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Special Report

Optimizing Available Tools for Achieving Result Standardization: Value Added by Joint Committee on Traceability in Laboratory Medicine (JCTLM)

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BACKGROUND: The JCTLM created a Task Force on Reference Measurement System Implementation (TF-RMSI) to provide guidance on metrological traceability implementation for the in vitro diagnostics (IVD) community.

CONTENT: TF-RMSI investigated the reference measurement systems (RMS) for 13 common measurands by applying the following procedural steps: (*a*) extracting data from the JCTLM database of available certified reference materials (CRMs) and reference measurement procedures (RMPs); (*b*) describing the RMS to which each recruited CRM or RMP belongs; (*c*) identifying the intended use of the CRMs, and, if used as a common calibrator for IVD measuring systems and/or trueness assessment of field methods was included, checking the CRM's certificate for information about commutability with clinical samples; and (*d*) checking if the CRM or RMP measurement uncertainty (MU) has the potential to be small enough to avoid significantly affecting the analytical performance specifications (APS) for MU of clinical sample results when the MU from the IVD calibrator and from the end-user measuring system were combined.

SUMMARY: We produced a synopsis of JCTLM-listed higher-order CRMs and RMPs for the selected measurands, including their main characteristics for implementing traceability and fulfilling (or not) the APS for suitable MU. Results showed that traceability to higher-order references can be established by IVD manufacturers within the defined APS for most of the 13 selected measurands. However, some measurands do not yet have suitable CRMs for use as common calibrators. For these measurands, splitting clinical samples with a laboratory performing the RMP may provide a practical alternative for establishing a calibration hierarchy.

Background

THE JOINT COMMITTEE ON TRACEABILITY IN LABORATORY MEDICINE (JCTLM)

The medical laboratory community is working toward global standardization to obtain equivalence of test results across space and time (1). Achieving this would eliminate the need for method-specific reference limits and decision levels allowing proper use of evidence-based information in clinical practice. The application of metrological principles is currently considered the best tool to achieve measurement standardization (2, 3). This relies on the implementation of a reference measurement system (RMS), essential components being the definition of the measurand with regards to the intended clinical use, together with the characterization of appropriate higher-order reference materials and methods. JCTLM, created in 2002, represents a part of this international movement toward comparability, reliability, and equivalence of measurement results in medical laboratories (4). In the last 20 years, the main

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objective of JCTLM has been to identify, through a transparent review process, reference materials and measurement procedures that fulfill the definition of "higher order," and laboratories offering a reference service. To achieve this goal, JCTLM is using appropriate International Organization for Standardization (ISO) standards and expertise of its members drawn from all international stakeholders who support standardization activities (5–7). The outcome of this work is a publicly available database listing reference materials, methods, and measurement services that meet the ISO standards (8). The JCTLM database is a highly valuable resource for implementing metrological traceability by the in vitro diagnostics (IVD) device manufacturers, both commercial and laboratory developed, on a global basis as described in the ISO 17511:2020 standard (9). Some countries or regions have regulations requiring metrological traceability to higher-order references, for example the European Union Regulation 2017/745 (10).

ADDING PILLARS TO THE TEMPLE OF LABORATORY STANDARDIZATION

The classical key elements of an RMS are higher-order certified reference materials (CRM), reference measurement procedures (RMP), and reference laboratory services (RLS) using these RMPs. However, additional components are essential to implementing the metrological traceability concept in a manner that is meaningful for clinical practice (Fig. 1) (11, 12). An additional pillar for sustaining what has been named the "temple of laboratory standardization" is the setting of analytical performance specifications (APS) for measurement uncertainty (MU) that are fit for the intended purpose (13, 14). This is an aspect not yet completely considered, substantially distinguishing the application of metrological science in laboratory medicine from that in other areas, i.e., the definition and use of the RMS concept for standardization of measurements must be closely associated with the setting of targets for MU to provide test results that are clinically suitable. Fulfilling APS ensures that measurement results in clinical samples have a MU that satisfies their intended use. If these targets are not objectively defined and fulfilled, there is a risk that measurement variability (including some bias, if any) obscures the clinical information derived from the result and reduces the advantages of metrological traceability implementation (12, 15).

Another pillar of the temple of standardization is participation in analytical quality control programs (internal and external surveillance) that appropriately assess the suitability of components used in the calibration hierarchy to establish metrological traceability. Surveillance programs intended to assess measurement procedures used in medical laboratories should provide adequate postmarket surveillance information (16–18). The recently revised ISO 17511:2020 standard includes these 2 additional components by requiring that the

