67th Meeting
SCIENTIFIC DIVISION
Minutes
Conference Call – June 9th, 2021

Members:		Abbr.	Term and Time of Office	
Philippe GILLERY (FR)	Chair	PG	2nd	2020 01 - 2022 12
Christa COBBAERT (NL)	Vice-Chair	CC	2nd	2020 01 - 2022 12
Garry JOHN (UK)	Secretary	GJ	1st	2021 03 - 2023 12
Barnali DAS (IN)	Member	BD	2nd	2021 01 - 2023 12
Konstantinos MAKRIS (GR)	Member	KM	2nd	2020 01 - 2022 12
Mario PLEBANI (IT)	Member	MP	2nd	2020 01 - 2022 12
Michael ROTTMANN (DE)	Corporate Rep.	MR	1st	2020 03 - 2022 12
Karen PHINNEY (US)	NIST Cons.	KP		
Liesbet DEPREZ (BE)	JRC Observer	LD		
Ian YOUNG (UK)	ICHCLR Observer	IY		
Chris BURNS (UK)	NIBSC Consultant	CB		
Greg MILLER (US)	JCTLM Chair/SD Cons.	GM		
Yang ZHEN (CN)	NIFDC Observer	YZ		

EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 67th MEETING
Conference Call – June 9th 2021
Present: Philippe Gillery (Chair), Christa Cobbaert (Vice-Chair), Garry John (Secretary), Barnali Das, Konstantinos Makris (Members), Michael Rottmann (Corporate Representative), Karen Phinney (NIST Consultant), Ian Young (SD Consultant/ICHCLR Observer), Greg Miller (JCTLM Chair/SD Consultant), Chris Burns (NIBSC Consultant), , Yang Zhen (NIFDC Observer) and Liesbet Deprez (JRC Observer) were in attendance.

Apologies received from Mario Plebani

*Documents mentioned as "**Appendix**" can be read on request*

5. CHAIRMAN'S REPORT
There is a move to improve relationships between scientific societies. Develop two MoUs with different societies for the management of our WGs; the first with ISTH is important for the WG-INR, the second related to WG-ID. MoU has been established between IFCC and IADMCT

5.4 EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE (EFLM)
CC updated the meeting on behalf of EFLM. It was decided last year to set up a TF to guide the transition from IVD directive to IVD regulation. Several members are also on the Clinical Device coordination group of the European Commission (EC); a high lever overarching committee.developed by the EC to have interaction with the field. Observership in WGs of the MDCG allows reviewing EC guidance documents. It was considered an advantage to collaborate and network with the other stakeholders of the IVD (IVD Industry). The IVD industries are

represented in Medtech Europe. There are a number of members that represent different job roles; important as implementation will mean different things for different groups. The IVDR are looking into safety on clinical effectiveness of medical tests.so decided to have one epidemiologist/methodologist in the group to look at the clinical evidence of tests on the market.

Composition of the group is good, started meetings about 8 months ago with monthly meetings; it is progressing well. IY is also a member for Biomed Alliance, this is a large organisation involving all the clinical organisations interactive with good lobby in Brussels. CC will send links so members can review. Progress has been slow because of COVID-19 and the MDR; the MDR is another organisation for regulating Medical Devises in Europe. There is huge under capacity from European Commission to work on implementation of IDV regulation for May next year. Alarming news from Branch organisations of Manufacturers that Certification pathway not working. EU has a large regulatory structure to be set up; all tests have to be reclassified (no Grandfather clauses) this means that 19,000 medical tests have to be classified as Class B or C tests to be available to go on the market for May next year. So far there not enough Notifying Body capacity, only 4 have been established; takes 2 years to set up a Notifying Body many Manufacturers do not have a Notifying Body with a 2 year waiting list. Dangers if pipeline not working tests will not have Certificates (most don't) are not available. This will result in 85-90% of tests will not be on the market. Smaller companies will be worse affected.

Alarm Bells must be sounded as this is undermining the whole European (maybe worldwide) health care system. National representatives and presidents of scientific organisations of European states have been asked discuss and arise awareness of this. Needs a longer implementation phase of IVDR.

MR commented that manufacturers fully support recommendations from CC. Companies are overloaded and do not have time to get all tests ready.

6.1 WORLD HEALTH ORGANISATION (WHO)

PG has received no communication regarding IFCC attendance at the WHO expert committees.

6.22.1 Joint Committee on Traceability in Laboratory Medicine (JCTLM)
Appendix 1

GM directed the Committee to Appendix 4 the Web page for World Metrology Day 20th May, several IFCC members submitted vignette about Metrology each are 6-8 minutes long explaining our profession and the importance of metrology.
GM also stated we are fully committed to IFCC SD, ICHCLR and JCTLM workshop. This will occur during the stakeholders meeting in December 6-10 and it will be a virtual workshop (European, American and Asian). The goal of the workshop is to develop a report with recommendations around advances needed in reference materials and regulatory cooperation to make it easier for the IVD industry to standardise their methods. Hoping to stimulate collaboration or at least corporation between regulatory bodies.
The JCTLM continues to carry on its work; there will be a new website but date not known. It will cut down on the number of pages that will need to be reviewed for information.

