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This Special Report presents the recommendations made by the IFCC WG on Commutability for assessing commutability of reference materials and which were published in a series of three articles in *Clinical Chemistry* in March 2018. This outlines the key recommendations for the experimental design of commutability assessement and two new statistical approaches for commutability assessment: one uses the difference in bias between a reference material and clinical samples and the second uses the calibration effectiveness of a reference material.

Commutability of certified reference materials

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Commutability is an essential property of a certified reference material (CRM) when it is used as a calibrator in the calibration hierarchy of an in-vitro diagnostics medical device (IVD-MD) as described in ISO 17511, In vitro diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values assigned to calibrators and control materials (1, 2). Commutability is defined in the International Vocabulary of Metrology (VIM) as a property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials (3). For medical laboratories, other specified materials are clinical samples (CSs) and the quantity intended to be measured is referred to as the measurand. Although the VIM definition refers to two measurement procedures, in practice commutability of the material with CSs is required for all combinations of measurement procedures for which the CRM is intended to be used.

CRMs are typically available as either pure substances characterized for mass balance or as matrix-based materials, with a certified property value for a stated measurand. A pure substance CRM cannot be evaluated for commutability, and is typically used (in current practice) for calibration of higher order reference measurement procedures. However, when a pure substance is prepared in a matrix similar to that of the intended CSs, for use as a calibrator for measurement procedures for the intended measurand in CSs, the CRM must be commutable with CSs.

Matrix-based CRMs (also known as secondary reference materials), including those prepared from pure substance CRMs, are typically used in a calibration hierarchy for an IVD-MD as calibrators for a manufacturer's selected measurement procedure or for a medical laboratory measurement procedure, also called an end-user IVD-MD. Note that in many cases a manufacturer's selected measurement procedure is the same technology as the IVD-MD, but operated with more stringent calibration and replication to reduce uncertainty. Commutability of matrix-based CRMs with CSs is an essential property for such matrix-based CRMs to be suitable for use in this context. Establishing traceability to a non-commutable matrix-based CRM in the calibration hierarchy of an IVD-MD may propagate any non-commutability bias to the final results for CSs measured with the IVD-MD. In such cases, results from one IVD-MD may not agree with results from other different IVD-MDs. Such differences among results for CSs among different IVD-MDs can lead to incorrect medical decisions if the results are interpreted using common decision criteria and/or guidelines for patient management.

Traceability of the assigned value of a calibrator for an IVD-MD to a common CRM is one important component in achieving standardized results among different IVD-MDs for the same measurand. It is also essential that all IVD-MDs purported to measure the same measurand demonstrate a degree of selectivity for the measurand in CSs that is suitable for the intended medical use.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Commutability (WGC) recently published recommendations for assessing commutability of reference materials. Part 1 provides recommendations for the experimental design of a commutability assessment (4). Parts 2 and 3 provide statistical procedures to evaluate the data from a commutability assessment (5, 6). When assessing commutability of a CRM with CSs, it is important to keep in mind that we are not assessing performance of the measurement procedures involved in the commutability assessment. However, performance of the measurement procedures can influence the assessment of commutability of a CRM. Key recommendations for the experimental design are summarized below; refer to the citations for details.