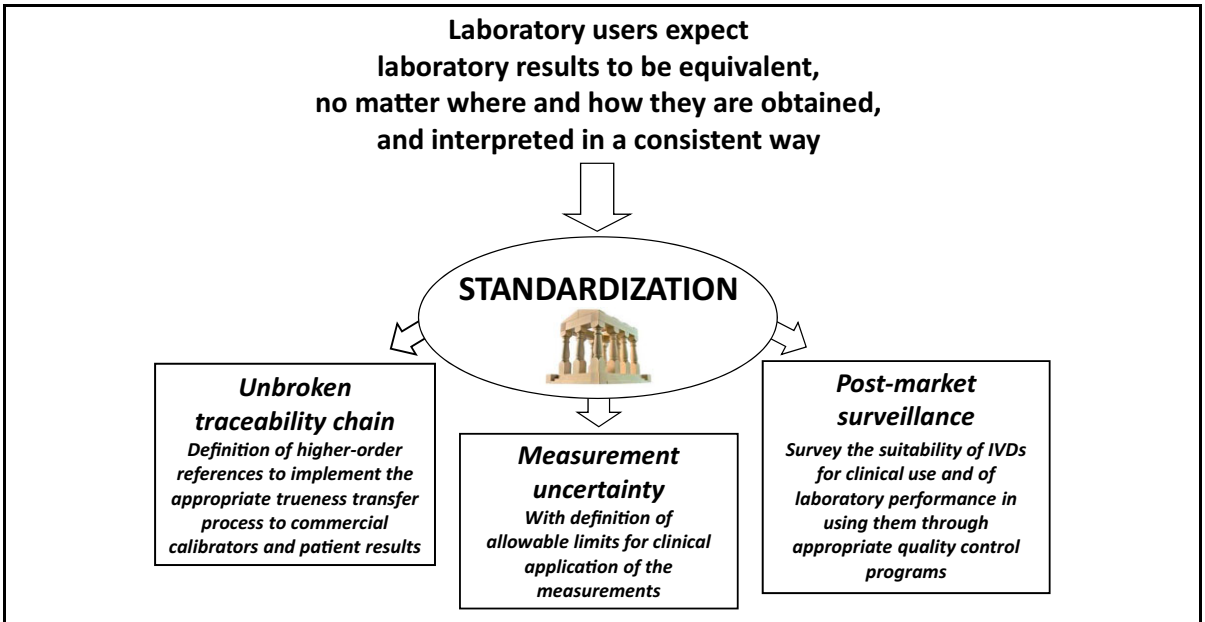

Fig. 1. Main components to be defined to produce standardized laboratory results. Modified with permission from Infusino and Panteghini (13).

MU of results obtained by end-users of IVD in clinical samples not exceed the predefined maximum allowable MU and mandating the inclusion in the IVD medical device developer's technical file of documentary evidence that metrological traceability is achieved (9).

THE JCTLM TASK FORCE ON REFERENCE MEASUREMENT SYSTEM IMPLEMENTATION (TF-RMSI)

IVD manufacturers usually provide only a short description of how metrological traceability was established for their commercially available measuring systems (12). The information provided is frequently limited to the name of the CRM and/or RMP to which the assay calibration is traceable, without any description of the implementation steps or the calibration hierarchy. Experience has shown that the type of traceability chain adopted by the IVD manufacturers and how it is implemented may lead to different combined MU at the level of commercial calibrators (12, 19). To address these observations, the ISO 17511:2020 standard requires appropriate documentation of the implementation steps for the calibration hierarchy as well as documentation of how metrological traceability to higher-order references was verified (9).

To aid IVD manufacturers in meeting these ISO 17511:2020 requirements, the identification and definition of available RMS and of all the calibration hierarchy components (i.e., not just CRMs and RMPs) may be helpful. With this in mind, in 2019 the JCTLM created the TF-RMSI, aiming to integrate the information historically provided in its database and to provide practical guidance on metrological traceability implementation to the IVD community. The TF-RMSI key objectives are to: (*a*) identify and describe available RMS and complete traceability chains, based on the information present in the JCTLM database; (*b*) illustrate the propagation of MU through the entire calibration hierarchy; (*c*) use APS derived according to an internationally recommended model to judge whether RMS components are fit for purpose; and (*d*) identify those measurands for which further advancements to existing RMS are needed or where some components of the RMS are lacking.

Considering major stakeholders in the field, TF-RMSI aims to:

- give to *IVD manufacturers* clarifications and recommendations for selecting the optimal approach for correctly implementing metrological traceability and identifying areas for improvement;
- be a stimulus for *higher-order reference providers* for improving the suitability of their products, if needed, and to assist with prioritizing future efforts; and
- help *laboratory professionals* in defining the analytical quality of their results.

Using serum creatinine as a case study, a preliminary exercise was carried out by employing an approach combining a critical review of what is available in the JCTLM database with a comparison of this information against derived APS for MU (20). Briefly, results showed that the most recently listed CRMs in the JCTLM database appeared to be suitable for correctly implementing metrological traceability (with commutability explicitly assessed) and has suitably small MU to allow APS to be met for measurements on patient samples. Splitting clinical samples with a laboratory performing mass spectrometry-based RMPs provided an alternative route to establishing a calibration hierarchy for measurement of serum creatinine. The TF-RMSI applied this approach for a group of 13 measurands covered within the JCTLM database, providing robust information about the state of the art of available RMSs and their impact on the ability of clinical measurements to meet APS. This report details the outcome of this work.

Methods

SELECTION OF MEASURANDS

We identified 13 common measurands selected among: (*a*) the most requested tests in a representative hospital laboratory, i.e., the laboratory of 'Luigi Sacco' academic hospital in Milan; (*b*) measurands for which the Consultative Committee for Amount of Substance (CCQM) comparisons were or are planned to be performed; and (*c*) different biochemistry categories (i.e., electrolytes, metabolites, enzymes, etc.). We investigated blood total hemoglobin (Hb), plasma/serum potassium, sodium, chloride, alanine aminotransferase (ALT), C-reactive protein (CRP), creatinine, urea, total calcium, total bilirubin, glucose, blood glycated hemoglobin (HbA_{1c}) [as measurand defined as molecules of Hb having a hexapeptide in common, which is the stable adduct of glucose to the N-terminal valine of the hemoglobin β-chain (βN1-deoxyfructosyl-hemoglobin) (21)], and serum 25-hydroxyvitamin D_3 [25(OH)D3].

