SCIENTIFIC DIVISION

63rd MEETING
Barcelona, Spain (May 18 and 19, 2019)
MINUTES *(FINAL)*

Members:	Abbr.	Term and Time of Office
Philippe GILLERY (FR) (Chair)	PG	1st 2017 01 - 2019 12
Christa COBBAERT (NL) (Vice-Chair)	CC	1st 2017 01 - 2019 12
Joseph PASSARELLI (US) (Secretary)	JP	2nd 2018 01 - 2020 12
Barnali DAS (IN)	BD	1st 2018 06 - 2020 12
Konstantinos MAKRIS (GR)	KM	1st 2017 01 - 2019 12
Mario PLEBANI (IT)	MP	1st 2017 01 - 2019 12
James PIERSON-PERRY (US) (Corporate Rep.)	JPP	2nd 2018 01 - 2020 12
Karen PHINNEY (NIST Representative)	KP	Consultant
Heinz SCHIMMEL (JRC Observer)	HS	Observer
Ian YOUNG (UK) (Chair JCTLM)	IY	Consultant
Chris BURNS (UK) (NIBSC Representative)	CB	Consultant
Greg MILLER (US) (ICHCLR Representative)	GM	Observer
Youchun WANG (CN) (NIFDC Representative)	YW	Observer

EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 63rd MEETING, Barcelona, Spain, May 18 – 19, 2019.

Present: Philippe Gillery (Chair), Christa Cobbaert (Vice-Chair), Joe Passarelli (Secretary), Barnali Das, Konstantinos Makris, Mario Plebani, (Members), Jim Pierson-Perry (Corporate Representative), Karen Phinney (NIST Representative), Heinz Schimmel (JRC Observer), Ian Young (SD Consultant/ChairJCTLM), Chris Burns (NIBSC Representative), and Greg Miller (ICHCLR Representative) were in attendance. Apologies received from Youchun Wang (NIFDC Representative).

5.4 EUROPEAN FEDERATION of CLINICAL CHEMISTRY and LABORATORY MEDICINE (EFLM):

The EFLM Science Committee and SD leadership once again agreed there should be close liaison and communication between the two groups. Professor Eric Kilpatrick is the EFLM SC chair. The Science Committee is responsible for scientific matters within EFLM and projects which further the scientific development of EFLM. Activities of the Committee particularly focus on promotion of research that translates the scientific results of clinical chemistry and laboratory medicine to clinical applications and improves patient outcomes through the appropriate use and interpretation of laboratory data in clinical practice. Within the EFLM SC there are working groups on cardiac biomarkers, biological variation, test evaluation, personalized laboratory medicine and a number of others but the general consensus of the SD is that these activities do not overlap with the IFCC SD.

PG has been in contact with the chair of the EFLM SC. Approaches to avoid overlap and work collaboratively continue to be discussed and explored.

6.1 WORLD HEALTH ORGANIZATION (WHO):

The WHO meeting occurs each autumn. PG attends and participates as the liaison from the SD. CB is also a full member of the WHO Expert Committee on Biological Standardization (ECBS) and will be able to provide a complete update from the WHO. There was a call for public comment with respect to the WHO Model List of In Vitro Diagnostics - https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sage-ivd-2nd-meeting/en/. Comments were sent in but so far no feedback has been received. PG had no other specific updates.

6.2 CLINICAL AND LABORATORY STANDARDS INSTITUTE (CLSI):

The link to these projects is under CPD: http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/clsi-ifcc-joint-projects/.
A project proposal was accepted by the CLSI Consensus Council for the update to EP28 (guidance document on Reference Ranges). This has direct implications to the Committee on Reference Intervals and Decision Limits (C-RIDL). As such, it is highly likely that Prof. Yeşim Özarda (chair of C-RIDL) will co-chair the CLSI Document Development Committee (DDC) for the revision to EP28. The CLSI Consensus Council is very supportive of this approach and are working through the logistics. A call for volunteers will go out soon.
The following new publications will be released in 2019:

1. Assessment of Equivalence of Sample Types (EP35)
2. Revision to the Reagent Stability Guidance Document (EP25)
3. Revision to the Linearity Assessment Guidance Document (EP06)
4. Revision to the Qualitative Assay Performance Evaluation Guidance Document (EP12)

6.22.1 Joint Committee on Traceability in Laboratory Medicine (JCTLM):

Dr. Gary Myers completed his second and final term as Chair, JCTLM Executive Committee. Professor Ian Young was nominated by IFCC and approved by the Executive Committee to serve a 2-year term (2019-2020) as the new Chair of the JCTLM Executive Committee. Dr. Myers was appointed by IFCC to replace Dr. Graham Beastall as a representative from IFCC to the JCTLM Executive Committee. Dr. Myers joins Dr. Anja Kessler (Referenzinstitut für Bioanalytik) as the two appointed representatives from the IFCC to the JCTLM Executive Committee.
The JCTLM Executive Committee continued its efforts to engage the International Council for Standardization in Haematology (ICSH) in collaborative programing activities in traceability. A joint leadership meeting with the ICSH and JCTLM was held 14-15 May, 2018 at BIPM, France.
Current JCTLM Database Content:

- 296 available certified reference materials;
- 194 reference measurement methods or procedures
- 176 reference measurement services delivered by 17 reference laboratories.

