

We are pleased to announce the International Council for Standardization in Haematology (ICSH) joined the JCTLM as a new Executive Committee Member. In this issue of the Newsletter we also report on new entries in the database resulting from the 2019 review cycle; the activities of JCTLM Working Groups and Task Force; and record attendance at the biennial Members and Stakeholders meeting in December.

1 Covid-19 Actions from the Chair of the JCTLM, Prof. Ian Young

As the work to develop this newsletter was starting, the world was struck by the Covid-19 pandemic. Many organizations active in the JCTLM have since been involved in the response to the crisis and in developing reliable diagnostic tools to tackle it. As I write to you today, countries are still dealing with the crisis as well as developing plans on how to ease control measures and restart their economies. Reliable diagnostic testing will continue to support these national efforts worldwide. We would like to dedicate a special edition of the newsletter to sharing and disseminating information on the efforts and on-going activities of JCTLM Members and Stakeholders in ensuring reliable diagnostic measurements for Covid-19. If you wish to provide information for consideration of inclusion in the newsletter, please send short summaries of your activities or projects, articles, or links to publications to jctlm@bipm.org by 15 July 2020.

2 ICSH: a new Executive Committee member of the JCTLM

The JCTLM has welcomed the International Council for Standardization in Haematology (ICSH) as a new Executive Committee Member, effective December 2019. The ICSH joins the International Bureau of Weights and Measures (BIPM), International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Laboratory Accreditation Cooperation (ILAC) on the Executive Committee.

The ICSH coordinates Working Groups of experts to examine laboratory methods and instruments for haematological analyses, to deliberate on issues of standardization and to stimulate and coordinate scientific work as necessary towards the development of international standardization materials and guidelines.

This important collaboration brings expertise in clinical laboratory haematology to the JCTLM and provides the opportunity to align the standardization and harmonization of haematology laboratory methods with the reference

measurement system of the JCTLM, further enhancing the aim of 'accurate results for patient care'.



Left to right: Martina Bednarova (ILAC); Terry Fawcett (ICSH); Gary Myers (IFCC) and Thomas Liew (CIPM)

3 Importance of metrological traceability of medical results

For those of us involved in implementing metrological traceability in laboratory medicine, we are well aware that it plays an important role. In the Special Report, Graham Jones describes some of the many different areas of medicine where this traceability is fundamental to good clinical care. Awareness of these scenarios reminds us of the importance of this work, and can help explain this to those whose support is needed for the work. It is also a reminder that we are all patients as well, and we can benefit from traceable laboratory results. Download the [Special Report on The importance of metrological traceability of medical results](#) by Graham Jones, June 2020, 2 pp.

4 Importance of harmonization for traceability in laboratory medicine

The Special Report discusses the importance of harmonization of several related activities needed to achieve metrological traceability in laboratory medicine. When laboratory test results differ, the potential exists for misinterpretation of results possibly leading to wrong diagnosis or treatments and adverse patient outcomes. The successful achievement of harmonized test results requires calibration traceability to reference systems of higher-order that now includes a harmonization protocol. Related activities that also require harmonization include: global coordination of harmonization activities, developing reference system components for high priority measurands, addressing issues with non-commutable reference materials, and coordinating global regulatory approaches for approving harmonized measurement procedures. The report includes a discussion of current resources for harmonization. Download the [Special Report on Why is harmonization important for traceability in laboratory medicine?](#) by Gary L. Myers and W. Greg Miller, June 2020, 3 pp.

5 New entries in the JCTLM database - www.bipm.org/jctlm/

The JCTLM review process conducted in 2019 has resulted in 30 new entries in the JCTLM Database for available higher-order certified reference materials, as well as a new published reference measurement method, and ten new measurement services delivered by reference laboratories. The new entries are listed below:

New entries for available Certified Reference Materials

| Analyte Category | Analyte |
|----------------------------|--|
| Drugs | 12 high purity certified reference materials of drugs of abuse |
| Non-peptide Hormones | 16 high purity certified reference materials of steroid hormones and their derivatives |
| Metabolites and Substrates | Creatinine in frozen human serum at two levels |

Complete information for each certified reference material entry can be retrieved by clicking on the Analyte name.