6.22.2 Joint Committee for Guide in Metrology (JCGM)
Report JCGM meeting (held in the morning) by PG

PG commented that all relevant documents had been circulated and are attached here. There is no need for additional discussion.

WG 1 (GUM): Graham White as IFCC representative
Appendix 1

WG 2 (VIM): Gunnar Nordin as IFCC representative
Appendix 1

Minutes of JCGM Meeting – December 7th, 2020
Appendix 1

International Vocabulary of Metrology (VIM), 4th edition
Appendix 1

6.22.3 BIPM Consultative Committees

6.22.3.1 Consultative Committee for Amount of Substance – Metrology in Chemistry (CCQM)
Appendix 1

CCQM Working Group on Protein Analysis (PAWG)
Appendix 1

CCQM requested that IFCC participate in a number of their WG one of which is the WG on Protein Analysis (PAWG). KM has agreed to represent SD on this WG

KM summarised the situation (Appendix 10a):

Growth Hormone is an area of interest and there is scope for collaboration.

Another area is HbA1c and suggested GJ would be appropriate to take this forward. GJ advised that the C-EUBD is now chaired by Dr E. English. It was questioned why CCQM was revisiting HbA1c as standardisation of this analyte is finalised.

IY suggests they look at IHCLR data base and pick a high priority measurand. CC spoke in support of selecting measurands with a clinical need especially as they are sponsoring for the EU collaboration with Lab Med.

PG commented that the CCQM recognises the importance of collaboration with IFCC-SD. CC suggested that we could use their facilities as Candidate Reference Measurement Labs, and we should work on a structured plan.

Next study they are to undertake is standardisation of BNP (Milena Quaglia). The candidate method is given in Appendix 10f. This will need participation from IFCC as samples likely to be used are not clinical samples. Also KM was unsure if the RM is appropriate CC stated that this is part of the EU Cardiomet project run by PTB and she is part of the study; CC stated in her experience they Would benefit from IFCC-SD lab med knowledge.

IY commented that he has been discussing the situation of various BNP and is happy to pick this up in his discussions. IY asked should this be a liaison of should there be more active involvement. KM asked should SD create a WG; but IY was worried there may be overlap. GM commented that CCQM should focus on the issues related to BNP measurement in the clinical situation (eg stability). There needs to be a clear position as to what CCQM want assistance with.

IY asked if there will be a joint IFCC CCQM WG; a decision will be made following further discussion.

KM reported that there was much discussion related to SARS-COV-2 Ab quantification.

6.22.3.2 CC for Units (CCU)
Appendix 1

There was no discussion on this item

6.23. INTERNATIONAL STANDARDS ORGANIZATION (ISO)

Appendix 1

IY reported the Committee on Reference Materials has been disbanded, and Published documents and current projects have been transferred to TC 334. One document is out for consultation on reference materials for particle size measurement; may be relevant for haematological methods and PCR related methods as well as infectious diseases.

6.31 JOINT RESEARCH CENTER (JRC)

LD submitted a status report on the CRM projects of the JRC in collaboration with the IFCC (June 2021).

1. CRMs for auto immune disorders [IFCC Committee on Harmonization of Autoimmune Tests (C-HAT)]

1.1 CRM for IgG anti-B2GP (antiphospholipid syndrome (APS)): ERM-DA477/IFCC
The matrix CRM has been intensively studied for commutability and the commutability is considered to be good (https://www.degruyter.com/document/doi/10.1515/cclm-2020-0995/html). However, the purified antibodies (intended to be used as a pure calibrant) seems to be non-commutable. Therefore, it was decided to work with arbitrary values. The material will be submitted to the WHO as a candidate for the international standard in spring 2022. If accepted the WHO will assign the arbitrary values. NIBSC has agreed to act as mediator and custodian of only a small part of the batch. JRC will take care of the distribution of the CRM to IVD manufacturers and clinical laboratories.

1.2 CRM for IgG and IgA anti tissue transglutaminase (anti-tTG) (Coeliac disease): ERM-DA487/IFCC
Several possible starting materials have been investigated in commutability study for both tTG IgA and tTG IgG. Based on the results the most suitable starting material was selected and a large amount was purchased. Processing of the material is planned for September 2021.

1.3 CRM for IgG anti-GBM (vasculitis): ERM-DA484/IFCC
A new commutability study was performed on three potential starting materials. Based on the results the most suitable starting material will be selected and a large amount will be purchased. Processing of the material is planned for the last quarter of 2021.