PROCEDURE

The following procedural steps for each selected measurand were adopted:

1. data were extracted from the JCTLM database of available CRMs and RMPs,
2. the RMS to which each recruited CRM belongs was described, with a focus on the certified values and their associated uncertainties;
3. the RMS to which each recruited RMP (including associated MU) belongs was described,

4. the intended use of matrix CRMs as stated in the materials' certificates of analysis was checked to confirm that providers intended them as higher-order calibrators for implementing IVD measuring system traceability. If the intended use included use as common calibrators or the assessment of trueness and validation of calibration of field methods used in medical laboratories, the CRM's certificate was examined for information about commutability with clinical samples for commercial procedures,
5. the MU of CRM certified values and the trueness and reproducibility characteristics of RMP measurements were examined for their potential to be small enough to avoid significantly affecting the MU of clinical samples, when uncertainties from IVD calibrator and end-user measuring systems are combined and compared to APS for total MU budget derived according to an internationally recommended model.

According to the metrological traceability concepts stated in ISO 17511:2020, to transfer trueness from higher-order references to commercial calibrators, IVD manufacturers have 2 possibilities: (*a*) directly calibrating their internal procedures for calibrator value assignment with a suitable matrix CRM, or (*b*) aligning to an RMP by a comparison study (9). The latter approach asks for the use of an appropriate panel of native (commutable by definition) or pooled (validated for commutability) human samples, whose values are assigned by the RMP and resulting MU for the clinical samples based on the inherent MU characteristics of the RMP and the specific value transfer protocol employed. This is usually done through a comparison experiment between a reference laboratory performing RMP and the IVD manufacturer performing its own internal procedure, defined in ISO 17511 as a selected measurement procedure. This approach makes it possible to correct systematic bias, such as calibration bias, if any, of an IVD measuring system and ensure the traceability of the calibration of the manufacturer's selected measurement procedure to the higher-order RMP and thus the assignment of metrological traceable values to the end-user IVD calibrators.

In our study, the information from the IFCC External Quality Assessment Scheme for Reference Laboratories in Laboratory Medicine (RELA) (22) was used to estimate a mean experimental MU on a given clinical sample characterized as a reference material by an RMP listed in the JCTLM database. When using an RMP in a calibration hierarchy to transfer trueness to commercial calibrators, a panel of appropriate clinical samples can be used, where the panel (in lieu of adequate commutable CRM) takes on the same role as a CRM. As such, the MU of the RELA samples, as reported in the RELA database, was assumed to be representative of the MU of higher-order reference materials in the calibration hierarchy (14, 23). Transferring this concept to our study, the MU reported for RELA samples by a given RLS using the specified RMP listed in the JCTLM database was used to assign the MU when reference samples were value-assigned in a calibration hierarchy intended to assign values to an IVD manufacturer's end-user calibrators.

Accredited RLSs were identified that used the RMP listed in the JCTLM database and participated in RELA. If more than one JCTLM-listed RLS was present in the RELA using the same RMP, a first look was taken at the MU reported for different RLSs to be sure that they were homogeneous in performance. In case of major differences in the MU for one RLS vs others (either markedly larger or smaller), this RLS was excluded from the analysis. After that, one of the JCTLM-listed RLSs was selected from the group using the listed RMP and displaying homogeneous MU (i.e., a MU comparable with most RLSs using that RMP) and this MU was attributed to the corresponding RMP in the final synopsis. It should be noted that using the described approach to estimate the MU contribution of the RMP may yield a worst-case MU estimate for the RMP contribution to the combined MU for the assigned value of a commercial calibrator. When IVD manufacturers work with an RLS to assign values to a panel of human samples, the robustness of the value transfer design and protocol may be enhanced by inclusion of multiple independent samples that may result in a reduction in MU propagation from the RMP (24).

ASSESSMENT OF COMMUTABILITY INFORMATION

To confirm that providers of matrix CRMs listed in the JCTLM database intended to offer them as higher-order calibrators for implementing traceability of IVD measuring systems, we examined the certificates of analysis. If the scope of intended use included use of the CRM as a calibrator for commercial measuring systems and/or the assessment of trueness of results obtained by field methods used in medical laboratories, we checked the information provided regarding commutability of the material. This information is essential to guarantee an unbroken sequence of calibrations needed to achieve implementation of metrological traceability because the use of CRMs that are noncommutable with the manufacturer's selected measurement procedure, as calibrators may introduce a significant bias, may lead to bias in values assigned to commercial calibrators and incorrect results for clinical samples (25). We investigated the

availability and quality of information regarding the commutability of matrix CRMs driven by the requirements defined by the IFCC Working Group on Commutability (26). Criteria for selecting clinical samples to be used in the experiment, their number, collection, and processing conditions, were assessed, together with the descriptions of the experimental design and of commutability criterion. Finally, the list of commercial measuring systems for which CRM commutability was tested was recorded, if available. In evaluating commutability information, it is important to remember that the requirements for demonstrating commutability of CRMs have significantly evolved between the 2002 and 2009 versions of the ISO 15194 standard, which have been used for the JCTLM assessment of CRMs (6, 27). Only when assessing a CRM for compliance with ISO 15194:2009 is a statement explicitly requested about commutability of the CRM with clinical samples for all measurement procedures with which it may be potentially used as a common calibrator for implementing metrological traceability. Because of this, the specific edition of the ISO 15194 standard used in the JCTLM review process is clearly indicated in the JCTLM listing of CRMs (8).

APS DERIVATION

The Strategic Conference organized in Milan in 2014 by the European Federation of Clinical Chemistry and Laboratory Medicine defined 3 models for establishing APS (28, 29). In model 1, APS are based on the influence of analytical performance on clinical outcomes. In model 2, APS are based on biological variation of the measurands. In model 3, APS reflect the state of the art of the measurement based on the analytical performance that is technically achievable. The 3 Milan models are based on different principles and model is selected that is appropriate for a measurand's biology and clinical use. Criteria have been proposed for selecting an appropriate model to determine APS for different laboratory measurands (30). Briefly, model 1 is suitable for measurands that are used to diagnose and monitor a specific disease; model 2 is appropriate for measurands under strict metabolic control; and model 3 is used for measurands that do not have the characteristics to be assigned to the first 2 models. Grading minimum and desirable levels for APS is also important because it stimulates the IVD community to improve the quality of their products to move, if necessary, from unacceptable or minimum performance to a desirable level.

