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IFCC Working Group Recommendations for Correction of Bias Caused by Noncommutability of a Certified Reference Material Used in the Calibration Hierarchy of an End-User Measurement Procedure

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Guests: Dr. Lindsey Mackay is General Manager at the National Measurement Institute in Canberra, Australia, and Dr. Greg Miller of the Virginia Commonwealth University Health System, chairs the IFCC working group on commutability.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

The term "commutability" as applied to reference and quality control materials was first introduced by workers at the New York State Department of Health in the January 1973 issue of *Clinical Chemistry*. Since that time, the concept has been proven to be critical in metrology, and in 2018 the working group on commutability of the International Federation of Clinical Chemistry and Laboratory Medicine, or IFCC, published a three-part set of recommendations for assessing commutability.

Now in the June 2020 issue of *Clinical Chemistry*, the IFCC working group has published a fourth article, this one concerned with correction of bias caused by non-commutability of reference materials. It was accompanied by an editorial by Dr. Lindsey Mackay from The National Measurement Institute in Canberra, Australia. She is our guest in this podcast and is joined by the Chair of the IFCC working group Greg Miller, from the Department of Pathology at Virginia Commonwealth University Health System in Richmond.

So, Dr. Miller, what type of certified reference material, or CRM, does this latest report address?

Dr. Greg Miller: This report addresses a matrix-based CRM, where the matrix is similar to that of the clinical samples intended to be measured. Such a CRM is intended for use as a secondary calibrator in the calibration hierarchy of an end-user measurement procedure that we use in the clinical laboratory. Because CRMs are expensive and have limited availability, they are not used directly as calibrators in the laboratory for our end-user measurement procedures.

Manufacturers use these CRMs to calibrate another measurement procedure that in turn is used to value-assign working calibrators and the end-user calibrator sold to and used by clinical laboratories.

A matrix-based CRM must be commutable with the clinical samples measured in a clinical laboratory to be suitable for use in this calibration hierarchy that achieves what we call metrological traceability from the clinical sample result to the value assigned to the CRM. Commutable means a CRM gives a measurement response equivalent to the measurement response of a clinical sample that has the same concentration of the measurand.

Bob Barrett: So Dr. Mackay, over to you, what is the issue caused by using a non-commutable matrix-based CRM in the calibration hierarchy of an end-user measurement procedure?

Dr. Lindsey Mackay: if a non-commutable theory was used in a calibration hierarchy, there'll be a bias introduced in the calibration sequence and that bias will be propagated down to the results for the actual clinical samples. What this means, is that the results for clinical samples from a measurement procedure for which the CRM is non-commutable, are biased compared with the results from other measurement procedures and these biases can cause erroneous medical decisions. So, it's important that this issue is addressed.

Bob Barrett: Now, Dr. Miller, how is the correlation applied in the calibration hierarchy of an end-user measurement procedure to achieve metrological traceability of results for clinical samples?

Dr. Greg Miller: Well, the ISO standard 17511 describes a sequence of measurand value transfers from higher-order reference materials using reference measurement procedures through a manufacturer's internal value transfer steps onto the end-user calibrator which is finally used to calibrate the instruments we use in the clinical laboratory.

A secondary matrix-based CRM is the final higher order component typically provided by a national metrology institute or similar provider. This CRM is used to calibrate a manufacturer's internal value transfer steps, typically including to a working calibrator which is also called the master lot of calibrator and to the end-user calibrator used by the clinical laboratory. If a correction for the non-commutability bias of the matrix-based CRM is needed, that correction can be added as an additional step in the calibration hierarchies between the CRM and one of the steps in the manufacturer's internal sequence.

Bob Barrett: And Dr. Mackay, what are the key requirements for developing a correction for non-commutability bias?

Dr. Lindsey Mackay: In simple terms, this approach involves incorporating a

correction factor into the calibration of a measurement procedure.

To determine an effective correction factor, the magnitude of a non-commutability bias associated with the CRM must be known with a small enough uncertainty that the correction for the bias can be incorporated and the measurement procedure will still be fit for purpose. The paper includes two examples that illustrate the experimental designs based on one of the approaches to commutability assessment published in 2018 from the IFCC working group. This is what's called the difference in bias approach.

The experimental designs that are presented aim to give the best estimate of the bias by ensuring that potential sources of variability are included. They also use a sufficiently large number of clinical samples and replicate measurements of the clinical samples and of the CRM to achieve a small uncertainty in the estimate of the non-commutability bias.

A key requirement for this approach to be effective is that the magnitude of the non-commutability bias remains constant over time. This is particularly important. The approach gives very small uncertainties for what can be quite large biases. The magnitude of the non-commutability bias can be influenced by stability of both the measurand and the matrix in the CRM.

It can also be affected by the stability of the batches of reagents and other components of the measuring systems used in the clinical laboratory. The paper recommends the periodic verification of the stability of the correction factor when using this approach to correct for bias. I think this will be really important whenever this approach to be used.

Bob Barrett: So, whose responsibility is it to develop and apply a correction for non-commutability of a matrix-based CRM?

Dr. Greg Miller: It's the manufacturer of the end-user measurement procedure that is responsible for this process. A non-commutability bias is a unique property of the combination of the CRM and a specific end-user measurement procedure.

Consequently, a correction for non-commutability bias only applies to the calibration hierarchy of that specific end-user measurement procedure. Only the manufacturer of that procedure has the technical knowledge of the internal steps in the calibration hierarchy and the ability to apply a correction to one of those steps. It is important to remember that a manufacturer is often an in vitro diagnostics company, but can also be an individual clinical laboratory that develops a measurement procedure for its own use. We call these laboratory developed tests.

Bob Barrett: Well, and finally, Dr. Mackay, what is the value to laboratory medicine of using a correction for non-commutability bias of a matrix-based CRM?

Dr. Lindsey Mackay: One of the biggest issues is that matrix-based CRMs are difficult to produce that are commutable with clinical samples to all measurement procedures for a given measurand.

When you are producing a CRM, it's also not practical to validate commutability for all measurement procedures and use worldwide. Applying a correction for any non-commutability bias that is identified for a CRM, allows a manufacturer to achieve metrological traceability to the value assigned to that CRM. When this bias correction is applied to a specific measurement procedure that is using the CRM as a calibrator, but for which the CRM is not computable, this enables results for clinical samples to be equivalent to results from other end-user measurement procedures from different manufacturers.

What really matters here is that patient care and patient safety based on results for that laboratory tests are improved and medical errors are avoided.

Bob Barrett: That was Dr. Lindsey Mackay, General Manager at the National Measurement Institute in Canberra, Australia. She was joined by the Chair of the IFCC working group on commutability, Dr. Greg Miller, from the Virginia Commonwealth University Health System. The latest report from the IFCC working group on commutability is available online now and appears in the June 2020 print edition of the journal *Clinical Chemistry,* along with Dr. Mackay's editorial.

I am Bob Barrett. Thanks for listening.