How aggregated EQA data contributes to harmonisation of clinical laboratory results

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Learning objectives

- How does EQA support harmonization
- Why commutability matters
- Value from aggregating EQA data

Clinical decisions need equivalent results from different measurement procedures

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

How to achieve equivalent results

1. **Calibration of all measuring systems is traceable to a common fit-for-purpose reference system**

2. **All measuring systems measure the same measurand**
   - **Acceptable influence by interfering substances, or molecular forms**

Joint Committee for Traceability in Laboratory Medicine

Database of reference materials, reference measurement procedures, and reference (calibration) laboratories that conform to the ISO standards

ISO 17511:2020 Metrological Traceability

ISO 15193:2009 Reference Measurement Procedures

ISO 15194:2009 Certified Reference Materials

ISO 15195:2018 Reference Measurement Laboratories

ISO 21151:2020 Harmonization Protocol

Database lists:

- **CRMs for 180 measurands**
- **RMPs for 160 measurands**
- **RMP services for 120 measurands**

Note that matrix-based CRM's reviewed against the older ISO 15194:2003 were not validated for commutability

STANDARDIZATION / HARMONIZATION
METROLOGICAL TRACEABILITY

Procedures for Identity and Purity Assessment

Assign value

Primary Reference Material (pure substance)

Reference Measurement Procedure for Calibrator (e.g. Gravimetry)

Assign value

Primary Calibrator

Calibrate

Reference Measurement Procedure for Measurand (e.g. IDMS)

- Consensus value assignment
- Harmonization Protocol

Assign value

IVD prepared
- From primary
- Arbitrary

Secondary Commutable Calibrator (matrix)