The fulfillment of APS related to the MU at the level of patient results depends on the MU contributions of each step of the calibration hierarchy (13, 14, 19, 31). It is necessary to accurately define all contributions and how much of the total MU budget is used across the different steps of the calibration hierarchy. Due to propagation of uncertainty in the calibration hierarchy, the MU of higher-order references may significantly affect the MU at the bottom level associated with patient results. It is therefore necessary that each contribution in terms of MU should be sufficiently small to allow fulfilling APS for MU at the clinical sample level, when the MU of the IVD calibrator and the end-user measuring system are included. Specific MU limits at different levels of the calibration hierarchy should be defined as fractions of the allowed total MU budget for the clinical sample result by applying an upside-down approach that starts with the APS of the end-user measurement results and then defining the goal for MU of the CRM or RMP for a given measurand by the performance needs of the clinical assays for that measurand (13). This 'uncertainty budget approach' is useful for identifying measurands for which the MU associated with the higher levels of the calibration hierarchy must be reduced (32).

It has been proposed that no more than one-third of the total MU budget should be used by higher-order references so that an adequate MU is available for the IVD manufacturer's calibrators and the imprecision of the commercial measuring system as implemented by each individual laboratory (19, 31). We recognize that this is an empirical recommendation and possibly alternate allocations of MU could reach the same goal. An IVD manufacturer should be able to allocate the MU budget into various parts as appropriate to the selected calibration hierarchy as long as the final combined MU does not exceed the maximum allowed MU as required to achieve fit for purpose performance.

In a preparatory work, we defined APS for MU for the measurands chosen for this work after their categorization according to the appropriate Milan model (33). Table 1 reports the Milan model allocation and APS for standard MU for the selected measurands that are applied in this paper to investigate if the status of the MU budget associated with a given calibration hierarchy is suitable for clinical application. When different options are available, IVD manufacturers should consider the suitability of higher-order references by selecting those with less impact on total MU budget.

Results

Table 2 reports the synopsis of higher-order matrixed CRMs and RMPs retrieved from the JCTLM database for the selected measurands, including their main characteristics for implementing metrological traceability and potentially fulfilling APS for suitable MU. All the listed CRMs made explicit in their certificates of analysis that the intended use was for evaluating the accuracy

Table 1. Milan model allocation and recommended analytical performance specifications (APS) for standard measurement uncertainty (MU) on clinical samples and at higher-order reference level for the selected measurands.

		APS for standard MU on clinical samples, %[a]		Allowable standard MU for higher-order references, %[b]	
Measurand	APS model	Desirable	Minimum	Desirable	Minimum
B-Total hemoglobin	Outcome-based	2.80	4.20	0.93	1.40
P-Potassium	Biological variation	1.96	2.94	0.65	0.98
P-Sodium	Biological variation	0.27	0.40	0.09	0.13
P-Chloride	Biological variation	0.49	0.74	0.16	0.25
P-Alanine aminotransferase	Biological variation	4.65	6.98	1.55	2.33
P-C-reactive protein	State of the art	3.76	5.64	1.25	1.88
P-Glucose	Outcome-based	2.00	3.00	0.67	1.00
P-Creatinine	Biological variation	2.20	3.30	0.73	1.10
P-Urea	Biological variation	7.05	10.6	2.35	3.53
P-Total calcium	Biological variation	0.91	1.36	0.30	0.45
P-Total bilirubin	Biological variation	10.5	15.7	3.50	5.23
B-HbA_{1c}	Outcome-based	3.00	3.70	1.00	1.23
S-25-hydroxyvitamin D3	Outcome-based	10.0	15.0	3.33	5.00

B, blood; P, plasma; S, serum.
[a]Derived from (33).
[b]Estimated as one-third of APS for standard MU for clinical samples.

of commercial procedures; therefore, the information about commutability assessment was included.

The results show that traceability to the highest metrological levels can be established by IVD manufacturers within the defined APS for most measurands. For Hb, ALT, urea, total bilirubin, HbA_{1c}, and 25(OH)D3, the MU of an IVD measuring system, if correctly traceable to the JCTLM-listed RMPs, has a high probability to fulfill the desirable APS for the total MU budget on clinical samples. For other measurands, distinctions need to be made among the different available options.

For plasma/serum potassium, the MU of an IVD measuring system when traceable to ion chromatography or inductively coupled plasma-mass spectrometry has a high probability to fulfill the desirable APS for the total MU budget, while traceability to inductively coupled plasma-optical emission spectrometry is likely to only fulfill minimum APS. IVD systems for measuring potassium using available CRMs as a basis for traceability have a lower possibility of fulfilling the APS.

For plasma/serum glucose, the MU of an IVD measuring system aligned to the isotopic dilution-mass spectrometry coupled to liquid chromatography (ID–LC–MS) has a high probability to fulfill the desirable APS for the total MU budget on clinical samples. The alignment to the isotopic dilution-mass spectrometry coupled to gas chromatography (ID–GC–MS) or the use of the available CRM are only suitable to fulfil the minimum APS.

For plasma/serum creatinine, splitting clinical samples with an RMS performing ID–GC–MS or ID–LC–MS should allow desirable APS to be fulfilled. As an alternative, the use of CRMs listed in the JCTLM database (with some exceptions) would allow at least the minimum quality level for APS related to MU to be achieved.