2. CRMs for CSF proteins [IFCC Working Group on CSF proteins (WG-CSF)]

2.1 CRM for Aβ1-42 in CSF: ERM-DA480/IFCC, ERM-DA481/IFCC, ERM-DA482/IFCC
The CRMs were released at the end of 2017. Re-calibration of commercial assays using the CRMs has been completed and a round-robin study has been organised to see the effect of re-calibration on the measurement of patient samples. The results are currently under discussion and will be presented at the next GBSC meeting during the AAIC conference in Denver summer 2021.
A paper on the release of the CRMs plus re-calibration of commercial immunoassays was published in the journal of the Alzheimer Association: Alzheimer and dementia (https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12145)

2.2 CRM for Aβ1-40 in CSF: ERM-DA480/IFCC, ERM-DA481/IFCC, ERM-DA482/IFCC
Studies to evaluate if the existing CRMs (ERM-DA480/IFCC, ERM-DA481/IFCC and ERM-DA482/IFCC) can also be certified for Aβ1-40 are ongoing. Homogeneity, short and long-term stability have been tested and results are good.
A calibrant peptide has been selected and quantified with amino acid analysis (AAA) by LNE, LGC and JRC. Purity assessment is ongoing in collaboration with LNE and LGC. The impurities have been identified, the quantification is planned for June/July 2021 and the final value assignment for August/September 2021.
A round-robin study of mass spectrometric candidate reference methods for CSF beta-amyloid 1-40 is currently organised by the IFCC WG on CSF protein with the aim to develop reference measurement procedures (RMPs). Four laboratories will participate and CRM that will be measured have been provided by the JRC.

2.3 CRM for Tau project: Development of a reference system for Tau
Within the IFCC WG on CSF protein laboratories are currently working on the development of reference measurement procedures (RMPs). A commutability study has also been organised. The University of Gothenburg (UGot) has developed an antibody-free MS method to measure several phospho- and non-phosphorylated peptides from Tau in CSF and this method might be a candidate reference method.
The JRC is involved in the measurement by AAA of potential calibrants. In the future, we might also be involved in the production of a CRM for the quantification of Tau protein in CSF.

2.4 Neurofilament light (Nfl): Project for the standardization of Nfl in blood (possibly in CSF).
A commutability study has been carried out by the IFCC WG on plasma/serum Nfl. In the study, samples from 40 patients were analysed on six platforms/assays and a few candidate CRMs were included. The results look encouraging, particularly with CSF spiked into serum/plasma.
In March 2021, UGot made a proposal to involve the JRC on the possibility to proceed with a future reference materials project. JRC is interested, but can only commit after having recruited of a new Contract Agent.

3. CRMs for Haemoglobin A2 [IFCC Working Group on Standardisation of Haemoglobin A2 (WG-HbA2)]

3.1 CRM for HbA2: ERM-DA485/IFCC and ERM-DA486/IFCC
For the calibrant materials: Recombinant haemoglobins (rHbA and rHbA2) have been purchased by JRC. The materials have been purified by PTB and 2 stock solutions have been prepared. These stock solutions have been quantified with amino acid analysis by JRC and PTB.
For the matrix CRM: 10 blood donations (4 with normal HbA2 levels and 6 with elevated HbA2 levels) have been processed into stabilised haemolysates. The final steps in the processing process (pooling, filling and lyophilisation) are planned in June 2021.

4. CRMs for apolipoproteins [IFCC Working Group on apolipoproteins by Mass Spectrometry (WG-APO MS)]
For the peptide calibrators for Lp(a): The JRC has produced the first batches of peptides calibrators that can be used to investigate the completeness of the digestion of Apo(a) in the candidate RMP. The purity check and AAA measurement on the peptides calibrators will be done by the JRC and LNE.

For the serum CRM for Lp(a): several candidate RM have been investigated in a commutability study. Results of this study indicate that CRM based on pools of human serums have the best commutability profile.

5. Work on standardisation/harmonization faecal immunochemical testing [IFCC working group in Faecal Immunochemical Testing [WG-FIT)]

A correlation/commutability study protocol was written and ratified by the IFCC-FIT WG. The analytical work has been carried out at the Bowel cancer screening hub in Guildford, UK. The JRC provided support by drafting the study protocol and performing the statistical evaluation of the results. The results of this study will be important to decide if the current FIT assays can be harmonised/standardized and which type of reference materials can be commutable with real life samples.

6. CRMs for enzymes [IFCC working Group on Pancreatic Enzymes (WG-PE)]

The JRC has received the request to produce a CRM for the catalytic activity for alkaline phosphatase (ALP). This request has been accepted in February 2020 but due to the COVID-19 crisis, the project had to be placed on hold.

There were no comments on the report.

6.33 NATIONAL INSTITUTE OF BIOLOGICAL STANDARDS AND CONTROL (NIBSC)

Update by Chris Burns

CB reported that NIBS have been focussed on the COVID response, both in terms of preparing reference standards (reported previously), and in terms of the vaccine testing and deployment. Many projects have been deprioritised including some reference standard projects.

NIBSC has been heavily involved in the UK and global response to Covid19 since February/March 2020. Many work programmes continue to be de-prioritised, but medicines-testing activities and standardisation activities continue – although outputs for the year are reduced as a result. The table below represents **draft list** of new International Standards that will be established by WHO at ECBS in October 2021. Additional projects may be added if collaborative study data is received in time. Projects of potential relevance to the work of the SD are shown in bold. More details can be provided for specific projects upon request.

