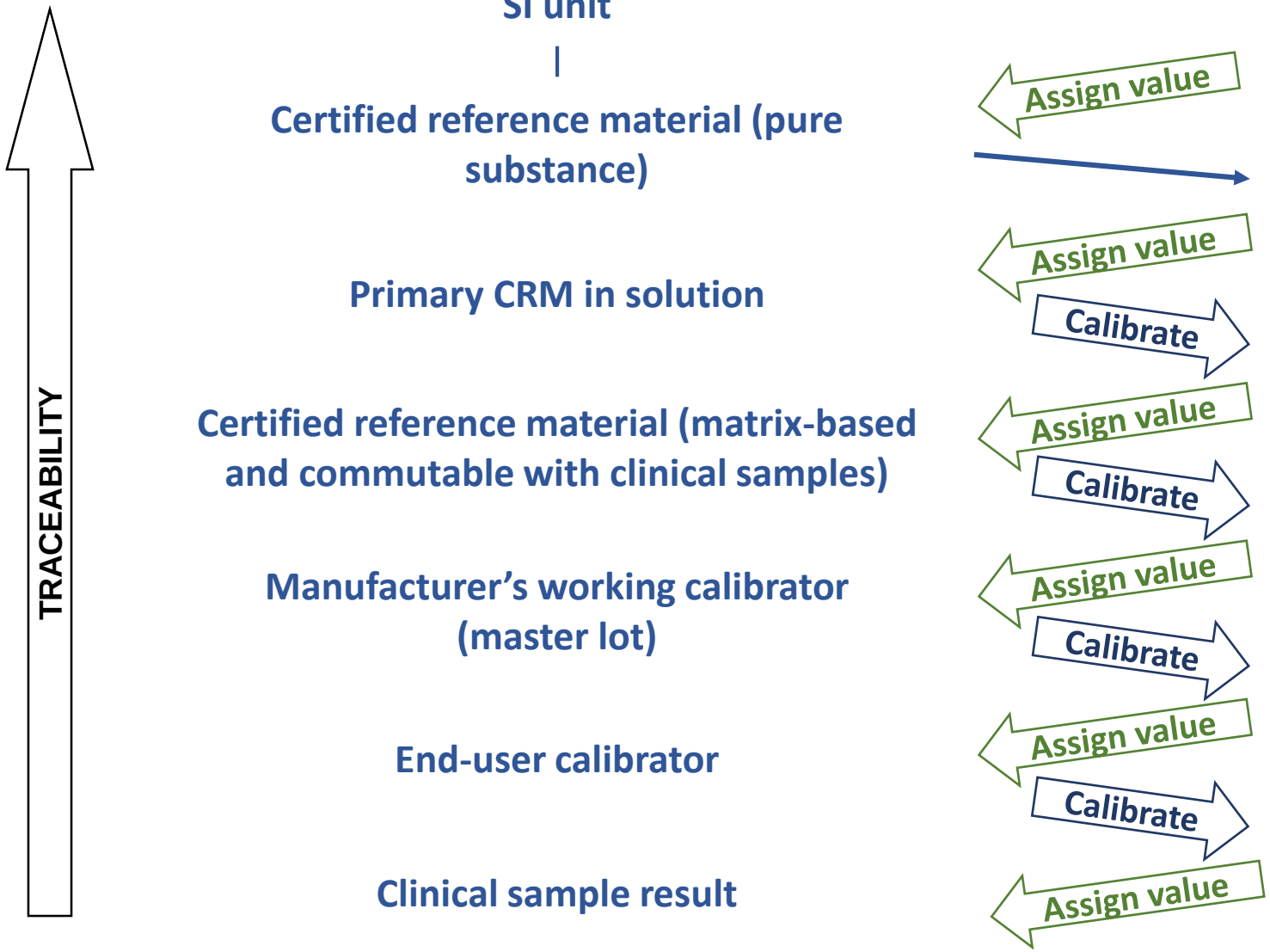


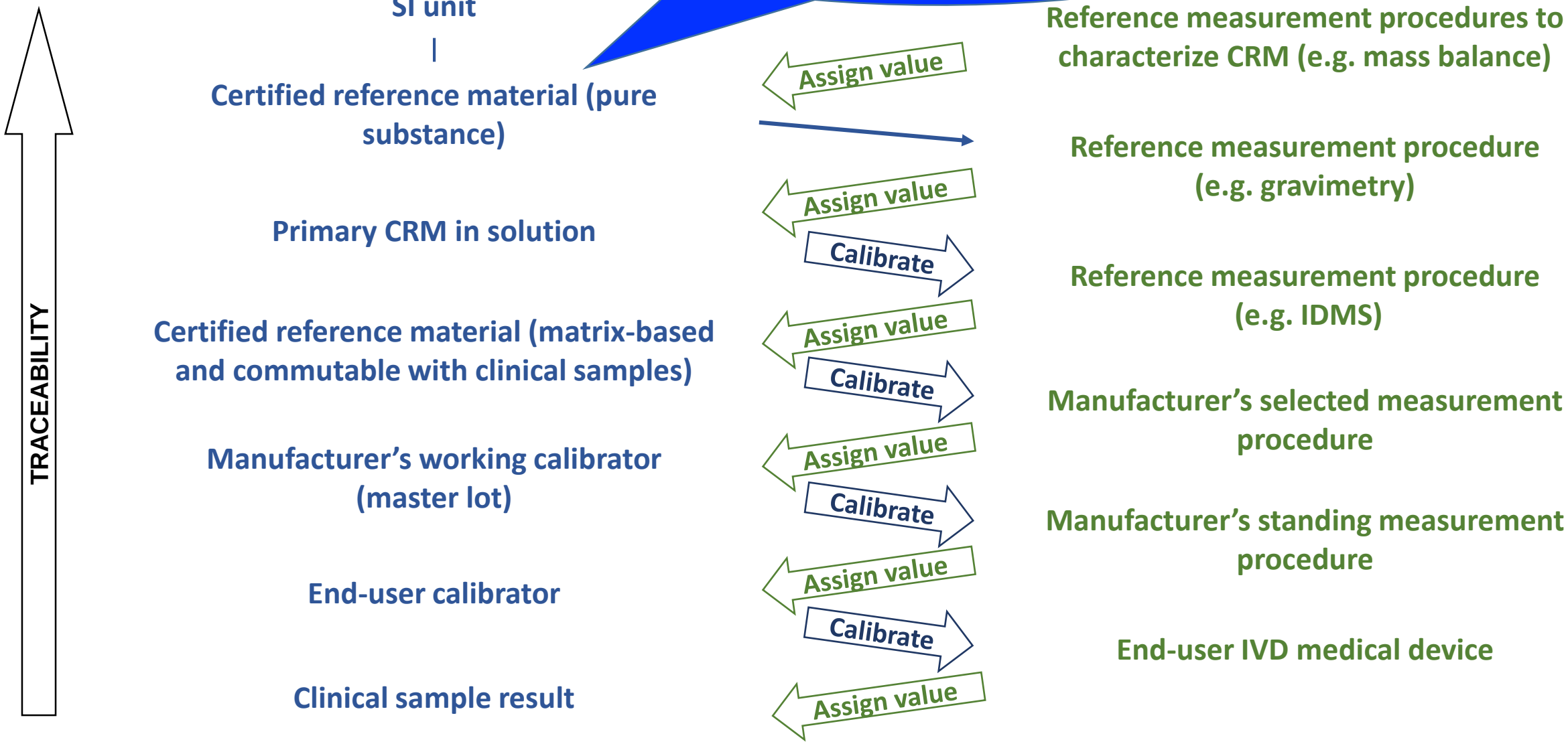
For results to be harmonized / standardized:

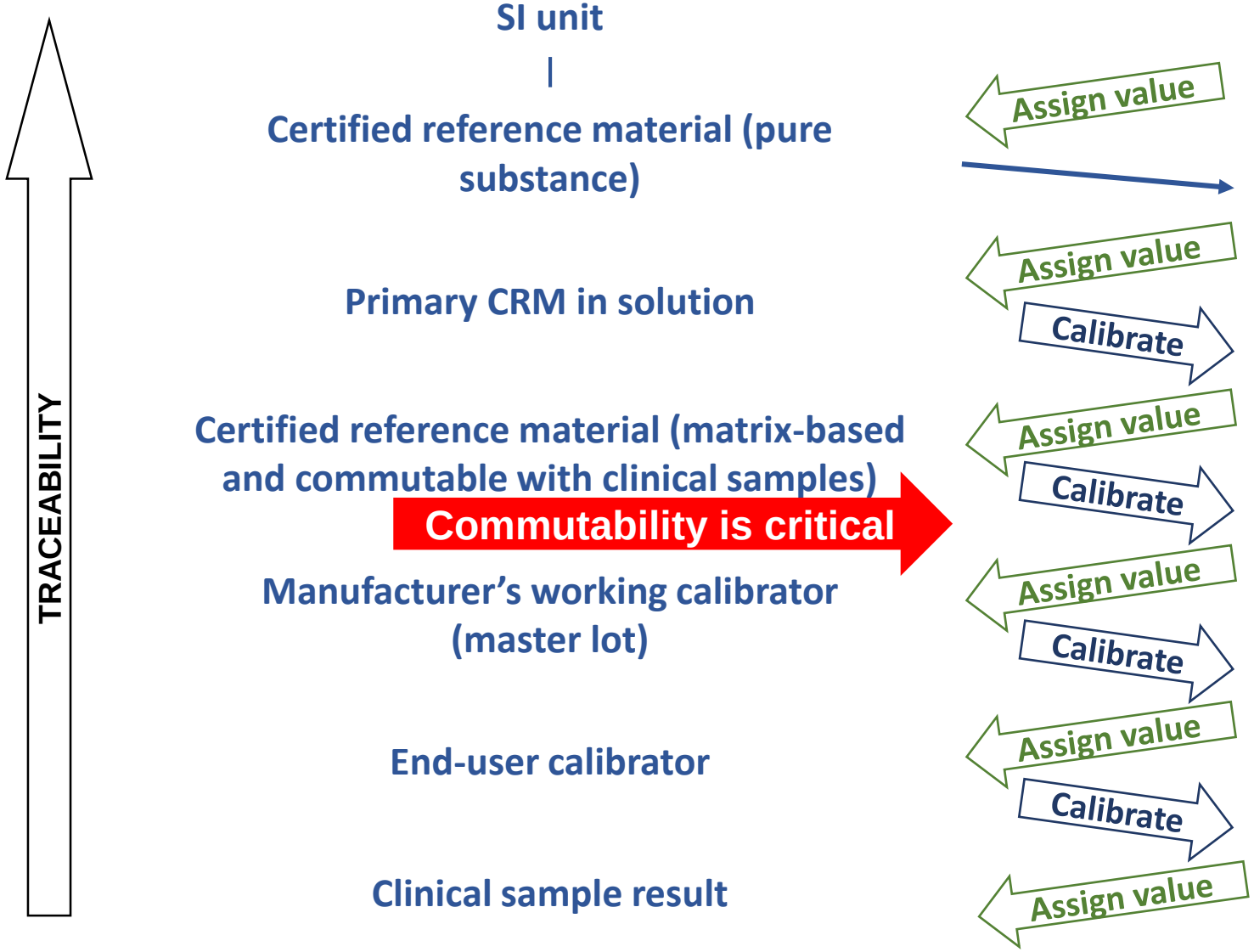
- ✓ **All IVD medical devices must have metrological traceability to the same higher order reference system**
  - **must be fit-for-purpose**

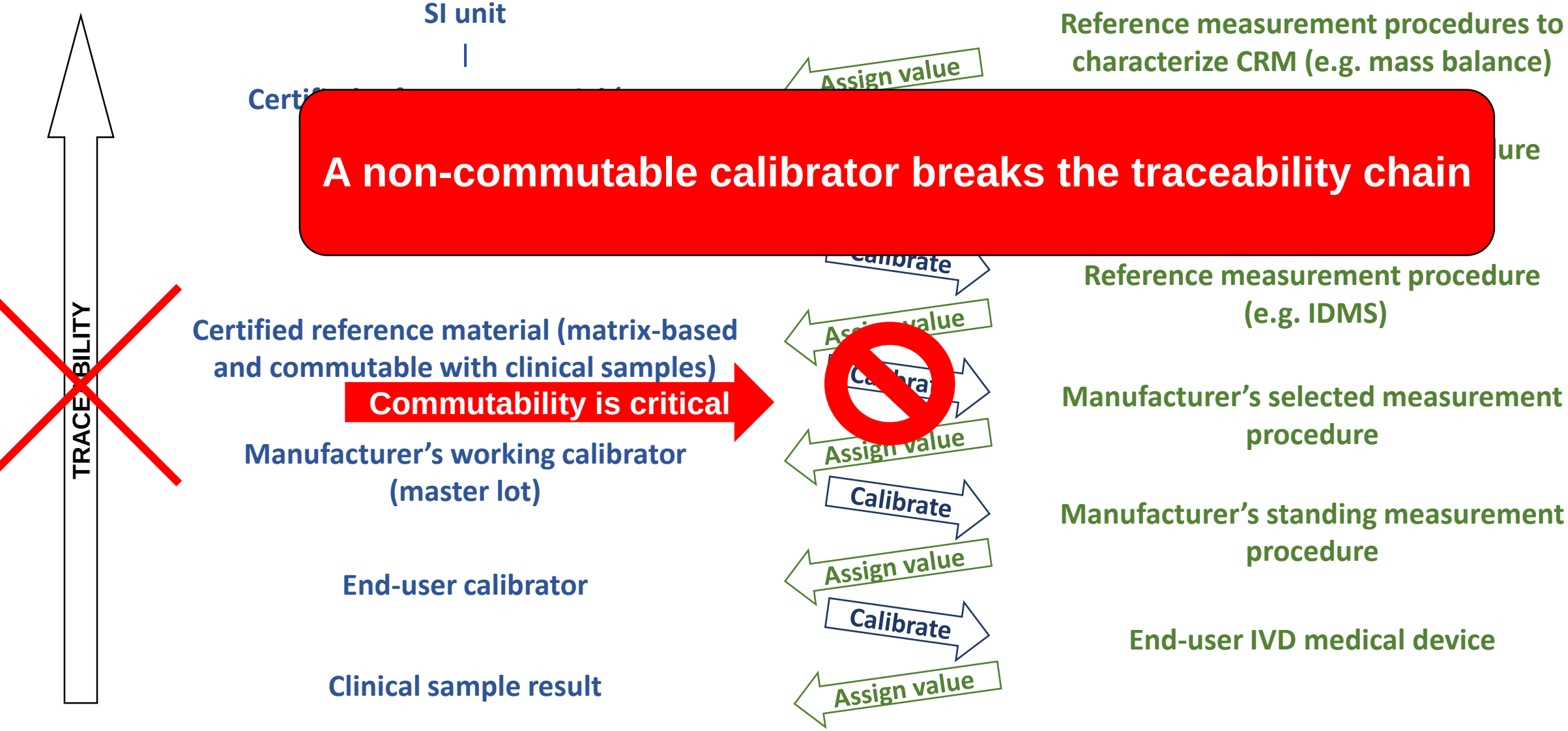
- ✓ **All IVD medical devices must measure the same measurand**
  - **must have adequate selectivity for the measurand**

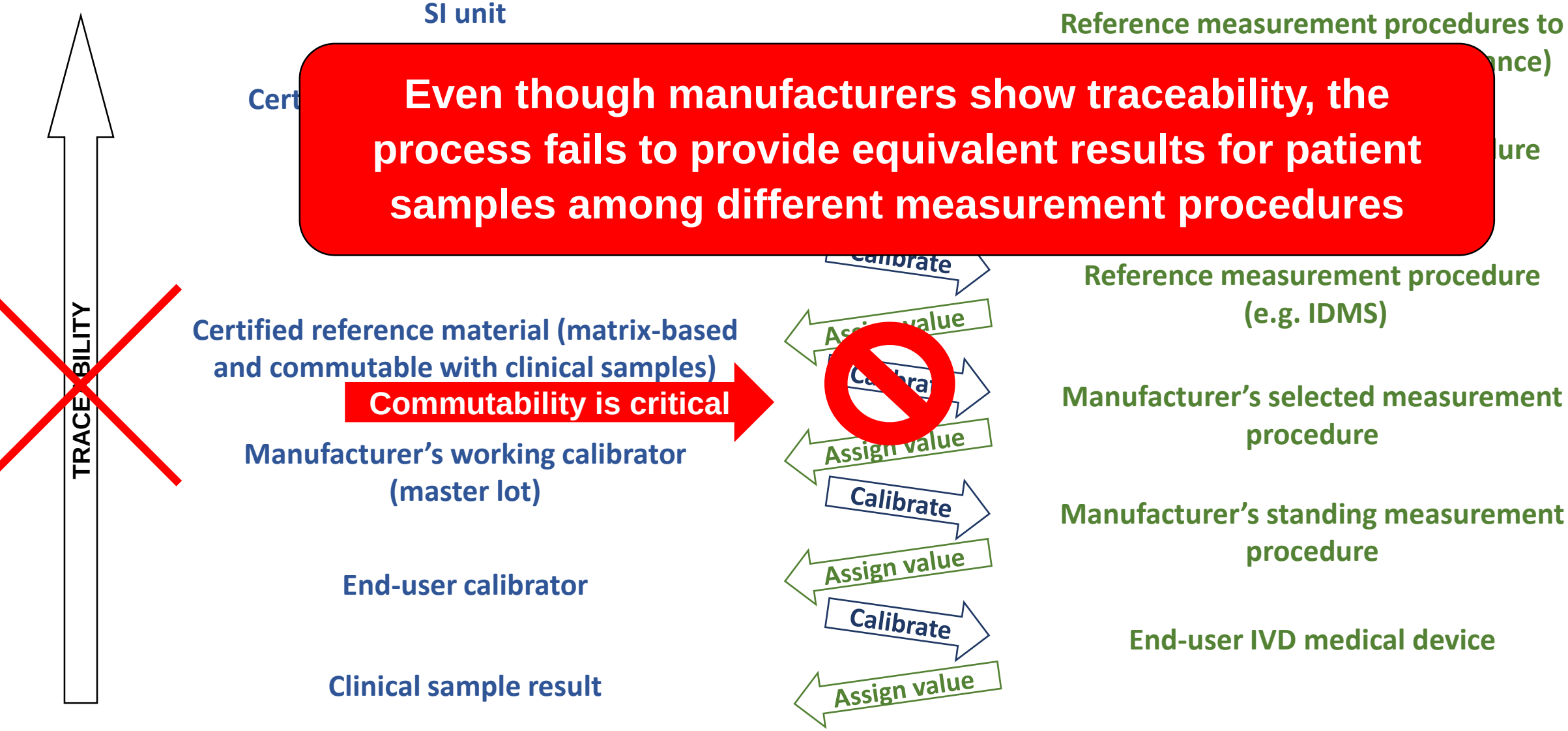
Metrological traceability: an unbroken chain of calibrations from a clinical sample result to a higher order reference system component (ISO 17511)