Plasma/serum sodium and calcium are similar showing that traceability of an IVD measuring system to ion chromatography is the only approach giving a realistic possibility to fulfil the APS for the total MU budget.

CRP is the only measurand among those evaluated with APS derived from the state-of-the-art model. Thus, CRP displays a unique situation where the elevated MU of the available CRM has less of an effect on the possibility to achieve APS on clinical samples, because the ERM-DA 474/IFCC MU (or that of historically related CRMs, i.e., CRM 470 or ERM-DA 472/IFCC) strongly influences the combined MU obtained on clinical samples by different measuring systems, the best of which is selected as APS (34).

The only negative situation is represented by plasma/serum chloride for which the MU of the current IVD measuring systems has almost no possibility to

Table 2. Synopsis of higher-order matrix CRMs and RMPs listed in the JCTLM database, including their characteristics for implementing traceability and fulfilling analytical performance specifications (APS) for suitable measurement uncertainty (MU).

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
B-Total hemoglobin					
Spectroscopy after reaction with KCN	Procedurally defined	154.1 g/L 156.3 g/L	**0.55**%[b] **0.54**%[b]	–	By definition
P-Potassium					
HSA HRM-2002A STY-0018-04 (frozen human serum) HSA HRM-2002A STY-0018-05 (frozen human serum) HSA HRM-2002A STY-0018-06 (frozen human serum)	By ICP–MS calibrated with the NIST Standard Reference Material® (SRM) 3141a Potassium standard solution	4.54 mmol/L 4.03 mmol/L 4.89 mmol/L	1.43% 1.24% *0.82%*	For validation of methods or as quality control material	Not available[c]
NIM CRM GBW09124 (frozen human serum) NIM CRM GBW09125 (frozen human serum) NIM CRM GBW09126 (frozen human serum)	By ICP–MS calibrated with the NIM GBW(E)080259	6.43 mmol/L 5.17 mmol/L 3.94 mmol/L	1.40% 1.35% 1.27%	For calibration and validation of procedures in clinical analyses	Not available[c]
Flame emission spectrophotometry	By calibration with high purity crystalline potassium chloride	4.96 mmol/L 2.8 mmol/L	*0.84%*[d] 1.16%[d]	–	By definition
ICP–MS	By calibration with high purity potassium solution	4.955 mmol/L 2.812 mmol/L	**0.44**%[e] **0.50**%[e]	–	By definition
ICP–OES	By calibration with high purity crystalline potassium chloride	2.776 mmol/L 4.942 mmol/L	*0.77%*[f] *0.81%*[f]	–	By definition
Ion chromatography	By calibration with high purity crystalline potassium chloride	4.998 mmol/L 2.813 mmol/L	**0.28**%[g] **0.37**%[g]	–	By definition

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
P-Sodium					
HSA HRM-2002A STY-0018-04 (frozen human serum) HSA HRM-2002A STY-0018-05 (frozen human serum) HSA HRM-2002A STY-0018-06 (frozen human serum)	By ICP-OES calibrated with the NIST SRM 3152a Sodium standard solution in turn value-assigned with ICP-OES calibrated with the NIST SRM 919a Sodium Chloride. Alternatively, ICP-OES directly calibrated with the NIST SRM 919b Sodium Chloride	139 mmol/L 124 mmol/L 153 mmol/L	1.44% 1.61% 1.31%	For validation of methods or as quality control material	Not available[c]
NIM CRM GBW09124 (frozen human serum) NIM CRM GBW09125 (frozen human serum) NIM CRM GBW09126 (frozen human serum)	By ICP-OES + flame emission spectrophotometry calibrated with NIM GBW(E)080127	134.7 mmol/L 150.4 mmol/L 164.5 mmol/L	1.29% 1.36% 1.20%	For calibration and validation of procedures in clinical analyses	Not available[c]
Flame emission spectrophotometry	By calibration with high purity crystalline sodium chloride	138.1 mmol/L 129.9 mmol/L	0.57%[h] 0.57%[h]	–	By definition
ICP-MS	By calibration with high purity sodium solution	130.2 mmol/L 155.4 mmol/L	0.46%[i] 0.32%[i]	–	By definition
ICP-OES	By calibration with high purity crystalline sodium chloride	131.9 mmol/L 155.5 mmol/L	0.75%[f] 0.75%[f]	–	By definition
Ion chromatography	By calibration with high purity crystalline sodium chloride	132.0 mmol/L 156.4 mmol/L	0.19%[g] 0.20%[g]	–	By definition
P-Chloride					
NIM CRM GBW09124 (frozen human serum) NIM CRM GBW09125 (frozen human serum) NIM CRM GBW09126 (frozen human serum)	By ICP-MS + ion chromatography[j] calibrated with NIM GBW(E)080268	100.8 mmol/L 112.8 mmol/L 126.0 mmol/L	1.23% 1.30% 1.12%	For calibration and validation of procedures in clinical analyses	Not available[c]

