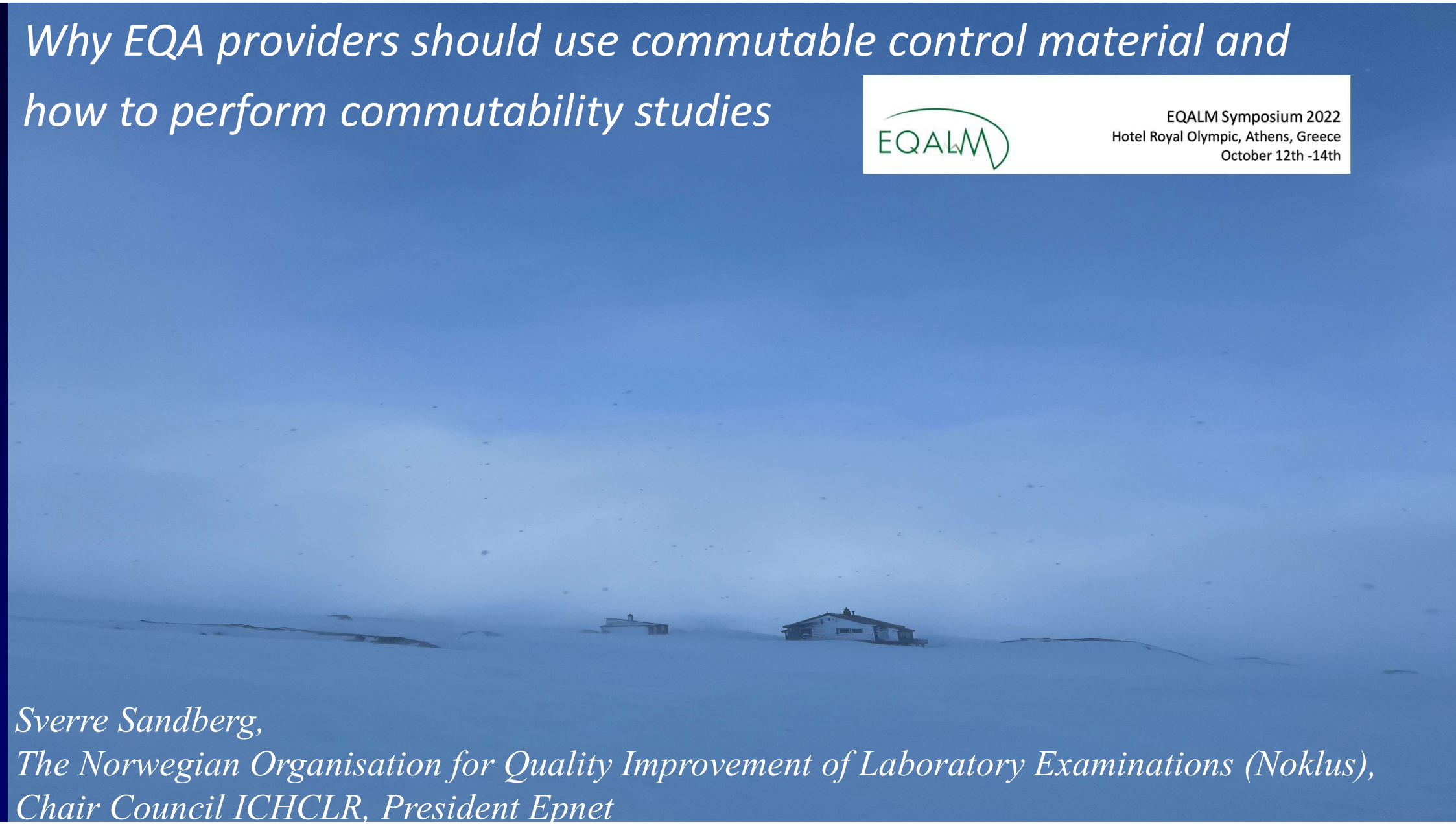
# *Why EQA providers should use commutable control material and how to perform commutability studies*

EQALM Symposium 2022
Hotel Royal Olympic, Athens, Greece
October 12th -14th



*Sverre Sandberg,*
*The Norwegian Organisation for Quality Improvement of Laboratory Examinations (Noklus),*
*Chair Council ICHCLR, President Epnet*

# Is EQA useful?

Do we need analytical EQA schemes if we can prove the metrological traceability of our assays?

**Actually: No**



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# EQA is used for three main purposes:

(1) to inform a laboratory of its results compared to other laboratories using the same measuring systems (MSs)

(2) to inform IVD manufacturers and the laboratories regarding the metrological traceability of their MSs with the goal to obtain equivalent results for CSs among *different* MSs.

(3) In addition, special EQA surveys are performed to inform laboratories and IVD manufacturers regarding the influence of for example interfering substances and selectivity for a certain measurand on results.



