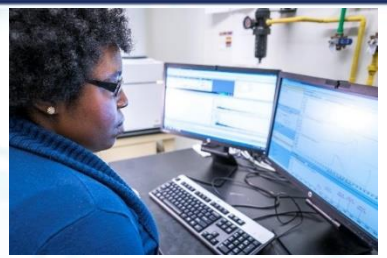




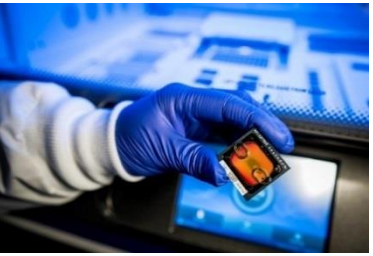
BIOMOLECULAR MEASUREMENT DIVISION

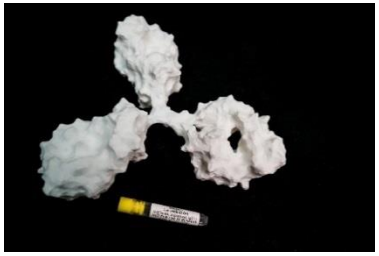
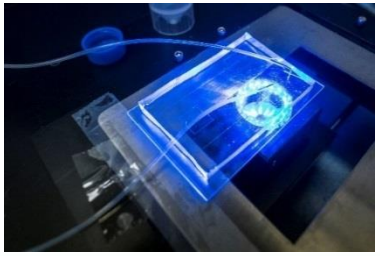
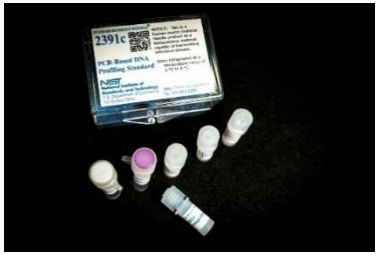
Developing CRMs for Diagnostics in Compliance with ISO 15194

Karen Phinney

National Institute of Standards and Technology
Vice-Chair, JCTLM Database Working Group