6.22.2 Joint Committee for Guide in Metrology (JCGM):

Report from Working Group 1 (GUM - Expression of Uncertainty in Measurement)
Dr. Martin Milton (JCGM Chairman) provided an update to the SD:
The circulation for review of the first Committee Draft of the document JCGM 103, Guide to the expression of uncertainty in measurement — Developing and using measurement models has been initiated. This document has been prepared by the Joint Committee for Guides in Metrology, of which the IFCC is a member, specifically by Working Group 1. This document is now being circulated for review amongst the

eight member organizations (BIPM, IEC, IFCC, ILAC, ISO, IUPAC, IUPAP and OIML), and to the Directors of National Metrology Institutes.
The chair proposed to use the review process that the JCGM has used previously.
Dr. Graham White is acting as IFCC representative.

Report from Working Group 2 (VIM)
The chair (Dr. Charles Ehrlich) of the Joint Committee for Guides in Metrology Working Group 2 (JCGM WG2) provided the following update to the SD:
The number of members of JCGM-WG2 has expanded since the last JCGM meeting by 3, from 12 to 15, with new representatives from IUPAP (1), OIML (1), and IUPAC (2), and one representative leaving (ILAC).
The main technical activity of JCGM-WG2 in the period May 2017 – November 2018 has been to develop a 'minimum change' version of a first "committee draft" (CD) of the fourth edition of the VIM that more fully incorporates entries on nominal properties and, to a much lesser extent, ordinal properties. The definitions of 'measurement' and 'measurement unit' have been given careful consideration in this regard. A longer-term 'evolutionary' version of the VIM4 CD has also been under development. Status of these two versions of these VIM4 CDs will be presented at the 3 December 2018 JCGM meeting.
Also to be discussed are publishing options of the VIM4 (e.g., electronic, hard copy, structure, languages).
Dr. Gunnar Nordin is serving as IFCC representative.

6.22.3 BUREAU INTERNATIONAL DES POIDS ET MESURES (BIPM) Consultative Committees
6.22.3.1 Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM):
The CCQM covers measurement standards and standardization in all branches of chemical and biological measurement science, and provides a forum where NMIs can be addressed collectively. A number of the CCQM WGs have programs in which a substantial portion of their activities are related to Laboratory Medicine, and notably for the Organic Analysis (OAWG) and Protein Analysis (PAWG) working groups. The OAWG has completed a comparison of metrology institutes with Vitamin D (D3 and D2) reference measurement procedure capabilities; this covered 7 institutes and will be published soon. The PAWG has mapped out a model system to look at the different types of pure peptide/protein types with respect to different challenges for purity assessment, with the aim of running comparisons to demonstrate NMI measurement capabilities for values assigning primary reference materials for peptides/small proteins.
The BIPM invited the IFCC-SD to a meeting of the BIPM's Consultative Committee for Metrology in Chemistry and Biology (CCQM), that was held on 10-12 April 2019 at the BIPM. Minutes from this meeting are forthcoming.
6.22.3.2 CC for Units (CCU): The IFCC is also a Member of the BIPM's CCU and has been invited to the 24th meeting of the Consultative Committee for Units which will take place at the BIPM from Tuesday 8 to Wednesday 9 October 2019 under the chairmanship of Prof. Joachim Ullrich. Professor Philippe Gillery as representative of the IFCC plans to attend. In addition, a BIPM Workshop entitled "Advanced Time and Frequency Transfer: the ultimate frontier for remote comparison methods" will be held on Thursday 10 October 2019 at the BIPM. This has been organized jointly by the CCU and the CCTF Working Group on Coordination of the Development of Advanced Time and Frequency Transfer Techniques (CCTF-WGATFT).

6.31 JOINT RESEARCH CENTER (JRC) – formerly the INSTITUTE FOR REFERENCE MATERIALS AND MEASUREMENTS (IRMM):

The status of JRC reference materials activity is mostly covered under the respective Cs and WGs. The JRC continues to collaborate with numerous SD Cs/WGs on a variety of projects. These include:

- Alzheimer's biomarker abeta 42 (ERM-DA480/IFCC, ERM-DA481/IFCC, ERMDA482/IFCC)
- Alzheimer's biomarker abeta 40 (ERM-DA480/IFCC, ERM-DA481/IFCC, ERMDA482/IFCC)
- Alzheimer's biomarker tau protein
- IgG anti-B2GP (ERM-DA477/IFCC)
- IgG anti-GBM (ERM/DA484/IFCC)
- IgG anti-tTG and IgA tTG (tissue transglutaminase)
- HbA2
- Pancreatic Amylase (ERM-AD456/IFCC)
- Lipoprotein (a)
- Faecal immunochemical testing

6.33 NATIONAL INSTITUTE OF BIOLOGICAL STANDARDS AND CONTROL (NIBSC)

NIBSC will propose 11 new or replacement WHO International Standards with diagnostic application. Those most relevant to the IFCC SD are as follows:

- **1st International Standard for AMH:** clinically, AMH in serum or plasma is measured in women, to assess ovarian reserve as part of assisted reproductive therapies and in paediatric medicine, to contribute to the diagnosis of disorders of sexual development.
- **Dual standard - 2nd WHO IS for Rheumatoid Factor and 1st WHO IS for Anti-Cyclic Citrullinated Protein Antibodies (ACPA):** data analysis on unitage and commutability studies are underway.
- **1st IS for insulin for immunoassay:** the aim is to provide a new International Standard for human insulin to replace International reference preparations which have been used by manufacturers of insulin assays for many years but also have recognized limitations relating to purity.