Calibrate

Manufacturer's Internal Procedures

Assign value

Manufacturer's End-user Calibrator

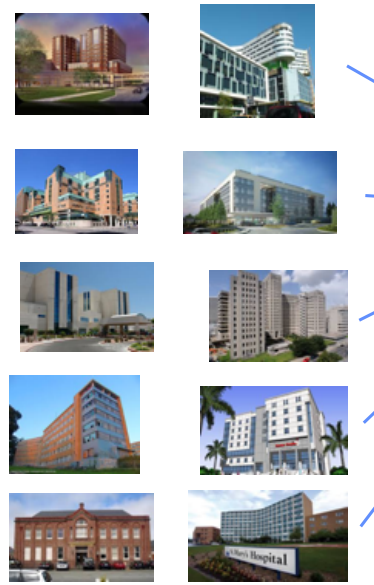
Calibrate

Medical Laboratory End-user IVD Device

Assign value

Patient's Sample Result

ASSESSMENT
EQA

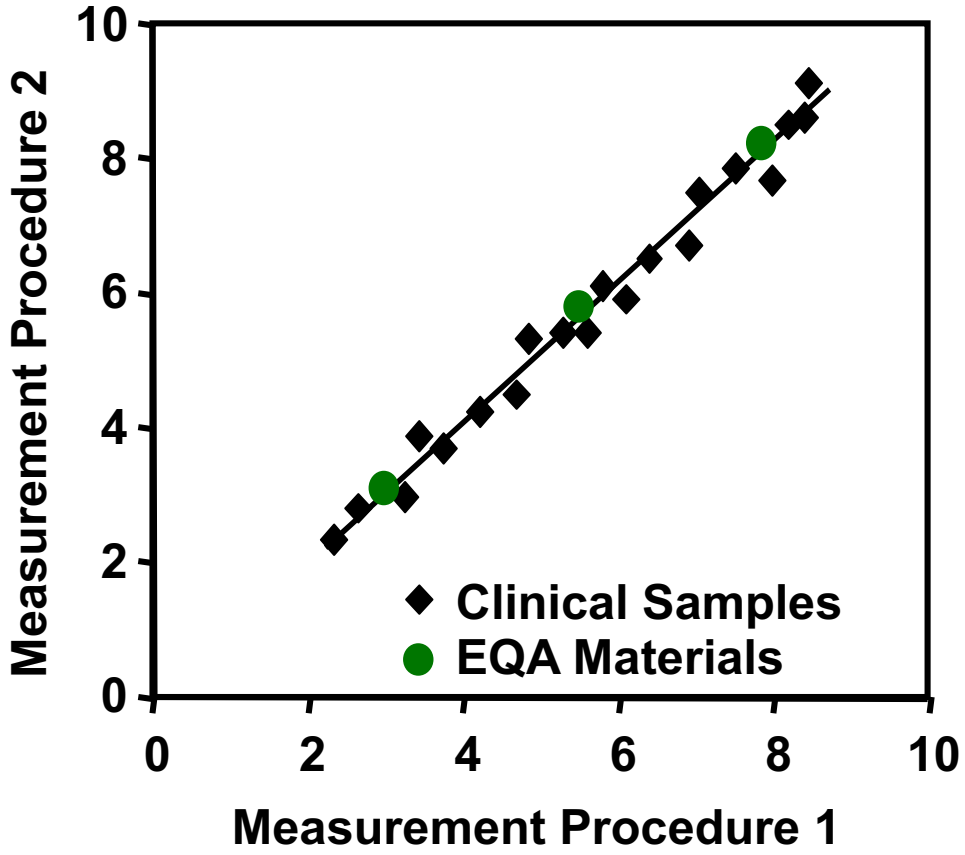


EQA Scheme Design

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		

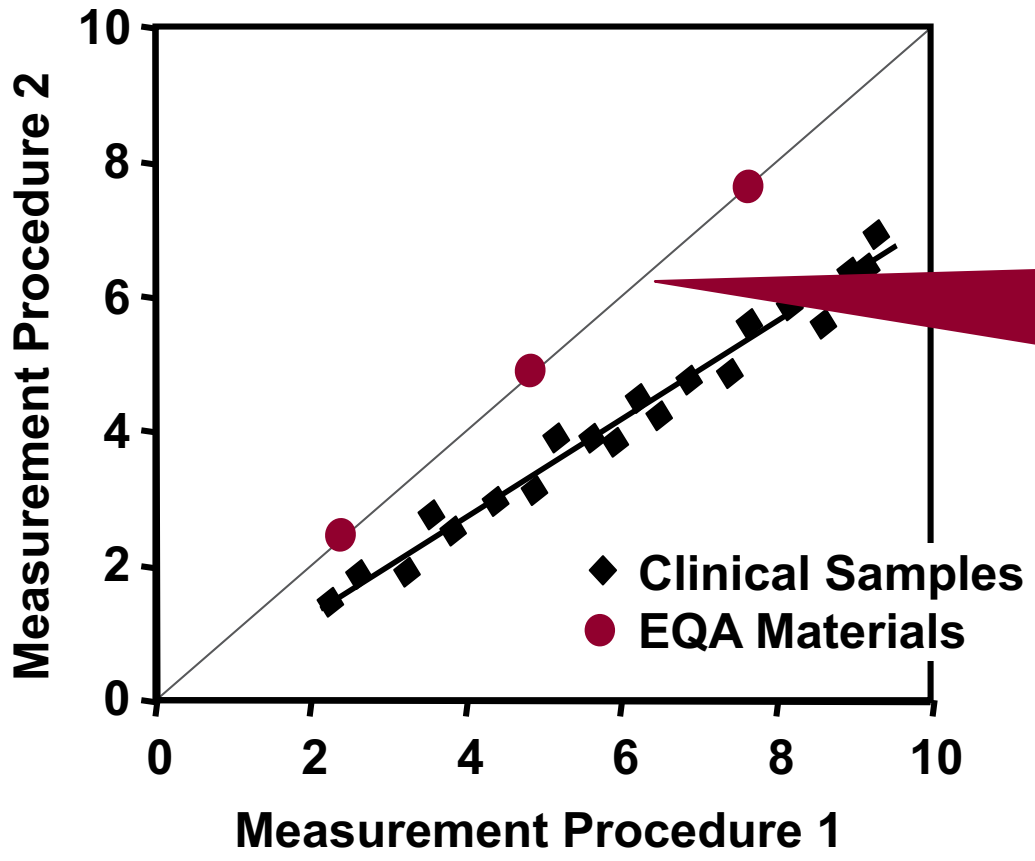
Adapted from Miller, Jones, Horowitz, Weykamp. Clin Chem 2011;57:1670-80