JCTLM
Accurate results for patient care



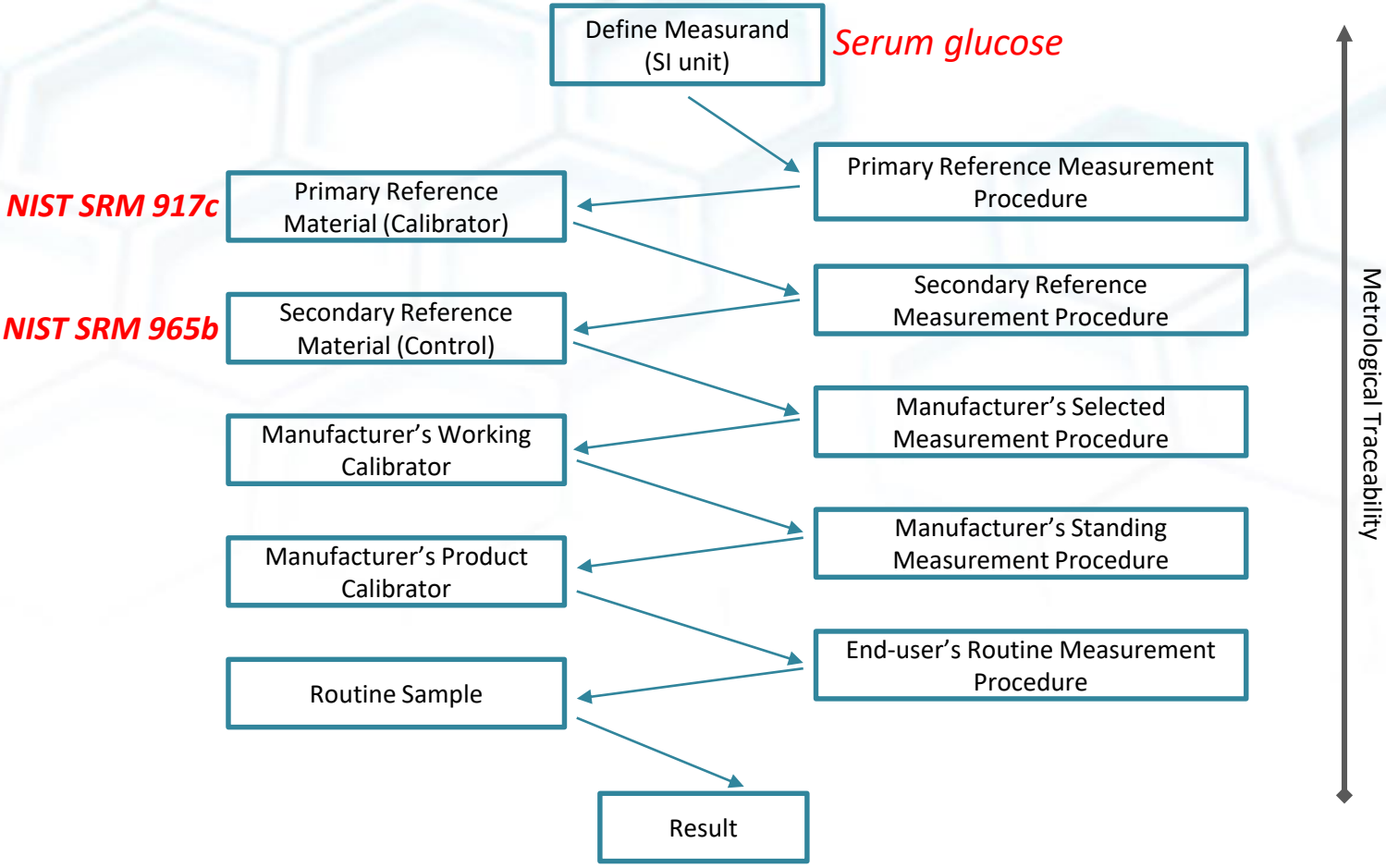




Goals of the JCTLM

- Promote worldwide equivalence of measurements in laboratory medicine
- Provide guidance on traceability to appropriate measurement standards
- Evaluate reference methods, materials, and laboratories against appropriate criteria and applicable ISO standards
- Provide diagnostic manufacturers with information on available reference materials and methods that may be suitable for establishing traceability

- Candidate reference measurement procedures, reference materials, and reference services are reviewed by a team of experts
- Those meeting the necessary criteria are listed in the JCTLM database: www.bipm.org/jctlm

An Example Reference Measurement System



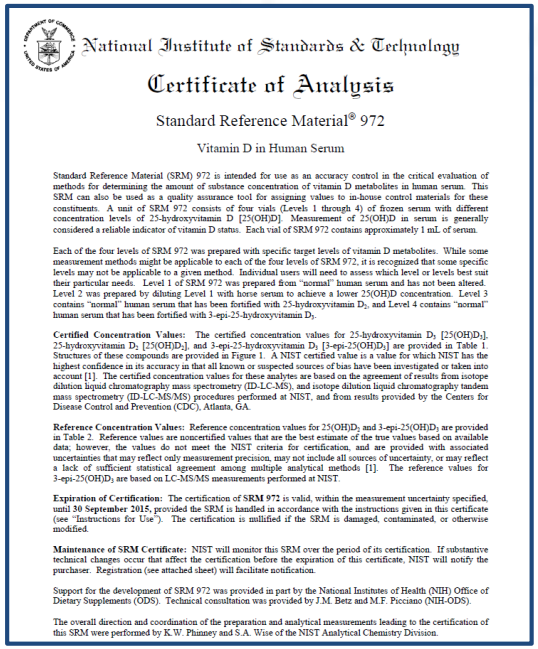
- Certified reference materials at the highest levels of the calibration hierarchy help ensure comparability of results across time, laboratory, and measurement procedure
- ISO 15194 describes CRM quality requirements and necessary documentation

Key Elements of ISO 15194

Material Properties

- Source and preparation
  - Matrix (serum, plasma, CSF, buffers)
  - Modifications (pooling, spiking, dilution)
  - Anticoagulants or preservatives
  - Lyophilization or sterilization
- Intended use
  - Calibrator
  - Trueness control
  - Evaluating new measurement procedures
- Commutability
- Instructions for use
  - Storage conditions
  - Reconstitution
  - Minimum sample size
- Metrological traceability
- Safety and health
  - Infectious disease testing
  - Disposal