New entries for Reference Measurement Methods

| Analyte Category | Reference Measurement Method (<i>JCTLM Identification Number</i>) |
|----------------------------|--|
| Metabolites and substrates | Liquid chromatography isotope dilution tandem mass spectrometry method for the measurement of urea in human serum and assignment of reference values to external quality assessment samples (JCTLM C15RMP7) Yong S. et al, <i>International Journal of Mass Spectrometry</i> . 2017, 414 , 87-93 |

Complete information for each method entry can be retrieved by clicking on the JCTLM identification number.

New entries for Reference Measurement Laboratory Services

| Analyte Category | Analyte | Location of Laboratory |
|----------------------------|--|------------------------|
| Enzymes | Alkaline phosphatase (ALP) in blood serum or plasma | China |
| Metabolites and Substrates | Glucose in blood serum/plasma and calibration solution | China |
| | Urea , Uric acid , Glucose and Cholesterol in blood serum/plasma | China |
| Non-Peptide hormones | Total Thyroxine in blood serum/plasma and calibration solution | China |
| | Progesterone and Testosterone in blood serum or plasma | China |
| Proteins | HbA1c in whole blood | China |

Complete information for each reference measurement service can be retrieved by clicking on the Analyte name.

6 JCTLM workshop reaches record attendance

The biennial workshop of the JCTLM was held at the BIPM in Sèvres, Paris, on 2-3 December 2019. The workshop reviewed recent developments in traceability in laboratory medicine and the impact that they are having on reducing between-method variability in the interests of better patient outcomes. The conference facilities at BIPM were fully utilized with a record number of participants and a record number of poster presentations. For the first time the workshop included parallel sessions in order to accommodate the expanding activity in this important area of laboratory medicine.

The scientific sessions included:

- Review of JCTLM activities and functions
- Challenging the status quo – plenary discussion of two controversial areas
- New concepts to improving quality in laboratory medicine
- International standards and regulation

- Meeting the challenge of method harmonization in haematology
- Measurement of specific nucleic acid sequences in healthcare
- Commutability
- Harmonization of methods for difficult analytes
- International projects to achieve standardization / harmonization
- Reference systems around the world
- Putting the patient first: clinical case studies
- What is the future for traceability in laboratory medicine – plenary discussion

The presentations and posters from the Workshop may be accessed at:

www.bipm.org/en/committees/jc/jctlm/workshop-2019.html.



A total of 120 delegates from 28 countries attended the biennial meeting of the JCTLM

7 JCTLM Members Report their activities for the Biennial JCTLM Members' and Stakeholders' Meeting

By Gary L. Myers, past President of JCTLM

At each biennial JCTLM Meeting members and stakeholders are requested to provide reports to the JCTLM Executive Committee of their work conducted during the past two years (2018-2019 in this case) in promoting traceability in laboratory medicine and towards implementing reference measurements systems which are applicable to their activities. The JCTLM Executive received 30 reports from the following National and Regional Members and Stakeholder Members:

National and Regional Members:

- All-Russian Scientific Research Institute for Metrological Service (VNIIMS)
- All-Russian Scientific Research Institute for Optical and Physical Measurements (VNIIOFI)
- Canadian Society of Clinical Chemists (CSCC)
- China Accreditation Service for Conformity Assessment (CNAS)
- Health Sciences Authority (HSA)

- Joint Research Centre (JRC)
- Korean Society of Clinical Chemistry (KSCC)
- Laboratoire National de Métrologie et d'Essais (LNE)
- National Institute of Metrology (NIM)
- National Institute of Standards and Technology (NIST)
- National Metrology Institute of Japan (NIMJ/AIST)
- National Metrology Institute of Turkey (TUBITAK-UME)

Stakeholder Members:

- Association for Quality Management in Laboratory Medicine (AQMLM)
- Buenos Aires External Quality Assessment Scheme (ProgBA CEMIC)
- Institution for Standardisation and Documentation in the Medical Laboratory (INSTAND e.v.)
- Interdepartmental Centre for Metrological Traceability in Laboratory Medicine (CIRME)
- International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR)
- Japan Association of Clinical Reagents Industries (JACRI)
- Japanese Committee for Clinical Laboratory Standards (JCCLS)
- Korean Association of External Quality Assessment Service (KEQAS)
- Maccura Biotechnology Co., Ltd (Maccura)
- MedicalSystem Biotechnology Co., Ltd (MedicalSystem)
- National Center for Clinical Laboratories (NCCL)
- Paul-Ehrlich-Institut (PEI)
- Quik S.A.S. (QUIK)
- RCPA Quality Assurance Programs (RCPA QAP)
- Ref4U, Laboratory of Toxicology, Faculty of Pharmaceutical Sciences, Ghent University (Ref4U)
- Shanghai Center for Clinical Laboratory (SCCL)
- Vitamin D External Quality Assessment Scheme (DEQAS)
- Wales External Quality Assessment Scheme (WEQAS)

The JCTLM Executive Committee thanks our members for submitting reports of their important activities that continue to advance traceability in laboratory medicine. We encourage our readers to review the reports posted on the JCTLM website. The full individual reports can be accessed and reviewed at: www.bipm.org/en/committees/jc/jctlm/members-jctlm.html then select Members' activity reports.

A selection of representative activities by members to promote traceability in laboratory medicine.

CSCC:

- The CSCC began to promote the JCTLM and its activities through the society's publication "CSCC News". The November 2018 issue featured the "Website of the Month" and described the resources available on the JCTLM website. The September 2019 issue featured an article on "Traceability and the role of JCTLM". This focus will continue as a series of articles with the next one planned regarding External Quality Assessment.

NIM, China:

- The "Protein and Peptide Therapeutics and Diagnostics: Research and Quality Assurance (PPTD-2018)" Workshop held in Chengdu (China) from 10-12 October 2018, organized by NIM (China) brought together metrology institutes, academic researchers, IVD and reagent manufacturers, regulators and pharmaceutical industry and clinical and government laboratories to present developments in establishing metrological traceability for *in vitro* diagnostics for accurate patient care. The three-day workshop attracted over 80 presentations and 50 posters covering three sessions: Advanced Methods for Peptide and Protein Drug Characterization and Quality Assurance; Standards and Advances in Peptide and Protein Diagnostics; Advances and Challenges in IVD Standards and Research. The workshop was organized under the auspices of the JCTLM, presenting developments in measurement methods and standards for characterizing therapeutic proteins and peptides. It focused on the importance of measurement standards and metrology for supporting *in vitro* diagnostic and pharmaceutical industries as well as underpinning innovative research and the development and quality of new products.

CIRME:

- The CIRME organized the following International Scientific Meetings under the auspices of the JCTLM:
 1. 12th International Scientific Meeting, 2018 - Standardization in Laboratory Medicine and Patient Safety
 2. 13th International Scientific Meeting, 2019 - The Internal Quality Control in the Traceability Era.

ICHCLR:

- The ICHCLR maintains the website www.harmonization.net as a global portal for information on harmonization activities. At present, 104 of the most frequently ordered measurands have been evaluated and recommendations for harmonization have been posted to the "Measurand" section of the web site. Links to organizations and resources for harmonization of measurands that are actively in progress or in a continuing status are also being added to the Measurand table.
- The ICHCLR's Council approved using a portion of the ICHCLR fund balance to support start-up costs for new projects to standardize/harmonize results for high-priority measurands conducted by other organizations. The funding is intended to support the following types of activity: an initial meeting of a working group to develop the detailed experimental

design for a project; and an initial experiment to launch a project. The expectation is the working group will obtain additional funding from other sources to complete the project. Apply at the website www.harmonization.net.

PEI:

- The Paul-Ehrlich-Institut is a designated WHO Collaborating Center for Quality Assurance of Blood Products and *in vitro* Diagnostic Devices and is part of the network of WHO Collaborating Centers involved in the WHO Biological Standardization Program.