Commutability is not relevant for a pure substance CRM
SI unit
Certified reference material (pure substance)
Primary CRM in solution
Certified reference material (matrix-based and commutable with clinical samples)
Manufacturer's working calibrator (master lot)
End-user calibrator
Clinical sample result
TRACEABILITY
Assign value
Assign value
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Reference measurement procedures to characterize CRM (e.g. mass balance)
Reference measurement procedure (e.g. gravimetry)
Reference measurement procedure (e.g. IDMS)
Manufacturer's selected measurement procedure
Manufacturer's standing measurement procedure
End-user IVD medical device


TRACEABILITY
SI unit
Certified reference material (pure substance)
Primary CRM in solution
Certified reference material (matrix-based and commutable with clinical samples)
Commutability is critical
Manufacturer's working calibrator (master lot)
End-user calibrator
Clinical sample result
Assign value
Assign value
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Reference measurement procedures to characterize CRM (e.g. mass balance)
Reference measurement procedure (e.g. gravimetry)
Reference measurement procedure (e.g. IDMS)
Manufacturer's selected measurement procedure
Manufacturer's standing measurement procedure
End-user IVD medical device


SI unit
Reference measurement procedures to characterize CRM (e.g. mass balance)
A non-commutable calibrator breaks the traceability chain
TRACEABILITY
Certified reference material (matrix-based and commutable with clinical samples)
Commutability is critical
Manufacturer's working calibrator (master lot)
End-user calibrator
Clinical sample result
Assign value
Calibrate
Reference measurement procedure (e.g. IDMS)
Manufacturer's selected measurement procedure
Manufacturer's standing measurement procedure
End-user IVD medical device


SI unit
Reference measurement procedures to
nce)
Cert
ure
Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures
TRACEABILITY
Certified reference material (matrix-based and commutable with clinical samples)
Commutability is critical
Manufacturer's working calibrator (master lot)
End-user calibrator
Clinical sample result
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Calibrate
Assign value
Reference measurement procedure (e.g. IDMS)
Manufacturer's selected measurement procedure
Manufacturer's standing measurement procedure
End-user IVD medical device

Approximately 100 measurands have reference system components

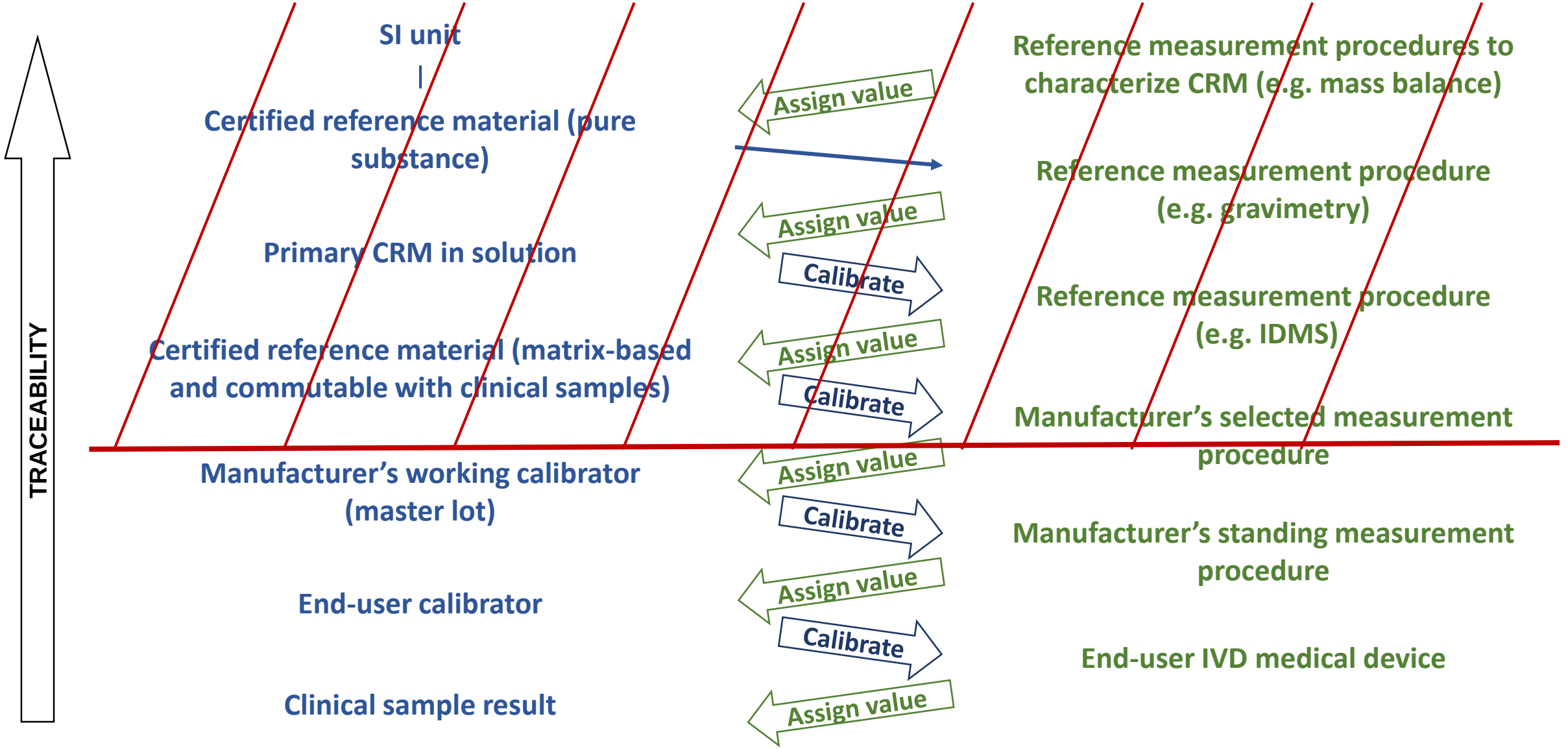
(Not all matrix-based CRM's have been validated for commutability)

WHO International Standards and Reference Preparations have historically not been validated for commutability and many are not commutable

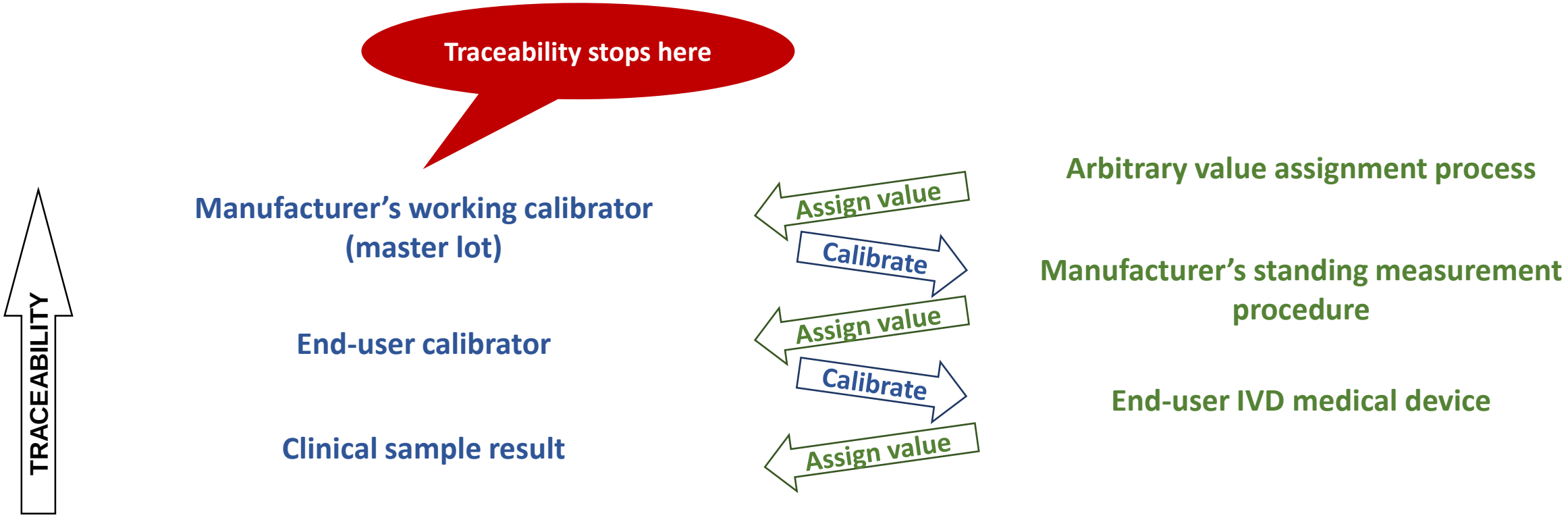
WHO Consultation on Commutability of WHO Biological Reference Preparations for In Vitro Detection of Infectious Markers.
WHO Headquarters, Geneva, 18-19 April, 2013

http://www.who.int/bloodproducts/norms/BS_2230_Addendum1_Commutability.pdf

Metrological traceability: an unbroken chain of calibrations from a clinical sample result to a higher order reference system component (ISO 17511)



Still traceable; however different working calibrators cause different results from different end-user IVD medical devices



Source of lab testing errors

46-68%	7-13%	20-45%
Pre-analytical	**Analytical**	**Post-analytical**
Ordering	???	Reporting
Collection		Received by MD
Transportation		Interpretation

Does not include contribution from medical errors caused by non-harmonized results

Plebani. Ann Clin Biochem 2010;47:101-10.

