Biennial activity report from JCTLM Member organizations

All JCTLM Members are invited to attend the Members' and Stakeholders' Meeting, which is held once every two years, and submit a report of their activities in support of traceability in laboratory medicine over the preceding period.

For that purpose this template document provides guidance to JCTLM Members for drafting their biennial activity report. Organizations are invited to provide the information below for submission to the Executive Committee.

Organization Name: Health Sciences Authority (HSA), Singapore

JCTLM Member status: National and Regional Member

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Period covered: 2022 – 2023

1. **Major achievement(s) in support of standardization in laboratory medicine**
   (Please describe what activities your organization has undertaken related to the implementation of reference measurement systems in laboratory medicine during the last two years, including but not limited to information on: the production of certified reference materials; the development of reference measurement methods; or the establishment of calibration (reference) measurement services. Outline the measurement area(s)/measurands covered, and provide a listing of the relevant technical/scientific publications.)

   - **Accuracy-Based External Quality Assessment (EQA) Programmes**

     HSA continues to organise accuracy-based EQA programmes for local clinical laboratories and medical clinics in Singapore, where metrologically traceable assigned (target) values determined by the Chemical Metrology Laboratory (CML) are used to evaluate the results of the participating laboratories/clinics.

     <u>HSA EQA Programme on HbA1c Testing</u>
     The HSA EQA Programme on HbA1c Testing is a mandatory programme for licensed hospitals, medical clinics and clinical laboratories which offer HbA1c testing for the diagnosis of diabetes mellitus. The programme comprises three cycles per year and two blood samples with different levels of HbA1c are provided in each cycle. Over 60 clinical laboratories and medical clinics participated in each cycle of the EQA Programme in 2023, reflecting a notable 10% increase in participation compared to 2021.

     <u>HSA EQA Programme in Clinical Chemistry</u>
     The HSA EQA programme for clinical laboratories is an on-going programme launched since 2011. The programme is intended to focus on chronic diseases affecting majority of the Singapore population. 17 Clinical markers are offered in this programme. The analytes include:
     (a) creatinine, glucose, total cholesterol, triglycerides (as 'total glycerides'), urea, uric acid, LDL-cholesterol, HDL-cholesterol, total protein, calcium, sodium, potassium, magnesium, iron, and chloride in human serum; and
     (b) albumin and creatinine in human urine.

     This programme comprises two cycles per year. Four serum samples and one urine sample are provided in each cycle. Close to 40 clinical laboratories, including all public and almost all private laboratories in Singapore participated in this EQA programme. Over the years, the results were continuously analysed to

identify any trends. In view of the continued high prevalence of diabetes among the Singapore population, HSA will further customize the EQA programmes to study biases between different methods and/or analysers where samples from diabetics pose a concern to the accuracy of measurements of other clinical markers.

- **Clinical Certified Reference Materials (CRMs) Maintained / Produced / Under Development**

HSA continues to maintain the following clinical CRMs through regular stability testing:

(a) HRM-3002B: Creatinine, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, total glycerides, free glycerol, urea and uric acid in human serum
(b) HRM-3003B: Haemoglobin A1c in human blood
(c) HRM-3004A: Albumin and creatinine in human urine
(d) HRM-2002A: Calcium, potassium and sodium in human serum
(e) HRM-2005A: Calcium, iron, potassium, magnesium, sodium and chloride in human serum
(f) HRM-2011A: Sodium, chloride, copper, selenium and phosphorus in human serum
(g) HRM-3005A: Cortisol in human serum
(h) HRM-3006A: Testosterone in human serum

HSA has produced the following clinical CRM between 2022 - 2023:

(a) HRM-3007A: Creatinine, glucose, urea and uric acid in human serum
(b) HRM-3008A: Total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol in human serum
(c) HRM-3010A: Glycated VHLTPE peptide solution (in conjunction with HRM-3011A as the calibrant for the determination of the amount-of-substance fraction of haemoglobin A1c)
(d) HRM-3011A: VELTPE peptide solution (in conjunction with HRM-3010A as the calibrant for the determination of the amount-of-substance fraction of haemoglobin A1c)

Certification of the following clinical CRMs is in progress:

(a) HRM-3009A: Human albumin solution
(b) HRM-3012A: SARS-CoV-2 antibody solution

Commutability study:
Commutability studies on two serum CRMs (HRM-3007A and HRM-3008A) and the urine CRM (HRM-3004A) were completed in 2022. The studies involved HSA, three clinical laboratories within public hospitals and a major private clinical laboratory in Singapore. The two serum CRMs (HRM-3007A and HRM-3008A) are now listed in the JCTLM database.

