IFCC C-STFT 2023 HYBRID MEETING

Monday, May 22nd, 2023

IFCC General Conference

Meeting Minutes

1) **Welcome and Introduction**

In-person participants:

Katleen Van Uytfanghe (Ref4U, Ref Lab Network, UGent, Belgium), **Hubert Vesper** (CDC, USA), **Alicia Lyle** (CDC, USA), **Stefaan Marivoet** (Tosoh, Belgium), **Oliver Lorenz** (Roche, Germany), **Rea Castro** (QuidelOrtho, USA), **Toshie Takora** (Tosoh, Japan), **Rie Konoma** (Tosoh, Japan), **Caroline Stobe** (RfB, Germany), Jean-Sebastien Blanchet (Beckman Coulter, France), **Jens P Berg** (University of Oslo and Oslo university hospital Oslo, Norway), **Okuno Koji** (Sysmex, Japan), **Takashi Aritsu** (Sysmex, Japan), **Gordon Avery** (Abbott, UK), **Susan Brophy** (Abbott, USA), **Valentina Vidranski** (CSMB, Croatia), **Stine Andersen** (Aalborg University Hospital, Denmark), **Veronique Raverot** (Hospices Civils de Lyon, France)

Virtual participants:

Akira Hishinuma (Japan Society of Clinical Chemistry, Japan), **Ben Cowper** (NIBSC, UK), **Uliana Danilenko** (CDC Ref Lab Network, USA), **Ashish Agravatt** (AMBI, India), **Kazuyuki Sugiyama** (LSI Medience Corporation, Japan), **Mina Ootsuka** (LSI Medience Corporation, Japan), **David Kiaei** (Siemens Healthineers, USA), **Paul Williams** (AACB, Australia), **Ashley Riberia** (CDC Ref Lab Network, USA), **Shuqi An** (Autobio Diagnostics, China), **Zengming Jin** (Autobio Diagnostics, China), **Chris Thomas** (QuidelOrtho, UK), **Violeta Raneva** (ReCCs, Japan), **zhangyifan**

For an overview of the IFCC-STFT Members, Corresponding Members and Consultants, see https://ifcc.org/ifcc-scientific-division/sd-committees/c-stft/ and slide 4 of the attached Annex 1.
There has been a change in chairman for the committee and some industry representatives have handed over their responsibilities to their colleagues. Thanks to all of them for their efforts and contributions to the C-STFT.

2) Approval of Meeting Minutes from the meeting in Brussels, October 28th 2022

Approved

3) **Review of Terms of Reference**

Slide 5-7 of the attached Annex 1

The terms of reference have not been changed. The main focus of the C-STFT is to implement and maintain the reference measurement systems (RMSs) that were developed by the IFCC Committee and to support the stakeholders with conducting standardization and harmonization activities.

The C-STFT developed a RMS for free T4 that conforms with ISO 17511.

- *There exists a primary reference material which is used to calibrate FT4 reference measurement procedures (RMPs), which in turn can be used by the manufacturers for the standardization and*

verification of their master and working calibrators, in-house methods and further down to the methods which are used in clinical practice.

- *A network of laboratories implementing the free T4 RMP is established and maintained.*
- *The task of the C-STFT here is to maintain the network of reference laboratories. As such, at all times interested parties have access to the RMS.*

For TSH, the RMS is also ISO 17511 compliant.

- *It relies on panels of human serum samples with TSH concentrations covering the entire measurement range of current immunoassays. These panels form the basis of harmonization.*
- *The panels are value assigned as a joined effort between as much as possible manufacturers, and in overlap with previous panels.*
- *Sustainability of the RMS needs a continues flow over time of value assigning targets to new follow-up panels.*
- *The task of the C-STFT is to coordinate this continuous effort.*

4) **Updates on the C-STFT activities - Develop and establish follow-up panel for TSH**
Slide 8-12 of the attached Annex 1

The establishment of the 3rd TSH Harmonization panel is ongoing. The objective of the panel is to ensure continuity of the established calibration set-point using a third harmonization panel and linking this panel to the second panel through overlapping measurements.