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**(2) to inform IVD manufacturers and laboratories regarding the metrological traceability of their MPs with the goal to obtain equivalent results for clinical samples among different MPs.**

**This is what we should do!!**

***We must focus on trueness / equivalence since we more and more use common decision limits and thresholds for diagnosis, screening and prevention of treatment error***

**All measuring systems should give the same results on the same clinical sample!**

**How can EQA organisers contribute?**



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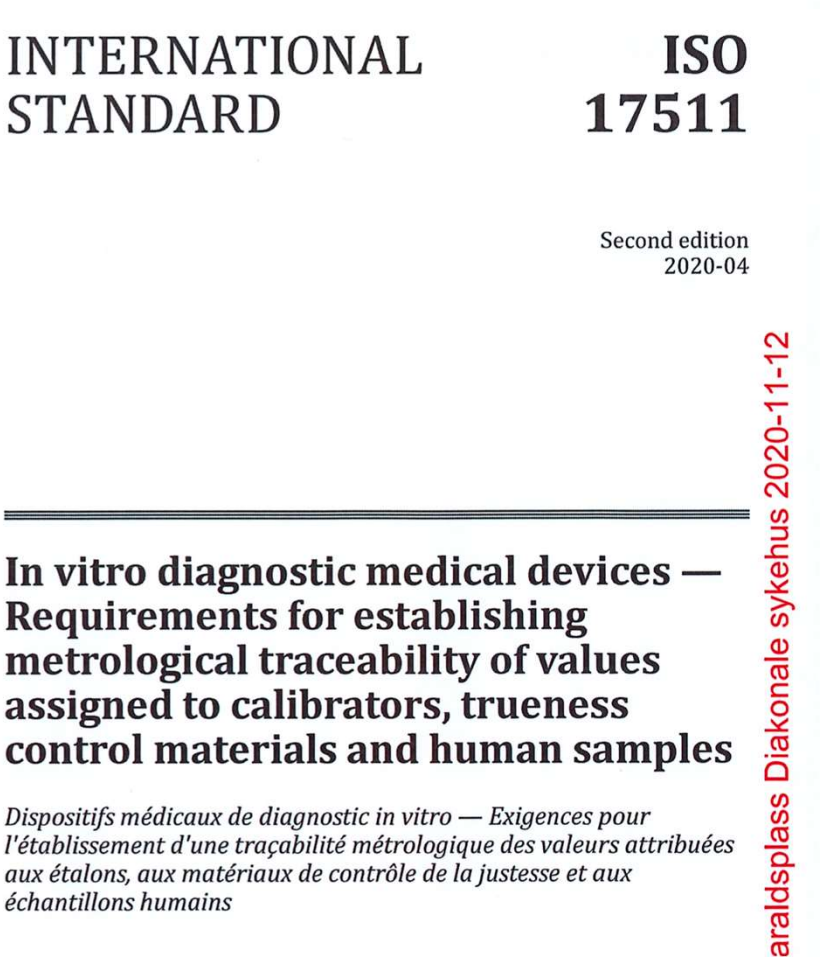
# Equivalence
(ISO 17511:2020, clause 3.13)

**equivalence of measured values** (**equivalent results)**

agreement of measured values among different *IVD MPs* intended to measure the same *measurand,* where the differences in measured values on the same human samples do not affect *clinical interpretation*



INTERNATIONAL STANDARD

ISO 17511

Second edition
2020-04

**In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples**

*Dispositifs médicaux de diagnostic in vitro — Exigences pour l'établissement d'une traçabilité métrologique des valeurs attribuées aux étalons, aux matériaux de contrôle de la justesse et aux échantillons humains*



# Presuppositions for obtaining equivalent results are that measuring systems are standardized / harmonised



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# Responsibilities

1. Establishing Standardization / Harmonization
   - IFCC
   - JCTLM – joint committee on traceability in laboratory medicine
   - ICHCLR – international committee on harmonisation of clinical laboratory results
   - IVD industry

2. Monitoring Standardization / Harmonization
   - EQA/PT
   - Patient Medians

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# Problems using EQA to monitor harmonisation/equivalence

- EQA providers cannot document commutability for their EQA material, but some of them assume commutability.

- For many measurands it will be difficult/impossible to produce commutable control material

- (It is of no use to have reference target values for measurands on EQA schemes if it is not possible to demonstrate commutability of the control material)



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# Commutability of External quality control material

**How can we show that we have commutable samples?**

**Two initiatives:**

IFCC – WG commutability

HALMA (Cooperation EQALM – ICHCLR)



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# WG – commutability in IFCC

- The WG is developing documents on how to set criteria for evaluating commutability for Certified reference material (CRM) and EQA material (EQAM).

- The criteria will be different because the different use of CRMs and EQAMs



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| Consideration | External Quality Assessment Material (EQAM) | Certified Reference Material (CRM) |
|---|---|---|
| Intended use | To assess suitability of results by each MS and of MP | To calibrate MSs |
| Prerequisites for including end-user MS in commutability assessment | | |
| Consequences of not having commutable material | | |

# The main difference when assesing commutability for CRMs and EQAMs

**CRM – certified reference material**

Evaluation of commutability will only be done for MS with an acceptable analytical quality
(both method evaluation and commutability evaluation)

**EQAMs – external quality assurance material**

Evaluation of commutability will done for all MSs

(only commutability evaluation) because method evaluation is done by APS set by the EQA organiser

# Principles for for commutability evaluations for EQAMs

General principles:

- 25-50 clinical samples are analysed in triplicate
- Prediction bands are constructed
- Control samples (EQAMs) are analysed in the same way as the clinical samples