A representative selection of member activities to develop Reference Method Procedures:

HSA:

HSA has developed or is in the process of developing the following reference method procedures:

1. LC-IDMS method for human growth hormone in human serum
2. LC-IDMS/MS method for the determination of concentration of insulin solution
3. LC-IDMS/MS method for the determination of concentration of amino acids solution
4. Spectrophotometry method for total protein in human serum (in progress)
5. LC-IDMS/MS method for amino acids in human serum (in progress)

LNE:

LNE actively participates in standardization activities in cooperation with different IFCC Working groups:

- As part of EMPIR project AntiMicroResist, LNE initiated the development of a candidate reference measurement procedure for procalcitonin measurement in human serum and the associated CRMs.
- As part of EMPIR project NeuroMet, LNE initiated the development of a candidate reference measurement procedure for Tau protein measurement in CSF and the associated CRMs.

NCCL:

NCCL's ID LC-MS/MS reference measurement procedure for glucose in blood serum was nominated and accepted for listing in the JCTLM Database in 2018.

WEQAS:

WEQAS has developed or is in the process of developing the following reference method procedures:

1. Reference Method for testosterone transferred from ID-GCMS to Tandem LC-MSMS
2. Reference Method for progesterone transferred from ID-GCMS to Tandem LC-MSMS (ongoing)
3. Reference Method for Salicylate Tandem LC-MS-MS (ongoing)
4. Reference Method for Paracetamol by Tandem LC-MS-MS (planned)
5. Reference Method for Vitamin D by Tandem LC-MS-MS (planned)

A representative selection of member activities to develop Certified Reference Materials:

HSA:

- HSA produced the following clinical CRM in 2018 - 2019: HRM-3005A: Cortisol in human serum

JRC:

- To support measurement standardization of biomarkers for the early detection of Alzheimer's disease, the JRC released a panel of three pooled CSF materials with different levels of amyloid- β 1-42 ($A\beta$ 1-42). This project was done in close collaboration with the IFCC WG CSF proteins. The CRMs, ERM-DA480/IFCC, ERM-DA481/IFCC and ERM-DA482/IFCC, were characterized with reference measurement procedures (RMPs) based on isotope dilution mass spectrometry.
- For the development of CRMs in the field of autoimmune disorders the JRC collaborates with the IFCC Committee on Harmonization of Autoimmune Tests. A CRM was produced for immunoglobulin G autoantibodies against proteinase 3 anti-neutrophil cytoplasmic (IgG PR3 ANCA). The CRM, called ERM-DA483/IFCC, was produced from a plasmapheresis sample of a patient diagnosed with vasculitis and certified for the mass concentration of IgG PR3 ANCA.
- JRC produced a new CRM for α -amylase (ERM-AD456/IFCC). The CRM consists of human pancreatic α -amylase in a buffered solution containing human serum albumin. The certified value was obtained through an interlaboratory comparison study with eleven expert laboratories applying the PRMP for the catalytic activity of α -amylase at 37 °C as established by the IFCC.

LNE:

- In 2019, nominations for certified reference materials LNE CRM HbA1c 401, 402, and 403 were accepted for listing in the JCTLM Database
- As part of EMPIR project CardioMet, LNE initiated the development of primary calibrators that will be used to calibrate candidate reference measurement procedures developed within IFCC WGApoMS for apolipoproteins apoA-I, B, C-I, C-II, C-III, E and apo (a).

NIST:

NIST issued the following new or renewal CRMs during 2019:

1. SRM 914b Creatinine
2. SRM 1949 Frozen Human Prenatal Serum (total thyroxine, total triiodothyronine, copper, selenium, zinc, 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, 3-epi-25-hydroxyvitamin D3, vitamin D binding protein)
3. SRM 971a Hormones in Frozen Human Serum (testosterone) SRM 2365 BK Virus DNA Quantitative Standard (BK virus DNA copy number)

- In addition, the Certificate of Analysis for SRM 1950 Metabolites in Frozen Human Plasma was updated to include a reference value for vitamin D binding protein.

TUBITAK UME:

- A certified reference material for 25-Hydroxy Vitamin D2 and 25-Hydroxy Vitamin D3 in Lyophilized Serum was completed and listed on the JCTLM database for higher-order reference materials.

