The Committee for Standardization of Thyroid Function Tests (C-STFT) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

IFCC C-STFT 2019 MEETING

WEDNESDAY, NOVEMBER 6 – THURSDAY, NOVEMBER 7, 2019
GENT UNIVERSITY

Meeting Minutes

List of Participants

Hubert Vesper (Chair, CDC, USA), Katleen Van Uytfanghe (UGent Ref Lab Network, Belgium), Uliana Danilenko (CDC Ref Lab Network, USA), David Halsall (Cambridge University Hospital Trust, UK); Iris Erlund (National Institute for Health and Welfare, Finland); Veronique Raverot (Hospices Civils de Lyon, France); Gordon Avery (Abbott, UK); Paul Sibley (Siemens, UK), Maria Patru (ORTHO, US), Jean-Sebastien Blanchet (representing Annette Adelmann, Beckman Coulter, France); Michael Rottmann (Roche, Germany); Teun van Herwaarden (Nijmegen Ref Lab Network, The Netherlands); Caroline Robberecht (representing Stefaan Marivoet, Tosoh, Belgium); Valentina Vidranski (UHC Sestre milosrdnice, Croatia); Derrick Xu (representing Vincent Chen, Snibe, China); Fidelia Pokuah (CDC Ref Lab Network, USA); Els Huyck (representing Vesna Kostanjevecki, Fujirebio, Japan)
Virtual participants: Annette Adelmann (Beckman Coulter); Jens Berg (Oslo university hospital, Norway)

1. Welcome and Roll Call

2. Reference Network Laboratory for FT4: consensus Reference Measurement Procedure (cRMP)

An overview of the Free Thyroxine cRMP and experiences with its implementation was given by Dr. Uliana Danilenko, of the CDC Ref Network Lab. Key points:

- cRMP employs Equilibrium Dialysis (ED) followed by ID-LC/MS/MS calibrated with certified reference material IRMM 468.
- Key parameters of ED (dilution, pH, temperature and ED time) have to follow the convention for consistent measurement results.
- ED time of 4 hours is sufficient to reach complete equilibrium dialysis; less time leads to inaccurate measurement, over 4 hours shows no major changes in results (these conditions are for the particular design of the dialysis cells used in this procedure).
- cRMP for FT4 has a high level of specificity through optimized chromatography
- Preanalytical factors such as the type of labware used with the cRMP can lead to loss of analyte, decreased sensitivity and inaccurate measurements
- Despite minor operational differences (in steps other than ED), FT4 reference laboratories demonstrate excellent agreement.

Reference laboratory network **candidates** are:
Ref4U *(Belgium),* ***CDC Clinical Reference Laboratories*** *(USA),* ***Radboud University Medical Center of Nijmegen*** *(The Netherlands), and* ***Reference Material Institute for Clinical Chemistry Standards*** *(Japan)*

Additional notes:
We would like to encourage more labs to join as Reference Laboratory Network. Candidate laboratories need to be able to achieve the analytical accuracy, imprecision and LOD for the cRMP. See presentation and info below for further details on requirements.

3. Reference Network Laboratory for FT4: Interlaboratory Comparison Study Update

Dr. Van Uytfanghe provided a summary of the previous study and a description of the ongoing study with some initial findings. Key findings:

- From the pilot method comparison, there is good agreement between the different labs. Measurement bias to the all method mean was within ±2.5% bias. Based on the data obtained in this study, calibration presumably is the major cause for bias.
- The first, ongoing method comparison includes samples covering the hypo-, eu- and hyperthyroid concentration range (3 – 121 pg/mL). All samples are unmodified sera from individual donors.
- Preliminary results from 2 laboratories were presented. The mean bias between both laboratories is about 1.4% and the imprecision is about 3% CV. Both methods used completely independent calibration.
- Timelines: given the workload of member laboratories, we anticipate the report on the ongoing method comparison study by May 2020.
- As a side note:
  The laboratory in Nijmegen uses immunoassays for routine measurements, and symmetrical dialysis when the result from the immunoassays need to be verified. In future, the laboratory is considering switching to a modified version of the cRMP to replace the symmetrical dialysis.