International Standards to be established

Project title	NIBSC Division	Project class
2nd IS for Diphtheria Antitoxin Equine	Bacteriology	Replacement WHO Standard
1st IS for Mycobacterium tuberculosis DNA	Bacteriology	New WHO Standard
3rd IS for VWF concentrate	Biotherapeutics	Replacement WHO Standard
4th IS Ferritin (human, recombinant)	Biotherapeutics	Replacement WHO Standard
1st IS for anti-thyroid peroxidase antibodies	Biotherapeutics	New WHO Standard
3rd WHO IS for Follicle Stimulating Hormone, human, recombinant	Biotherapeutics	Replacement WHO Standard
1st IS VZV DNA	Infectious Disease Diagnostics	New WHO Standard
1st IS for Lassa virus antibody	Virology	New WHO Standard

Additional activities of note

4th WHO IS for pituitary TSH

The current 3rd WHO International Standard (IS), 81/565, established in 2003, is a native TSH preparation, stocks of which are depleting and, at the current rate of sales, will be exhausted in 2022. As a result, there is now a requirement to prepare a replacement; the 4th WHO IS.
There are well-established problems with the commutability of the IS, 81/565, in current TSH immunoassays, which have resulted in a lack of harmonization of TSH measurements between methods/laboratories. A Committee for the Standardisation of Thyroid Function Tests (C-STFT) was established by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to address this issue. C-STFT have focused their efforts on harmonization of TSH measurements based on a multi-assay method comparison study using a panel of clinical serum samples, calibrated in IU. The need to replace the IS coincides with the replacement of the IFCC serum panel for harmonization of TSH measurements. We have been working with the C-STFT to distribute their panels of samples and we are proposing a joint study for the replacement of these materials.
It is expected that the IS will continue to co-exist with IFCC serum panel. The IFCC panel will continue to be used to ensure harmonisation of TSH measurements between methods/laboratories. Meanwhile, the IS will continue to find use as the physical definition of the IU, as a globally available stable reference material for TSH and for manufacturers to use for internal quality control purposes (e.g. verification of immunoassay performance).

European Metrology Network on Traceability in Laboratory Medicine – TraceLabMed

NIBSC continues to be a member – EMN contribution to JCTLM here: https://www.linkedin.com/feed/update/urn:li:activity:6801094127200038912/
Replacement panel for TSH will ensure continuity. Currently discussion is going on between NIBSC and Hubert about study organisation; when the reference material is taken to WHO it will be a joint proposal between NIBSC and the IFCC WG.

6.37 NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST)

NIST's lab activities remain limited because of the COVID-19 pandemic. Status information on RM/SRM projects that may be of interest are included in the table.

NIST Clinical Certified Reference Materials; June 2021 update reflecting changes within the last 12 months.

Analyte	NIST Identifier	Release Date	Description
Glucose in Frozen Human Serum	SRM 965c	2022	• Renewal material • Material acquisition in progress
Creatinine in Frozen Human Serum – Low Level	SRM 967b	2022	• Renewal material • Material acquisition in progress
Bovine Serum Albumin (7% solution)	SRM 927f	Summer 2021	• Renewal of SRM 927e • Certification measurements in progress
Human Cardiac Troponin Complex	SRM 2921a	Late 2021	• Renewal of SRM 2921
^{15}N-Labeled Recombinant Human Insulin-like Growth Factor 1	SRM 2927	July 2020	• New reference material
Toxic Metals and Metabolites in Frozen Human Blood	SRM 955d	July 2020	• New matrix (human not caprine)
Vitamin D Metabolites in Frozen Human Serum (Total 25-Hydroxyvitamin D Low Level)	SRM 2969	Summer 2021	• Certification measurements complete • Lower concentration of 25(OH)D than SRM 972a
Vitamin D Metabolites in Frozen Human Serum (25-Hydroxyvitamin D2 High Level)	SRM 2970	Summer 2021	• Certification measurements complete • Higher concentration of 25(OH)D_2 than SRM 972a
Albumin and Creatinine in Frozen Human Urine	SRM 3666	Late 2021	• Certification measurements in progress
Homocysteine in Frozen Human Serum	SRM 1955a	2022	• Material acquisition in progress
Cardiac Troponin I in Frozen Human Plasma	RM 8121	2021	• Material acquisition
Electrolytes in Frozen Human Serum	SRM 956e	2022	• Material acquisition
Bilirubin	SRM 916b	Summer 2021	• Renewal of SRM 916a • Certification measurements in progress
Glucose	SRM 917d	Late 2021	• Renewal of SRM 917c • Procurement of material in progress
Cortisol	SRM 921a	July 2020	• Renewal of SRM 921
Tripalmitin	SRM 1595a	2022	• Renewal of SRM 1595 • Procurement of material in progress
JC Virus DNA Quantitative Standard	SRM 2367	Late 2021	• Candidate materials acquired

			• Certification measurements in progress
SARS CoV-2 Synthetic RNA Fragments	RGTM 10169	June 2020	• Distributed and awaiting feedback on material properties
COVID-19 Serology	RGTM 10196	Late 2021	• Material acquisition in progress

6.38 THE INTERNATIONAL CONSORTIUM FOR HARMONIZATION OF CLINICAL LABORATORY RESULTS (ICHCLR)

IY reported that the IFCC/ ICHCLR has continued its work; the harmonisation oversight group meets monthly and has added around 15 measurands to the data base this year. Additionally looking at measurands previously listed and revised the documentation; BNP being an example.