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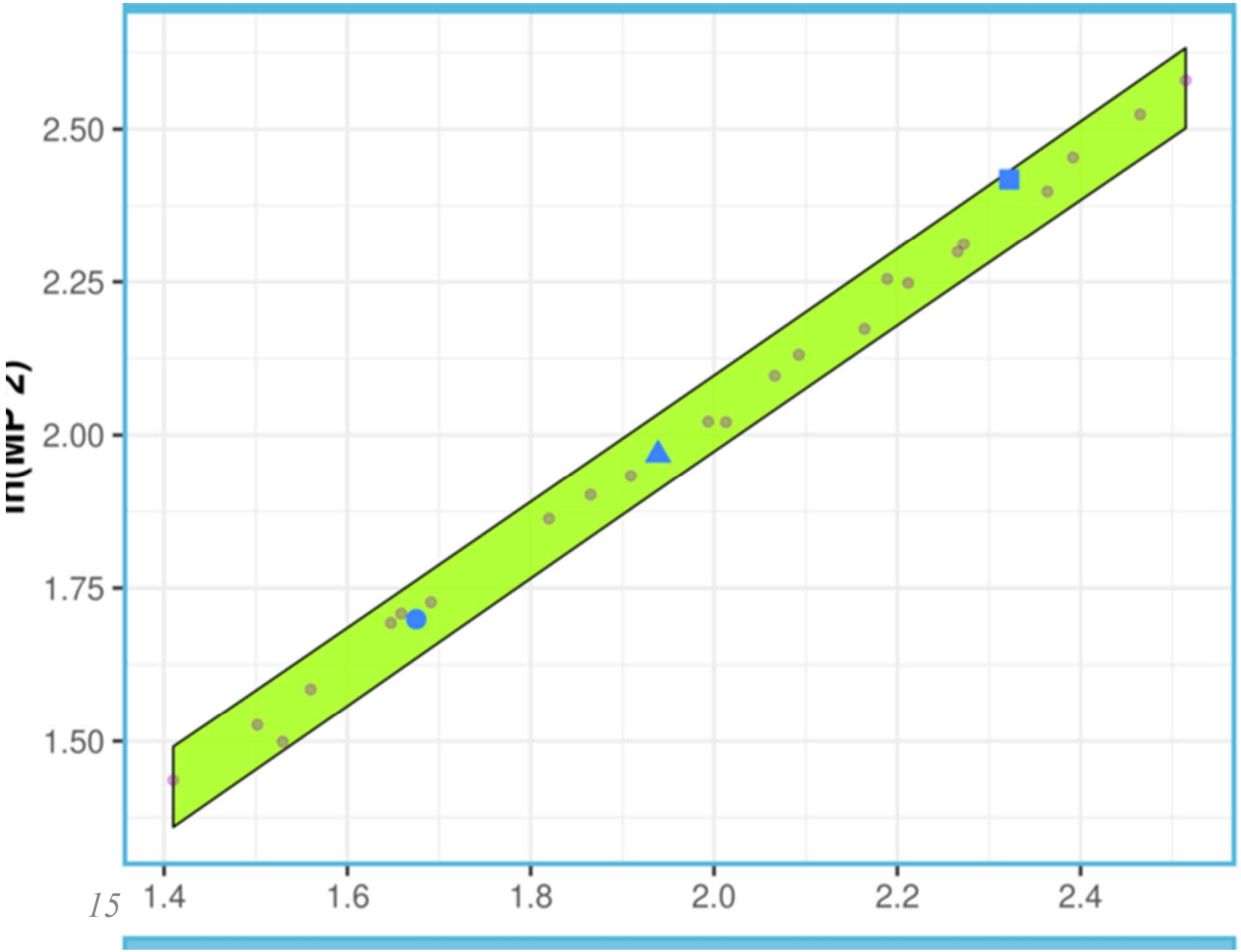
ln(MPG)
2.50
2.25
2.00
1.75
1.50
1.4
1.6
1.8
2.0
2.2
2.4


2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.4
1.6

# Problem

## The presence of non-selectivity

which is not taken into account in the CLSI (EP14) guideline



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# *Selectivity* of a measuring system

is a property whereby the measured value of a measurand is independent of other measurands or other quantities in the sample (VIM definition).

Other measurands or quantities may be metabolites of the measurand, molecular forms of the measurand, other ions or molecules, or influences on the measurement from any source other than the measurand itself.

***Relative selectivity*** is the degree of relative differences in selectivity between any two measuring systems (MSs)



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# Problem
# The presence of non-selectivity

- The presence of non-selectivity will increase the width of the prediction bands

- As non-selectivity often will be present, the question is:

How much «non-selectivity» can be tolerated?