4. Reference Network Laboratory for FT4: Network organization

Dr. Vesper provided an outline of proposed network structure and operation including analytical performance criteria for network laboratories. Key points:

- The aim of the reference laboratory network is to ensure consistent accuracy and traceability of RMP measurements over time, and to increase RMP laboratory capacity for manufacturers and laboratories.
- The suggested analytical performance requirements for the FT4 RMP are:
  Imprecision: ≤5%,
  Bias: ±2.5%,
  Expanded measurement uncertainty: 7.6%,
  LoQ: 1.3 pmol/L (0.10 ng/dL) and an LoD: 0.5 pmol/L (0.04 ng/dL)
- To join network, laboratory must be able to perform cRMP and meet analytical performance criteria. In addition, it was suggested that candidates need to participate successfully in two conservative network studies. Further it was suggested that network member laboratories need to successfully pass studies to continue participation and participate in regular meetings/ communications.

- The proposed network study design: 2 challenges per year, 5-10 samples per challenge with 2 replicates per day on 2 days, use of common QCs and calibrators
- Candidate laboratories should also be trained in understanding the background and rationales behind the convention of the cRMP. E.g. pH is determining the equilibrium between bound and free T4, therefore the pH of the sample before ED should be set to 7.4 (at 37°C). Perhaps, this kind of training should also be shared with clinical labs wanting to adopt a FT4 ED based LC/MS procedure.

During the discussion, it was emphasized that the focus of this standardization work is on analytical performance, expressed i.e., in bias to the cRMP and imprecision. Thus, manufacturers and laboratories can use any technology or antibody they deem most suitable for their purpose.

5. TSH Harmonization: Preparation of 3rd TSH Harmonization Panel

Dr. Van Uytfanghe presented a draft for the protocol for creating 3rd panel.

During the discussion, it was pointed out that the panel should be as similar as possible to the previous panels to avoid any risk of jeopardizing comparability of results between the different panels used in time. Therefore, the following were suggested:

- Not to change the protocol regarding in- or exclusion criteria, but gather more information on the samples collected (e.g. add biotin explicitly to the overview with information on supplements taken)
- The group agreed to have 500 µL aliquots.

Next steps:

- Share the draft protocol to the committee and start contacting collection sites.
- Work with collection sites to help with ethics review and other procedures

5. Updates on national/regional efforts to standardize and harmonize thyroid function tests

Dr. Vesper presented an update on activities and experiences in selected countries such as the U.S. and Japan. This was followed by a discussion on expanding efforts to other countries/regions.

U.S.

- CDC Clinical Standardization Programs are working on a standardization program for thyroid function tests (FT4 only at this point) with projected launch in late spring of 2020; CDC Clinical Reference Laboratory for FT4 can assign target values to individual donor samples and provide samples to participants – official announcement to be made.
- CDC already assigned target values to College of American Pathologists (CAP) accuracy-based survey for thyroid function tests; the survey uses materials prepared according to CSLI 37 using single donor, non-pooled sera. However, it was found that with the samples selected at this point, the concentration range in the CAP survey was too small.
- American Thyroid Association formed a working group to review analytical performance criteria for FT4 and TSH; data on Westgard website is over 30 years old and need to be reviewed to

ensure that it is still accurate for current assays and populations. We do not have information on the timelines of this working group.

- Partnership for the Accurate Testing of Hormones (PATH) – released list of priority analytes to be standardized. TSH and FT4 are among the top of list.
- As we work on implementing standardization for FT4, this will involve a significant shift in values. Prof. Thienpont performed a survey among professional organizations and physicians on whether this shift will be of concern for patient care. Dr. Vesper will compile the information. Initial review of the information suggests that there are no major concerns in changing the values. Info from the survey will be provided to stakeholders to support the proposed recalibration process.