SRM 972



National Institute of Standards & Technology

Certificate of Analysis

Standard Reference Material® 972

Vitamin D in Human Serum

Standard Reference Material (SRM) 972 is intended for use as an accuracy control in the critical evaluation of methods for determining the amount of substance concentration of vitamin D metabolites in human serum. This SRM can also be used as a quality assurance tool for assigning values to in-house control materials for these constituents. A unit of SRM 972 consists of four vials (Levels 1 through 4) of frozen serum with different concentration levels of 25-hydroxyvitamin D [25(OH)D]. Measurement of 25(OH)D in serum is generally considered a reliable indicator of vitamin D status. Each vial of SRM 972 contains approximately 1 mL of serum.

Each of the four levels of SRM 972 was prepared with specific target levels of vitamin D metabolites. While some measurement methods might be applicable to each of the four levels of SRM 972, it is recognized that some specific levels may not be applicable to a given method. Individual users will need to assess which level or levels best suit their particular needs. Level 1 of SRM 972 was prepared from "normal" human serum and has not been altered. Level 2 was prepared by diluting Level 1 with horse serum to achieve a lower 25(OH)D concentration. Level 3 contains "normal" human serum that has been fortified with 25-hydroxyvitamin D_3, and Level 4 contains "normal" human serum that has been fortified with 3-epi-25-hydroxyvitamin D_3.

Certified Concentration Values: The certified concentration values for 25-hydroxyvitamin D_3 [25(OH)D_3], 25-hydroxyvitamin D_2 [25(OH)D_2], and 3-epi-25-hydroxyvitamin D_3 [3-epi-25(OH)D_3] are provided in Table 1. Structures of these compounds are provided in Figure 1. A NIST certified value is a value for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias have been investigated or taken into account [1]. The certified concentration values for these analytes are based on the agreement of results from isotope dilution liquid chromatography mass spectrometry (ID-LC-MS), and isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) procedures performed at NIST, and from results provided by the Centers for Disease Control and Prevention (CDC), Atlanta, GA.

Reference Concentration Values: Reference concentration values for 25(OH)D_2 and 3-epi-25(OH)D_3 are provided in Table 2. Reference values are noncertified values that are the best estimate of the true values based on available data; however, the values do not meet the NIST criteria for certification, and are provided with associated uncertainties that may reflect only measurement precision, may not include all sources of uncertainty, or may reflect a lack of sufficient statistical agreement among multiple analytical methods [1]. The reference values for 3-epi-25(OH)D_3 are based on LC-MS/MS measurements performed at NIST.

Expiration of Certification: The certification of **SRM 972** is valid, within the measurement uncertainty specified, until **30 September 2015,** provided the SRM is handled in accordance with the instructions given in this certificate (see "Instructions for Use"). The certification is nullified if the SRM is damaged, contaminated, or otherwise modified.

Maintenance of SRM Certificate: NIST will monitor this SRM over the period of its certification. If substantive technical changes occur that affect the certification before the expiration of this certificate, NIST will notify the purchaser. Registration (see attached sheet) will facilitate notification.

Support for the development of SRM 972 was provided in part by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). Technical consultation was provided by J.M. Betz and M.F. Picciano (NIH-ODS).

The overall direction and coordination of the preparation and analytical measurements leading to the certification of this SRM were performed by K.W. Phinney and S.A. Wise of the NIST Analytical Chemistry Division.

Key Elements of ISO 15194

Value Assignment

- Measurement procedure(s) used
- Homogeneity assessment
- Stability assessment
- Statistical evaluation of data
- Certified values*
- Derivation of uncertainties

*Need to describe how unit conversions were done (e.g., ng/g to ng/mL)