A Memorandum of Agreement has been signed with EQALM and 2 sub groups established; one to help define commutability criteria for EQA materials (chair GM) and one to define a core data set which will be sought from EQA schemes in order to inform assessment of comparability between assays (Chair Tony Killeen).

IFCC are considering if there should be any modifications to the existing MOU; ICHLR has suggested the possibility if groups are successful with funding of establishing WG that would report through the SD structure.

ICHCLR has written to clinical societies with a view to establishing greater liaison and involvement of clinicians to identify potential measurands that clinical groups consider would benefit from harmonisation.

8.2 MAIN ACTIVITIES OF COMMITTEES

8.2.6 C-NOMENCLATURE, PROPERTIES AND UNITS (C-NPU) - Appendix 1

Video Meeting on 6th April 2021

Present: Prof P. Gillery (PG); Prof G. John (GJ); Prof I. Young (IY); Dr Y.B.L. Hansen (YH)

YH introduced himself as the new chair of C-NPD and give a summary of his background.
C-NPU has 5 members including the chair, and works in in collaboration with International Union of Pure and Applied Chemistry (IUPAC)
There is a steering committee that will support the continued development of NPU Terminology.

YB outlined the current ToR and discussed the need for change. Historically C-NPU has worked closely with the Nordic region; while continuing to work in this region, would like the committees influence be expanded into wider geographical areas.

There are obstacles to overcome with expansion, notably many countries and regions have national guidelines for terminology (SNOMED CT, LOINC etc) relating to IT regulations.
Try to get more involved in Laboratory informatics; develop a clear understanding of need and agreement on terminology.

IY added some additional information regarding the NPU data base; there are two issues:

Potential alliance with SNOMED; this was discussed 7-8 years ago. Two competing data bases LOINC and CNPU the latter has some advantages particularly in relation to definition of measurand but LOINC is more widely used. SNOMED has developed a mapping process with LOINC which enables SNOMED to offer LOINC functionalities in areas where SNOMED is used. SNOMED now wishes to create a liaison with CNPU which will allow it to used CNPU functionality as an alternative or in addition in countries were LOINC operates. There is an advantage to SNOMED in this and probably some advantages to CNPU; CNPU are interested in progressing this.

GM suggested is this an opportunity to recommend the world adopt one system. IY recognises the advantage to this and if starting from scratch this is what would be done; but Scandinavian counties are wedded to CNPU whereas most of the rest of the world use LOINC. IFCC has been involved with CNPU for many years and recognises that it is predominantly a regional activity; it would be very costly for the Scandinavian countries to switch to LOINC.

8.2.11 C-MOLECULAR DIAGNOSTICS (C-MD) - Appendix 1
Video Meeting on 20th April 2021
Present: Prof P. Gillery (PG); Prof C. Cobbaert (CC); Dr B. Das (BD); Prof G. John (GJ); Prof P. Ahmad-Nejad (PA-N)
PA-N would like to change the ToR to include:

- to evaluate the current status of molecular SARS-CoV2 testing worldwide
- surveys providing information about SARS CoV2 testing and cT-DNA in routine diagnostics

Suggested ToR:

- provide reports about the current status quo in MDX
- To produce guidelines on molecular techniques and their validation for routine diagnostics
- To create a network of locus-specific IFCC Molecular Diagnostics Centres

Current Projects:

- *surveys providing information about SARS CoV2 testing and ct-DNA in routine diagnostics;* EQA update
- Guidelines: how to set up PCR/ Primer Design/ RFLP/ ct-DNA Assay/… how to validate…how to report → cooperation with C-CMBC?
- Establish an International Network of IFCC Reference Centres in Molecular Diagnostics→ feedback needed/really working?

8.2.23 C-TRACEABILITY IN LABORATORY MEDICINE (C-TLM)

- Data entry of RELA 2021 is closed since end of May. We received more than 680 results which have to be evaluated within the next weeks.
- We still have to search for the different results of RELA2020, HbA1c. The samples had been measured by the participants for a 2nd time and these results will now be compared with the results of the first campaign.
- The procedure manual for RELA has to be revised by the members of C-TLM
- Next meeting: 29 November 2021, 14-18 h, EuroMedLab Munich

There were no special topics to discuss. There are many opportunities to develop the work of the committee. However, this is currently difficult due to a lack of resources.