NCCL:

- A CRM GBW 09181a, 09182a & 09183a “Glycated Hemoglobin in Human Hemolysate buffer” was nominated and accepted for listing in the JCTLM Database in 2018.

8 Activities of the Working Group for Traceability, Education and Promotion (WG-TEP)

Graham Beastall, Past Chair of the JCTLM Working Group for Traceability, Education and Promotion (WG-TEP)

Website:

The website www.jctlm.org continues to be updated on a regular basis with news items and additional freely available resources. The website is well used with an excellent global profile and feedback is positive. Revision of the home page took place in March 2019.

Webinars and presentations from conferences:

WG-TEP completed its task of publishing ten short webinars on the IFCC eAcademy. These can be accessed from www.jctlm.org. The WG-TEP has now facilitated 34 presentations on traceability in laboratory medicine in 23 countries. Many of these presentations may be found on www.jctlm.org.

Auspices:

JCTLM Auspices were awarded to scientific meetings in three countries. To apply for JCTLM auspices, access the form from the Publications section of www.jctlm.org.

Publications:

Google scholar reveals >350 publications mentioning traceability and laboratory medicine in 2019, almost 100 of these mentioned JCTLM. Key publications are listed in the Publications section of www.jctlm.org. To list other key publications, contact the Secretariat at jctlm@bipm.org.

Newsletter:

The annual Newsletter was published in April together with a special report on ‘Metrological traceability for EQA’ by Tony Badrick.

JCTLM Workshop: ‘Accurate results for patient care’

A separate item on this meeting appears in this Newsletter.

Future work streams:

The WG-TEP has commenced two active projects:

- Traceability in laboratory medicine and laboratory accreditation
- Traceability in laboratory medicine and the harmonization of clinical laboratory results.

Membership of WG-TEP:

The WG has refreshed its membership. Graham Beastall (UK) and Nanette Brouwer (NL) have completed their terms of office. The WG welcomes to its membership Aida Caicedo (CO); Penny Manganyi (ZA); Albert Tsui (CA); Maxim Vonsky (RU); Paul Yip (CA).

9 Future meetings

Meetings held under the auspices of the JCTLM

- 30 November 2020: 14th International Scientific Meeting of the Centre of Metrological Traceability in Laboratory Medicine (CIRME) “Implementation of metrological traceability in laboratory medicine: where we are and what is missing”, Milan (Italy). See [Meeting programme](#)

Future JCTLM meetings

- 2 December 2020: JCTLM Database Working Group meeting, BIPM, Sèvres
- 3-4 December 2020: 22nd Meeting of the JCTLM Executive Committee, BIPM, Sèvres
- 6-10 January 2021: JCTLM Symposium on traceability at IFCC World lab, Seoul, Republic of Korea

10 Providing higher order references that are fit for purpose: a call for action

Mauro Panteghini

Chair of the JCTLM Task Force on Reference Measurement System Implementation (TF-RMSI)

In 2019, the JCTLM created the Task Force on Reference Measurement System Implementation (TF-RMSI) with the aim to provide guidance on traceability implementation to the IVD community. The main objectives of the TF-RMSI are:

- to identify and describe available reference measurement systems (RMSs) and traceability chains in their entirety, based on the information present in JCTLM database;
- to illustrate the evolution of measurement uncertainty (MU) through the entire metrological traceability chains;
- by using appropriately derived analytical performance specifications (APS), to judge whether RMS components are fit for purpose;
- to identify those measurands for which further advancements to existing RMSs are needed or some components of the RMS are lacking.

Using serum creatinine as a case study, a preliminary exercise was recently carried out by checking what type of information is available in the JCTLM database and comparing this against derived APS for MU of this measurand. As this represents a novel approach that should be more widely tested, the TF-RMSI is now planning to review a greater number of measurands covered within the JCTLM database, chosen based on their frequency of measurement in medical laboratories and on their clinical importance, for providing more robust information about the state of the art of available RMSs and their impact on the ability of clinical measurements to meet APS.