6.37 NATIONAL INSTITUTE FOR STANDARDS AND TECHNOLOGY (NIST):

The status of NIST reference materials activity is mostly covered under the respective C's and WGs.

In addition, the NIST website (www.nist.gov) can provide information on materials and services available today.

The most relevant projects to the IFCC and SD are:

- Albumin in urine
- Cardiac troponin
- Prenatal serum focused on hormones
- Vitamin D binding proteins

8.2 MAIN ACTIVITIES OF COMMITTEES:

8.2.6 C-NOMENCLATURE, PROPERTIES AND UNITS (C-NPU):

As a reminder, in 2014 a formal agreement between IFCC and IUPAC was put in place. Wikipedia presence for the NPU was created 2015 (edited by the chair with input from many NPU members). The Wikipedia entry is a useful introduction: (https://en.wikipedia.org/wiki/NPU_terminology) and the NPU Website is performing well.

The C has written a manuscript entitled: “Recommendation on measurement units - why and how” intended for submission in the electronic Journal of the International Federation of Clinical Chemistry and Laboratory Medicine.
In a current C-NPU activity, an online manual of NPU terminology is under development. The goal is to have a sort of encyclopedia for medical laboratory terminology that is accessible for any medical laboratorians. The project is funded by IUPAC (https://iupac.org/projects/project-details/?project_nr=2016-044-2-700). The project is in an iterative stage of establishing, reviewing and revising homepages.
The C planned to meet in Barcelona in conjunction with EuroMedLab 2019 and at the IUPAC meeting in Paris in July.

8.2.11 C-MOLECULAR DIAGNOSTICS (C-MD):
The C initiated a document which lists molecular genetic reference materials and their distributors. The document is to be discussed at the Euromedlab meeting in Barcelona. The final document will be placed on the C-MD website (in addition to the listed EQAs for MDX). The goal is to list commercial reference materials and reference materials from independent organizations (e.g. WHO) and is intended to help laboratories setting up genetic assays in infectious diseases.
The C will provide a plenary session at COLABIOCLI 2019 entitled “Quality Considerations for Molecular Diagnostics”. Three members and one corresponding member of the C-MD will be presenting talks covering different aspects to the aforementioned topic.
The C initiated a first draft to create a checklist for verification of a molecular diagnostics assay. The draft has been disseminated within the C-MD and will be discussed at the Barcelona meeting.
The network of IFCC Molecular Diagnostics Centres has expanded within the last months. The C-MD has granted certificates to nine new IFCC Molecular Diagnostics Centres.
Finally, at the end of last year, the C carried out a survey on important features of molecular diagnostics (IFCC-MD Survey 2018 on external quality assessments, alternative evaluation programs, tests of critical and significant risks, test methods). For the first time the C prepared an additional Spanish survey version. Both the data and possible improvements to the survey will be discussed by the C-MD in Barcelona.

8.2.23 C-TRACEABILITY IN LABORATORY MEDICINE (C-TLM):
The annual meeting of the committee will be held in Barcelona on May 20th, 2019. Two new members will attend the meeting.
The committee plans to discuss its active contribution to the work of JCTLM (e.g. as review team members, author of web presentations, etc.) to establish and promote the concept of traceability.
The results of RELA2018 are currently being processed for evaluation and the preliminary results will be presented for discussion at the annual meeting. JCTLM database laboratories look for an international scheme which provides frequent surveys for total hemoglobin. To this end, 4 of 6 laboratories using different procedures have submitted results for total hemoglobin. The evaluation is in progress.
The committee also plans to discuss the need to further extend the RELA portfolio. The chair of C-TLM will present the work of the committee at the annual meeting of WG-ID and discuss the support to establish comparison studies with the newly developed methods in the future. Further points for discussion will be the progress of the CDT and HbA1c networks, respectively.
In addition, C-TLM plans to discuss proposals on how to focus and publish the data of RELA collected in 16 years.

8.2.24 C-REFERENCE INTERVALS AND DECISION LIMITS (C-RIDL):

Articles published on behalf of the C-RIDL:

1. Jones GRD, Haeckel R, Loh TP, Sikaris K, Streichert T, Ozarda Y,; IFCC Committee on Reference Intervals and Decision Limits. Indirect methods for reference interval determination - review and recommendations. Clin Chem Lab Med. 2018 Apr 19. pii: /j/cclm.ahead-of-print/cclm-2018-0073/cclm-2018-0073.xml. doi: 10.1515/cclm-2018-0073 [Epub ahead of print].
2. Ozarda Y, Sikaris K, Streichert T, Macri M, on behalf of IFCC-Committee on Reference intervals and Decision Limits (C-RIDL). Distinguishing Reference Intervals and Clinical Decision Limits – A review by the International Federation of Clinical Chemistry Committee on Reference Intervals and Decision Limits". Critical Reviews in Clinical Laboratory Sciences, 2018 Sep;55(6):420-431.

Article published directly related to the C-RIDL projects;

- Ozarda Y, Higgins V, Adeli K. Verification of reference intervals in routine clinical laboratories: practical challenges and recommendations. Clin Chem Lab Med. 2018 May 5. pii: /j/cclm.ahead-of-print/cclm-2018-0059/cclm-2018-0059.xml. doi: 10.1515/cclm-2018-0059 [Epub ahead of print]

CLSI will soon start a revision project of EP28 (Reference Ranges) and the chair of C-RIDL, Dr. Ozarda has accepted the position to co-chair the CLSI committee ensuring alignment of activities and content publications.

The C met during the General Conference in Budapest in Hungary.