8.2.24 C-REFERENCE INTERVALS AND DECISION LIMITS (C-RIDL) – Appendix 1
C-RIDL meeting has been planned on 28 November during the EUROMEDLAB 2021 in Munich.

Would like to invite the president of IFCC, Prof. Khosrow Adeli to the C-RIDL meeting in Munich to talk about 'The new IFCC Taskforce on Global Reference Interval Database' that was announced in the IFCC website that it will also work closely with the C-RIDL.

PG stated it is important that there is good communication between this committee and the new TF on Reference Intervals; although goals are different.

8.2.25 C-STANDARDIZATION OF THYROID FUNCTIONS TESTS (C-STFT)- Appendix
Second Interlab fT4 comparison study ongoing.
Development of Harmonisation sample set ongoing.
NIBSC will collaborate with C-STFT to coordinate TSH reference material development.
Stability assessment of current TSH panel complete. Statistical analysis awaited.

8.2.27 C-BONE METABOLISM (C-BM) – Appendix 1
Term of reference 1:

PTH standardization

CS has sent pools to EC's lab by the end of May for the commutability study. EC's team will perform the study in June 2021.

- RMP for PTH:
Candice Ulmer has presented the first results of the RMP LC-MS/MS method on which she's currently working at the CDC facilities. She will present the updates during the meeting of the C-BM that is planned on May 20th in Barcelona.

- Liaison with other societies: the C-BM is endorsed by the IOF and ERA-EDTA. No further initiatives have to be expected regarding this term of reference.

Contacts have been made with the Protein analysis Working group (PAWG) from the International Committee for Weights and Measures (CIPM). This Group is interested in PTH. Collaboration between C-BM and them would definitely be an added value.

Term of reference 2

Bone markers assays

The good commutability level of materials prepared by diluting IDS-Orion top dose with Roche Universal diluents were not confirmed when Roche top dose was diluted with Roche universal diluents.
The CVs obtained in EC's team hands with Orion RIA were are far too elevated, which does not allow formal statistical analysis and leads to too high rate of inconclusive levels

Conclusions of the PINP commutability study: IDS–Orion top dose diluted in Roche sample diluents is commutable with all the 3 assays. This should be used by manufacturers to harmonize the kits.

List accomplishments for PINP
A manuscript has been accepted in CCLM
An equation allowing harmonization has been proposed
A commutability study is ongoing
A study on biological variation of PINP and other markers on remaining samples from EuBIVAS has been performed, and a paper has been published.
An Editorial on PINP has been written.
A commutable calibrator has been defined.

List planned activities in 2020-2021 for PINP
Evaluate the opportunity to develop a RMP for PINP
Prepare commutable standard to calibrate the assays (with the help of the LNE)

- CTX

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

Samples have been exchanged between Greece and Belgium and run in the 2 labs: results confirm that the problem of the Cobas in GR were punctual and show a good agreement now between centres.

CTX has also been run on the EuBIVAS samples. MS has been published.

List accomplishments for CTX

Exchange samples between 2 centres: data presented in Paris

A study on biological variation of CTX on remaining samples from EuBIVAS has been performed and the paper has been published in Osteoporosis International.
Multicentre study results are completed

Term of reference 3:

Vitamin D metabolites assay standardization

A manuscript “Analytical Performance specifications for 25(OH)D examinations” has been accepted in Nutrients 2021 Jan 28;13(2);431
EC is working on a paper on the application of MU on NIST samples
EC is working on a paper on APS for 24,25(OH)2D
Collection of samples from pregnant women is ongoing

8.3 MAIN ACTIVITIES OF WORKING GROUPS

8.3.35 WG – STAND. OF HEMOGLOBIN A_2 (WG-SHbA_2) - Appendix 1

Candidate reference measurement procedure for HbA_2

The stock solutions of the recombinant haemoglobins to be used for calibration have been shipped to JRC for distribution to the four reference laboratories (2 in China and 2 in Germany). The JRC has endorsed a third party for the preparation of the documentation to be shipped to the Chinese customs.

Certified reference material (CRMs) for HbA_2

The stabilized haemolysates have been prepared before the Covid-19 lockdown at the JRC and are waiting for the lyophilisation, already scheduled for both levels (normal and high) before the end of June 2021. Approximately 3000 vials per level are expected. A first set of vials will be shipped soon afterwards to Milano for a preliminary characterization.

IFCC-ICSH joint group on standardization of HbA_2 – manufacturers

We keep constant contacts with the ICSH group, last information being sent to them on March 6th, 2021. An update on the production of the CRMs was sent to the manufacturers (attending the JCTLM meeting in Paris in December 2019) in date 9 April 2021.

KM commented most of the work has been done and WG collaborating with ICSH to implement this reference method. Are expecting reference material. LD commentated all donations are collected and pools will now be made and stability and value assignment will be performed.

8.3.36 WG - STAND. OF CARBOHYDRATE-DEF. TRANSFERRIN (WG-CDT) - Appendix 1

CC reported the WG is working with several manufacturers and in different countries. Chromsystems are working towards the endorsed CDC standardisation; Siemens are working on a comparability study. Sebia have developed several webinars to campaign for standardisation.

