C-STFT Meeting

June 29, 2021 7:30 am – 10:00 am EST

Minutes

1) **Welcome and Introduction**
   - *Virtual participants*: Hubert Vesper (CDC, USA), Katleen Van Uytfanghe (UGent Ref Lab Network, Belgium), Uliana Danilenko (CDC Ref Lab Network, USA), Teun van Herwaarden (Nijmegen Ref Lab Network, The Netherlands), Fidelia Pokuah (CDC Ref Lab Network, USA), Stine Anderson (New member – Denmark), Bilek Radovan (Czech Society of Medical Biochemistry), Carol Dauscher (SIEMENS), David Halsall (Cambridge University Hospital Trust, UK), Dr. Barnali Das, Gordon Avery (Abbott, UK), Iris Erlund (National Institute for Health and Welfare, Finland), Jens Peter Berg (Oslo university hospital, Norway), Maria Patru (ORTHO, US), Michael Rottmann (Roche, Germany), Wataru Motsuchi (FRI), Nino Bekaia (Laboratory Medince Aossciation of Georgia - GLMA), Paul Williams (Australia), Stefaan Marivoet (Tosoh, Belgium). Stephan Fellner (DiaSys Diagnosic System), Veronique Raverot (Hospices Civils de Lyon, France), Vincent Chen (Snibe, China), Robert Payne (Siemens), Teda, Violeta Raneva (ReCCS), Tanja Dubravcic (Siemens), Shanti Narayanan (Tosoh), Ron Archer (Beckman), Karen, Simeon Adebisi (Association of Clinical Chemists of Nigeria)
   - *Reviewed C-STFT Terms of Reference*

2) FT4 Standardization updates

a) FT4 Reference Laboratory Network

- Status of inter-lab comparison study: 2nd network method comparison study aims to assess agreement among candidate ref labs over broader concentration range to identify potential sources of bias among the labs.
- Results: all labs are able to perform within pre-set specifications:
  - CV (3-5%), further review of individual samples with higher CVs underway
  - Compared accuracy data between 4 labs: data shows good agreement between the 4 labs, existing bias (-2% – 5%) does not seem to be concentration dependent. All labs used independent calibration (no common calibrators used)
- Way Forward:
  - Additional review of data to evaluate in depth higher CVs as well as all data sets.
  - Evaluate 2 NIST reference materials;
  - Prepare manuscript,
  - Refine RMP SOP based on feedback from the labs,
  - Formalize network and seek additional reference labs.

b) Reference Laboratory Activities/Reference Value Assignments

- UGent: 2011 RMP listed in JCTLM and ISO 17025 & 15195 accredited; defined specification that is used for validation. Provides services to IVD manufacturers, EQA organizations, individual labs and support C-STFT activities. As well actively measure FT4 on yearly basis
- CDC: RMP submitted to JCTLM for review. Currently planning on ISO 17025 & 15195 audit for accreditation in early 2022. Currently recruiting clinical labs for inter-lab comparison study.

Provides free thyroxine services to metrological organizations, accuracy-based EQA providers, CDC HoSt and support C-STFT activities. CDC set to establish formal standardization programs for FT4 in late fall 2021

- Radboud University: Completed method measurements and performing comparisons with CDC and UGent. Provides services to EQA programs with 80 labs to monitor FT4/TSH with the intent to see whether the current standardization status of manufactures is reflected in the EQA scheme.

3) TSH Harmonization updates

a) Creating new Follow-up panel

- Need to collect 3rd panel of samples before the 2nd set of samples is running out. The latter is already used by manufacturers to verify their performance internally compared to the targets set in 2016. The third panel should link to the 2nd panel, in order to keep the traceability to the original basis for harmonization (panel one).
    - Samples should cover the entire concentration range, more samples in the lower concentration range should be added, compared to the previous panels
    - Aim for panel to be ready by 2021 but delayed due to COVID; therefore, plan to have ready by 2023 after collection and validation; using same protocol
    - C-STFT budget will cover collection and perform viral testing on samples; UGent can support with ethical approval for collection; CDC will receive, aliquot, store and distribute samples

b) Harmonization project in Japan

- Japan 2nd report on study to harmonize TSH; Stakeholders involved included Japan societies, industry and IVD manufacturers
    - Ref ISO 21151- harmonization protocol; New ISO 17511 traceability of lab medicine includes harmonization protocol as one way to establish metrological traceability
    - 120 healthy donors (no thyroid disease or medications that can affect thyroid function)
    - Mean avg: 5.15%-7.29%; highest IVD manufacturer 9.27%
    - Concluded that study validated C-STFT, and re-calibration values will be used without further adjustment in Japan.