Commutable EQA/PT



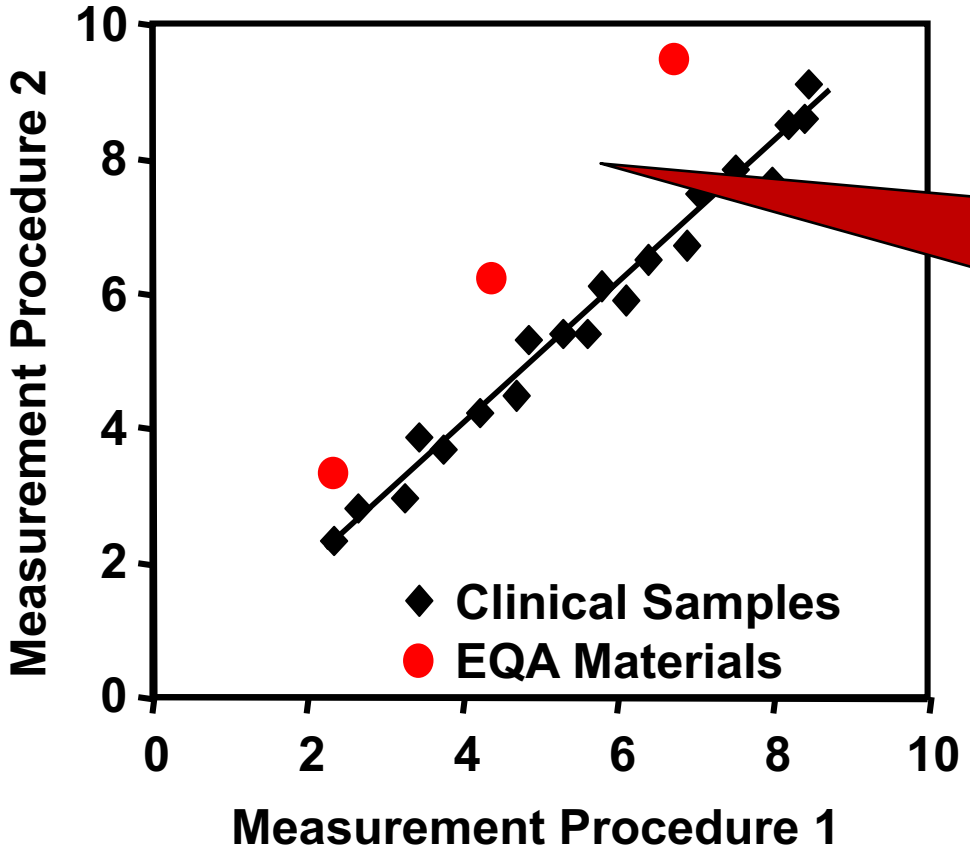
EQA/PT results reflect status of clinical sample results

Non-Commutable EQA



Apparent agreement means patient results DO NOT AGREE

Non-Commutable EQA



Disagreement does NOT mean patient results are different

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**

Challenges: EQA for harmonization assessment

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

ICHCLR and EQALM conducted a pilot feasibility study

DE GRUYTER

Clin Chem Lab Med 2021; 59(1): 117–125

Eline A. E. van der Hagen, Cas Weykamp, Sverre Sandberg, Anne V. Stavelin, Finlay MacKenzie and W. Greg Miller*

Feasibility for aggregation of commutable external quality assessment results to evaluate metrological traceability and agreement among results

- **Creatinine as example measurand**
- **Four EQA providers: CAP (US), NEQAS (GB), NOKLUS (NO), SKML (NL)**
- **Commutable EQA materials**

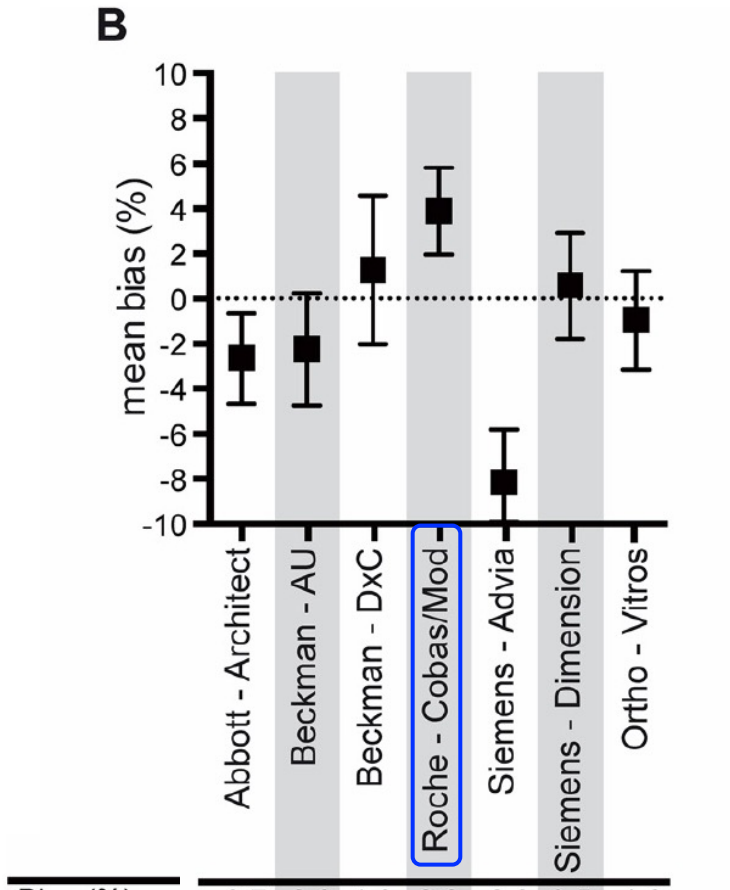
Challenge: how to determine an EQA material is commutable