WG waiting on mediation; discussion ongoing about calculation of uncertainty; the IFCC endorsed CDT method is currently not JCTLM endorsed. Stephen Westward will mediate.

8.3.37 WG – STAND. OF ALBUMIN ASSAYS IN URINE (WG-SAU)

GM reported that this group has been relatively stagnant due to COVID. Recently GM talked with Jesse Seegmiller and J. Lieski who are now actively getting back to continuing the validation of the candidate reference procedures being developed. Most work has been done; major work now to transfer values from NIST material to working in house calibrators and to improve precision performance of MS method to meet requirements for uncertainty at the level of the reference procedures.

The goal to conduct a round robin exercise using authentic patients samples in early 2022 which will in addition include the NIST reference procedure which has been fully validated and a RMP from NMI in Singapore who have recently published a fully validated MS procedure. If the timelines are met, publications and submission to JCTLM should happen in May 2023.

8.3.40 WG – STAND. OF PREGNANCY-ASS. P-PROTEIN A (WG-PAPPA)

BD has had no communication from the Chair of this group. There has been no response and BD was wondering if email address is correct.

8.3.41 WG – GROWTH HORMONE (WG-hGH) - Appendix 1

P1 Defining the accuracy base for hGH standardization.
A mass-spectrometry (MS)-based RMS will be implemented. Christian Arsene has an isotope dilution mass spectroscopy based GH quantification assay up and running.
Method is also available at NML at LGC group. Both laboratories could and are willing to potentially serve as reference laboratories.

P2 Development of an MS-based Reference Measurement Procedure for the measurement of hGH.
See P1, method setup by Christian Arsene. Method can be used as a candidate RMP with standardization on 22kDa Growth Hormone isoform.
For the next meeting the requirements for the candidate RMP in relation to ISO17511, ISO15193, ISO15194 will be discussed.

P3 Establish the suitability of recombinant human growth hormone preparations as primary reference material with appropriate properties.
Use of 15N labelled GH as internal standard discussed. No further actions op P3 yet.

P4 Establish the performance of commercially available hGH assays compared to the MS-based RMP
Commutability study setup by Eef Lentjes. Protocol is ready for rollout. Still budget required for fee participants (participating donors & physician).

P5 Determination of the effect of freeze/thawing on measured hGH
No progress on P5.

CC has no information relating to harmonising methods mentioned in P1; we should not have two methods if possible.

Michel Vos will be the new chair of this committee; he is very active. The WG will discuss what is the best method to support the clinical need.

8.3.42 WG – STAND. OF INSULIN ASSAYS (WG-SIA)

CC commented on the report from Michael Steffes (below). GM was part of the meeting but CC could only partly join. There has been good progress on the MS method; this is a good candidate, but CC believes they do not align with IFCC goals. CC is unsure if they will develop an IFCC RMP, and has asked for an update on the IFCC goals for a candidate RMP.

Michael Steffes report: The meeting went very well, with some nice comments from colleagues at the US National Institutes of Health, our primary (and original) source of support. We have had additional interactions with those who presented. Jesse is leading the writing of a manuscript describing our work to develop an MS assay for insulin and the glargine analog and its metabolites. Overall the GRADE study, for which we developed the assay, will report results later this month at the American Diabetes Association meeting. In addition many GRADE manuscripts are planned with several at advanced stages. We are the Central Laboratory for GRADE, and we remain the Central Laboratory for DCCT/EDIC.

GM stated he has been involved with this for many years. Michael Steffes has several hundred clinical samples from patients who has insulin levels stimulated by a glucose drink and collected at different times; so a wide range of samples suitable to prepare a panel to be used as a

secondary reference material. There are two or three active groups setting up MS methods which could be used as a Network. Not sure the organization commitment is there to get JCTLM approval.

CC stressed her concern over the ongoing issue related to resources available to accomplish many of these tasks. GM stated that Michael Steffes probably sees this as a research activity rather than standardization imitative; CC also believes this to be the case.

8.3.49 WG – CSF Proteins (WG-CSF) - Appendix 1
Video Meeting on 24th April 2021
Present: Prof P. Gillery (PG); Prof C. Cobbaert (CC); Dr B. Das (BD); Prof G. John (GJ); Dr J. Gobom (JG)

Neurofilament light chain
JG discussed a promising new biomarker for neurodegeneration; Neurofilament light chain (Nfl) which can be measured both in the brain cerebrospinal fluid (CSF). The clinical relevance of this measurement is still being debated.
There is no standardisation of Nfl. There are many platforms (Manufacturers/in-house) but compare well. All are sandwich immunoassays. Nfl concentration is very low so methods need to be very sensitive.
Measurand not defined. Recombinant Nfl used as a standard but not performing well.