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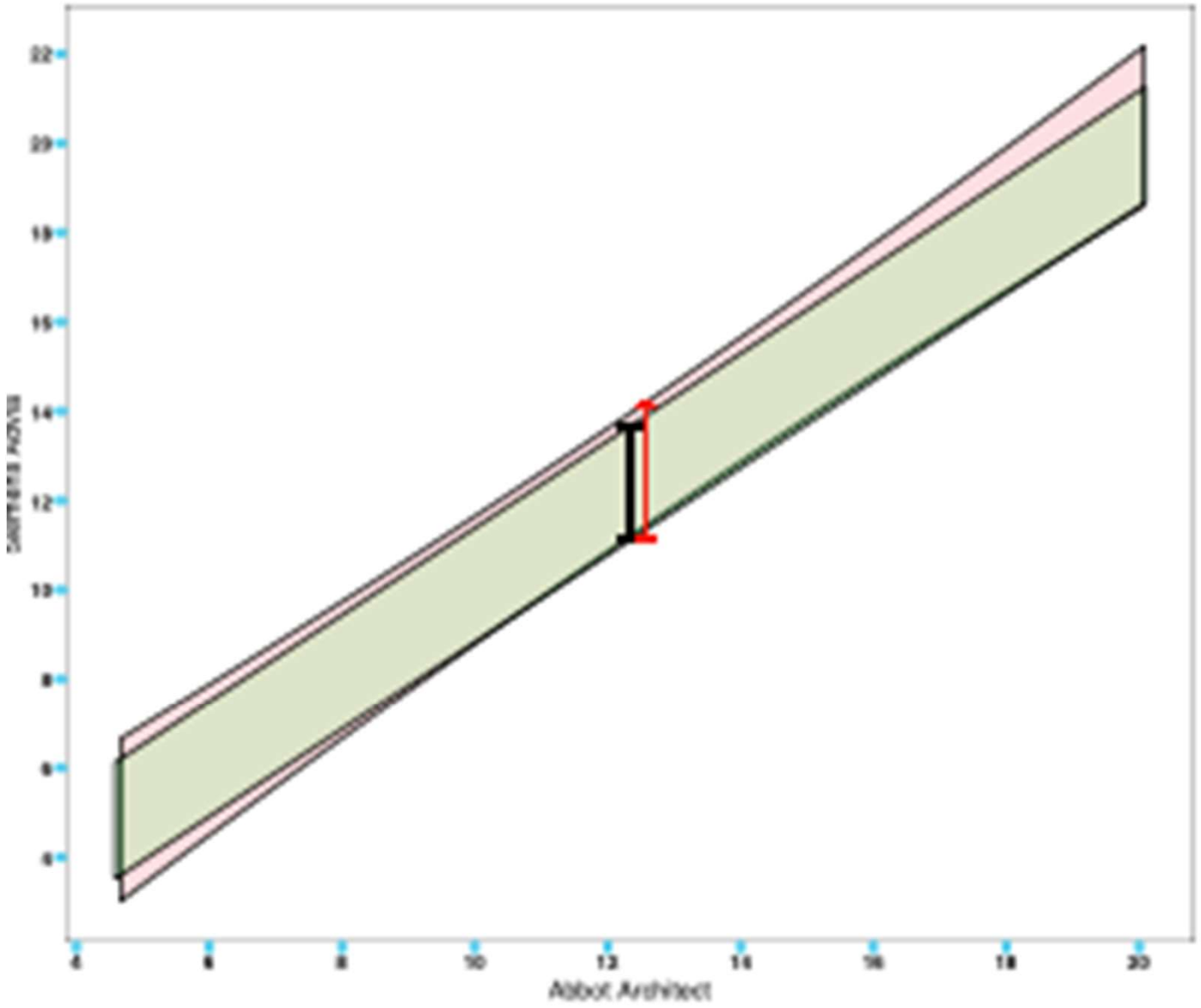


*How much «non-selectivity» can be accepted?*
*- what is an acceptable increase in the width of the prediction band (M)*

How much «non-selectivity» can be accepted?

- what is an acceptable increase in the width of the prediction band (M)

$SD^2_{MS_1}$ *is the variance of* $MS_1$

$SD^2_R$ *is the variance of the residuals*

A quantitative measure of non-selectivy is

$$\zeta = \frac{\mathrm{SD}_\mathrm{R}^2}{\mathrm{SD}_{\mathrm{MS}_1}^2 + \mathrm{SD}_{\mathrm{MS}_2}^2}$$

*ζ is in principle the ratio of the variances of the residuals and the sum of the variances of each MS*

*ζ is related to M*



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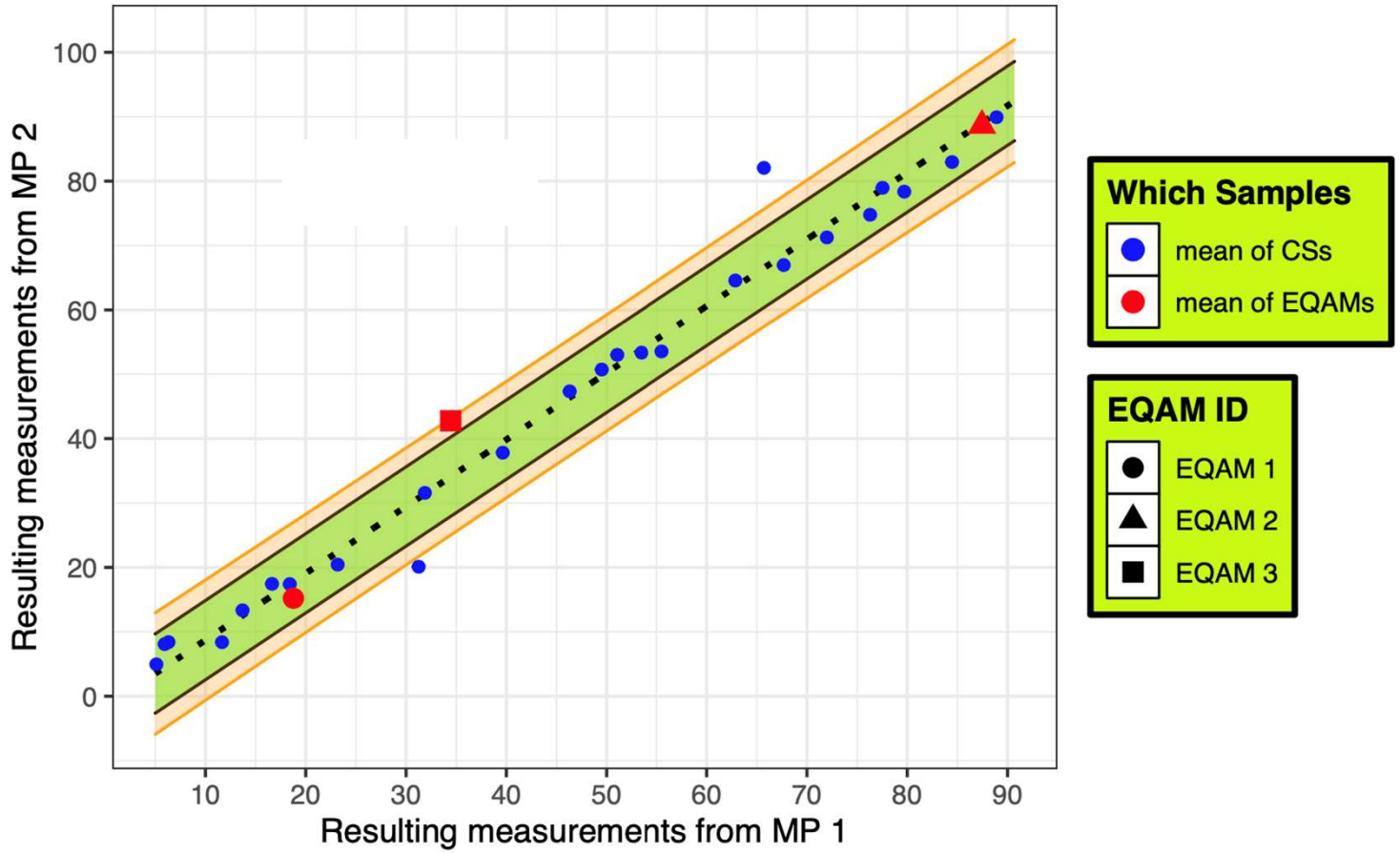
*ζ is in principle the ratio of the variances of the residuals and the sum of the variances of each MS and is related to M*