Harmonization

One of the most important challenges in laboratory medicine

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]

- **International Forum organized by *AACC* in October, 2010**
- **Agreement that metrological traceability to higher order CRM and RMP is preferred when possible**
- **Endorsed a harmonization approach when no CRM or RMP**

International Consortium
for Harmonization of Clinical Laboratory Results

Search

HOME ABOUT OVERSIGHT MEASURANDS RESOURCES CONTACT US

www.harmonization.net

International Consortium
for Harmonization of Clinical Laboratory Results

Search

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Resources

/ Resources

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

Content
Council/HOG Meeting Summaries
Council/HOG Meeting Summaries
Read more

Content
ICHCLR Activity Reports
ICHCLR Activity Reports
Read more

Document
International Consortium for Harmonization of Clinical Laboratory Results: Operating Procedures
Read more

Document
Toolbox of technical procedures for developing a process to achieve harmonization for a measurand
Read more

www.harmonization.net

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journal homepage: www.elsevier.com/locate/clinchim

A "Step-Up" approach for harmonization

Katleen Van Uytfanghe, Linde A. De Grande, Linda M. Thienpont *

Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, Gent University, Harelbekestraat 72, 9000 Gent, Belgium

A harmonization protocol based on clinical samples when there are no certified reference materials or reference measurement procedures

Clin Chim Acta 2014; 432: 62-67

Clinical Chemistry 63:7
1248–1260 (2017)

Endocrinology and Metabolism

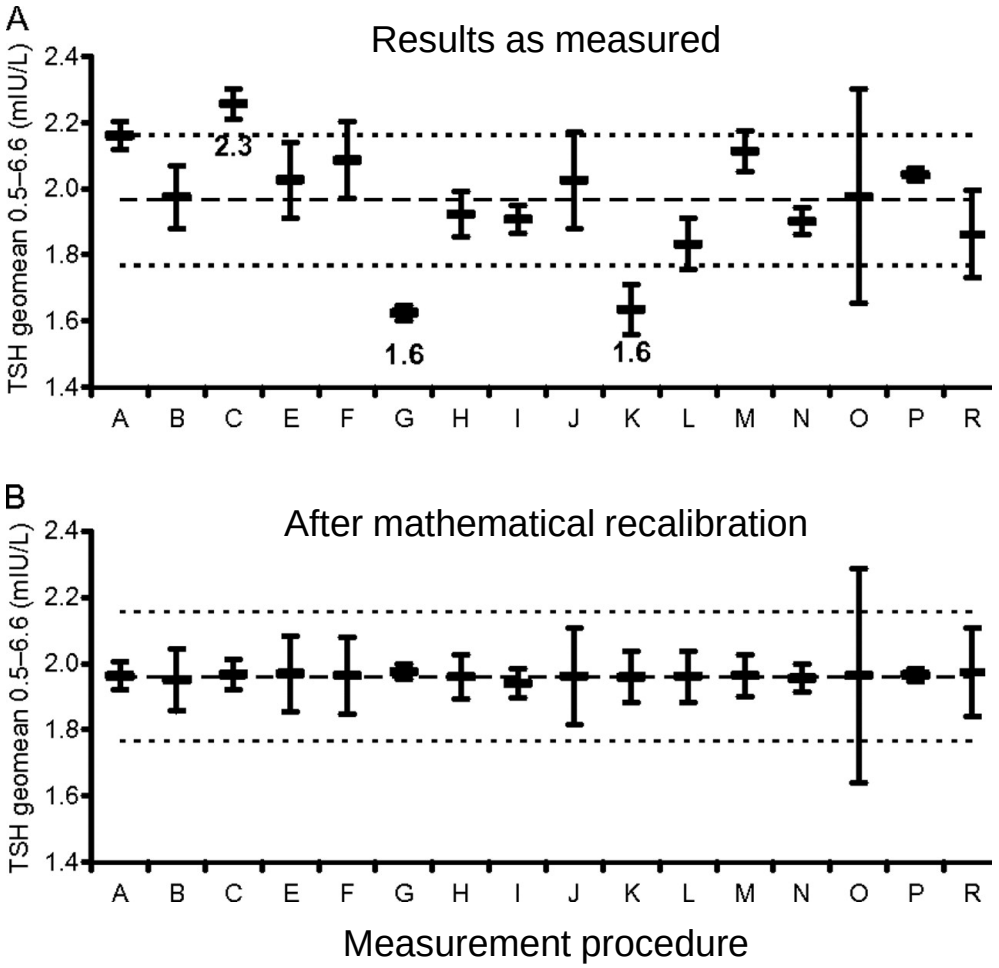
Harmonization of Serum Thyroid-Stimulating Hormone Measurements Paves the Way for the Adoption of a More Uniform Reference Interval

Linda M. Thienpont,[1,2*] Katleen Van Uytfanghe,[3] Linde A.C. De Grande,[1] Dries Reynders,[4] Barnali Das,[5] James D. Faix,[6] Finlay MacKenzie,[7] Brigitte Decallonne,[8] Akira Hishinuma,[9] Bruno Lapauw,[10] Paul Taelman,[11] Paul Van Crombrugge,[12] Annick Van den Bruel,[13] Brigitte Velkeniers,[14] and Paul Williams[15] on behalf of the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

IFCC Committee for Standardization of Thyroid Function Tests developed much of the science supporting a practical harmonization protocol.

Step 1: A panel of individual clinical samples is used to assess the state of the art

- Commutable because uses the samples intended to be measured
- Can identify methods that need improvement
- Can simulate recalibration to examine feasibility



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

Key procedures developed for value assignment:

Sofie K. Van Houcke, Stefan Van Aelst, Katleen Van Uytfanghe and Linda M. Thienpont*

Harmonization of immunoassays to the all-procedure trimmed mean – proof of concept by use of data from the insulin standardization project Clin Chem Lab Med 2013; 51: e103-5.

APTM for individual samples was equivalent to a value assigned by a RMP

Clin Chem Lab Med. 2014 Jul;52(7):965-72. doi: 10.1515/cclm-2013-1038.

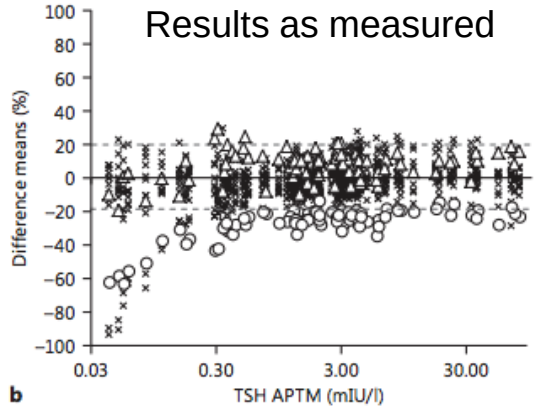
A statistical basis for harmonization of thyroid stimulating hormone immunoassays using a robust factor analysis model.

Stöckl D, Van Uytfanghe K, Van Aelst S, Thienpont LM.

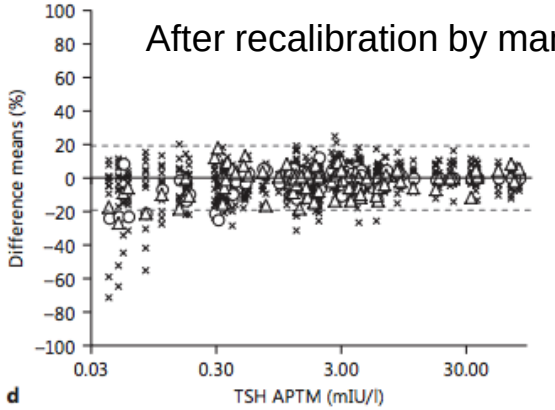
Step 2: A panel of healthy and diseased clinical samples that covers the measuring interval

- Master calibrators included
- Each manufacturer determines a correction algorithm for their calibration hierarchy
- The correction algorithm is applied to the clinical samples

