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

AACC 2018 Annual Meeting Notes

07/30/18 (5:30 PM-7:30 PM)

Speaker: Hubert Vesper, PhD – The C-STFT

Introduction of new committee members

Update on the current committee members and corresponding members nominated by National Societies. An overview can be found at http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/.

Summary of Previous Progress

- The previous committee made progress with establishing a system to maintain traceability of free thyroid hormone and TSH measurements-now, it is time to implement these systems.
- A network of laboratories operating the FT4 RMP (4 labs in network) is being established.
- There are panels of individual donor samples with reference values assigned (FT4; TSH), and network labs will be contacted for future assignment of sample panels. The table below provides an overview of the remaining sets of samples, currently stored at the NIBSC:

Panel	number of sets left	stored at	content
TSH harmonization panel	5	NIBSC	2 times 0.5 mL
FT4 standardization panel	1	NIBSC	2 times 0.5 mL
TSH follow-up panel	30	NIBSC	1 times 0.5 mL
FT4 follow-up panel	32	NIBSC	1 times 0.5 mL
TSH reference interval panel	25	NIBSC	1 times 0.5 mL
FT4 reference interval panel	17	NIBSC	1 times 0.5 mL

Present and Future Progress

The terms of reference, see http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/, have changed. The focus is now on implementation and sustainability.

Coordination of Programs

- Need to link national and regional standardization/harmonization programs to the reference system established by the C-STFT
- CDC intends to develop a program like their current standardization programs for Testosterone and Estradiol, which will be linked to the C-STFT through CDC's participation in the C-STFT reference laboratory network.
- In Japan, a harmonization project is currently on-going. Our TSH harmonization project was presented to the government officials in the Ministry of Health, Labour and Welfare on behalf of four scientific societies, Japan Thyroid Association, Japan Society of Clinical Chemistry, Japanese Society of Laboratory

Medicine, and Japanese Committee for Clinical Laboratory Standards, the government officials contacted Japan Association of Clinical Reagents Industries (JACRI) in order to explore the practical issues to discuss the IVD companies. The government agreed that IVD companies present conversion factors when they do not change the reagent systems. JACRI expressed concerns about the reference intervals reported in Clinical Chemistry because the study was performed in the Caucasian population. Therefore, a project to develop Japanese RI is running. In this project, 10 different manufacturers, which sell their products to the Japanese market will participate. The samples to establish the RI are currently collected and will be measured under the same conditions as the samples for the RI which the C-STFT published in Clin. Chem, i.e. with the technically harmonized TSH-assays.
Also, ReCCS, Japan is part of the C-STFT reference laboratory network making sure standardization efforts in Japan are linked to the C-STFT.

- In addition to working with measurements performed in patient care, there is a need to support clinical and epidemiological studies to ensure study data are traceable to the established reference measurement systems.
- C-STFT will support PT programs in order to make them traceable to the established reference measurement systems.

Developing Reference Intervals

- We are identifying studies and data sources suitable for defining reference intervals.
- We need to look at existing cohorts and generate new data to determine what is “normal”.

Promoting use of standardized thyroid tests

- We are communicating with public health communities about the importance of accurate and reliable tests.

Current Projects and Activities

- New panels for TSH and Free T4 have to be established well in time, so that they are available before the current panels are depleted. Note that for collecting samples we might need 1 – 1.5 year.
- We will consolidate the sample inventory at NIBSC.
- We will collaborate with metrological institutes to develop reference materials that are in line with our efforts.

Q&A (after Dr. Vespers presentation)

Q: Manufacturers are concerned about how changes to products will be addressed going forward:

C-STFT, in collaboration with CDC, will inform the clinicians about the upcoming changes. One organization that will be used to distribute this information will be the Partnership for the Accurate Testing of Hormones (PATH, http://www.hormoneassays.org/). Manufacturers are represented in this organization, which provides them the opportunity to review and assist with the formulation of messages. This organization is mainly U.S. focused and other organizations for other countries and regions need to be identified.