*Different ζ depending on study design and increase in the prediction interval accepted (M),*

| | | $\zeta_{upper}$ values for different Ms | | | | |
|---|---|---|---|---|---|---|
| **Number of clinical samples** | Number of replicates | M = 15% | M = 20% | M = 25% | M = 30% | M = 40% |
| **20** | 2 | 2,50 | 2,73 | 2,93 | 3,19 | 3,69 |
| **20** | 3 | 1,97 | 2,14 | 2,32 | 2,52 | 2,92 |
| **20** | 4 | 1,80 | 1,95 | 2,12 | 2,30 | 2,66 |
| **25** | 2 | 2,32 | 2,51 | 2,74 | 2,94 | 3,42 |
| **25** | 3 | 1,88 | 2,05 | 2,22 | 2,40 | 2,78 |
| **25** | 4 | 1,73 | 1,89 | 2,05 | 2,22 | 2,57 |
| **30** | 2 | 2,19 | 2,38 | 2,58 | 2,79 | 3,23 |
| **30** | 3 | 1,82 | 1,98 | 2,15 | 2,32 | 2,69 |
| **30** | 4 | 1,69 | 1,84 | 2,00 | 2,16 | 2,50 |
| **40** | 2 | 2,03 | 2,21 | 2,38 | 2,58 | 3,01 |
| **40** | 3 | 1,74 | 1,89 | 2,05 | 2,22 | 2,58 |
| **40** | 4 | 1,63 | 1,78 | 1,93 | 2,09 | 2,42 |