- **Reference Measurement Methods Developed / in Development**

(a) LC-IDMS/MS method for 17β-estradiol in human serum
(b) LC-IDMS/MS method for procalcitonin in human serum
(c) High resolution IDMS method for human growth hormone in human serum (in progress)
(d) LC-IDMS/MS method for Vitamin D metabolites (25-hydroxyvitamin D2 and 25-hydroxyvitamin D3) in human serum (method re-validation for inclusion of Vitamin D metabolites in the HSA EQA Programme in Clinical Chemistry in 2024)
(e) LC-MS-MS and LC-UV methods for the purity assessment of parathyroid hormone (in progress)
(f) dPCR method for the quantification of SARS-CoV-2 RNA
(g) ^{31}P qNMR and ion chromatography methods for phosphate in human serum (in progress)

New capability on nucleic acid measurement

HSA started to develop new capability on nucleic acid measurement in 2021. After two years of research, HSA has successfully developed a dPCR method for the quantification of SARS-CoV-2 RNA and used this method to participate in a CCQM pilot study.

- **International Comparisons Related to Healthcare Co-organised / Participated**

  HSA co-organised the following comparisons:
  (a) CCQM-K115.c Key comparison on peptide purity: HbA1c glycated hexa-peptide, GE
  (b) CCQM-K115.2018 Key comparison on peptide purity: HbA1c hexa-peptide, VE
  (c) CCQM-P219 Pilot study on determination of the amount-of-substance fraction of [Hb1c/(HbA1c+HbA0)] in human hemolysate (in progress)

  HSA participated in the following comparisons:
  (a) CCQM-K177 Key comparison on human growth hormone in serum
  (b) CCQM-P227 Pilot study on SARS-CoV-2 RNA copy number quantification
  (c) CCQM-P232 Fire drill influenza RNA copy number quantification (in progress)
  (d) 2023 IFCC RELA on 17β-estradiol

2. Planned activity(ies) in support of standardization in laboratory medicine

(Please outline R&D project(s) and/or programme(s) planned by your organization in the next two years including information on: new measurement area(s)/meaurands of interest for your organization; new CRMs and renewals of materials; development of methods (new measurands and improved measurement technique/principle); and extensions of your calibration measurement service(s) portfolio.)

- **Development of Clinical CRMs**
  (a) Vitamin D metabolites in human serum
  (b) Steroid hormones (progesterone and estradiol) in human serum
  (c) HbA1c in human blood

- **Method development**
  (a) Cystatin C in human serum
  (b) Influenza RNA copy number quantification

3. Promoting traceability in laboratory medicine

(Please describe activities your organization has undertaken during the last two years for promoting traceability in laboratory medicine including but not limited to a listing of your publication(s), presentation(s) and other communication(s) on traceability at international and national conferences or congresses, or other forums for clinical laboratory medicine)

- **Publications Related to Healthcare**

  (a) Commutability assessment of human urine certified reference materials for albumin and creatinine on multiple clinical analyzers using different statistical models
  Liu H, Ng CY, Liu Q, Teo TL, Loh TP, Wong MS, et al. Analytical and Bioanalytical Chemistry. 2023; 415:787-800.

  This paper reported the first systematical commutability study on urine albumin and creatinine certified reference materials (CRMs). The commutability of two urine CRMs for albumin and creatinine was evaluated using three statistical models on five different brands/models of clinical analyzers from four major clinical chemistry in vitro diagnostic manufacturers. The urine CRMs were found to be commutable on all five clinical analyzers when evaluated using all three statistical models, suggesting that these CRMs should be commutable for most clinical analysers. With good commutability for both

albumin and creatinine, these urine CRMs can potentially be used as candidate materials for standardization of urine albumin measurement as well as albumin-creatinine ratios.