Japan

- Japan is making fast progress on TSH harmonization and completed their study on harmonized reference intervals for TSH.
- Initial findings suggest that the harmonization procedure is suitable and can be used to ensure comparable results over time.
- The group hopes to be able to view the final report on TSH in May 2020 at the IFCC WorldLab 2020 meeting in Seoul/South Korea.
- The committee reached out to IFCC C-RIDL to coordinate work on reference intervals. So far, no response was received.
- The group discussed the best way to determine reference intervals, and the type of factors to consider such as circadian variation, or geographic location of blood collection (i.e., iodine deficient regions).
  The group agreed that reference intervals should be used together with other clinical signs and symptoms and should not be used as the only clinical decision tool.

China

- The group would like to have a better understanding on how standardization is implemented in China. Prof. Thienpont once had a discussion with the Chinese FDA, but the group has no information whether additional actions towards standardization have been initiated in China. Mr. Derrick Xu will follow up on Chinese harmonization and standardization activities and will get back to the group with a report.
- The group would like to encourage manufacturers to participate in the Seoul meeting. Dr. Maria Patru suggested that her Chinese colleague could help with translation if needed.

Australia

- No updates were available about their reference interval project. Dr. Vesper will reach out to collect information.

Europe

- The group emphasized that standardization/harmonization activities need to be in line/support compliance with the new IVD regulation (effective May 2022).
- EUthyroid Project: A big epidemiological study towards the elimination of iodine deficiency and preventable thyroid-related diseases in Europe. Ideally, we want to ensure that the PIs use standardized tests so that results will be aligned with standardized tests used in patient care. (It

was pointed out that the same applies to large studies in other countries e.g. NHANES in the U.S.). EUthyroid is interested to know when standardized FT4 test would become available.

Nepal

- There has been a request from Nepal to provide a system and share experience in harmonizing results. The request has also been forwarded to Dr. Philippe Gillery, the SD chair, and the IFCC C-RIDL. It is planned to discuss this project further at the meeting in Seoul/South Korea.

Croatia

- It was reported that in Croatia there is another project ongoing to develop reference intervals.
- A subset of samples from 140 patients is collected along with other relevant clinical information.
- 5 manufacturers will be included for measurement of TSH, FT4 and thyroid antibodies.
- Results from this study are anticipated in May 2020.
- There is an interest in having these reference ranges standardized as well.
- Further discussions are needed to define approaches for aligning these reference intervals with the IFCC reference system.

Finland

- Finland will have a follow-up of its 2000-2011 studies in 2022, inviting 10,000 participants. In addition, a special cohort with teenagers and children will be added.
- The PI would like to have the study aligned to the IFCC reference system. Further communications will occur to discuss potential approaches to achieve alignment.

The committee discussed further:

- Timelines for implementation of standardized FT4 tests:
  The group agreed that it is very unlikely to introduce a change in calibration and alignment to the IFCC system at one specific time point because of differences in how manufacturers operate and different requirements from country specific regulatory agencies. The educational activities conducted by C-STFT, initiated by Prof. Thienpont, will continue to inform stakeholders about the changes occurring as a result of standardization/harmonization.
- The group agreed to reach out to EQA providers who try using accuracy-based surveys to make sure target values are assigned with cRMPs and harmonization protocols.

6. Educational Activities and Website

Educating the clinical, public health and regulatory stakeholders about the work performed to standardized and harmonize thyroid function tests remains an important topic.

- It was suggested to invite FDA representatives to meetings to inform them about the standardization activities and related changes in measurement results.
- The group agreed that there is a further need to educate physicians, end-users on recalibrations of results.
- Website content should be reviewed to provide information suitable for non-scientific audiences (https://ifcc-cstft.org/).

- The group will reach out to national professional organizations in order to better inform these groups about the work and related changes in measurement results.

7. Next Meetings

- It was recommended that separate meetings outside of scientific meetings are more valuable to have. Anyone willing to host next year's meeting can volunteer. Ghent is willing to host 2020 meeting.
- The committee will have a meeting at the IFCC WorldLab in Seoul in 2020 on Monday May 25th.

8. Information provided with these minutes

1. Presentations given at the meeting
2. Contact information of participants
3. Group picture