Plans/suggested work items:

1. Comparison of alternative approaches (conventional and big data) for the determination of reference intervals
2. Individual reference intervals
3. The update of the CLSI Guideline EP28-A3

8.2.25 C-STANDARDIZATION OF THYROID FUNCTION TESTS (C-STFT):

Establishing a system to maintain traceability of free thyroid hormone and TSH measurements has been completed and now the focus is on implementation.

Next interlaboratory comparison study planned for June 2019 using euthyroid as well as hyper and hypothyroid samples:

- Revising current SOP for free thyroid to facilitate setup and implementation of RMP.
- Drafting rules for network operation.
- Samples were consolidated at NIBSC and an inventory was created.

Next Steps:

- Have fT4 network operational by end 2019.
- Provide calibration and standardization services for fT4 through Network by spring 2020.
- Assess TSH harmonization efforts in Japan and implement harmonization in other countries based on experiences obtained starting spring 2020.
- Once the IFCC reference system is operational, approach relevant organizations to assist with implementation and development of reference intervals starting spring/summer 2020.
- Collaborate with reference material providers and accuracy-based EQA programs to make materials traceable to the IFCC reference system, and to monitor impact of standardization and harmonization.

The Committee plans to meet twice in 2019 at EuroMedLab and at the AACC.

8.2.26 C-HARMONIZATION OF AUTOIMMUNE TESTS (C-HAT):

The committee continues to focus on the preparation of reference materials in collaboration with the JRC. The C continues developing plans for introducing and implementing reference materials for IgG anti MPO and IgG anti PR3. The committee is facing a similar issue as C-STFT with implementation of harmonized assays systems in that there is the need to work with manufacturers and regulatory agencies worldwide and in particular the FDA. At present IVD manufacturers have to submit a full new 510k dossier after they have re-calibrated their assay, including sometimes very expensive clinical studies. This requires considerable resources (financial, people, time) and is often a barrier to standardization/harmonization. There have been discussions with the FDA and they are supportive but their focus is primarily on comparisons to predicate devices.

Future plans:

- Anti mitochondrial antibodies (M2 subtype)
- Other anti DNA method/materials
- Developing criteria for reference methods:
    - defining the antigen or even important epitopes
    - which class of antibody is being detected
    - developing a reference panel of samples
    - harmonize methods where possible so it can be defined which method detects which antibody to which antigen
- harmonize the clinical interpretation of results
    - formulating guidance

The C has planned a face-to-face meeting in Barcelona Sunday May 19th 2019 in conjunction with EuroMedLab.

8.2.27 C-BONE METABOLISM (C-BM):

The Committee was constituted in January 2019 after the closure of three previous WGs (PTH, Bone Markers, and Vit D).

PTH standardization:

The Committee plans to achieve and finalize the commutability study of WHO IS 95/646 and to continue working on PTH RMP.

Bone markers assays:

PINP:

A paper on the results of the multicentre study has been accepted by CCLM.

During the IOF-IFCC held in Paris on April 3rd 2019, an equation to “recalibrate” the kits against each other based on 10% of the results of the multicentre study was proposed. This equation has been “validated” on another set of independent samples. This shows that harmonization of PINP is possible.

With the help of Vincent Delatour, a preliminary commutability study will be organized in Liège.

Future plans are to:

- Perform the commutability study
- Evaluate the opportunity to develop a RMP for PINP
- Prepare commutable standards to calibrate the assays (with the help of the LNE)
- Write a paper on biological variation of PINP (and other bone markers)

CTX:

A paper on the multicenter study has been written, but it has been put on hold because of the poor quality of the results.

Future Plans:

- Manufacturers to work to improve the issues observed on the multicentre study. This is mandatory for the future of the marker.
- Write a paper on biological variation of CTX (and other bone markers)

Vitamin D metabolites assay standardization:
In collaboration with NIST, a study has been organized to evaluate the performance of different assays on a single donor panel. The LCMS reference method of the NIST has been used to assign the value of the samples and they have all been measured in Liege with most of the different immunoassays available on the market according to the VDSP protocol. A paper is currently under redaction.
Future plans:

- Write and submit the paper on the study
- Propose an "external" validation of IVD certified assays for VDSP
- Work on current VDSP performance guidelines for 25(OH)D

The C met in Paris with IOF and IVD representatives on April 3rd, 2019
Future Meetings:

- Meeting in Barcelona on May 20th, 2019 in conjunction with EuroMedlab
- Meeting in Budapest during ERA-EDTA congress (June 12th-16th) if agreement of endorsement by ERA-EDTA
- Potentially meeting in AACC in August 2019 if needed and decided during the meeting of May 20th.

8.3 MAIN ACTIVITIES OF WORKING GROUPS:

8.3.35 WG - STANDARDISATION OF HEMOGLOBIN A2 (WG-HbA2):

A joint committee with ICSH (The International Council for Standardization in Hematology) has been formed.
Candidate reference measurement procedure for HbA_2:
The method developed is an HPLC-IDMSMS measurement procedure based on peptide mapping and calibration with recombinant expressed HbA0 and HbA2 standard materials, traced back to SI units. The experimental work to prepare the second paper on the method (description of the candidate IFCC reference method) is at present under pause because the WG is waiting for the recombinant hemoglobins to be used for calibration.
Certified reference material for HbA_2:
A first pilot batch at the normal level (non beta-thalassemia carrier) of HbA_2 has been prepared at the JRC. A preliminary characterization of such batch is under way. A first version of the SOP to prepare such materials has been written. Various actions have been decided (supply of fresh blood, protocol for blood collection, informed consent by the donors, commutability study, information to the WG corresponding members and manufacturers) to finalize the preparation of the large batch.
IFCC-ICSH joint group on standardization of HbA_2:
The WG keeps in constant contact with the ICSH group, by teleconferences every 3-4 months. A conference call was held on December 3rd, 2018, and another one on May 14, 2019. They are informed of the activities of the WG, and the chair is waiting for data from them on studies recently performed on a residual batch of the NIBSC material for HbA_2.