(b) Evaluation of low-density lipoprotein cholesterol equations by cross-platform assessment of accuracy-based EQA data against SI-traceable reference value
Tan HT, Yong S, Liu H, Liu Q, Teo TL, Sethi SK. Clinical Chemistry and Laboratory Medicine. 2023;61(10):1808-1819.

Three equations (Friedewald, Martin/Hopkins, and Sampson) for the calculation of low density lipoprotein-cholesterol (LDL-C) were evaluated against SI-traceable reference value from beta-quantification IDMS. The conventional Friedewald equation always under-estimates LDL-C when the levels exceed the optimal range (≥ 150 mg/dL or 1.7 mmol/L) and the under-estimation worsens with rising triglycerides levels due to the inherent limitation of the equation. This can result in a misdiagnosis or under-treatment of patients at risk of cardiovascular disease events. The Martin/Hopkins equation was concluded to be more robust and led to the least misclassification of LDL-C results when evaluated against traceable reference values.

- **Presentations/Seminars Related to Healthcare**

(a) 2022 HSA EQA Programme Symposium for participating clinical laboratories of EQA programme, February 2023.

(b) "Understanding HSA HbA1c EQAP and Investigating Failed Proficiency Testing", Sharon Yong, invited seminar for Singapore Association of Clinical Biochemists Education Programme, Singapore, October 2022.

(c) "Accuracy-Based External Quality Assessment – Importance, Key Factors and Experience", Liu Qinde, invited keynote presentation at the 8th China Experimental Medicine Conference, Nanchang, China, May 2023.

(d) "Application of Proteomics in Metrology: Identification of Impurities in Parathyroid Hormone", Tan Hwee Tong, invited presentation at the Asia-Oceania Mass Spectrometry Conference/Annual Meeting of the Korean Society for Mass Spectrometry, Jeju Island, Korea, August 2023.

(e) "Measurement Uncertainty in Clinical Laboratories", Cheow Pui Sze, invited presentation at the 6th Singapore General Hospital Clinical Pathology Frontiers in Technology Workshop, Singapore, November 2023.

- **Courses for Healthcare Sector**

(a) Self-directed online course *via* Moodle platform on "Measurement Uncertainty for Clinical Laboratories" for local and overseas clinical laboratories in September 2022.

(b) Self-directed course on "Measurement Uncertainty for Clinical Laboratories" open online from January 2023.

4. Reference laboratory networks /collaborations focusing on developing /implementing reference measurement systems

(Please describe your participation in laboratory networks, forums or professional/technical committees linked to reference measurements system development/implementation, and contributions to JCTLM Working Group activities.)

- Four HSA staff members are currently serving in the JCTLM Database Working Group:
  (a) Dr Qinde Liu
  Vice-Chair of Analyte Group 1

Team Leader of Non-Peptides Hormones Review Team
Member of Metabolites and Substrates Review Team

(b) Dr Richard Shin
Member of Non-Electrolyte Metals Review Team

(c) Dr Hwee Tong Tan
Member of Proteins Review Team

(d) Ms Hong Liu
Member of Vitamins and Micronutrients

- IFCC Standardization of Procalcitonin Assay (WG-PCT)

HSA supported Laboratoire National de Métrologie et d'Essais (LNE, France) on the standardisation effort by developing a standard addition method based on LC-MS/MS and has since completed a bilateral comparison with LNE.

- NIDDK Urine Albumin Standardisation Programme

In collaboration with NIST, University of Minnesota, and Mayo Clinic, a round robin for standardisation of the reference measurement procedures is ongoing. The study materials were provided to the three US reference laboratories by HSA. All four reference laboratories have completed the measurements and the analysis of the results is ongoing.

- Collaboration with US CDC

(a) HSA continued to collaborate with US CDC on the measurement LDL-cholesterol and HDL-cholesterol in human serum programme, aiming to standardise the reference measurement procedure based on beta-quantification.
(b) HSA and CDC have planned to carry out a collaborative project on evaluating the performance of point-of-care devices for lipid testing, including total-cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides.

5. Open questions and suggestions to be addressed by JCTLM

(Suggestions on issues related to standardization and metrological traceability that should be considered by the JCTLM)

Note: The information of this report will be accessible publicly on the relevant JCTLM Members webpage, unless the author of the report states otherwise. In the case the organization does not authorizes the publication of the report in part or full, the author will add a statement to clarify which part(s) of the report will /will not be rendered public.