Common practice is to assume commutability based on how samples are prepared

- **Collected and processed the "same way" as patient samples**
  - ✓ **Freeze thaw influences**
  - ✓ **Pooling influences**
  - ✓ **Supplementation and preservative influences**
- **Not scientifically defensible without evidence**

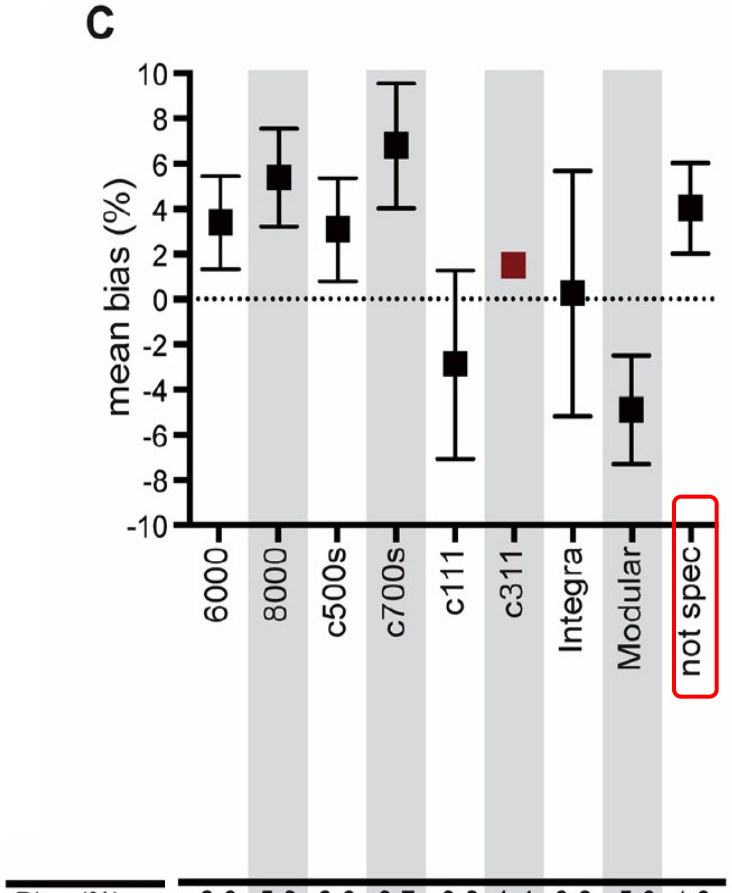
An approach is in development by the IFCC WG-CMT

Aggregated data by instrument, enzymatic methods



Bias (%)	-2.7	-2.3	1.2	3.8	-8.2	0.5	-1.0
ExpU (%)	2.0	2.5	3.3	1.9	2.4	2.4	2.2
n	85	30	10	314	42	20	48
% Outlier	1.2	-	-	0.6	-	-	-

Heterogeneity within a single manufacturer



Bias (%)	3.3	5.3	3.0	6.7	-3.0	1.4	0.2	-5.0	4.0
ExpU (%)	2.1	2.2	2.3	2.8	4.2	-	5.4	2.4	2.0
n	78	39	50	23	5	1	3	2	113
% Outlier	-	5.1	-	-	-	-	-	-	-

Van der Hagen, et al. CCLM 2021; 59:117-25

Challenge: sufficient information about the measuring systems

Table 3: Participant information needed for aggregation of results from different EQA providers.