8.3.36 WG - STAND. OF CARBOHYDRATE-DEF. TRANSFERRIN (WG-CDT):

The following is a summary and a description of the current focus of this WG:

1. JCTLM – The document was updated and resubmitted during 2018. Unfortunately, the method was rejected due mostly to how the uncertainty was calculated. The WG and JCTLM are in discussion to resolve the situation.
2. There have also been continuous communication and updates requested from commercial manufacturers towards final development and release of their CDT_{IFCC} methods.
3. Current laboratories for the HPLC RMP are: Sweden, The Netherlands, France, United States, Italy and United Kingdom.

4. Sustainability and performance of network laboratories and participating commercial manufacturers are assessed by the yearly distribution of IFCC calibrators, controls and blind samples from Dr. Weykamp's laboratory. Laboratory performance is assessed on a pass/fail criterion and HPLC RMP performance is assessed in further detail by Dr. Schellenberg.
5. WG members have been raising awareness of CDT_{IFCC} with local authorities at regional level.
6. The C plans to meet in Barcelona (closed and open sessions) and with the SD including the chair of JCTLM – Professor Ian Young to address point #1.

8.3.39 WG – STAND. OF ALBUMIN ASSAYS IN URINE (WG-SAU):
All activities of the WG-SAU are a joint effort with the Laboratory Working Group (LWG) of the National Kidney Disease Education Program (NKDEP), USA.
Reference measurement procedure for UA (funded by NKDEP and NIST):
Candidate isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) reference measurement procedures for UA are under development by the Mayo Clinic Renal Testing Laboratory, University of Minnesota Advanced Research Diagnostic Laboratory and NIST.
NIST and Mayo will continue to develop and validate their reference measurement procedures and will work identifying sources of disagreement among the methods, and pursue validation of the candidate reference measurement procedures in accordance with ISO 15193 and other relevant standards for the purpose of JCTLM listing. Univ of Minn will share preliminary data at the NKDEP-LWG in August 2019.
Reference materials for UA and urine creatinine:
To facilitate standardization of routine methods, NIST SRM 3666 is currently being developed based on the specifications recommended by the WG-SAU and the LWG of the NKDEP. Once developed, a commutability assessment of the materials will be conducted. The acquisition of frozen single-donor urine samples for preparation of NIST SRM 3666 has been completed as of December 2018. Value-assignment of SRM 3666 for urine albumin and creatinine will be conducted by NIST.
Publications:
Miller WG, Bachmann LM, Fleming JK, Delanghe JR, Parsa A, Narva AS. Recommendations for reporting low and high values for urinary albumin and total protein [Letter to the Editor]. Clin Chem 2019; 65(2):349-350.
A joint IFCC/WG-SAU is planned to be held in conjunction with the AACC Annual meeting in August 2019.

8.3.40 WG – STAND. OF PREGNANCY-ASS. P-PROTEIN A (WG-PAPPA):
The WG main goal is to harmonize the PAPP-A measurements of the various methods commercially available. Currently, the WG is evaluating different PAPP-A preparations in relation to the major assay constructs presently being used in routine prenatal testing.
The work with evaluation of different PAPP-A preparations has continued in phase 3, in which endogenous materials of PAPP-A (PAPP-A in second trimester and third trimester sera diluted in various materials and compared to first trimester serum pools) were analyzed with assays systems of the companies involved in the WG in order to study the commutability of these materials.
The phase 3 results (3rd and 2nd trimester pregnancy plasma serum pools in different diluents by company assays) were distributed to the whole working group.
A new NIST standard reference material in preparation has been identified as a promising candidate reference material for PAPP-A. The issue of commutability will be further assessed moving forward.

The plans for the next phase of the work are to be discussed in the next WG meeting in Barcelona EuroMedLab.

8.3.41 WG – GROWTH HORMONE (WG-GH)

The overall goal of the WG-GH is to achieve standardization of growth hormone through secondary reference materials and a reference measurement procedure.
To achieve this goal, a pilot study was started testing commutability of potential GH calibrators among 25 individual patient samples. Several potential calibrators were included: pools of patient sera and the WHO standard IS 98/574 in a serum matrix. All available routine methods were included and also a LCMS-MS method. All results were analyzed again after the LCMSMS results became available, but it was concluded that the patient pools were not commutable, nor the international standard at the higher concentration. However, it could be concluded from the LCMSMS results that the isoform ratio of the 22 and 20 KDa GH was not the cause of this. The secondary calibrators and also the individual patient samples were pooled from patient serum, which had been frozen and thawed several times, which may have an effect on the commutability results. A report was made with the results and sent to the members of the working group.
The chair is now organizing a blood draw from healthy volunteers who have been cycling at maximum exercise. This will be done probably before the summer of 2019, at the Rehabilitation and Sports Medicine department of the UMCUtrecht, the Netherlands (Prof Dr Backx). The chair hopes to be able to construct at least five levels of GH from this material, which will be processed freshly and then aliquoted and frozen. Once complete, a commutability study will be organized, internationally, with the help of the working group members.
Develop a reference method for the measurement of the 22KDa growth hormone:
Until now only the laboratory of Dr. Christian Arsene was approached to measure samples. Fortunately, Dr. Milena Quaglia, LGC, London, UK has agreed to join the working group.