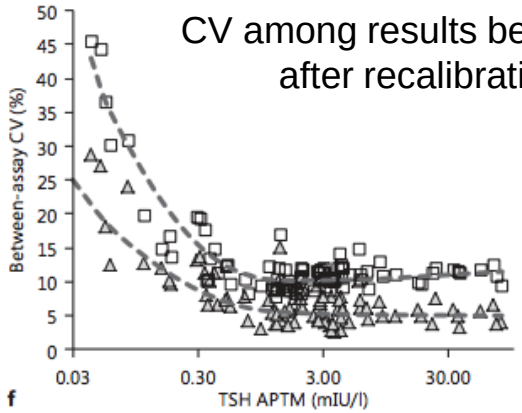
Results as measured



After recalibration by manufacturers



CV among results before and after recalibration

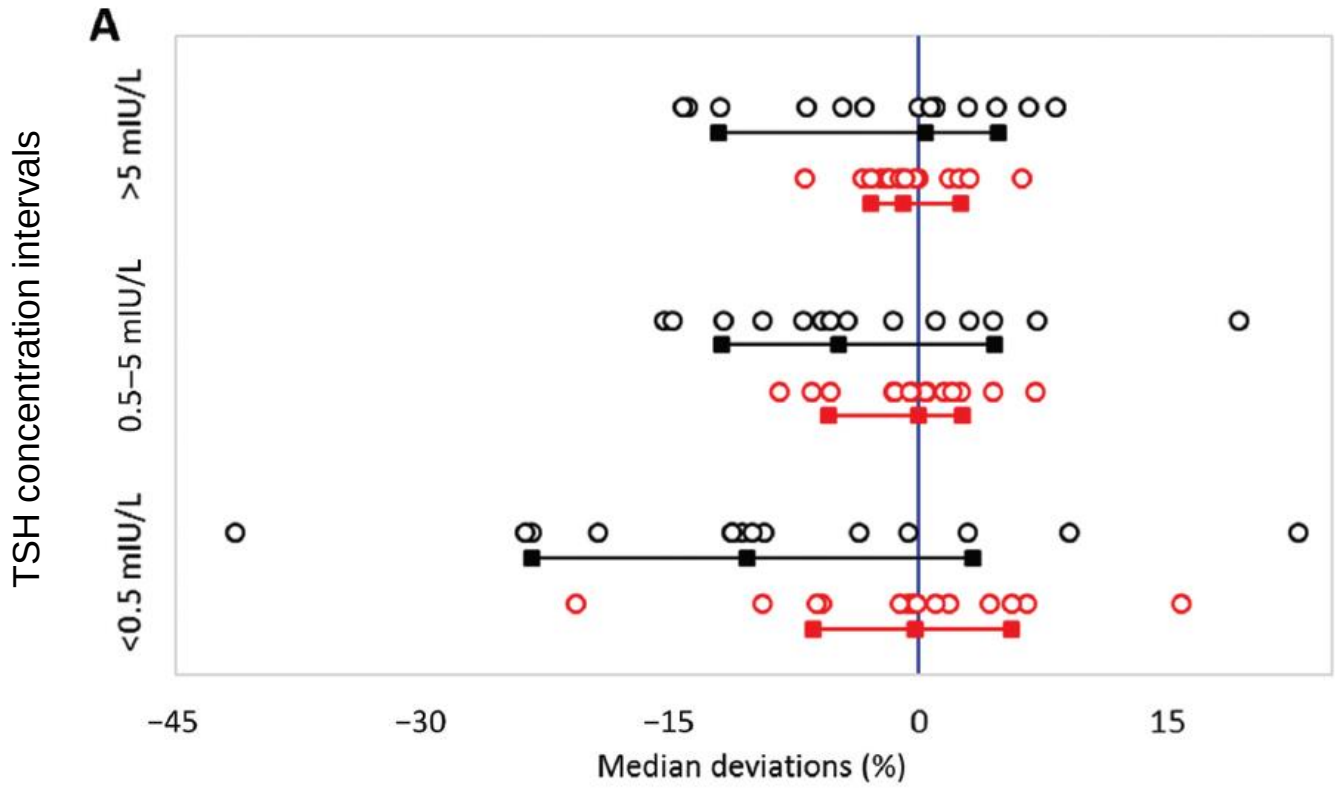


before

after

Thienpont et al. Eur Thyroid J 2014;3:109–116.

Step 3: New patient panel, linked to preceding, for validating recalibration algorithms and for sustaining the harmonization process



Original calibration

Recalibration applying each manufacturer's harmonization algorithm

Thienpont et al. Clin Chem 2017; 63(7): 1248-60

Step 4: Assess sustainability of recalibration using aggregated clinical data from laboratories worldwide

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journal homepage: www.elsevier.com/locate/clinchim

Monitoring the stability of the standardization status of FT4 and TSH assays by use of daily outpatient medians and flagging frequencies

Linde A.C. De Grande [a], Kenneth Goossens [a], Katleen Van Uytfanghe [b], Barnali Das [c], Finlay MacKenzie [d], Maria-Magdalena Patru [e], Linda M. Thienpont [a,*], for the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT):

Can the TSH approach be generalized?

NEW PROJECT
NOT PUBLISHED
NOT AN ISO STANDARD

NP 21151: *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin -* ***Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and human samples***

New project approved (2014)

Committee draft (2018)

-- vote --

HERE

Draft international standard (2019)

-- vote --

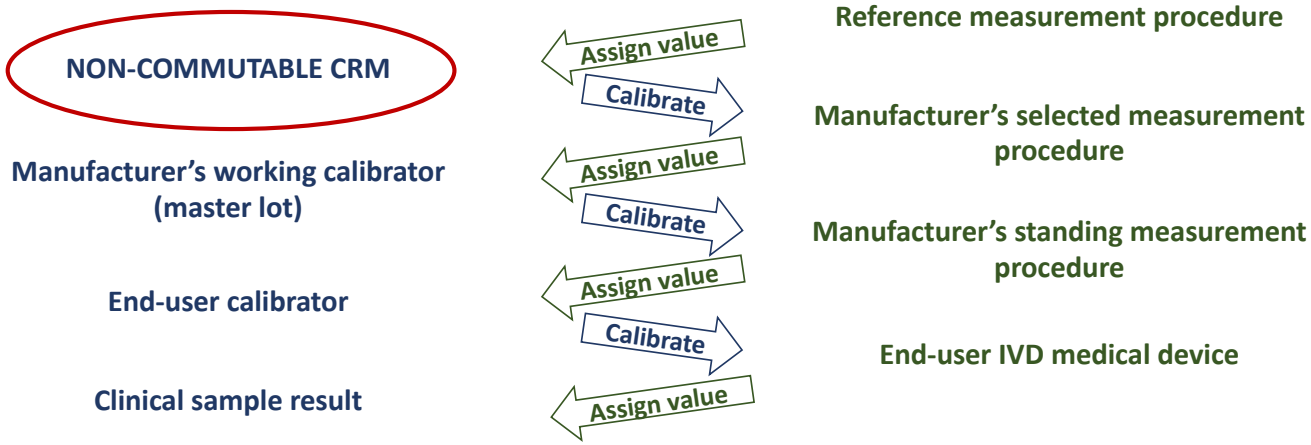
[Final draft international standard]

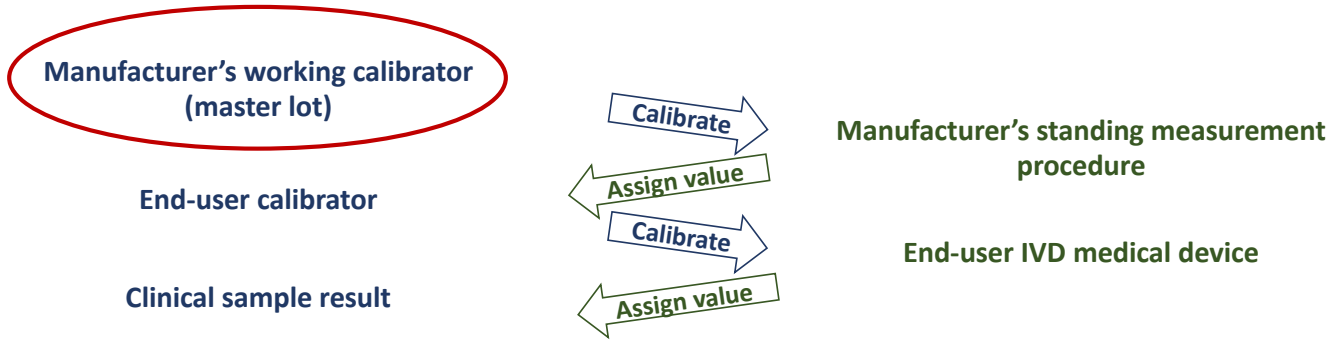
-- vote --

International standard

Metrological traceability: harmonization protocol

Replace these inadequate calibration hierarchies …





Metrological traceability: harmonization protocol

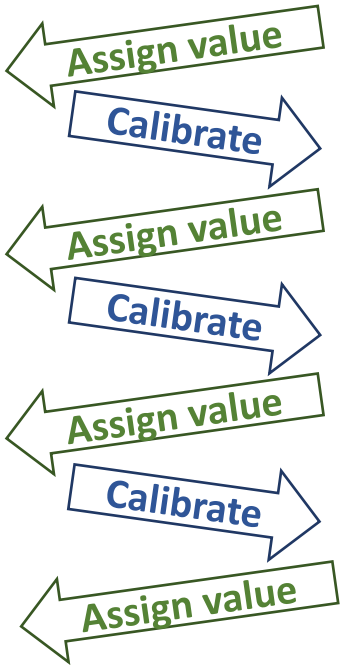
… with metrological traceability to the same harmonization protocol

Harmonization reference material (e.g. a panel or pools of clinical samples)

Manufacturer's working calibrator (master lot)