- Note: The first TSH panel was established in 2015 – the feasibility of the use of such a panel as basis for harmonization was published in 2017 in Clinical Chemistry. At same time a 2nd follow-up panel was created with 95 samples, which were assigned target values in overlap with the harmonization panel. The 2nd panel was meant to be used by all manufacturers to actually verify or work further on the harmonization of their assays.
- At this point of time, we will target the 3rd panel. We will use primarily the same protocol and requirements as we have used in the previous study and use samples covering the entire measurement range and include more samples close to the limits of quantitation.
- The protocol has two phases:
    - 1st phase (2023 IFCC TSH Study Phase 1, 2023 ITS Phase 1). This phase has multiple objectives: (i) Verification of the status of harmonization using the 2nd follow-up panel and its target values as previously set; (ii) recalibration of the assays to these target values if deemed necessary, (iii) characterization of the candidate 4th WHO international standard for human TSH (81/615).
    - 2nd phase: This phase has one objective: Value assignment of the 3rd TSH harmonization panel. These samples will be provided in a second shipment.

a) 2023 IFCC TSH Study Phase 1
Slide 13-38 of the attached Annex 1

This part of the study is finished, data-analysis is ongoing.
Details on the materials and methods can be found in slides 13 – 17.

The data presented during the meeting focused on the results for the native samples, without removal of possible outliers. One assay was left out for the presentation of the data after recalibration. The target is the APTM as calculated in 2015.
Note, at this point in time the data are presented anonymously because some questions popped-up for which the respective manufacturers will be contacted upon further detailed data-analysis.

Details on the results can be found in slides 20-37.
In summary:

- There is a good agreement of the mean of all replicates over all assays and the target set in 2015.
- In the 0.5-5 mIU/L concentration range the status before recalibration seems to be somewhat better than in the previous method comparison.
- Recalibration brings further improvement, primarily at the level of the individual manufacturers
  What needs to be document is whether or not different/new assays compared to previous method comparison study were used by some manufacturers.
- No numerical data were reported for 6 assays in the <0.5 mIU/L or lower concentration range
  No numerical data were reported for 4 assays in the >50 mIU/L or higher concentration range

In the previous study, it was explicitly asked to report all numerical values, also for samples which were outside the reportable range of these assays. This was done to increase the number of results that form the basis of the calculation of the APTM. For the current study manufacturers did not do so.

- ➔ The question was raised whether these data could be of value, and hence be reported retrospectively.
  One argument not to do so, is that these results probably have a high uncertainty.
- ➔ Do we need to take the measurement range into account when we randomize the subset of samples per manufacturer in phase 2 of this project. See also further.

The NIBSC is doing a separate and independent assessment for the study on the 4th WHO international standard for human TSH (81/615). As replacement, the 4th WHO international standard is very similar to the 3rd international standard, there is already a good idea of its value. This study will focus on the suitability of the 4th international standard with current TSH assays and its commutability will be assessed. Data analysis was ongoing at the time of the meeting. The report was due to be filed in July, all manufacturers got a chance to comment on beforehand, see also the post meeting report at the end of these minutes.

In the follow-up discussion some questions were raised:

- Dr. Berg asked whether the recalibration functions had been published. This has not been done. The clin chem manuscript from 2016 was a proof of concept study. It was left to the manufacturers responsibility to effectively implement harmonization. Dr. Vesper added that the C-STFT committee we will not promote that laboratories do a recalibration on their on the basis of published algorithms.
- Dr. Vesper raised the question whether or not something is going on in the low concentration range that is not related to a calibration bias, as we see negative biases for quite some assays. Could this be related to the particular glycosylation of the disease states that lead to such low concentrations? It is an intriguing hypothesis stated by some researchers that the assays perhaps do not pick up

some glycosylation forms, or not to the same extend.
→ The detailed data-analysis that will follow can perhaps bring additional knowledge.
However, overall based on (i) the better agreement of the TSH assays, and (ii) the lesser effect of recalibration suggest that there is improvement amongst harmonization of TSH assays.

b) 2023 IFCC TSH Study Phase 2

Slide 39-47 of the attached Annex 1

Some practical questions needed an answer:

- ➔ Is the proposed timing fine?
  - Update contact details: September 2023
    If possible, use the same contacts, also within subcontracting couriers
  - Ship samples: November 2023
  - Report: January 2024

  Yes!
- ➔ Do we need more samples, in which concentration range?
  From a calibration perspective, the number of samples is probably fine, from a research perspective, more samples in the low concentration range might help to find out the source of the negative bias. We will collect samples as long as possible in order not to compromise the timelines above.
- ➔ Do we need samples from healthy donors?
  In the past, CDC has stated that some samples from there repository could be added.
- ➔ Do we need to take the concentration range of the assays into account upon randomization?
  This could be done in order to have enough numerical values for each of the samples, however care should be taken that the APTM is not affect by the bias of a few assays.
- ➔ Will we include the samples of patients on recombinant TSH?
  These can be included, but care should be taken upon final data-analysis. Randomization should also be done carefully in order to mix the samples well with authentic samples.