1. The criterion for acceptable commutability is established as a fraction of the maximum allowable uncertainty required for the CRM's assigned value at the position it is intended to be used in a calibration hierarchy for an IVD-MD. The criterion should enable agreement of results for CSs among different IVD-MDs, frequently described as the total allowable error, such that medical decisions can be made, and the probability of occurrence and severity of harm to patients is acceptably low. The statistical approaches in parts 2 and 3 of the IFCC WGC recommendations use the same fixed criterion for all measurement procedures participating in a commutability assessment.
2. Individual CSs are preferred because these are the samples that IVD-MDs are intended to measure and with which a CRM used as a calibrator must be commutable.
3. The presence of sample specific influences (e.g. complex molecular forms, or interfering substances) can confound a commutability assessment by creating outlier results for some CSs, or by increasing the uncertainty. Consequently, the individual CSs included in a commutability study should not contain known interfering substances or unusual molecular forms where these factors are known to negatively affect all or most of the available measurement procedures for the measurand.
4. The concentrations of measurand in the individual CSs do not need to cover the full measuring interval for the measurement procedures included, but should bracket the concentration of measurand in the CRM being evaluated.
5. The number of clinical samples and the number of replicate measurements is derived from the uncertainty required in the commutability assessment.
6. The CSs must be collected, processed, stored and transported such that the measurand and matrix are not altered from that of samples used for typical medical laboratory testing. A preliminary experiment may be needed to validate the conditions.
7. Pooled CSs can be used when sample volume requirements cannot be met using individual CSs. However, the pooling process can alter the matrix and validation is required to demonstrate that pooled CSs can be substituted for individual CSs.
8. When CRMs are diluted prior to use or to prepare several concentrations of the material, the diluted materials must be validated to be commutable with CSs.
9. It is desirable that a commutability assessment includes all measurement procedures for which a CRM will be used. For logistical reasons, a limited number of measurement procedures are typically included. Those measurement procedures included should represent commonly used measurement procedures and different technologies when applicable.
10. Measurement procedures included must have acceptable performance characteristics for precision and selectivity for the measurand. Calibration is not important for commutability assessment. However, results among the different measurement procedures included in the study must be correlated for adequate assessment of commutability of a CRM intended for use in the calibration hierarchies of those measurement procedures.
11. Ideally a CRM will be commutable with CSs for all measurement procedures for which it is intended to be used. In practice, this goal is not always met. There is no fixed fraction of measurement procedures for which a CRM must be commutable for that CRM to be useful. Market share, number of people for whom results will be provided from the measurement procedures and impact on health improvement can be considered when determining the fraction of measurement procedures for which a CRM should be commutable to be suitable for use.

Traditional methods for assessing commutability have been based on statistical procedures with criteria defined by the distribution of the differences in results for clinical samples. This approach can lead to different criteria for each pair of measurement procedures examined because the criteria reflect the random errors that are frequently different for each measurement procedure. Variable acceptability criteria for commutability assessments among comparisons between different pairs of measurement procedures can confound the determination of the suitability for use of a CRM in the calibration hierarchies of IVD-MDs. Determining that results for a CRM are within the prediction interval from regression plots or within the limit of agreement from difference plots does not consider the uncertainty of the measurements. For example, a result for a CRM that falls on the prediction interval or limit of agreement has a probability of approximately 50% of having a value within the criterion.

One of the new statistical approaches for commutability assessment reflects the VIM definition of commutability by estimating the difference in bias between a CRM and the average bias of CSs at the concentration of the CRM (5). This approach uses an error model that estimates the difference in bias and its uncertainty because most random error components including the sample specific effects are determined in the experimental design. The criterion for commutability is the same for all combinations of measurement procedures and can be based on medically relevant differences between results for the CRM and clinical samples. A panel of clinical samples and the CRM are measured by each measurement procedure in the commutability assessment. Figure 1 shows an example of commutability conditions for a pair of measurement procedures. A commutable CRM has a difference

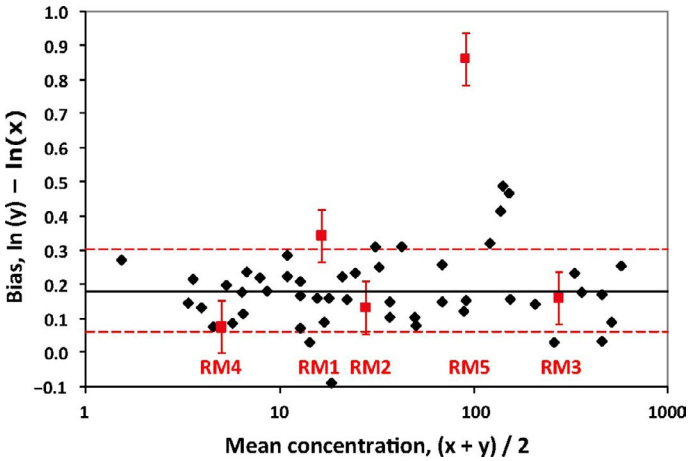

Figure 1. Difference in bias between RMs (red squares) and CSs (black diamonds) vs mean concentration of the 2 measuring systems.
The solid black line is the mean bias between the 2 measurement procedures for the CSs. The red dashed lines are the commutability criteria. The red squares are the mean bias between the 2 MPs for the RMs, and the bars are the uncertainty in the difference in bias between RM and CS mean bias. RM1, RM2, and RM4 are indeterminate; RM3 is commutable; RM5 is non-commutable. Reproduced with permission from the American Association for Clinical Chemistry (see Reference 5).