If excess non-selectivity

commutabiity cannot be assessed



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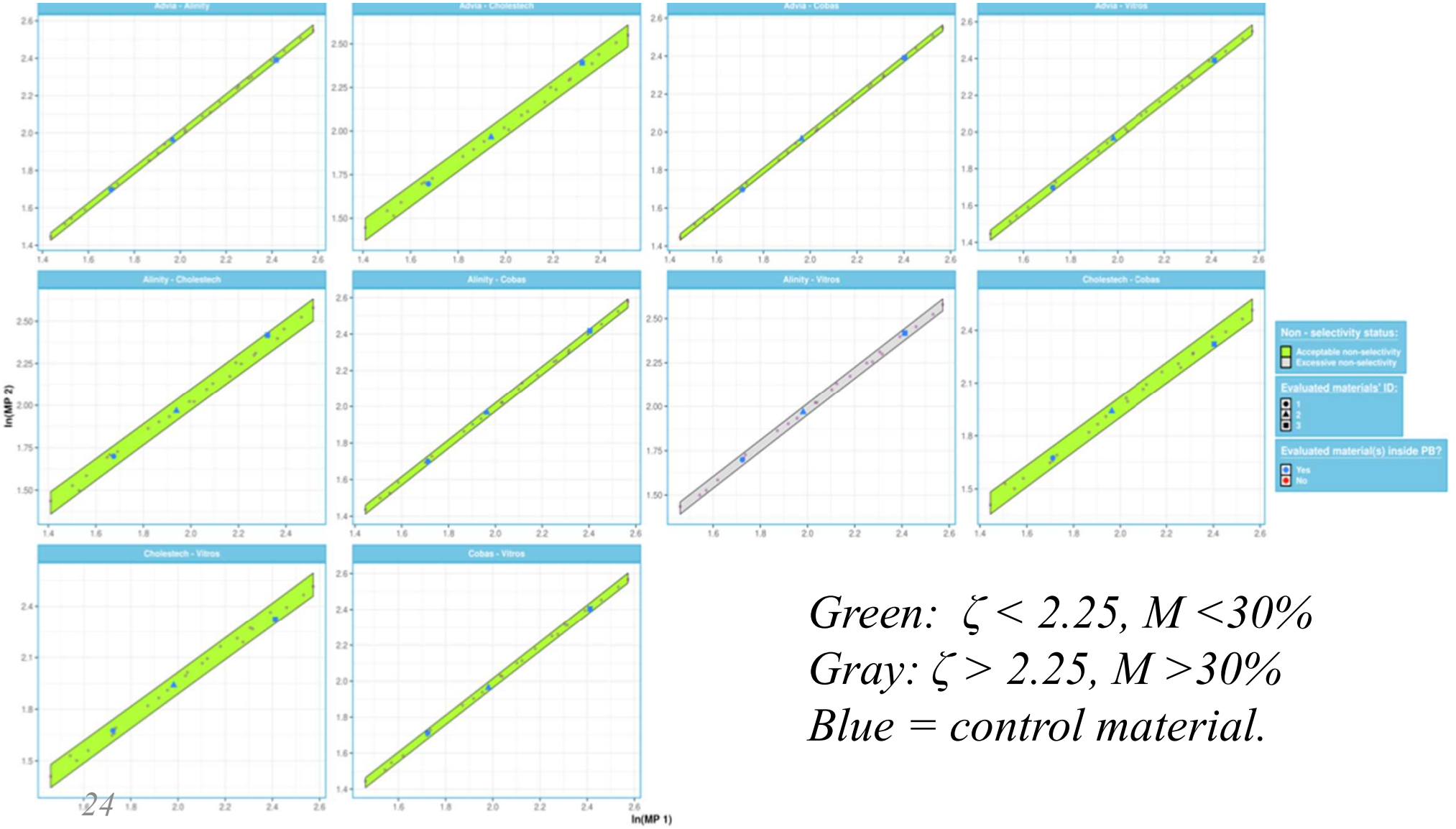
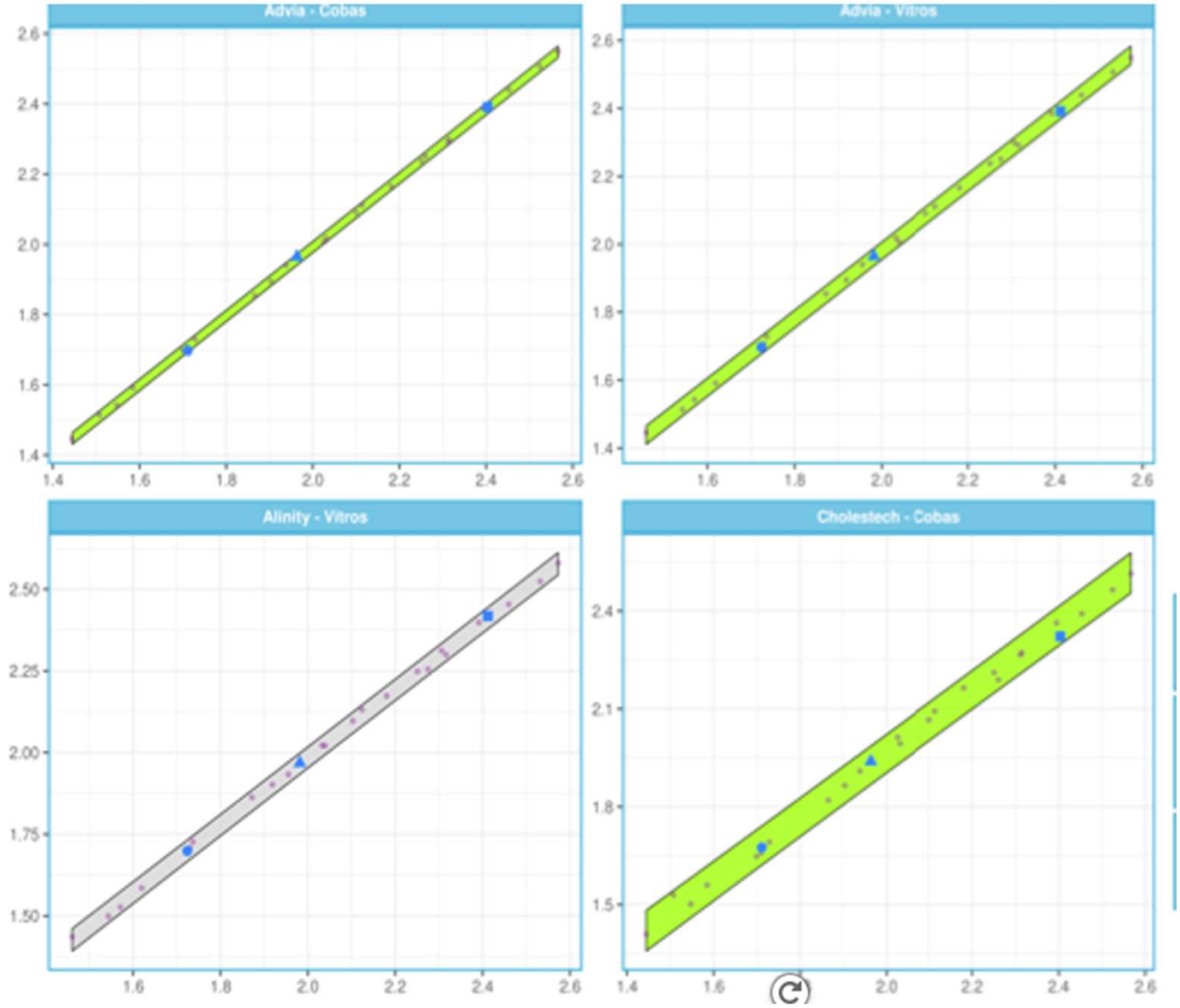
# *Commutability study Glucose*




*Green: $\zeta < 2.25$, $M < 30\%$*
*Gray: $\zeta > 2.25$, $M > 30\%$*
*Blue = control material.*




*Green: $\zeta < 2.25$, $M < 30\%$*
*Gray: $\zeta > 2.25$, $M > 30\%$*
*Blue = control material.*

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# Commutablity of EQAMs is a presupposition for aggregation of EQA results – the HALMA initiative

Cooperation between ICHCLR (International Cooperation for Harmonisation of Clinical Laboratory Results) – www.harmonisation.net

and EQALM (www.eqalm.org)