Tau Protein
Many different forms of Tau Protein.
Laboratories are producing vary different results. Difference may be due to the use of different Heavy Labelled Peptides. ? problems in producing Heavy Standards.
Attempt to develop a MS based Reference Method. Measure Total Tau Protein not phospho-Tau

8.3.51 WG- COMMUTABILITY IN METROLOGICAL TRACEABILITY (WG-CMT)
GM reported working on draft manuscripts for recommendations around criteria for commutability assessment for CRMs and for EQA materials. EQA materials has required rethink how to assess commutability for these materials. Overall good progress.

8.3.53 WG-IMMUUNOSUPPRESSIVE DRUGS (WG-ID) – Appendix 1
Video Meeting on 24th April 2021 (minutes GJ)
Present: Prof P. Gillery (PG); Prof C. Cobbaert (CC); Prof G. John (GJ); Dr C. Seger (CS).
Following its formation in 2018 CS reported that the WG had been very active, but activities have been stopped due to the COVID pandemic. Most members of the WG-ID are active members of the IATDMCT (Immunosuppressive Drugs Committee).
Immunoassay methods were discussed in depth; should these methods be discontinued from clinical use. They have significant cross reactivity; reference material is not commutable to immunoassays
Calibrators remain a problem as they have to be whole blood.
Many members use LC-MS for their ISD-TDM service. The higher level of imprecision may mean that LC-MS is not superior to HPLC.
The Isotope Dilution MS/MS Reference Methods published by Taibon et al for:

- Cyclosporin A
- Tacrolimus
- Sirolimus
- Everolimus

are listed by JCTLM
Method needs verification by independent laboratories.
Currently there is no active Laboratory Network.

8.3.54 WG – APOLIPOPROTEINS BY MASS SPECTROMETRY (WG APO-MS) - Appendix 1
CC commented that the WG has progressed well; focused on Lp(a) standardisation which is independent on kringle size or polymorphism. Now have a harmonised Standardised RMP which will be published soon; there has been a commutability study performed twice with different

reference materials with different numbers of kringles. Native pools will be chosen as reference material. This is a difficult analyte. It is hoped the candidate RMP and the commutability data for the choice of reference materials written up within the next few months.

8.3.55 WG - PANCREATIC ENZYMES (WG-PE)

CC commented business as usual. They will do a survey this summer based on comments from SD; some countries use Lipase whereas now they use Pancreatic Amylase; they will chart that.

8.3.56 WG FECAL IMMUNOCHEMICAL TESTING (WG-FIT) - Appendix 1

PG reported that the WG is working on a harmonisation study, results to be available at the end of June, and will be discussed during the next meeting.

Sally Benton prepared a report:

Meetings

- The whole FIT-WG last met in October 2020 via zoom. This meeting was well attended as always with over 20 attendees representing all corporate companies involved in the group and group members. The main areas of discussion were
    - Preparation of a publication for CCA journal summarising the work of the group
    - Harmonisation study
- The group intend to have a face to face meeting at the end of November 2021 at the Euromedlab congress in Munich

Projects

- Harmonisation study – the group are coming to the end of a harmonisation study. All analytical work has been carried out and the results are being reviewed for discussion later in June. A final report will be prepared by the sub group and this then shared with the whole group, including the manufacturers of FIT methods. This work will enable the group to consider whether the FIT for Hb assays can be harmonised.

8.3.58 WG STANDARDIZATION OF PROCALCITONIN ASSAYS (WG-PCT)- Appendix 1

KM stated WG progressing well; method has been developed but there is a problem with sensitivity; focussing on sample preparation to work on this. There is a publication, not of a candidate RMP but on the preparation of samples to be applied to method they have developed.

The second ToR is to document the variability of commercial methods for PCT. These are divided into Brahms and new methods; sample collection is difficult to perform a commutability sturdy and also a variability study.

Their third ToR is a little controversial; this is to investigate standardisation especially those standardised to Brahms. There is a lot of negative reaction from companies. MR commented the negative reaction is relative depending on the standardisation used; discussion is around recovery in native and spiked samples. Brahms state that when there is RMP (LC/MS or other) there will be a general shift in values which will result in a change in clinical cut offs.

PG stated the Manufacturers are important in the continuation of this programme.

8.3 60 WG CONTINUOUS GLUCOSE MONITORING (WG-CGM)- Appendix 1

KM made reference to the flow chart in Appendix 29d. This WG will look at traceability of CGMs; Issues are outlined in the flow chart. There are problems related to standardisation; a secondary reference methods needs to be specified.

The issue is the CGMs measure glucose in interstitial fluid not blood (as glucose meters do); statistical methods have to be developed.

PG stated this WG will be discussed in more detail at next meeting.

8.3.61 WG DEVELOPMENT OF A REFERENCE MEASUREMENT SYSTEM FOR SUSTAINABLE PT/INR STANDARDIZATION (WG PT/INR) - Appendix 1

MoU signed

This WG was not discussed.

8.8 PROJECT PROPOSALS

Project proposal on **"Laboratory Calculated tests: Quality Regulation, Validation and Implementation"**- **Appendix 31**
Not discussed – Comments will have to be sent to PG.