Compliance demonstration		Return to Reference Material Template Spreadsheet				
Nominating Organization	**Contact Information**	**Reference Material Identifier / Name**	**JCTLM Reference Material Nomination Number**	**Review Team Name**	**Review Team Leader's Name**	**Date of review**
ISO 15194, 2nd Ed - 2009-05-01		**Compliance demonstration of the nominated reference material with ISO 15194: 2009 (E) requirements**		**For Review Team Use**		
Paragraph number	**Title of the paragraph**	**Please enter "Yes" or "No" in each of the cells below as appropriate**	**A short description on how the compliance is achieved must be added in each of the field below**	**Mandatory element (Yes/No)**	**Observations**	**Classification: Critical, Major or Minor non-compliance, or observation**
4	Systematic format of properties in the supporting documentation of a certified reference material					
4.1	Format of properties					
4.1.1						
4.1.2						
4.1.3						
4.1.4						
4.1.4.1						
4.1.4.2						
4.1.4.3						
4.1.4.4						
4.2	Construction of systematic designations and trivial names					
4.3	Trivial names					
5	Properties, production, and characterization of a certified reference material					
5.1	Hierarchical position					
5.2	Properties					
5.3	Production and characterization					
6	Content of supporting documentation					
6.1	Supporting documentation					
6.2	Label					
6.3	Certificate					
6.3 a)						
6.3 b)						
6.3 c)						
6.3 d)						
6.3 e)						

CRM Intended Use (Scope)

SRM 2389a (Amino Acid Solution)

This Standard Reference Material (SRM) is intended primarily for use in calibration of chromatographic instrumentation for the determination of amino acids.

SRM 2668 (Toxic Elements in Urine)

This Standard Reference Material (SRM) is intended primarily for validating analytical methods and measurements for the determination of toxic elements in human urine.

SRM 972a (Vitamin D Metabolites in Serum)

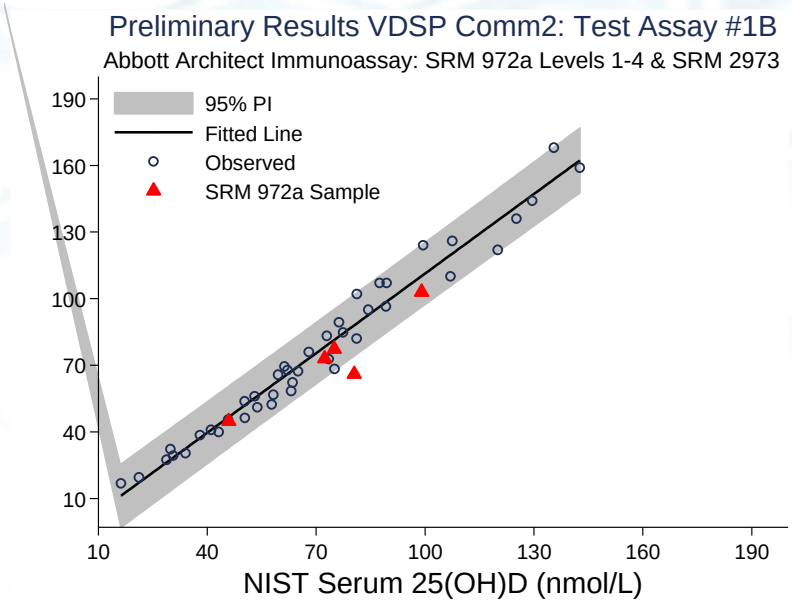
This Standard Reference Material (SRM) is intended for use as an accuracy control in the critical evaluation of methods for determining the amount-of-substance concentration of vitamin D metabolites in human serum….Each of the four levels of SRM 972a was prepared with a specific target level of 25(OH)D. While some measurement methods might be applicable to each of the four levels of SRM 972a, *it is recognized that some methods may not be applicable to some levels. Individual users will need to assess which level or levels best suit their particular needs.*

Commutability Assessment Through Interlab Study – SRM 968e (Fat-Soluble Vitamins)