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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

https://doi.org/10.1515/cclm-2020-0736
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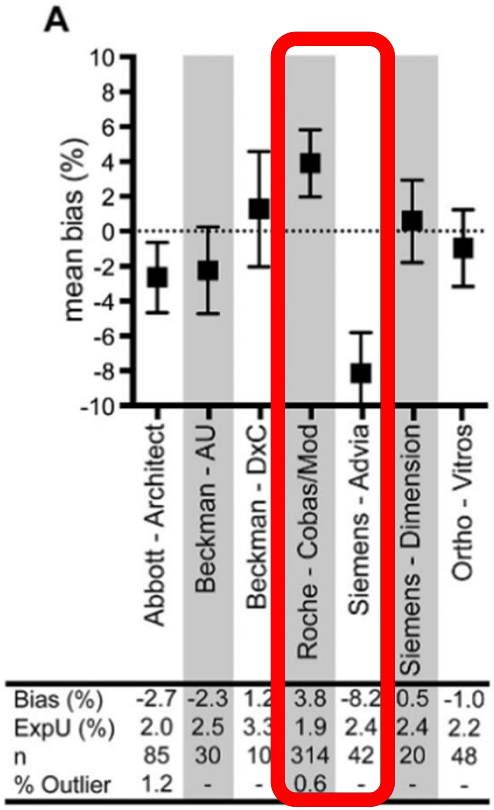
## Abstract

**Objectives:** External quality assessment (EQA) with commutable samples is used for assessing agreement of results for patients' samples. We investigated the feasibility to aggregate results from four different EQA schemes

**Conclusions:** EQA data could be aggregated from four different programs using different commutable samples to determine bias among different measurement procedures. Criteria for commutability for EQA samples as well as standardization of reporting the measurement methods, reagents, instrument platforms and models used by participants are needed to improve the ability to aggregate the results for optimal assessment of performance of measurement procedures. Aggregating data from a larger




## Creatinine

Mean % bias for the aggregated results from 4 EQA providers

# Aggregation of EQA results

**A**ggregation aims to collect and aggregate results from different EQA providers that use commutable samples. The purpose is to evaluate and assess harmonization and standardization of measurands through aggregated EQA data on an international basis.

Read more at:
http://www.eqalm.org/site/halma/halma.php



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# Commutable EQAM

A flowchart and two check lists have been developed to assess the probability that the control material is commutable even.



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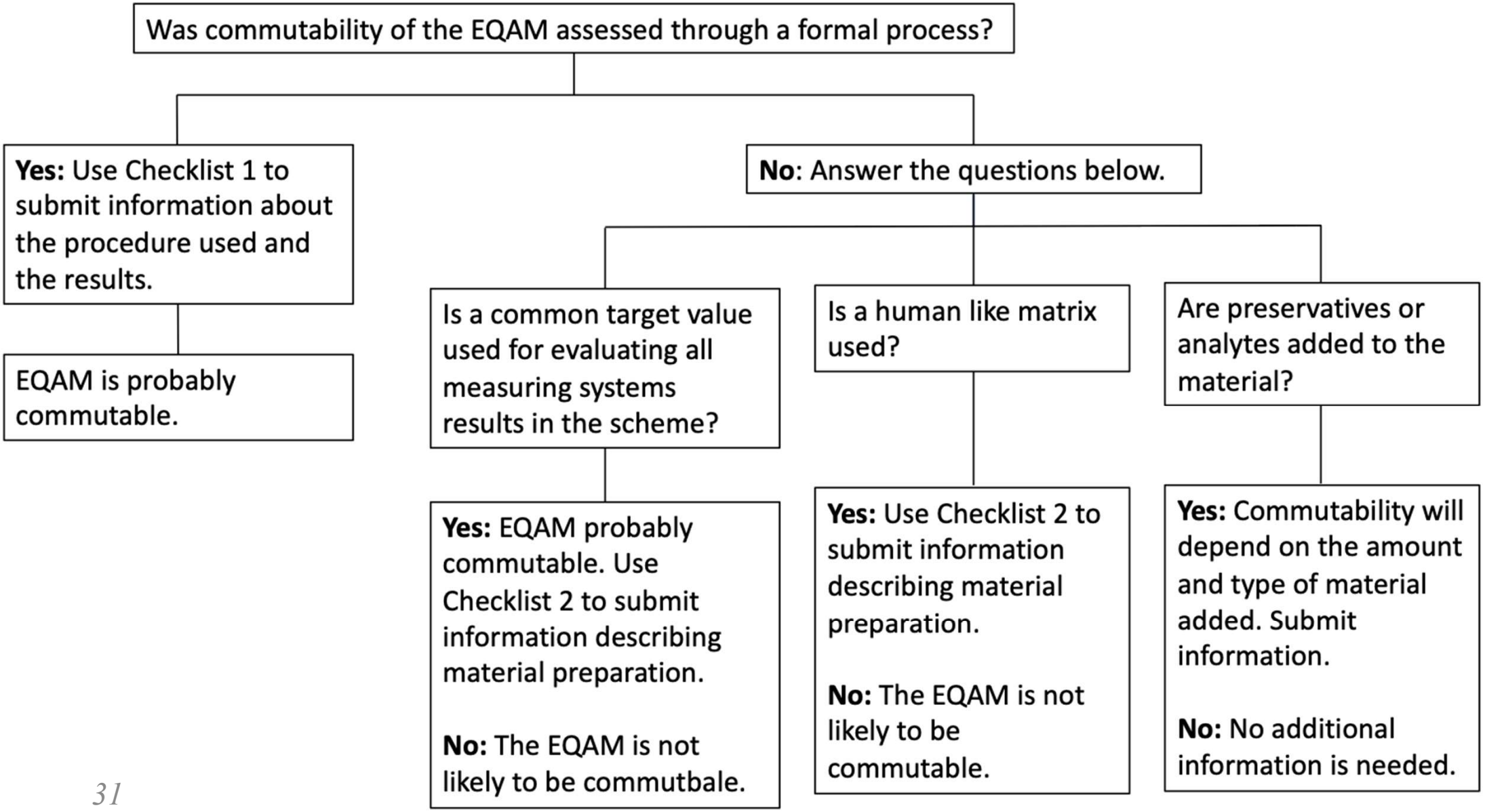
Was commutability of the EQAM assessed through a formal process?
**Yes:** Use Checklist 1 to submit information about the procedure used and the results.
EQAM is probably commutable.
**No**: Answer the questions below.
Is a common target value used for evaluating all measuring systems results in the scheme?
**Yes:** EQAM probably commutable. Use Checklist 2 to submit information describing material preparation.
**No:** The EQAM is not likely to be commutbale.
Is a human like matrix used?
**Yes:** Use Checklist 2 to submit information describing material preparation.
**No:** The EQAM is not likely to be commutable.
Are preservatives or analytes added to the material?
**Yes:** Commutability will depend on the amount and type of material added. Submit information.
**No:** No additional information is needed.