5) **Updates on the C-STFT activities - Establishment of a reference laboratory network for FT4**
Slide 48-55 of the attached Annex 1

The aim is to sustain the network of FT4 reference laboratories. The different members of the network provide different services to all interested parties. So as an IVD manufacturer, provider of QC materials, … you can actually work with the different laboratories within the network.

- There are currently 4 Network members: CDC Clinical reference laboratory - USA; Radboud University Medical Center of Nijmegen -The Netherlands; Reference Material Institute of Clinical Chemistry Standards - Japan; Ref4U, Ghent University - Belgium
- There are requests to join network from Autobio-China and Government of Western Australia, and others. New laboratories should:
  - Provide in writing to the network coordinator their intent to join the network
  - Demonstrate that they correctly perform the latest version of the FT4 cRMP and meet analytical performance criteria
  - Successfully participate in two consecutive network studies

- The network members have defined the network rules. Participants should:
    - Operate the cRMP for FT4 based on the current version of the network approved SOP
    - Participate in regular meetings/communications
    - Participate in regular network studies to monitor the analytical performance of the member laboratory. To maintain membership, network members need to successfully pass two consecutive network studies.
    - Meet analytical performance requirements for FT4 cRMP
- The network rules and the results of the interlaboratory comparison are currently being summarized in a joint manuscript
- The network prepares a follow-up method comparison by the end of 2023, to which candidate members will also be invited
- The network members have submitted 3 manuscripts, see also see also the post meeting report

In the follow-up discussion it was questioned whether spiking samples with T4 would be feasible in order to create samples with FT4 concentration in the high end of the FT4 concentration range. Based on our past experience, we reported on spiking experiments in 2012, spiked samples turned out to have a much higher FT4 concentration than expected, moreover, the concentrations did not fit the regression equations between the target (ED-ID/MS) and the average of all manufacturers results. Hence it was concluded that the samples were not commutable.

In addition to the discussion, Dr. Vesper also mentioned that:

- CDC has developed a routine FT4 procedure in with dialysis in a 96-well plate format.
- CLSI is drafting a document on the practical considerations of establishing metrological traceability, which will include FT4 as an example.
- JCTLM might broaden its scope of activities and support networks of reference laboratories

6) **Updates on the C-STFT activities - Educational activities**
Slide 56-58 of the attached Annex 1

No further details were discussed.

7) **Updates on C-STFT National/Regional Activities and Member Activities**
Slide 56-66 of the attached Annex 1, and Annex 2

No further details were discussed.

8) Updates of the terms of reference – future activities
Slide 67 of the attached Annex 1

The IFCC encourages us to at least think and consider whether an update of the terms of reference is needed, and the scope of our activities should be broadened. This should not be decided on short notice, and can be the results of discussion with other experts in the field.

A dedicated C-STFT meeting could be organized, at which we could take time to discuss this topic. Possible future analytes could be: thyroglobulin, autoantibodies, …

9) IFCC meeting options

Slide 67 of the attached Annex 1

Seeing the timelines of the next round of TSH-measurement, it was decided to have the next in-person afterwards so that results can be discussed.

This will then be in conjunction with the XXVI IFCC WORLDLAB in Dubai 2024, May 26 – May 30.

Meeting Adjourn

Post meeting report

Per August 1st 2023, some post meeting updates can be reported as well:

1. The report on the 4th WHO international standard report was sent out to all participants in order to give each of them a change to comment. The report was submitted to the WHO and now posted on their website for public consultation, so we may receive some comments from the wider "public" in the next few months Please see https://www.who.int/groups/expert-committee-on-biological-standardization#:~:text=The%20WHO%20Expert%20Committee%20on,with%20the%20establishment%20of%20WHO if you whish to read and comment.