End-user calibrator

Clinical sample result



International harmonization protocol for a calibration hierarchy

Manufacturer's selected measurement procedure

Manufacturer's standing measurement procedure

End-user IVD medical device

Steps in the ISO 21151 Draft International Standard

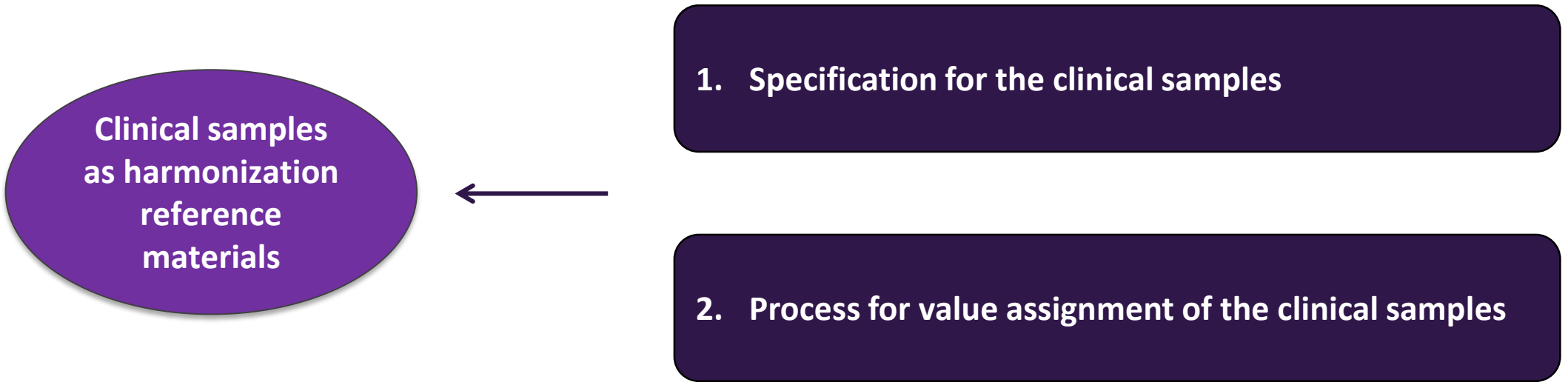
NOT PUBLISHED
NOT AN ISO STANDARD

Harmonization protocol: qualify measurement procedures for inclusion

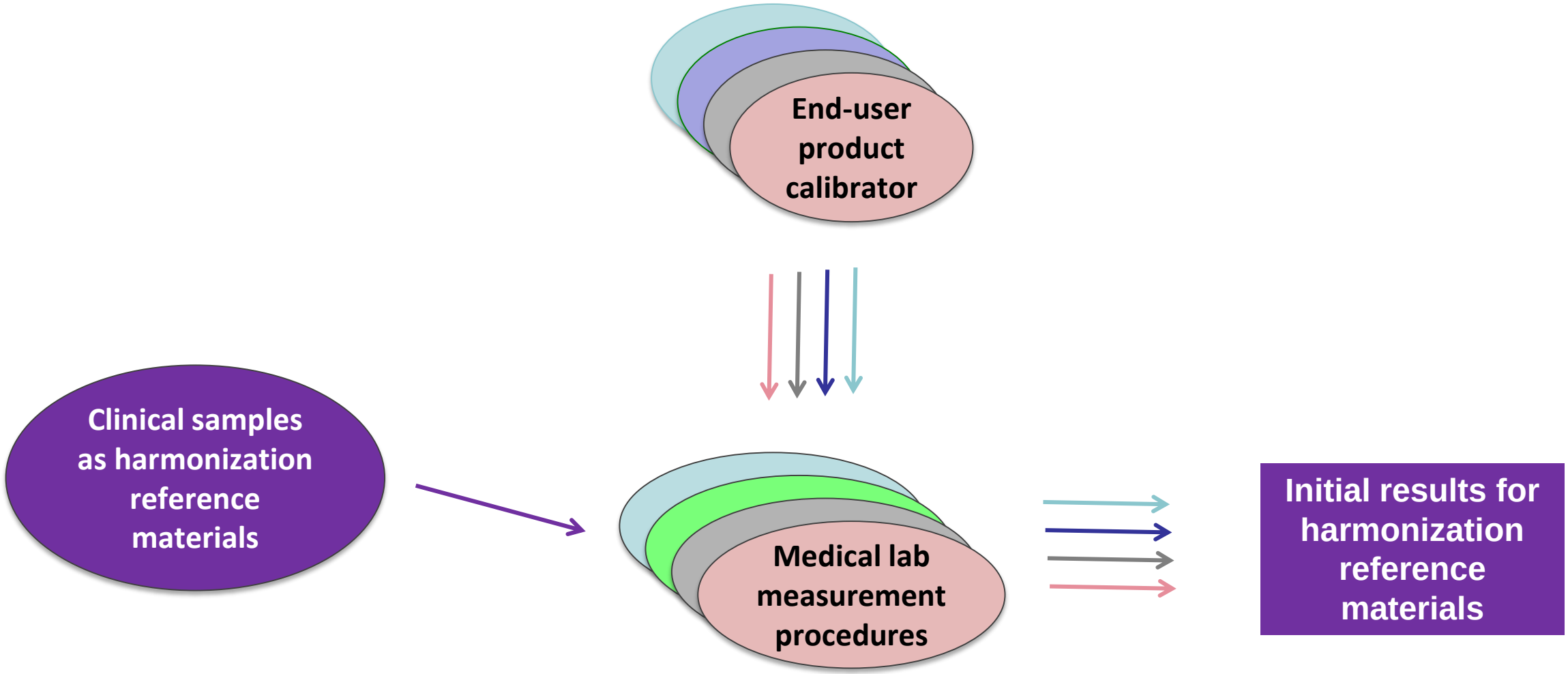
1. **Measure the same quantity (molecular form)**
   - **Correlated measurement responses**
   - **Similar specimen specific influences = similar selectivity for the measurand**

2. **Adequate performance**
   - **Precision**
   - **Proportional response over concentration**

Harmonization protocol: reference materials



Harmonization protocol: initial results

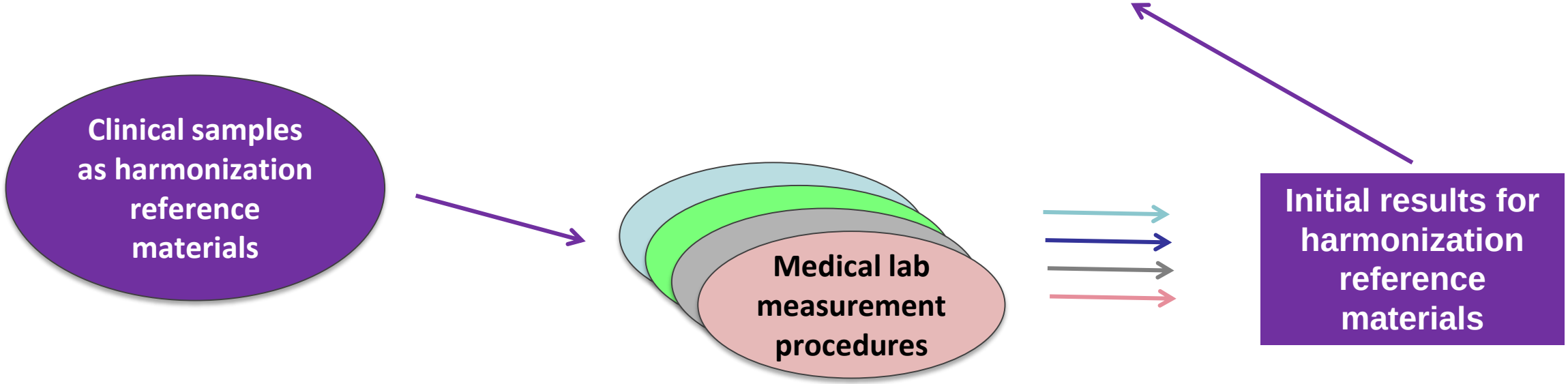


Harmonization protocol: IVD-specific correction algorithm

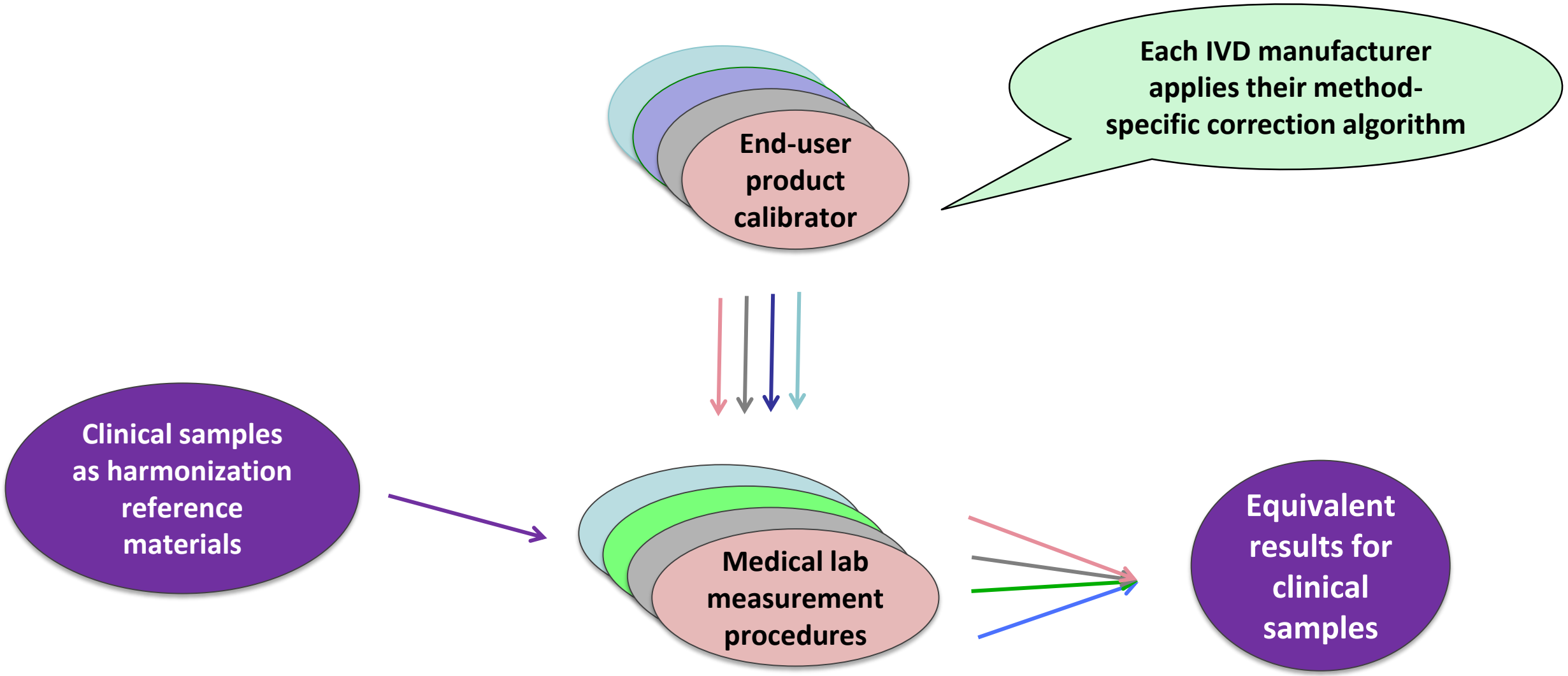
Each IVD manufacturer develops a method-specific correction algorithm to achieve equivalent results for clinical samples.