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
Coulometry	By calibration with high purity crystalline sodium chloride	118.6 mmol/L	0.75%[f]	–	By definition
		143.4 mmol/L	0.75%[f]		
ICP–MS	By calibration with high purity crystalline sodium chloride	119.5 mmol/L	0.50%[k]	–	By definition
		146.2 mmol/L	0.51%[k]		
P-Alanine aminotransferase					
Kinetic spectrophotometry IFCC RMP (37 °C)	Procedurally defined	106.0 U/L	**1.24%**[k]	–	By definition
		178.0 U/L	**1.25%**[k]		
P-C-reactive protein (CRP)					
ERM-DA474/IFCC (frozen human serum)	To WHO 1st International Standard 85-506 through ERM-DA470	41.2 mg/L	3.03%	To calibrate serum-based protein standards and control materials of organizations that offer such preparations for the quantification of CRP by immunoassays	Only commutability of a pilot batch assessed
P-Glucose					
LNE CRM Bio 101a level 1 (frozen human serum) LNE CRM Bio 101a level 2 (frozen human serum)	By ID–GC–MS calibrated with the NIST SRM 917c D-glucose (Dextrose)	4.148 mmol/L	*0.77%*	For use as quality control material to assess the bias or MU of measurement procedures for the determination of glucose in human serum	Available
		11.663 mmol/L	*0.71%*		
Enzymatic method	By calibration with high purity crystalline glucose	4.295 mmol/L	1.25%[l]	–	By definition
		6.489 mmol/L	1.33%[l]		
ID–GC–MS	By calibration with high purity crystalline glucose	4.261 mmol/L	*0.86%*[m]	–	By definition
		6.510 mmol/L	*0.90%*[m]		
ID–LC–MS	By calibration with high purity crystalline glucose	5.15 mmol/L	**0.49%**[n]	–	By definition
		11.69 mmol/L	**0.47%**[n]		

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
P-Creatinine					
JRC BCR-573 (lyophilized human serum) JRC BCR-574 (lyophilized human serum) JRC BCR-575 (lyophilized human serum)	By ID-GC-MS and HPLC[j] calibrated with the NIST SRM 914a Creatinine	68.7 µmol/L 105.0 µmol/L 404.1 µmol/L	*1.02%* **0.62%** *0.88%*	For assessing accuracy of routine methods and studying transferability of RMPs	Not available[o]
LGC ERM-DA250a (frozen human serum) LGC ERM-DA251a (frozen human serum) LGC ERM-DA252a (frozen human serum) LGC ERM-DA253a (frozen human serum)	By ID-LC-MS calibrated with the NIST SRM 914 Creatinine	358.0 µmol/L 197.0 µmol/L 27.5 µmol/L 449.0 µmol/L	5.87% 5.58% 15.6% 3.56%	For validation and ongoing monitoring of methods of analysis for the determination of creatinine in human blood samples	Not available[o]
LNE CRM Bio 101a level 1 (frozen human serum) LNE CRM Bio 101a level 2 (frozen human serum)	By ID-GC-MS calibrated with the NIST SRM 914a Creatinine	53.04 µmol/L 550.54 µmol/L	*1.09%* **0.56%**	For use as quality control material to assess the bias or MU of measurement procedures for the determination of glucose in human serum	Available
KRISS CRM 111-01-014 (frozen human serum) KRISS CRM 111-01-015 (frozen human serum)	By ID-LC-MS calibrated with the NIST SRM 914a Creatinine	55.1 µmol/L 254.34 µmol/L	*0.80%* *0.81%*	As a secondary measurement standard, intended primarily for use in evaluating the accuracy of procedures for the determination of creatinine in human serum	Available
ID-GC-MS	By calibration with high purity crystalline creatinine	151.9 µmol/L 352.9 µmol/L	**0.49%**[p] **0.50%**[p]	–	By definition
ID-LC-MS	By calibration with high purity crystalline creatinine	152.1 µmol/L 350.5 µmol/L	*0.82%*[n] **0.40%**[n]	–	By definition

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
ID-SERS	By calibration with high purity crystalline creatinine	345.7 μmol/L	1.23%[q]	–	By definition
		492.0 μmol/L	2.24%[q]		
P-Urea					
Spectrophotometry	By calibration with high purity crystalline urea	30.71 mmol/L	**1.14**%[r]	–	By definition
		19.57 mmol/L	**0.84**%[r]		
ID-GC-MS	By calibration with high purity crystalline urea	31.03 mmol/L	**0.50**%[s]	–	By definition
		19.41 mmol/L	**0.49**%[s]		
ID-LC-MS	By calibration with high purity crystalline urea	31.44 mmol/L	**1.46**%[t]	–	By definition
		19.56 mmol/L	**1.05**%[t]		
P-Total calcium					
JRC BCR-304 (lyophilized human serum)	By atomic absorption spectrometry (6 labs) + other methods not listed in the JCTLM database as higher-order RMP (6 labs) calibrated with $CaCO_3$ of stated purity, diluted in appropriate solutions	2.201 mmol/L	*0.43*%	For use as calibration material and as quality control standard for the evaluation of routine methods	Not available[o]
HSA HRM-2002A STY-0018-04 (frozen human serum) HSA HRM-2002A STY-0018-05 (frozen human serum) HSA HRM-2002A STY-0018-06 (frozen human serum)	By ICP-OES calibrated with the NIST SRM 3109a Calcium standard solution in turn value-assigned with ICP-OES calibrated with the NIST SRM 915 b Calcium Carbonate	2.56 mmol/L 2.23 mmol/L 2.71 mmol/L	1.37% 1.57% 1.29%	For validation of methods or as quality control material	Not available[c]
NIM CRM GBW09124 (frozen human serum) NIM CRM GBW09125 (frozen human serum) NIM CRM GBW09126 (frozen human serum)	By ICP-MS calibrated with the NIM GBW(E)080118	3.14 mmol/L 2.655 mmol/L 2.096 mmol/L	1.62% 1.44% 1.28%	For calibration and validation of procedures in clinical analyses	Not available[c]