8.3.42 WG – STANDARDIZATION OF INSULIN ASSAYS (WG-SIA)

This is a joint project between ADA/EASD and IFCC. The overall goal of the WG is to establish a reference system for serum/plasma insulin measurement to achieve standardization of all commercial methods to assay insulin.
Current status:

1. Ongoing development and validation of MS/MS method for intact insulin at University of Minnesota. Significant progress has been made following prioritization and financial support for development of the LC-MS/MS insulin assay at the University of Minnesota.
2. Continued collaboration with other laboratories (Quest Diagnostics, Mayo Clinic) developing insulin methods by mass spectrometry and sustained efforts to evolve reference method procedures in these laboratories.
3. In collaboration with the College of American Pathologists (CAP), established criteria for ongoing accuracy based evaluation of serum pools for testing of insulin, C-peptide, and glucose.
4. Continued collaboration with NIBSC to evaluate insulin candidate reference material and will ultimately utilize that to calibrate the mass spec method and establish it as a higher order reference method.

Future Plans and activities:

1. Implement accuracy based proficiency testing survey using serum pools for insulin (and c-peptide) via the College of American Pathologists; results will allow for assessment of comparability of results across assays, using a commutable matrix,

as the WG moves towards standardization or harmonization. Implementation target date: Q2 2019.

2. Working group report or peer-reviewed publication regarding either insulin/c-peptide serum pool data across hundreds of laboratories/assays and/or lack of harmonized conversion factor across insulin assays.

The WG plans to meet next in conjunction with EuroMedLab, Barcelona, Spain May 2019 and again at the AACC Annual Meeting, Anaheim, CA 2019.

8.3.43 WG – STANDARDIZATION OF TROPONIN I (WG-TNI)

The following provides a brief summary of the status of WG-TNI:

1. Patient samples from myocardial infarction patients for producing RM 2922 continue to accumulate by recruitment and collection. Currently there are approximately 25 mLs of serum from each of 25 subjects, for a total of approximately 620 mLs of cTnI material
2. Dr. Lowenthal is initiating the procurement processes at NIST. A draft Statement of Work has been written.
3. Dr. Lowenthal has received the names and contact information of three vendors that have expressed interest in bidding on the blending and aliquoting of RM 2922.
4. In a separate effort, the WG-TNI is in the last phases of designing a Round Robin Study for high-sensitivity cTnI methods using common pools of commutable samples from de-identified residual samples collected at Dr. Christenson's laboratory under an IRB protocol. Dr. Robert Payne, an expert in high sensitivity assays has agreed to spearhead this activity. All manufacturers with hsTnI assays will be invited to participate. A primary objective will be to characterize the relationships between the hsTnI methods.
5. The WG-TNI will meet at the AACC Annual Meeting in Anaheim, tentatively scheduled for 7am on Monday August 5th for 2-3 hours. Topics on the meeting agenda will include:
   A. An update on the status of producing RM 2922.
   B. Discuss the pros and cons of depleting TnI from the normal serum blending material.
   C. The feasibility of producing an 'app' that would make available evidence of the relationship of the various hsTnI assays from the round robin activity.
   D. Discussion of a possible project with the Maastricht cardiac biomarker group. The purpose of this collaboration would be to investigate the subforms of TnI in acute myocardial infarction versus chronic disease.
   E. Start of a list of scientific meetings that might be good venues for presenting the work of WG-TnI.
   F. Discuss what materials and methods should be focused on for use in development of an SRM in the future.
   G. Examine the possibility of a round robin activity with the CAP.

8.3.49 WG – CSF PROTEINS (WG-CSF):

The WG is in contact with NMIs for the standardization of the Tau proteins. There seems to be some coordinated activities. So far the following have been accomplished:

- Two RMPs for CSF amyloid β 1-42 have been published and approved by the JCTLM (C12RMP1 and C11RMP9).
- A method for measurement of CSF amyloid β 1-40 by SRM has been published and validation of a RMP is ongoing.
- Mass spectrometric methods for measurement of CSF tau have been developed by several of the work group members.

- Three CRMs for CSF amyloid β 1-42 have been developed (ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC).
- Collection of CSF for development of CRMs for tau is ongoing.
- Round-Robin study of CSF-amyloid beta 1-42/1-40 ratio RMPs by mass spectrometry is in the planning stage.
- Round-Robin study of CSF tau RMPs by mass spectrometry is being planned.
- There has been reluctance by industry to adopt the new reference system and the WG has prepared training materials and trying to move this forward.

8.3.51 WG – COMMUTABILITY (WG-C):

The WG published the first three papers last March 2018 in Clinical Chemistry.
Three additional manuscripts are being written:

1. IFCC working group recommendations for assessing commutability part 4: Correction of bias caused by non-commutability of a certified reference material used in the calibration hierarchy of an end-user measurement procedure. The manuscript will include supplemental worked examples that are in the final stages of refinement. The WG will focus its discussion on this manuscript at its meeting during EuroMedLab Barcelona to advance the manuscript to final or close to final form. The manuscript will be submitted in 2019.
2. IFCC working group recommendations for assessing commutability part 5: Validation of a replacement batch of a reference material.
3. IFCC working group recommendations for assessing commutability part 6: Approaches to establish criteria for commutability assessment. This manuscript will be a difficult undertaking and will try to address how to define the degree of commutability which is required for a given reference material, taking into account its intended use and the intended use of the measurand.