Can apply the correction to:

1. **Working (master) calibrator, or**
2. **End-user calibrator, or**
3. **Clinical sample result**

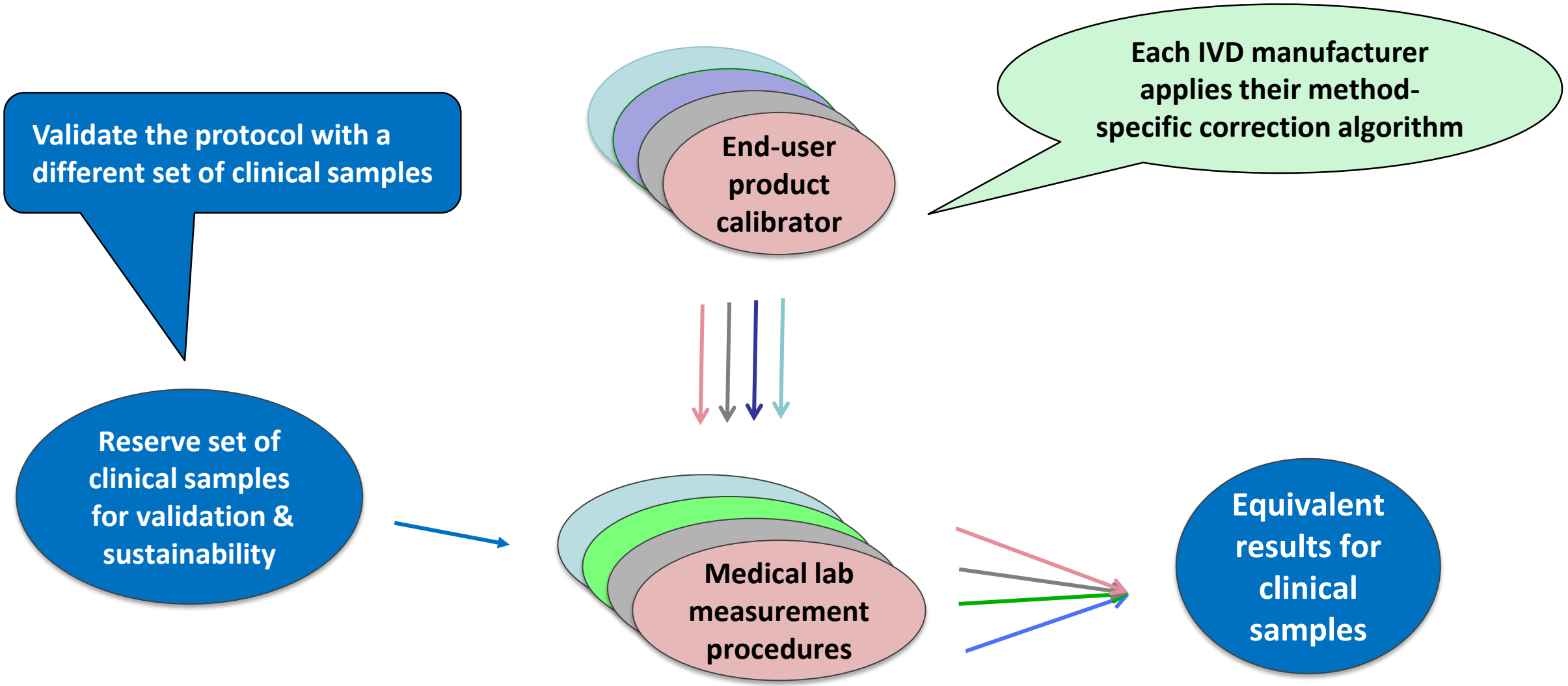


Harmonization protocol: equivalent results



Harmonization protocol: validation / sustainability

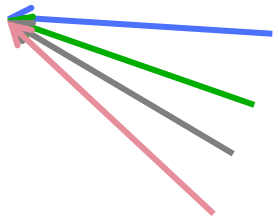
Harmonization protocol: validate the protocol



Harmonization protocol: surveillance over time

1. Feedback to labs and IVD manufacturers
2. Repeat harmonization protocol if needed (reserve set)
3. Provision for harmonization of new or improved measurement procedures

Equivalent results

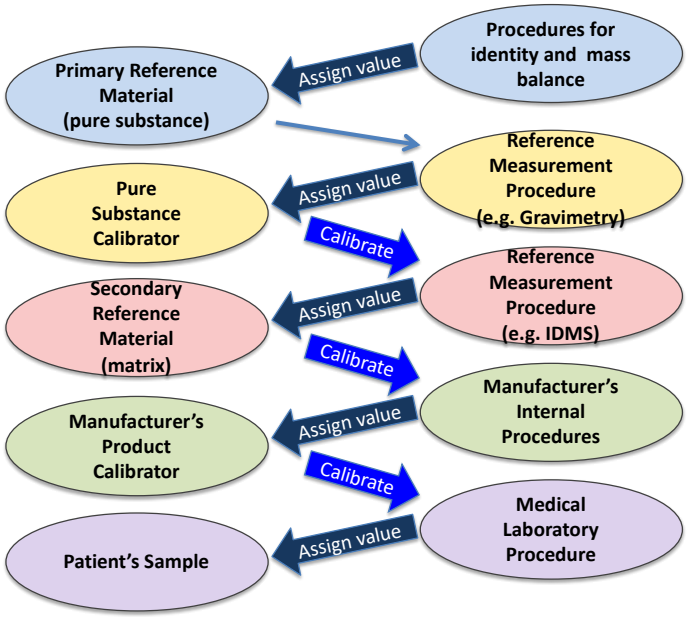


Medical lab measurement procedures

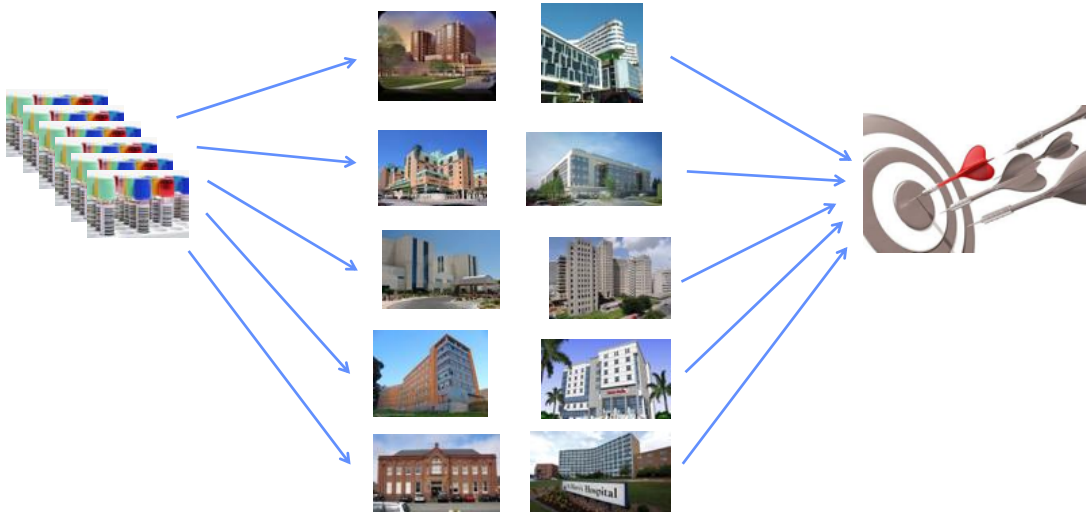
Surveillance of harmonized results

- **EQA/PT** (commutable samples)
- Other scheme; e.g. patient medians

STANDARDIZATION / HARMONIZATION
METROLOGICAL TRACEABILITY



ASSESSMENT
EQA



Clinical Chemistry 63:7
1184–1186 (2017)

Editorials

Harmonization: Its Time Has Come

W. Greg Miller[1*]

How can EQALM help?