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
Atomic absorption spectrophotometry	By calibration with high purity calcium carbonate	3.53 mmol/L	0.65%[u]	–	By definition
		2.05 mmol/L	0.66%[u]		
ICP-MS	By calibration with high purity calcium carbonate	3.504 mmol/L	0.50%[k]	–	By definition
		1.969 mmol/L	0.51%[k]		
ICP-OES	By calibration with high purity calcium carbonate	1.968 mmol/L	0.76%[f]	–	By definition
		3.527 mmol/L	0.77%[f]		
Ion chromatography	By calibration with high purity calcium carbonate	3.02 mmol/L	**0.20%[v]**	–	By definition
		2.841 mmol/L	**0.23%[v]**		
P-Total bilirubin					
Spectrophotometry	By calibration with high purity bilirubin	25.5 µmol/L	**0.75%[r]**	–	By definition
		32.0 µmol/L	**0.75%[r]**		
B-HbA_{1c}					
NCCL CRM GBW 09181a (human hemolysate buffer-based) NCCL CRM GBW 09182a (human hemolysate buffer-based) NCCL CRM GBW 09183a (human hemolysate buffer-based)	By HPLC–LC-MS/MS[w] calibrated with ERM-AD500/IFCC	31.4 mmol/mol	1.59%	For validating performance of routine methods and in trueness control of RMPs	Available
		51.49 mmol/mol	*1.11%*		
		78.6 mmol/mol	*1.12%*		
LNE HbA1c 401 (lyophilized human blood hemolysate) LNE HbA1c 402 (lyophilized human blood hemolysate) LNE HbA1c 403 (lyophilized human blood hemolysate)	By HPLC–ESI-MS calibrated with ERM-AD500/IFCC	32.5 mmol/mol	2.77%	For use as quality control material to assess the bias or MU of measurement procedures for the determination of HbA_{1c} in hemolysate or whole blood	Available
		50.9 mmol/mol	2.06%		
		80.4 mmol/mol	1.43%		
HPLC–ESI-MS	Procedurally defined	34.65 mmol/mol	**0.75%[k]**	–	By definition
		36.36 mmol/mol	**0.76%[k]**		
HPLC-CE	Procedurally defined	61.3 mmol/mol	**0.91%[x]**	–	By definition
		34.03 mmol/mol	1.38%[x]		
HPLC–LC–MS/MS[w]	Procedurally defined	71.43 mmol/mol	**0.73%[y]**	–	By definition
		45.15 mmol/mol	**0.91%[y]**		

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Combined standard MU ($k = 1$)[a]	Stated intended use in the CRM certificate of analysis	Commutability information
S-25-hydroxyvitamin D_3					
UME CRM 1308 (lyophilized horse serum)	By IDMS. Calibration stated as traceable to the SI, but calibration material not specified	49.8 μg/L	**2.71**%	For method performance check and validation purposes of 25-hydroxyvitamin D_3 measurement in serum with ID–LC–MS and HPLC–UV methods	Not available[c]
ID–LC–MS	By calibration with high purity 25OHD3 solution	61.97 μg/L	**2.10**%[z]	–	By definition
		118.7 μg/L	**2.10**%[z]		

KCN, potassium cyanide; HSA, Health Sciences Authority; ICP–MS, inductively coupled plasma-mass spectrometry; NIST, National Institute for Standards and Technology; NIM, National Institute of Metrology; ICP–OES, inductively coupled plasma-optical emission spectrometry; LNE, Laboratoire National de Métrologie et d'Essais; ID–GC–MS, isotopic dilution-mass spectrometry coupled to gas chromatography; ID–LC–MS, isotopic dilution-mass spectrometry coupled to liquid chromatography; JRC, Joint Research Centre; KRISS, Korea Research Institute of Standards and Science; ID–SERS, isotope dilution surface-enhanced Raman scattering; NCCL, National Center for Clinical Laboratories; HPLC–ESI–MS, treatment with endoproteinase Glu-C followed by HPLC and electrospray ionization mass spectrometry; HPLC–CE, treatment with endoproteinase Glu-C followed by HPLC and capillary electrophoresis; UME, Ulusal Metroloji Enstitüsü.

[a] Higher-order references fulfilling minimum quality APS for MU are in italics and those fulfilling desirable quality APS are in bold. The others do not fulfill specifications.

[b] From RELA 2018, Labcode 154.

[c] Reviewed for compliance with ISO 15194:2009 standard.

[d] From RELA 2018, Labcode 39.

[e] From RELA 2018, Labcode 54.

[f] From RELA 2018, Labcode 3.

[g] From RELA 2018, Labcode 87.

[h] From RELA 2017, Labcode 25.

[i] From RELA 2018, Labcode 51.

[j] Not listed in the JCTLM database as higher-order RMP.

[k] From RELA 2018, Labcode 27.

[l] From RELA 2018, Labcode 6.

[m] From RELA 2018, Labcode 5.

[n] From RELA 2017, Labcode 18.

[o] Reviewed for compliance with ISO 15194:2002 but not been reviewed against ISO 15194:2009.

[p] From RELA 2017, Labcode 1.

[q] From RELA 2010, Labcode 111.

[r] From RELA 2018, Labcode 47.

[s] From RELA 2018, Labcode 1.

[t] From RELA 2018, Labcode 65.

[u] From RELA 2018, Labcode 25.

[v] From RELA 2017, Labcode 8.

[w] This procedure is a modification of the JCTLM-listed HPLC–ESI–MS and needs to be nominated for appropriate review by the relevant JCTLM review team.

[x] From RELA 2015, Labcode 43.

[y] From RELA 2016, Labcode 18.

[z] From RELA 2018, Labcode 11.

fulfil APS for the total MU budget on clinical samples regardless of the higher-order reference selected. To this regard, it would be interesting to determine whether the use of a RMP based on the ion chromatography principle may significantly improve the associated MU and permit the MU for chloride to get close to the APS as already observed for other plasma/serum ions (35, 36).