The overall goal is to propose standard terminology to describe the degree of commutability of a reference material, taking into account its intended use. In addition, to provide guidance to manufacturers and laboratories about what information should be provided by manufacturers in relation to the commutability of reference materials used to establish the calibration traceability of a measurement procedure.
The first 3 papers built on the concepts as described in the CLSI guidance document on commutability as they now account for uncertainty of the measurement. The next paper planned will bring in the concept of bias. It is believed that if bias is large it can be corrected; if it is small it may be ignored.

8.3.53 WG – IMMUNOSUPPRESSIVE DRUGS (WG-ID):

The WG is devoted to the establishment of candidate reference procedures and reference materials for immunosuppressive drugs (ISDs) such as cyclosporine, sirolimus, tacrolimus, everolimus, and mycophenolic acid (MPA). Demonstration of the current state of the art in ISD – TDM by measurement comparison will define the need for harmonization or – if feasible – standardization of measurement services
The group will be meeting in Barcelona and this really represents the first meeting of the WG with wide participation. Some of the topics that will be discussed are as follows:

- WG-ID: terms of references, deliverables and expectations Christoph Seger (CS)
- IATDMCT liaison – aims and reasoning Loralie Langman (LL)
- Reflection of ISD-TDM status quo in proficiency testing data (CS)
- TALKS:
    - The need for ISD-TDM standardization – the clinical / pharmacological view - Teun van Gelder
    - The RELA PT scheme / PT provider as hub for harmonization efforts? - Anja Kessler

- Uncertainty and traceability of ISD measurements - Raül Rigo
- The candidate reference method on cyclosporine A - Denis Grote-Koska
- Towards a candidate reference method for ISD-TDM - Judith Taibon

DISCUSSION:

- Top 1 … Harmonization, round robin 1… Where do we stand, can we make a significant RR?
- Top 2 … Dissemination of methods? Where do we stand, what are the needs?
- JCTLM clearance as starting point? Transparency in the publication process
- Top 3 … Dissemination of materials? Where do we stand, what are the needs? Availability of ISO34 certified reference materials
  - Can ISD samples be provided and distributed? "frozen" vs. "fresh" sample issue.
- Top 4 … Uncertainty calculations. Where do we stand, what are the needs? Can reference method requirements be met?
- Upcoming publication efforts:
  - eIFCC – enhance the visibility of WG-ID - position paper

The minutes of this meeting will give a much better "evidenced based" insight on how to proceed from 2019 to the future.

8.3.54 WG – APOLIPOPROTEINS BY MASS SPECTROMETRY (WG-APO MS):

The WG is progressing very well and investigating both reference materials and reference methods. The digestion conditions have been optimized to obtain a sample preparation procedure which supports complete digestion of all apolipoproteins, including apolipoproteins CI and CIII. Using this approach, complete and stable digestion for all apolipoproteins in one single sample preparation has been achieved. This has the advantage that one single MS-based method for the multiplexed quantitation of all seven apolipoproteins can be developed.

Transgenic pig EDTA plasma from Japanese mini pigs holding human apo(a) with a specified number of kringles for evaluation as a secondary cRM has been obtained. Moreover, peptides have been ordered, of which the first ones have been received, as primary cRM for apo(a). An outline for an initial commutability study was drafted, and serum samples to perform such studies have been ordered.

Moving forward, the WG plans to develop a harmonized SOP for the cRMP procedure, and evaluate the transferability and the degree of harmonization between the three calibration laboratories. Initial evaluation of the equimolarity of the digestion is also planned for Q3 and Q4 2019.

A literature study was performed to review the current evidence at the genetic and proteomics level for the quantitation of apolipoproteins in CVD risk assessment. Based on these outcomes, an alternative clinical care pathway was proposed (Ruhaak LR, Van der Laarse A, Cobbaert CM). An invited review was written, entitled: Apolipoprotein profiling as a personalized approach to the diagnosis and treatment of dyslipidaemia. Annals of Clinical Biochemistry. 2019 https://doi.org/10.1177/0004563219827620).

By a joint task group of EAS and EFLM members, a consensus statement was developed on quantifying atherogenic lipoproteins, for better defining the residual CV risk, beyond LDLc and classical lipid parameters. The potential added value of serum apolipoprotein profiling is mentioned in Clin Chem. 2018; 64: 1006-33, and is entitled: Quantifying Atherogenic Lipoproteins: Current and Future Challenges in the Era of Personalized Medicine and Very Low Concentrations of LDL Cholesterol. A Consensus Statement from EAS and EFLM. Langlois MR, Chapman MJ, Cobbaert C, Mora S, Remaley AT, Ros E et al.; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative.