International Consortium
for Harmonization of Clinical Laboratory Results

Search

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Frontpage / Measurands

This section provides information on the status of harmonization or standardization of measurands. Priorities based on medical impact are provided for measurands for which harmonization is needed or that have an incomplete or inactive implementation of a harmonization activity. Additional information regarding the harmonization status and medical impact is available by clicking on the measurand name. Information on reference materials, reference measurement procedures, and reference laboratory services is provided by the links in the JCTLM column. Links to organizations actively addressing harmonization of particular measurands are provided for additional information on those projects.

Comments on measurand status can be sent using the Contact Us tab. Download the form to submit a new measurand.

Summary of Measurand Harmonization Activities

Measurand	Matrix	Medical Impact of Harmonization [1]	Harmonization Status [2]	Resources [3]	Organization [4]
Akaline Phosphatase (ALP)	Serum	Medium	Incomplete	JCTLM	IFCC
Alanine Aminotransferase (ALT)	Serum	Medium	Incomplete	JCTLM	IFCC EU-JRC (IRMM)
Albumin	Urine		Active		NKDEP IFCC JSCC
Albumin	Serum	Medium	Needed	JCTLM	
Alpha Fetoprotein	Serum		Adequate		
Amylase	Serum		Active	JCTLM	IFCC
Anti-DNA antibody (qualitative)	Serum	Low			
Anti-DNA antibody (quantitative)	Serum	Medium	Needed		
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)	Serum		Adequate		
Antinuclear antibody (ANA)	fixed cells or serum		Active		International Workshops and Consensus Conferences
Antistreptolysin O	Serum	Low	Needed		
Aspartate Aminotransferase (AST)	Serum	Medium	Incomplete	JCTLM	IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		

Measurand	Matrix	Medical Impact of Harmonization [1]	Harmonization Status [2]	Resources [3]	Organization [4]
Akaline Phosphatase (ALP)	Serum				IFCC
Alanine Aminotransferase (ALT)	Serum				IFCC EU-JRC (IRMM)
Albumin	Urine				NKDEP IFCC JSCC
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Alpha Fetoprotein	Serum				
Amylase	Serum				IFCC
Anti-DNA antibody (qualitative)	Serum				
Anti-DNA antibody (quantitative)	Serum				
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)	Serum				
Antinuclear antibody (ANA)	fixed cells or serum				International Workshops and Consensus Conferences
Antistreptolysin O	Serum				
Aspartate Aminotransferase (AST)	Serum				IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		

B-type Natriuretic Peptide (BNP)

B-Type natriuretic peptide (BNP) is a marker of cardiac function and is used for diagnosis, risk stratification and follow-up of patients with chronic or acute heart failure. Laboratory assessments have determined that the agreement among results for different measurement procedures is not suitable to support uniform clinical decision values for interpretation of results (1,2). Both a candidate reference material (2) and a candidate reference measurement procedure (3) have been recently reported.

References

1. Clerico A, Zaninotto M, Prontera C, et al. State of the art of BNP and NT-proBNP immunoassays: The CardioOrmoCheck study. Clin Chim Acgta 2012;414:112-9.
2. Semenov AG, Tamm NN, Apple FS, et al. Searching for a BNP standard: Glycosylated proBNP as a common calibrator enables improved comparability of commercial BNP immunoassays. Clin Biochem 2017;50:181-5.
3. Torma AF, Groves K, Biesenbruch S, et al. A candidate liquid chromatography mass spectrometry reference method for the quantification of the cardiac marker 1-32 B-type natriuretic peptide. Clin Chem Lab Med 2017;55:1397-1406.

Measurand	Matrix	Medical Impact of Harmonization [1]	Harmonization Status [2]	Resources [3]	Organization [4]
Akaline Phosphatase (ALP)	Serum	Medium	Incomplete	JCTLM	IFCC
Alanine Aminotransferase (ALT)	Serum	Medium	Incomplete	JCTLM	IFCC EU-JRC (IRMM)
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Albumin					
Alpha Fetoprotein					
Amylase	Serum		Active	JCTLM	IFCC
Anti-DNA antibody (qualitative)	Serum	Low			
Anti-DNA antibody (quantitative)	Serum	Medium	Needed		
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)	Serum		Adequate		
Antinuclear antibody (ANA)	fixed cells or serum		Active		International Workshops and Consensus Conferences
Antistreptolysin O	Serum	Low	Needed		
Aspartate Aminotransferase (AST)	Serum	Medium	Incomplete	JCTLM	IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		

Links to commutable EQA programs

Challenges: EQA for harmonization assessment

- **Commutable samples can be difficult and expensive to prepare in adequate amounts**
- **RMP value assignment is expensive and not always available**
  - **Information on equivalence of results is very useful**
- **Adequate number of participants are needed for meaningful assessment of IVD devices**

Challenges: EQA for harmonization assessment

- **EQA is frequently national or regional**
- **Need to assess performance globally**
  - **Global IVD manufacturers**
  - **Different calibration requirements in different countries**

Need EQA feedback to the IVD industry

We need a mechanism for EQA providers to cooperate to:

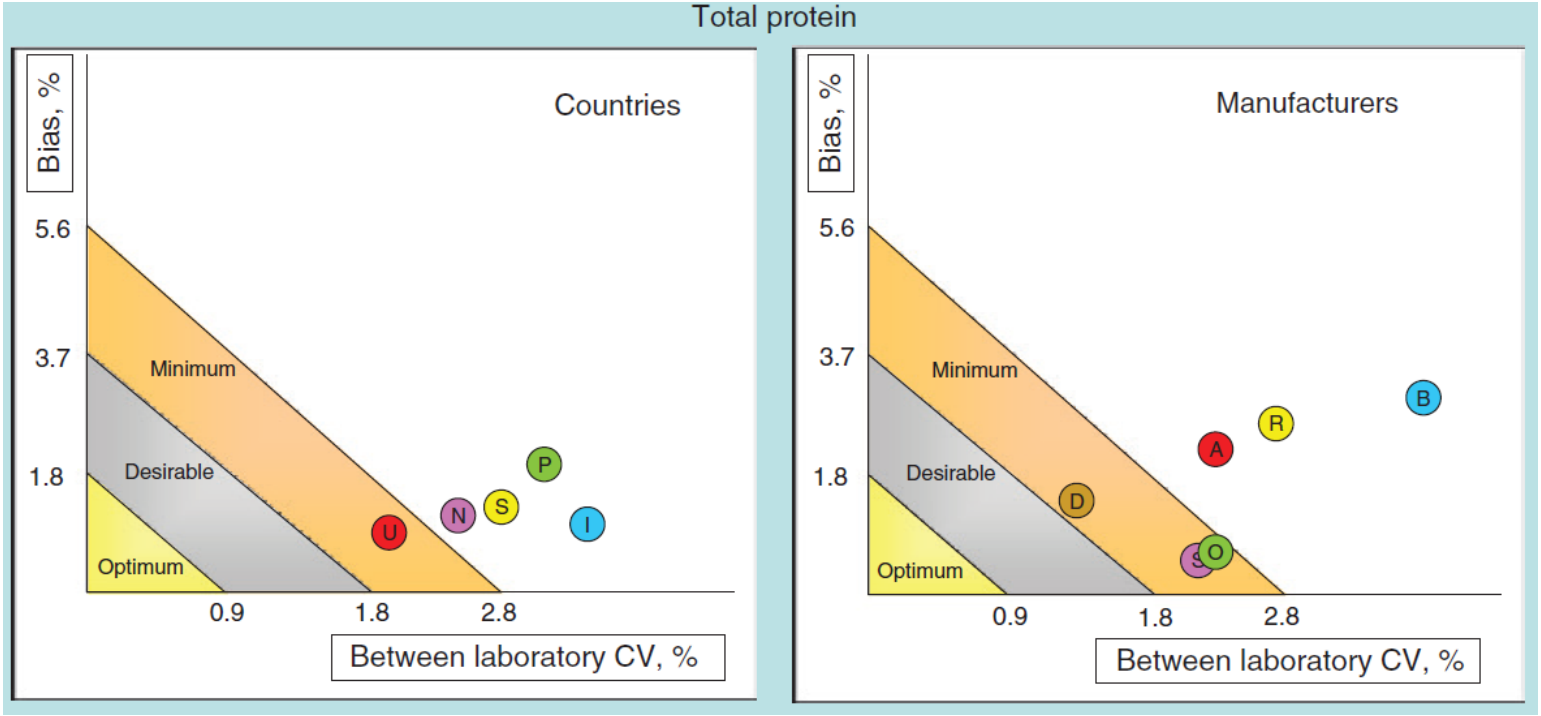
1. **Cover measurands on an annual or biennial cycle**

2. **Prepare aggregated data summaries among schemes**

An organizing role for EQALM?

Should EQALM become GQALM?

Commutable samples provided by SKML



Develop an algorithm to aggregate results from different EQA samples in different schemes

Weykamp et al. Clin Chem Lab Med 2017;55:203-211

Opinion Paper

Ferruccio Ceriotti* and Christa Cobbaert

Harmonization of External Quality Assessment Schemes and their role – clinical chemistry and beyond

1. We conclude that harmonization of EQAS has still a long way to go, and much technical and organizational work has to be done, but important milestones indicating the way to follow have been defined [1, 7, 9, 11, 18]. Intensive
2. collaborations or alliances between country-specific EQA organizations under the umbrella of the European Organization for External Quality Assurance in Laboratory Medicine are urgently needed, as well as efforts to merge EQAS in countries where different schemes for the same measurands are in use. These efforts should allow to

Conclusions

- **Harmonization of results is important to reduce medical errors**
- **EQA with commutable samples has an essential role in the process**
- **Global cooperation is needed to support harmonization**