List of selected measurands to be evaluated by the TF-RMSI

- B-Total hemoglobin
- P-Potassium
- P-Sodium
- P-Alanine aminotransferase (ALT)
- P-C-reactive protein
- P-Glucose
- P-Total calcium
- P-Total bilirubin
- B-HbA_{1c}
- S-25-hydroxyvitamin D₃ [25(OH)D₃]

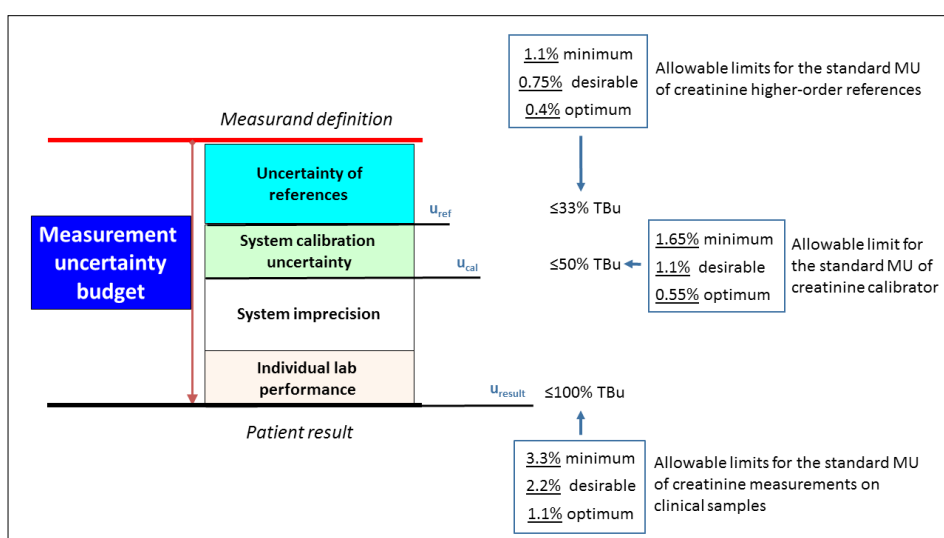
As APS relate to the total MU budget (TBu) that should

be fulfilled at the level of patient results, the fulfilment of APS depends on the MU contributions of each step of the metrological traceability chain. It is essential to accurately define the entity of all those contributions and how much of the TBu is used across the different steps of the traceability chain. The uncertainty of higher order references (u_{ref}) represents the first contribution to the TBu. Due to uncertainty propagation in the calibration hierarchy, u_{ref} may significantly affect the MU of patient results. It is therefore intuitive that this contribution in terms of MU should be sufficiently small to allow APS to be fulfilled for MU at the clinical sample level, when IVD calibrator and random uncertainties have been added. Therefore, specific MU limits at different levels of the traceability chain should be defined as fractions of allowed TBu. Using serum creatinine as an example, the Figure reports how to derive the allowable limits for the standard MU of higher order references in order to not exceed with a high probability TBu at the level of clinical samples.

Recruited TF-RMSI members will work on the selected measurands using APS derived from appropriate models to judge whether available higher order references are fit for purpose and if something is still lacking for the correct implementation of metrological traceability of these measurands.

Selected references

- Panteghini M, Braga F. Implementation of metrological traceability in laboratory medicine: where we are and what is missing. *Clin. Chem. Lab. Med.* 2020 Feb 18. pii: /j/cclm.ahead-of-print/cclm-2019-1128/cclm-2019-1128.xml. doi: 10.1515/cclm-2019-1128. [Epub ahead of print]
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Allowable limits for the standard measurement uncertainty (MU) of serum creatinine results on clinical samples (derived from the biological variation model) (u_{result}) and corresponding limits for creatinine higher-order references (materials or procedures) (u_{ref}) and commercial calibrators (u_{cal}), expressed as a fraction of the total uncertainty budget (TBu). Adapted from Braga F, Panteghini M. The utility of measurement uncertainty in medical laboratories. *Clin. Chem. Lab. Med.* 2020 Mar 3. pii: /j/cclm.ahead-of-print/cclm-2019-1336/cclm-2019-1336.xml. doi: 10.1515/cclm-2019-1336.