8.3.55 WG – PANCREATIC ENZYMES (WG-PE):

The WG was established as a result of the closure of the previous C-RSE.
At the meeting in Budapest (2018-11) Denis Grote-Koska presented the first results of investigation with the aim of developing a reference system of pancreas amylase in serum and he presented the important theoretical background.
Successful investigations covered the following:

- Determination of inhibitory constants for pancreas and salivary amylase by mAb's
- Spiked solutions: Comparison of calculated vs. experimentally determined enzyme activities
- Serum pool: Comparison of calculated vs. experimentally determined enzyme activities
- Absorption kinetics
- Correlation to total amylase activities measured in the clinical routine laboratory (n = 51)
- Correlation to lipase activities measured in the clinical routine laboratory (n = 51)
- Influence on the inhibition of glucosidase by matrix due to adding inhibitory mAb's

After the meeting in Budapest two other laboratories (Francesca Canalias, Spain and Friederike Weber, Roche, Germany) performed reproduction of the investigation protocol. Measurements were done in March 2019 at both sites.
Theoretical work was done by Ferruccio Ceriotti, who was listing the uncertainty budget and roughly estimating contributions of each uncertainty component.
At the upcoming meeting in Barcelona (2019-05) those results will be compared and discussed to find issues and mention noteworthy hints to be considered for further studies. The estimated measurement uncertainty is required to discuss if the needs for a reference system can be met.
A basis for discussion is the next step, namely an inter laboratory comparison of e.g. 4-5 reference laboratories and the potential source of sufficient sample material.

8.3.56 WG – FECAL IMMUNOCHEMICAL TESTING (WG-FIT):

The group continues to have extremely good engagement and support and has met at least twice since its inception. There is now a member from the Turkish Society of clinical chemistry as well as a Japanese SCC representative.
Project/ TOR updates:
Reference material:
A reference material study has been carried out as a collaboration between the JRC lab in Geel and the South of England bowel cancer screening hub. The initial findings were shared at the October 2018 meeting; final findings will be presented in May 2019. It is unlikely that the methods will be standardized; however, the hope is to be able to harmonize the methods. The details of this will be discussed at the May 2019 meeting at Euromedlab.
EQA:
A review of EQA material has been completed and the plan is to prepare a publication
Pre-analytical variation:
It is very challenging to improve the pre-analytical variation that occurs with FIT. Group members continue to carry out research to help understand these variabilities and impact on FIT results. Results are regularly presented at the meetings for discussion.
IQC:
There is no 3rd party IQC available for FIT analysis. The group will discuss a project that has been agreed to address this using FIT suppliers on-board IQC material.
The WG plans to meet again in Barcelona in May 2019 in conjunction with EuroMedLab. A second meeting is planned, 19th October 2019: World Endoscopy Organization (WEO) meeting, Barcelona.

8.3.57 WG – CELL FREE DNA AND RELATED CIRCULATING BIOMARKERS (WG-cfDNA):

The WG has reached out for corporate member sponsorships to enable face-to-face meetings.

Terms of Reference:

- To identify and provide guidance on preanalytical and analytical aspects for obtaining good and reproducible results for cfDNA and related circulating biomarkers for clinical use, and to guide the correct clinical implementation of these biomarkers.

Current projects:

- Defining pre-analytical aspects / drafting guideline
- Defining minimal analytical performance
- Setting up proficiency testing for cfDNA
- Organizing international workshops
- Defining grant proposals to address unmet needs

The chair and WG have prepared a paper about the pre-analytical aspects and the paper is currently being reviewed by the WG. The chair believes the WG members will provide expertise in lung cancer, organ rejection, and other broad areas (such as exosomes). The WG also plans to be involved early on with NMIs.

8.3.58 WG – PROCALCITONIN (WG-PCT):

The following is the status of WG-PCT to date:

Objective 1: Develop and validate a reference measurement procedure for PCT absolute quantification by stable isotope dilution mass spectrometry (SIDMS) in order to establish metrological traceability of results to the SI Units:

- For now, the IDMS reference method will measure total PCT (PCT 1-116 + PCT 2-116 + PCT 3-116)
- Different primary calibrators have been produced. Their purity is being characterized by high resolution mass spectrometry
- Different separation methods to purify PCT in biological samples are under development
- Suitability of recombinant PCT and/or synthetic peptides as possible primary calibrators are being investigated
- A candidate reference measurement procedure for absolute quantification of PCT by IDMS is under development. Good progress was made with peptide-based calibration. The work on protein–based calibration will be initiated in September 2019.

Objective 2: Document and understand the variability of results provided by the different commercially available PCT assays:

- Residual samples from patients with different PCT concentrations (frozen serum) have been collected in different hospitals with the objective to prepare pools
- Discussions on the design of the commutability study have started and the following prerequisites have been identified:
  - Investigation of the freeze thaw effect to determine if frozen samples can be used instead of fresh clinical specimens
  - volume needed by each routine assay to measure each sample
  - assays precision to determine the number of replicates needed to minimize uncertainties and reduce the rate of inconclusive results
  - Identification of the main sources of variability (e.g. lot to lot variations)
- An EQA scheme relying on commutable materials will be organized after study materials have been prepared and commutability is demonstrated
- Each assay manufacturer is expected to provide preliminary information on how their assay is calibrated and what epitope is targeted by antibodies

- A decision whether standardization is needed or not will be made after the variability of results provided by the different commercially available PCT assays has been documented and understood

A meeting of IFCC WG-PCT will take place on May 20th 2019 during EuroMedLab Barcelona.

8.19 MEETINGS

8.19.63 63rd SD Meeting – Barcelona, Spain, May 18th and 19th, 2019 (Saturday and Sunday), before the EuroMedLab Congress.

8.19.64 64th SD Meeting – Milano, Italy, October 11th and 12th, 2019 at the IFCC office.

8.16.65 65th SD Meeting – exact dates to be determined but will be held in conjunction with WorldLab 2020 – Seoul, South Korea