2. The IFCC has generated guidelines for its functional groups in order to guarantee regular meetings. This will primarily impact the frequency by which the members meet.
   These are the requirements given:
   The EB encourages all IFCC functional groups (Committees, Taskforces, Working Groups) to meet on a monthly or bi-monthly schedule to enhance communication and increase productivity.
   In addition:
   a) At minimum, IFCC functional groups are expected to meet a minimum of 4 times a year, one in person and three virtual meetings.
   b) The annual in-person meeting should be a minimum of 4 hours (half a day) or longer.
   c) Virtual meetings should be a minimum of 2-3 hours in duration.

3. The following manuscripts have been published:
   a) Ribera A, Zhang L, Dabbs-Brown A, Sugahara O, Poynter K, van Uytfanghe K, Shimizu E, van Herwaarden AE, Botelho JC, Danilenko U, Vesper HW. Development of an equilibrium dialysis ID-UPLC-MS/MS candidate reference measurement procedure for free thyroxine in human serum. Clin Biochem. 2023 Jun;116:42-51. doi: 10.1016/j.clinbiochem.2023.03.010. Epub 2023 Mar 20. PMID: 36940844.
   b) Jansen HI, van der Steen R, Brandt A, Olthaar AJ, Vesper HW, Shimizu E, Heijboer AC, Van Uytfanghe K, van Herwaarden AE. Description and validation of an equilibrium dialysis ID-LC-MS/MS candidate reference measurement procedure for free thyroxine in human serum. Clin Chem Lab Med. 2023 Mar 31;61(9):1605-1611. doi: 10.1515/cclm-2022-1134. PMID: 36994743.
   c) Ribera A, Zhang L, Ribeiro C, Vazquez N, Thonkulpitak J, Botelho JC, Danilenko U, van Uytfanghe K, Vesper HW. Practical considerations for accurate determination of free thyroxine by equilibrium dialysis. J Mass Spectrom Adv Clin Lab. 2023 Jun 23;29:9-15. doi: 10.1016/j.jmsacl.2023.06.001. PMID: 37449264; PMCID: PMC10336244.
   d) Van Uytfanghe K, Ehrenkranz J, Halsall D, Hoff K, Loh TP, Spencer CA, Köhrle J. Thyroid Stimulating Hormone and Thyroid Hormones (Triiodothyronine and Thyroxine): An American Thyroid Association-Commissioned Review of Current Clinical and Laboratory Status. Thyroid. 2023 Sep 1. doi: 10.1089/thy.2023.0169. Epub ahead of print. PMID: 37655789.

IFCC Committee
Standardization of Thyroid Function Tests (C-STFT)

Meeting May 22, 2023

(EuroMedLab, Rome)

Agenda

Time	Topic
14.00 – 14:15	Welcome and introduction
14:15 – 14:30	Approve of meeting minutes from Brussels meeting
14:30 – 14:45	Review of terms of reference and C-STFT membership Develop and establish follow-up panel for TSH
14:45 – 15:45	Discuss preliminary results of 2023 ITS Phase 1 Preparation of Phase 2
15:45 – 16:00	Break
16:00 – 16:30	Establishment of a FT4 reference laboratory network
16:30 – 16:45	Updates on educational activities
16:45 – 17:00	Updates on C-STFT member activities
17:00 – 18:00	Other agenda points - discussion
18:00	Adjourn

1. Welcome and Introductions

IFCC-STFT Members, Corresponding Members and Consultants

List of Members
Katleen Van Uytfanghe, Chair, BE
Akira Hishinuma, JP
Veronique Raverot, FR
Stine L. Anderson, DK
To be determined

Consultants
Iris Erlund, FI
Michael Rottmann, DE
Linda Thienpont, BE
Henry Völzke, DE

Past Chair
Hubert Vesper, Chair US

Reference Laboratory Network candidates:
- ***Ref4U*** *(Belgium)*
- ***CDC Clinical Reference Laboratories*** *(USA)*
- ***Radboud University Medical Center of Nijmegen*** *(The Netherlands)*
- ***Reference Material Institute for Clinical Chemistry Standards*** *(Japan)*