For many measurands it will be difficult to make commutable EQAMS

# Patients samples are usually commutable

- Patient medians from a large population for certain measurands are rather stable.
- Patient medians  from different laboratories can be compared if their originate from similar populations.
- Patients medians monitor both pre-analytical and analytical (including lot to lot variation, calibration, sample tubes etc) harmonisation
- Patient medians can evaluate equivalence and not metrological traceability



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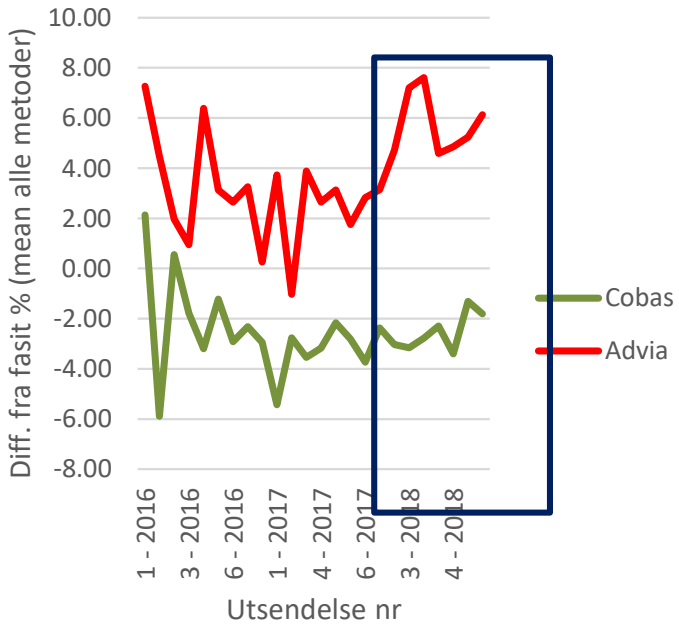
# The Noklus percentiler and flagger program (150 labs worldwide)

**New software under development**

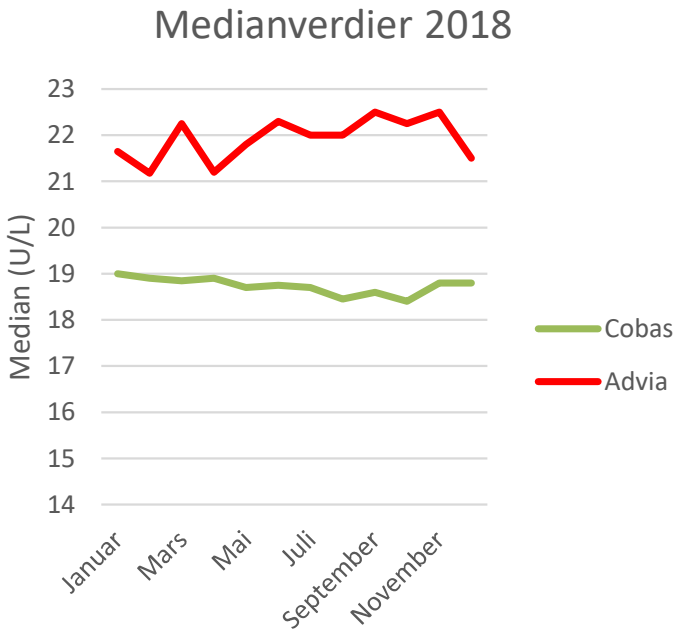
**Program will be offered in 2023 to EQA providers that can enrol their participants (see poster)**

# Example: ALT

## EQA program




## Patient medians

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# Conclusions

- One of the main purposes of EQA is to be able to monitor harmonisation and standardisation
- EQA providers should prioritise to circulate commutable EQAM
- EQA providers must prove that they have commutable material
- An updated method for how this should be done will soon be published.
- Data from different EQA-providers using commutable material can be aggregated.
- Patient medians can provide a supplement/replacement to EQA



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CUTTING EDGE OF LABORATORY MEDICINE IN EUROPE
ANALYTICAL PERFORMANCE SPECIFICATIONS: MOVING FROM MODELS TO PRACTICAL RECOMMENDATIONS
The aim of this conference is to go through and discuss the three different models agreed by the Milan 2014 EFLM Strategic Conference to set APS for the medical laboratory and to give practical examples on how this can be done.
Prague, Czech Republic, Charles University | October 12–13, 2023


Thank you