c) Collaboration between NIBSC and C-STFT

- C-STFT was approached by NIBSC – to assist in linking the new lot for the WHO TSH material to the IFCC C-STFT harmonization basis.
    - The WHO material is used to define International Units which are used with the harmonization panel. This will not be a commutability study. Given the nature of the material, it is assumed that this material is not commutable and therefore cannot be used as calibrator. Study design and planning are in progress

4) Activities in support of thyroid function test standardization

a) Stability of serum reference panels stored at NIBSC

- Along with samples for 1st and 2nd panel, additional samples were set aside (subset off 1st and 2nd panel) to verify stability of the samples over time to ensure that the protocol of transferring the target from one panel to another will not be jeopardize by the stability of the samples

- The isochronous stability study started in 2015 and was splitted in 2 timeframes with measurements in 2017 and 2020. Two sets of samples were stored as time point, continuously at liquid nitrogen. All other sets were stored at -70° degrees and moved to liquid nitrogen along the way. Each set of samples contained 9 samples for FT4 and 9 samples for TSH. Roche performed all measurements with their assay and provided data (2017 & 2020 time points)
    - Part I Results: the noticeable difference between the different storage conditions was statistically not relevant, thus samples were considered stable when stored at -70 up to 24 months
    - Part II Results: noticeable variations among samples; average values for TSH and FT4 appears to slightly increase over time. Changes currently seen may be due to differences in assay (lot-to-lot variability); Further statistical review on the data is underway

b) Review of biological variability data

- IFCC committee is working with American Thyroid Association (ATA), which convened a working group to look into biological variation (BV) of thyroid tests. Data on BV are over 30yrs ol, but are still being used to determine analytical performance criteria based on BV. Katleen is representing IFCC. The ATA working group consists of international members and with different area of expertise and will develop a document to Provide an update of current practices on thyroid hormone measurements, Comparability of current assays will be included and to review of analytical performance criteria for thyroid function tests. Work on this in progress

c) Reference interval studies

- Implementation of standardization of thyroid function would allow reference intervals to also be linked to the reference system. Helpful to lab and clinical communities if regional reference intervals are linked to IFCC system as needed. For example:
    - Reference system for TSH in Japan linked to harmonize system.
    - In the US, NHANES population to establish reference intervals for TSH and FT4
    - Europe – different study cohorts standardize to reference system to do the same
    - TSH values it is anticipated that those from US or Japan may not be appropriate due to the differences in iodine supplement use. Further investigations are necessary once data become available.
    - Finland – cross-sectional study in 2021-2022; collecting about 10k samples from healthy adult for reference interval study for TSH along with urinary iodine study; would be good to have harmonize assays by then. (FinHealth Survey – done every 5 years)
    - *Australia – studies on reference intervals; working on harmonize assays (difficult to get full agreement among assays); work is anticipated to continue 2023-2025*

5) Education/Communication

- An update on the IFCC activities was written: Clin Chim Acta. 2021;519:183-186
- ATA Working Group, see above
- Reach out to other organization on activities related to Thyroid Function tests and Standardized test, i.e. Work with PATH in the U.S.
- AACC Scientific Meeting session – 32222 Current Sue of Thyroid Function Tests and Work to Improve their Comparability and reliability

- AACC Roundtable
- CDC CSP Events and Newsletters to reach lab and clinical communities
- C-STFT Website
- Scientific Conferences and Meetings: Euromedlab and World Congress

6) Member Updates and Other items

- Australia – 9 assays harmonize ref intervals; *working on gathering data for other assays. FT4 ref interval around normal range not far apart unless go away from normal ranges which isn't helpful for clinical community*
- Japan – need various stakeholders to ensure harmonization implementation on a national level is successful (scientific community, IVD community and government/regulatory)
- Biologic Variation database on different assays – EFLN website (biologicvaration.eu)

Meeting adjourned at 10 a.m.