Information	Minimum requirement	Desirable information	Example
Instrument manufacturer	X		Abbott
Instrument name	X		Architect
Instrument measuring system designation	X		C8000
Method type (reagent type)	X		Enzymatic
Reagent manufacturer		X	Abbott
Reagent lot number		X	R49872
Calibrator manufacturer		X	Abbott
Calibrator lot number		X	C43256
Calibration traceability (when applicable)		X	IDMS listed by JCTLM

Van der Hagen, et al. CCLM 2021; 59:117-25

Collaboration between EQALM and ICHCLR

Harmonization of Measurands in Laboratory Medicine through Data Aggregation

The HALMA initiative

http://www.eqalm.org/site/halma/halma.php

International Consortium
for Harmonization of Clinical Laboratory Results

EQALM
European Organisation For External Quality Assurance Providers in Laboratory Medicine

HALMA:

The primary purpose is to assess harmonization of the IVD industry through aggregated EQA data for different measurands on an international basis.

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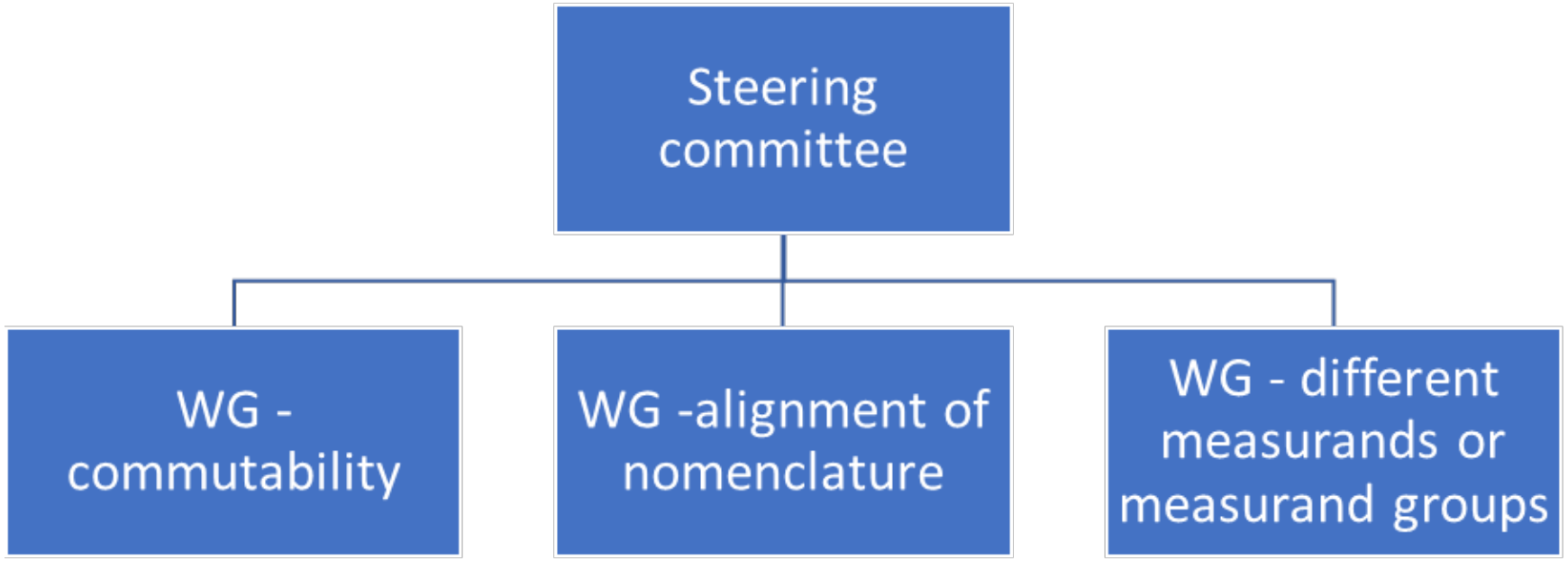
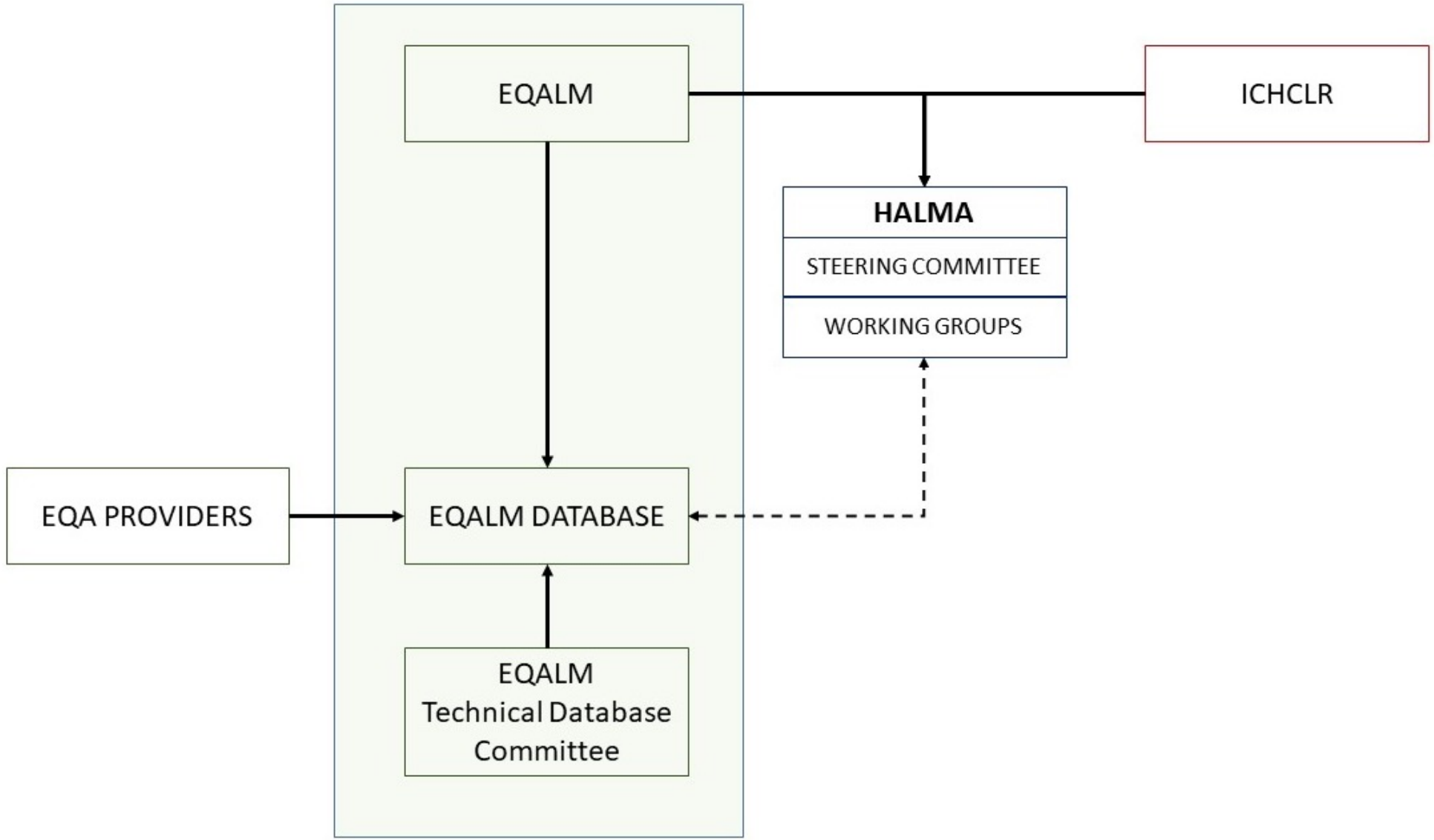


WGs for Measurands

1. Creatinine, Calcium
2. TSH and free T4
3. ALT and AST
4. HDL-cholesterol


EQALM
ICHCLR
HALMA
STEERING COMMITTEE
WORKING GROUPS
EQA PROVIDERS
EQALM DATABASE
EQALM
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Committee

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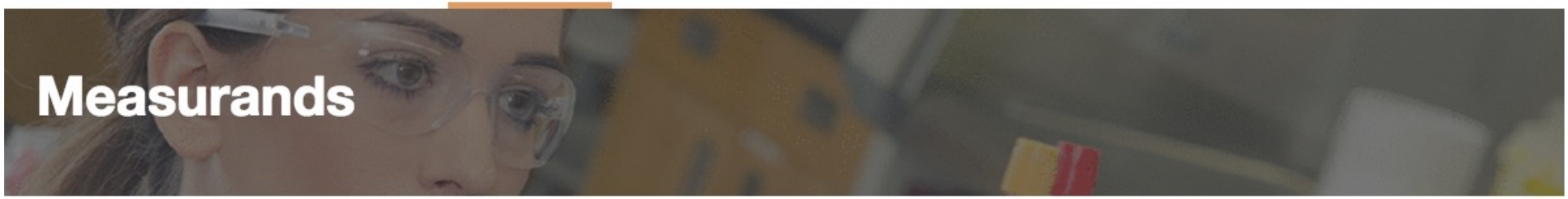