With standardization services that are linked to C-STFT being available through the CDC, manufacturers can demonstrate accuracy of measurements. This may help with addressing potential concerns with regards to regulatory issues.

The previous C-STFT conducted a survey among clinicians and researchers about the potential impact of changing the calibration to the new reference system. the new working group will review the findings of this survey, and provide a report to manufacturers and stakeholders.

C-STFT will work with manufacturers and other stakeholders to make the transition as smooth as possible. C-STFT understand that each manufacturer may have to make the changes within their timelines and constraints.

For FT4, this also emphasizes the importance of the reference laboratory network, because FDA and other organizations look at this system to make future decisions (see also further on in the discussion).

Q: There are concerns that the current reference range will change for free T4 in terms width also, because of the small sample size that was used in the current reference interval study. The higher end does not seem to be clearly reflected.

We never stated that the established reference interval, based on 120 people, was the final one. On the contrary, we were very aware of the limited number of study subjects. Therefore we intend to look at existing data and generate new data to take a more in-depth look at the reference ranges with a larger sample size in order to more accurately define the lower and upper limits of the reference range.

C-STFT is exploring the possibility of using a similar approach for defining normal ranges as was done for testosterone by PATH and the Endocrine Society (Travison et al. JCEM 2017;102:1161-1173).

Q: There is a concern about the ability of simultaneous operations of FT4 and TSH measurements in these efforts:

Already at the last meeting in Athens, it was decided to address TSH and FT4 separately.

Q: There are concerns on how the FDA will accept this method, because this will help determine how other countries' regulatory services will act:

Tracey Bosworth from the FDA confirmed that they are well aware of the activities of the C-STFT and the reference measurement systems developed by the C-STFT. They are also very supportive to what we have done so far.
As mentioned before, the Japanese authorities accepted conversion factors, based on the method comparisons to assign new values to the assays calibration. In this Japanese effort, only one manufacturer added new points to their calibration.

Q: There is a concern that the CDC would not be able to solely handle the kind of throughput required to have all manufacturers align properly:

To address the increasing need for reference measurements, a network of reference laboratories will be established, which will increase measurement capacity.

Q: There are concerns that estimating the calibration status by means of a method comparison, as was done, does not necessarily fulfill the internal requirements of IVD-manufacturers for calibration. As this type of calibration process has not the same deepness as the internal protocols, and might be not powerful enough.

The C-STFT and its partner laboratories will always be willing to establish new studies, as needed, so that we can further work together to generate the needed data with enough statistical power – be it at an individual level (if the manufacturers requirements are to different) – or as a group.

Q: There are concerns that due to the fact that the deviation from the reference values cannot be expressed by just a single factor and if the proper amount of reference values aren't developed, the calibration of assays will be skewed.

We provided an extensive concentration range for the harmonization and standardization panels. We could always certify additional samples if needed. C-STFT is asking manufacturers to provide information about concentration ranges and other sample requirements as it is developing new panels.

Q: There is a concern regarding stability of the samples that are collected and stored for future use…mainly, some internal procedures require samples to not be older than 60 days:

Tracey Bosworth from the FDA stated that frozen samples can be used.

C-STFT has an ongoing stability study with samples that were collected together with all other panels (TSH and FT4). The first phase of the study is completed and included in the last two manuscripts we published (Clinical Chemistry 2017;63:1248-1260 and Clinical Chemistry 2017;63:1642-1252). The second phase will last until 2020 (i.e. it will end after 5 years).

Q1: Manufacturers want to send calibrators to be value assigned using the reference laboratories, because laboratories are running out of materials:

The C-STFT reference laboratories can provide such measurements.

Q2: But what do manufacturers do for TSH?

For TSH the harmonization procedures developed by the previous C-STFT will be used. As mentioned, developing a new panel for TSH is a priority for C-STFT to ensure continuity. Note, some manufacturers already requested their set of samples from the TSH-follow-up panel. As agreed upon in the past, these samples are available for each of the participating manufacturers.

Q: In the low concentration range, for TSH the scatter in results is still high – can this be due to the reliability of the targets.