in bias and its uncertainty within the criterion; commutability is indeterminate when the uncertainty exceeds the criterion; and a non-commutable decision is made when the difference in bias and its uncertainty are outside the criterion. All combinations of measurement procedures are examined in this manner. The assessment is simplified when a reference measurement procedure is available because results from the different measurement procedures only need to be compared to those from the reference measurement procedure. The difference in bias approach is also suitable for assessing commutability of trueness controls and proficiency testing / external quality assessment materials. Citation 5 includes complete statistical details and a worked example.

The second new statistical approach for commutability assessment is based on the effectiveness of a CRM to fulfill its intended use as a higher order calibrator in the calibration hierarchies of IVD medical devices (6). As in the preceding approach, the criterion for commutability is the same for all IVD medical devices. In this approach, the CRM is used in the calibration hierarchy of each IVD medical device in the commutability assessment. A panel of clinical samples is measured by each IVD medical device and the difference from the target values for each sample is determined vs a reference measurement procedure, when available, or vs another target such as the trimmed all methods mean. The median of the results for the panel of clinical samples for each IVD medical device is used to determine an inter-measurement procedure bias range that is compared to the criterion. The CRM is commutable for use with those IVD medical devices whose median results are within the criterion. Figure 2 shows an example of commutability conditions for seven measurement procedures. The CRM is commutable for use with six of

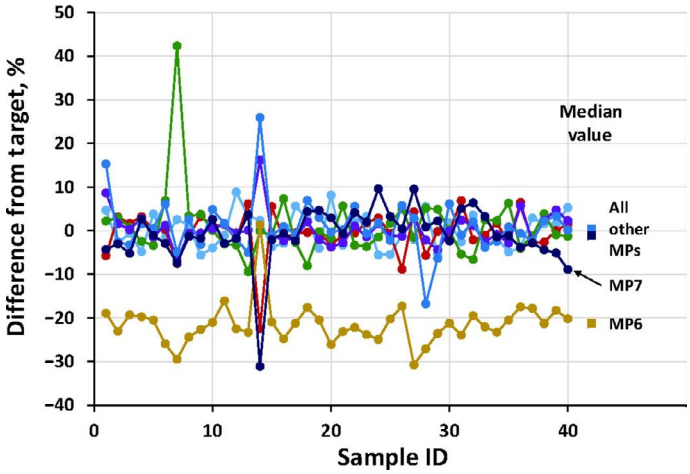

Figure 2. Difference in percent from the target value for the same 40 CS results after recalibration of the 7 MPs shown in Fig. 3 with traceability to the RM.
The median difference for each MP is shown as the square symbol, along with the MP labels to the right. Note that the MP6 median is separated from the other medians that are difficult to distinguish from each other. The MP colors are the same as in Fig. 3. MP7 is the dark blue symbol as pointed out on the figure. Reproduced with permission from the American Association for Clinical Chemistry (see Reference 6).

the seven measurement procedures because their inter-measurement procedure bias range met the criterion with the CRM used in each of their calibration hierarchies. The CRM is non-commutable for use with measurement procedure MP6 because its results are not within the criterion. Note that this approach is not influenced by a small number of clinical samples with sample specific effects observed for some measurement procedures as seen for samples 7 and 14. Citation 6 includes complete statistical details and a worked example.

In conclusion, commutability with clinical samples is an essential property of matrix-based CRMs intended for use as calibrators in a calibration hierarchy for IVD medical devices. JCTLM now requires commutability assessment data for listing of new CRMs in its database. The IFCC WGC has developed comprehensive recommendations for performing a commutability assessment including new statistical approaches that consider the uncertainty in the data and use a fixed criterion applicable to all measurement procedures in an assessment.

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