Measurands

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

www.harmonization.net

Measurand	Matrix	Medical Impact of Harmonization	Harmonization Status	Resources	Organization
Elastase I	Fecal, Serum	Low	Unknown		
Fetal fibronectin	Cervical fluid	Low	Unknown		
Albumin	Serum	Medium	Needed	JCTLM	
Anti-DNA antibody (quantitative)	Serum	Medium	Needed		
Anti-HBs Quantitative	Serum, Plasma	Medium	Needed		
Anti-Hepatitis B Surface Antigen (Anti-HBsAg)	Serum, Heparin Plasma	High	Needed	WHO	
Anti-myeloperoxidase (MPO) antibody, IgG	Serum	High	Needed	JCTLM	IFCC
Anti-SSA antibody IgG	Serum	Medium	Needed		
Antistreptolysin O	Serum	Low	Needed		
Bilirubin, conjugated	Serum	Medium	Needed		
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		
CA 125	Serum	High	Needed		
CA 15-3	Serum	High	Needed		
CA 19-9	Serum	High	Needed		
Calcium, ionized	Blood	Medium	Needed		

Measurand	Matrix	zation	Resources	Organization
Elastase I	Fecal, Seru			
Fetal fibronectin	Cervical fl			
Albumin	Serum		JCTLM	
Anti-DNA antibody (quantitative)	Serum			
Anti-HBs Quantitative	Serum, Pla			
Anti-Hepatitis B Surface Antigen (Anti-HBsAg)	Serum, He Plasma		WHO	
Anti-myeloperoxidase (MPO) antibody, IgG	Serum		JCTLM	IFCC
Anti-SSA antibody IgG	Serum			
Antistreptolysin O	Serum			
Bilirubin, conjugated	Serum			
B-type Natriuretic Peptide (BNP)	Serum			
CA 125	Serum			
CA 15-3	Serum			
CA 19-9	Serum			
Calcium, ionized	Blood			

Anti-Hepatitis B Surface Antigen (Anti-HBsAg)

1. **Medical Impact:**

Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs Ab). Anti-HBs Ab also appears as the immune response following hepatitis B vaccination. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection.

There has been recent renewed interest in measuring serum levels of HBsAg as a surrogate marker to predict HBsAg loss and monitor anti-HBV therapy. During the natural history of HBV infection, the loss of serum HBsAg is generally associated with their seroconversion to anti-HBs, the hallmark of a successful immunological response to HBV infection. The speed and amplitude of the decline in HBsAg levels are suspected to be a good predictors of sustained virological response and HBsAg loss.

Therefore, the concordance among different assays for HBsAg and anti-HBs Ab is very important.

2. **Harmonization Status:**

According to the EQA data from the College of American Pathologists in 2015 (non-commutable samples), the agreement of the test results from 11 manufacturers' test kits was very good. The overall concordance of HBsAg from 2,252 laboratories using kits manufactured by 11 companies was 99.7% for positive samples and 99.8% for negative samples. The overall concordance of anti-HBs Ab from 1,820 laboratories using kits manufactured by 11 companies was 99.3% for the positive samples and 99.7% for the negative samples.

A comparison report in 2012 [1], the quantitation of HBsAg levels in routine clinical samples by four different test systems appeared overall to be accurate, showing low variability and little discrepancy. HBsAg levels were compared among 80 patients using Abbott Architect, Diasorin, Bio-Rad and Roche.

Another head-to-head study evaluating the performance of 3 assays (Abbott Architect, DiaSorin LiaisonXL and Roche Elecsys HBsAgII).measuring the HBsAg level [2] also showed good correlation between all current systems [2].

Conclusions

- **Harmonization/standardization of results is important to reduce medical errors**
- **EQA with commutable samples has an essential role in the process**
- **EQA data aggregated from different schemes informs IVD manufacturers, clinical laboratories, and regulatory bodies**
- **Global cooperation is needed to support harmonization**