That might be a reason. Not all manufacturers did report values for the lower concentrated samples, because of their assays LoD. We did explicitly ask to report all numerical values, even if they were below the established LoD, in order to have a reliable estimate of the targets when n was lower. Also here, if needed, an additional study could be done.

Final thought after all questions:

We should go ahead with creating awareness – to this end, it's time to update the informational slides for common use. They can help each of us to get the message out to other stakeholders/organizations and to get suggestions and even to bring on new contacts.

Speaker: K. Van Uytfanghe, PhD – The FT4 reference laboratory network

Summary of Past Decisions/Objectives

- The reference laboratory network was established in order to ensure consistent accuracy and traceability over time, and to increase RMP laboratory capacity for manufacturers and laboratories. All laboratories were asked to implement the IFCC endorsed FT4 RMP.
- We decided to assess current agreement among candidate RMP laboratories, align measurement results as needed, and use the network to establish target values based on all-laboratory means.
- Candidate members: Ref4U (Belgium), CDC (USA), Radboud University Medical Center of Nijmegen (The Netherlands), Reference Material Institute for Clinical Chemistry Standards (Japan)
- The IFCC endorsed FT4 RMP uses ED with ID-LC/MS/MS and has specific conditions for the ED process.
- The CRM used is IRMM 468 for calibration traceability.
- The suggested analytical performance requirements are: Imprecision: ≤5%, Bias: ±2.5%, Expanded measurement uncertainty: 7.6%, LoD/LoQ: 0.5/1.3 pmol/L (0.04/0.10 ng/dL)

Current Progress/first network method comparison

- The objectives for this initial method comparison were threefold: (i) assess agreement among laboratories, (ii) identify potential sources of bias and (iii) review and refine RMP SOP as needed
- For the experimental design we decided to use 20 blinded euthyroid, single-donor samples and measure them on 3-4 independent occasions. This should rule out any influence of possible protein leakage on the assessment of bias, and gives us the possibility to study intra-laboratory variation.
- Preliminary results:
    - The correlation of the 4 lab results to the overall mean is very good, the RMP SOP can be reproduced in different labs.
    - The mean bias of labs are within +-2.5% bias, but there is room for improvement. Labs show consistent bias across the concentration range, and this indicates calibration differences rather than sample related issues.

Future efforts

The reference laboratory network members will

- improve the calibration status of network laboratories,
- refine RMP SOP based on feedback from network members,
- define performance criteria for the network laboratories and develop protocol for network operation.
- After these tasks are completed, a new method comparison will be performed. This new study will include samples in the hypo- and hyperthyroid concentration range.

Comments (after Dr. Van Uytfanghes presentation)

- We will publish the data, but we will publish it based on the final method comparison using the hypo- and hyperthyroid samples. Here the group suggested to that it might be good to publish the current information for educational purposes. C-STFT will consider this sugegstion.
- A potential timeline for the second method comparison isn't currently available. We intend to discuss the results in detail with the network members in September. Dr. Vesper pointed out that the bias among laboratories is already within 2.5%, and results indicate that further improvements can be achieved with reasonable efforts.

- Work is being done to determine analytical performance criteria for manufacturers. This work is being conducted in collaboration with clinical organizations.
- C-STFT is working to ensure that the reference method, specifically the ED step is sustainable.
- The T4 primary reference material is 100% synthetic T4. The material has been developed during the course of the G6RD-CT-2001-00587 European project. The material was certified and later on commercialized by the IRMM.

Other

- For those who want to recapitulate what we have done, or are looking for information which they could share in order to help disseminate our work – you can find a compilation of what we have done on our website, which we will continue to update. https://ifTcc-cstft.org/
- Next meeting
    - November 9th, 2018 at the IFCC General Conference (Budapest). From 9 - 12 a.m. for *members and corresponding members*, and an open meeting from 1 p.m. - 2 p.m. *(industry partners invited*).
    - May 20th, in parallel with the next EuroMedLab Congress to be held in Barcelona from 19 to 23 May 2019.