Final Remarks

Establishing traceability of measured results for clinical samples must be inseparably linked to the allowable MU to fit the intended clinical application (11, 13). MU contributions should be defined across the entire traceability chain, starting with the higher-order references, extending through the IVD manufacturers and their processes for assignment of calibrator values, and ultimately to the results reported to clinicians by clinical laboratories (13, 19, 31). Therefore, the MU allowed for each step of the traceability chain should be specified to obtain a final combined MU of the patient's sample result that fulfills APS. In general, when one-third (or less) of the total MU budget is consumed by the MU of higher-order references, the remaining MU is suitable for the manufacturer's calibration and value transfer protocol together with the end-user measuring system imprecision and individual laboratory performance (19, 31). To date, reference entries on the JCTLM database have not been methodically evaluated from this point of view and, therefore, no information about the potential suitability of available higher-order references for contributing to the fulfillment of total MU budget is available. The top of the traceability chain is vital for transferring trueness, so that criteria to select higher-order references must be carefully fulfilled. Among those, MU should become a priority aspect (12, 19).

One could argue that these higher-order references are as good as they can be, and improvement, when needed, may not be easily achieved. Our study suggests, however, that the impact of the MU of higher-order references on the MU of clinical sample results and thus on clinical decisions is inadequately recognized by higher-order reference providers. RMPs with better performance, such as ion chromatography for chloride, represents a target for the work of developers of RMPs and for providers of RMSs. Furthermore, our analysis showed that suitable commutable CRMs to be used as common calibrators of IVD measuring systems are still lacking for clinically important measurands, such as Hb, ALT, urea, bilirubin, and 25(OH)D3. In these cases, using clinical samples as reference materials with value assigned by an RMS may provide the sole practical alternative for establishing a calibration hierarchy.

For many measurands, different calibration hierarchies may be applied to transfer trueness from the measurand definition to commercial calibrators. By selecting one of these calibration hierarchies, IVD manufacturers may spend very different amounts of the total MU budget in implementing metrological traceability of their measuring systems. In a previous paper (12), we reported the strategies implemented by 4 major IVD companies for establishing traceability of their commercial systems for plasma glucose determination. To assign traceable values to commercial calibrators at least 4 different types of calibration hierarchy, each with differences in MU accumulation, were used resulting in differences in the clinical suitability of patient results. Therefore, the quality of laboratory measurements may be dependent on the type of calibration hierarchy selected by manufacturers for transfer of trueness. Accordingly, when different options are available in making a choice, IVD manufacturers should consider the suitability of higher-order references in terms of MU by selecting ones with less impact on the total MU budget. In the case of plasma electrolyte measurement, we recently reported the importance of the selection by the manufacturers of higher-order references with less impact in terms of MU for improving performance of measuring systems (36). The simple replacement of flame emission spectrophotometry with ion chromatography as RMP in the sodium value assigning process of manufacturer calibrators could decrease MU on clinical samples from about 0.80% to 0.55%. Additional options, such as the implementation of statistically well-defined testing and value transfer study protocols, should also be employed by manufacturers to reduce MU contribution of existing RMS.

Another issue sometimes inadequately considered is commutability when CRMs are intended to be used either as common calibrators for implementing metrological traceability or as trueness control materials. Historically, assessment of CRM commutability with commercial measuring systems was not recognized as a mandatory practice and ISO 15194:2002 did not emphasize the issue adequately (27). Consequently, there are CRMs, particularly the oldest ones, for which commutability information is partial or not satisfactory. The responsibility of CRM providers to ensure that their products are assessed for commutability is now laid down in ISO 15194:2009 and this should be done by using guidelines available in the literature (6, 37, 38). For the more recently JCTLM-listed CRMs, the commutability was indeed investigated, and the related information documented in the certificate of analysis.

Conclusion

This study demonstrated that data available in the JCTLM database are an important resource for higher-

order references that are suitable for use in calibration hierarchies of end-user measuring systems for a representative group of common measurands used for medical decisions. The JCTLM database relies on voluntary submission of information. Therefore, this database is not fully comprehensive and additional higher-order materials and methods that meet requirements outlined in ISO standards may be available. The value of the JCTLM process is that the higher-order references are carefully reviewed to meet the requirements in the ISO standards and thus are generally suitable for use. However, the information on CRMs, RMPs and RLSs must be carefully assessed for MU and for commutability in the case of matrix CRMs to establish a suitable calibration hierarchy for end-user measuring systems (IVD devices) that meet the MU requirements for patient sample results. In addition, the information in the database is valuable to providers of CRMs and RMPs to assess that their proposed references have MU suitable for use at the intended levels in a calibration hierarchy and to identify when improved quality or performance of the references is needed.

Nonstandard Abbreviations: JCTLM, Joint Committee for Traceability in Laboratory Medicine; RMS, reference measurement system; ISO, International Organization for Standardization; IVD, in vitro diagnostics; CRM, certified reference materials; RMP, reference measurement procedure; RLS, reference laboratory service; APS, analytical performance specifications; MU, measurement uncertainty; TF-RMSI, Task Force on Reference Measurement System Implementation; CCQM, Consultative Committee for Amount of Substance; Hb, blood total hemoglobin; HbA_{1c}, blood glycated hemoglobin; ALT, alanine aminotransferase; CRP, C-reactive protein; 25(OH)D3, serum 25-hydroxyvitamin D3; RELA, Reference Laboratories in Laboratory Medicine; ID–LC–MS, isotopic dilution-mass spectrometry coupled to liquid chromatography; ID–GC–MS, isotopic dilution-mass spectrometry coupled to gas chromatography.

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