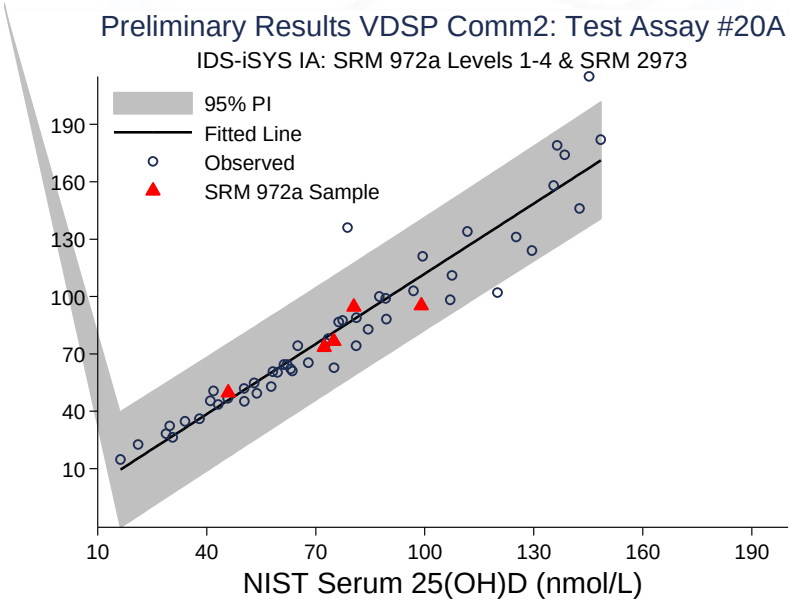
Analyte	NIST LC-UV 1	NIST LC-UV 2	Study median
Total retinol	0.346 (0.016)	0.326 (0.008)	0.351
γ/β-Tocopherol	2.03 (0.10)	1.84 (0.03)	1.72
α-Tocopherol	6.96 (0.34)	5.84 (0.10)	6.75
Total lutein	0.069 (0.004)	0.059 (0.003)	0.072
Total lycopene	0.173 (0.004)	0.294 (0.008)	0.236
Total β-carotene	0.114 (0.004)	0.093 (0.004)	0.090
Total zeaxanthin	0.029 (0.003)	0.029 (0.001)	0.037

Data for Level 1 of SRM 968e from NIST methods and from participants in the NIST Micronutrients Measurement QA Program (MMQAP). All results in μg/mL.

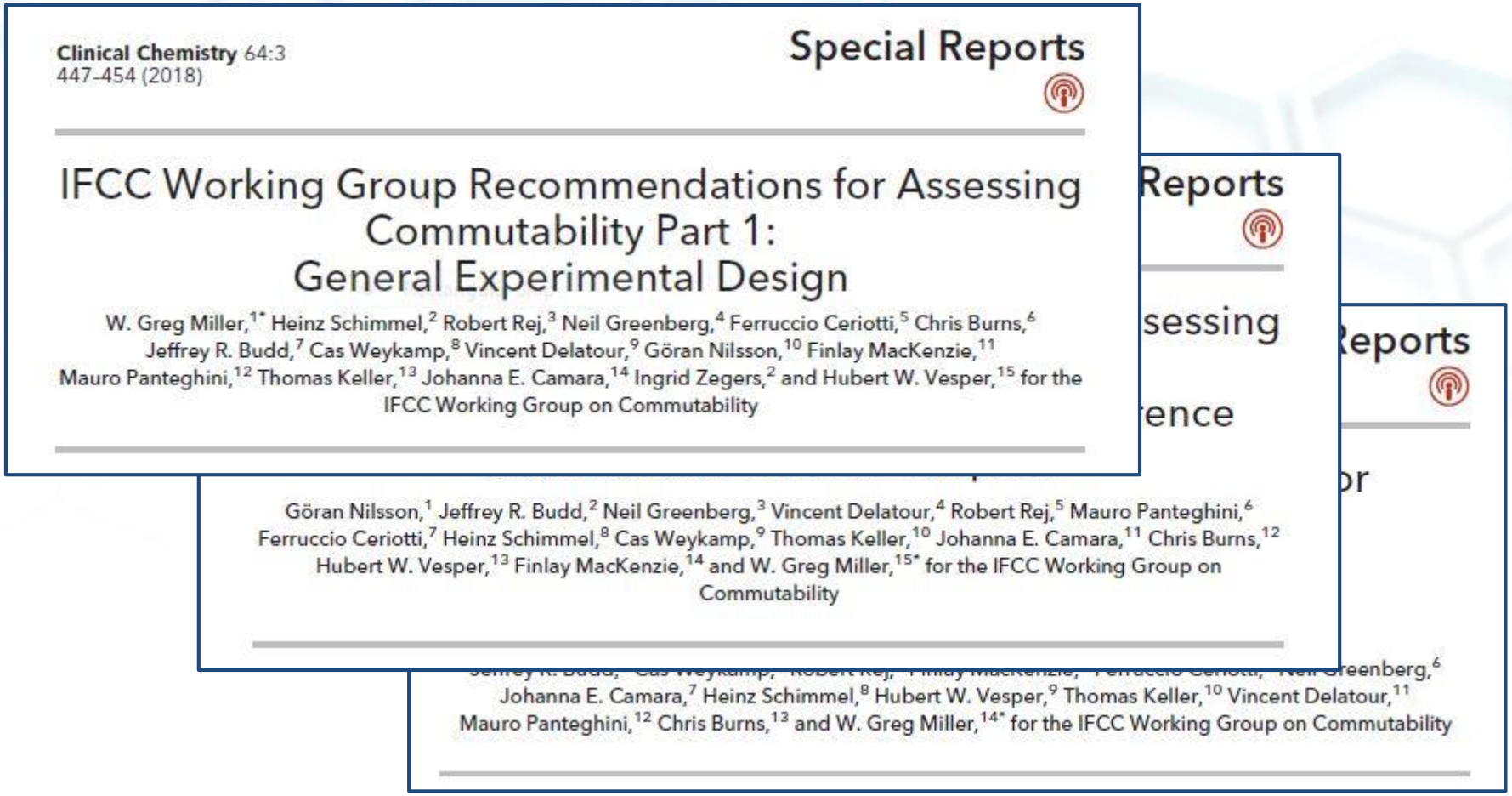
Commutability Assessment Through Commutability Study



- Study performed as part of the Vitamin D Standardization Program (VDSP)
- 50 single donor patient samples were distributed to participants
- Study included SRMs and PT/EQA materials

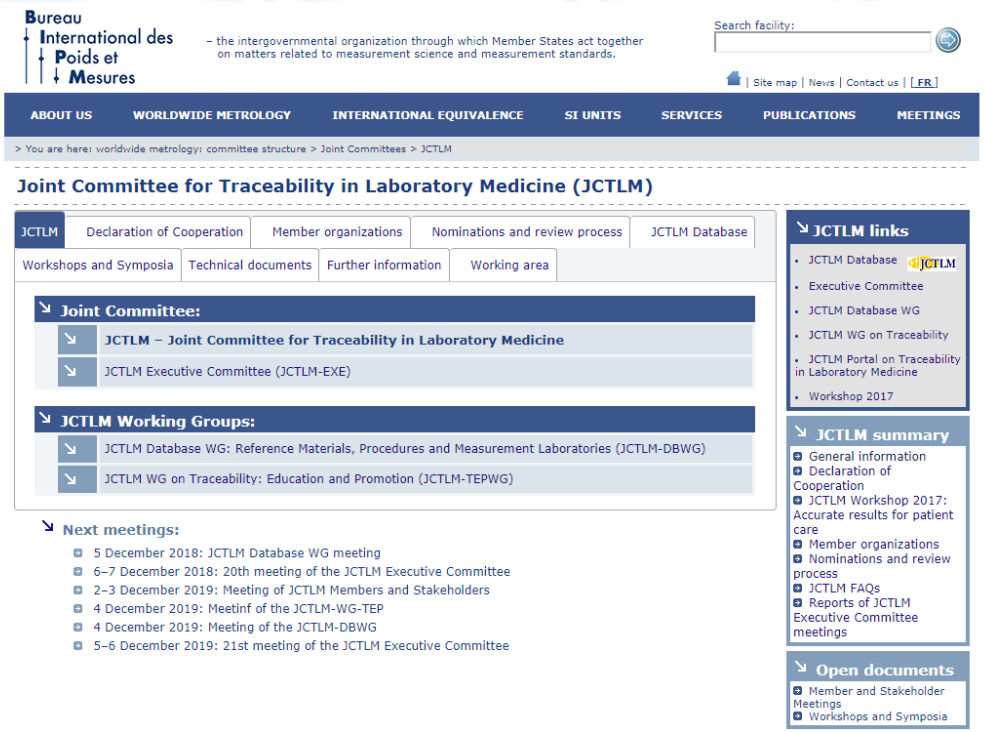


Guidance on Commutability Studies



IFCC Working Group on Commutability

For More Information



https://www.bipm.org/en/committees/jc/jctlm/