List of Corresponding Members, nominated by National Societies:
Paul Williams, Australasian Association for Clinical Biochemistry and Laboratory Medicine (AACB)
Valentina Vidranski, Croatian Society of Medical Biochemistry and Laboratory Medicine
Radovan Bílek, Czech Society of Clinical Biochemistry (CSKB)
Nino Bekaia, Laboratory Medicine Association of Georgia (GLMA)
Poornima Manjreka, Association of Clinical Biochemists of India (ACBI)
Ashishkumar Agravatt, Association of Medical Biochemists of India (AMBI)
M. Reza Bakhtiari, Iranian Association of Clinical Laboratory Doctors
Suprita Gupta, Nepalese Association for Clinical Chemistry (NACC)
Simeon Adebisi, Association of Clinical Chemists Nigeria (ACCN)
Jens Berg - Norwegian Society of Medical Biochemistry
Sheharbano Imran, Pakistan Society of Chemical Pathologists
Lakminda Thilakarathna, Association for Clinical Biochemistry, Sri Lanka
Yasemin Ucal, Turkish Biochemical Society (TBS)
David Halsall, Association for Clinical Biochemistry (ACB) - UK

List of Corresponding Members, nominated by Corporate Members
Gordon Avery, ABBOTT Diagnostics
Zengming Jin, AUTOBIO Diagnostics
Annette Adelmann → Jean-Sebastien Blanchet, BECKMAN COULTER
Stephan Fellner, DiaSys Diagnostic Systems
Tao Yang MACCURA Biotechnology Co., Ltd
Laura-Leena Kiiskinen → Maiju Palokangas, MEDIX BIOCHEMICA
Jian Xie, MINDRAY
Rea Castro, QUIDELORTHO
Carole Dauscher, SIEMENS Healthineers
Jiazhen Shen → Ran Xu, SNIBE

2. Review terms of reference

C-STFT Terms of Reference

- Establish a system to maintain traceability of free thyroid hormone and TSH measurements
- Coordinate programs to evaluate free thyroid and TSH assays with regards to their analytical performance
- Develop reference intervals for free thyroid hormones and TSH
- Liaise with key stakeholders to promote the use of the standardized assays in routine clinical practice and public health, to ensure analytical performance requirements meet clinical needs, and to help with developing and establishing reference intervals.

➢ Implement and maintain the reference system developed by the IFCC Committee

➢ Support stakeholders with conducting standardization and harmonization activities

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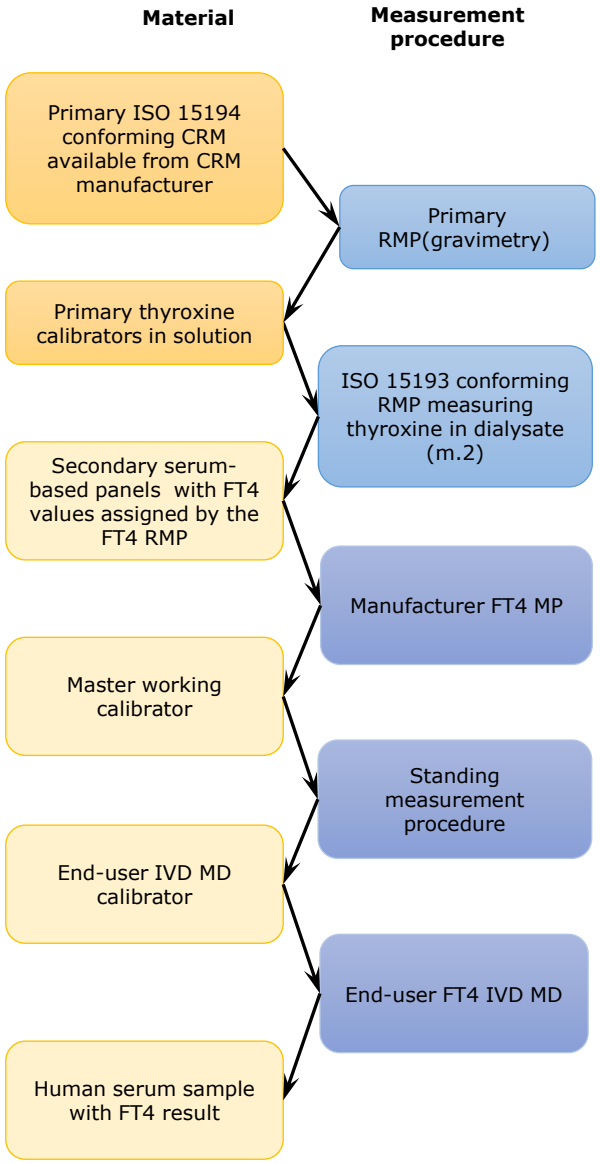
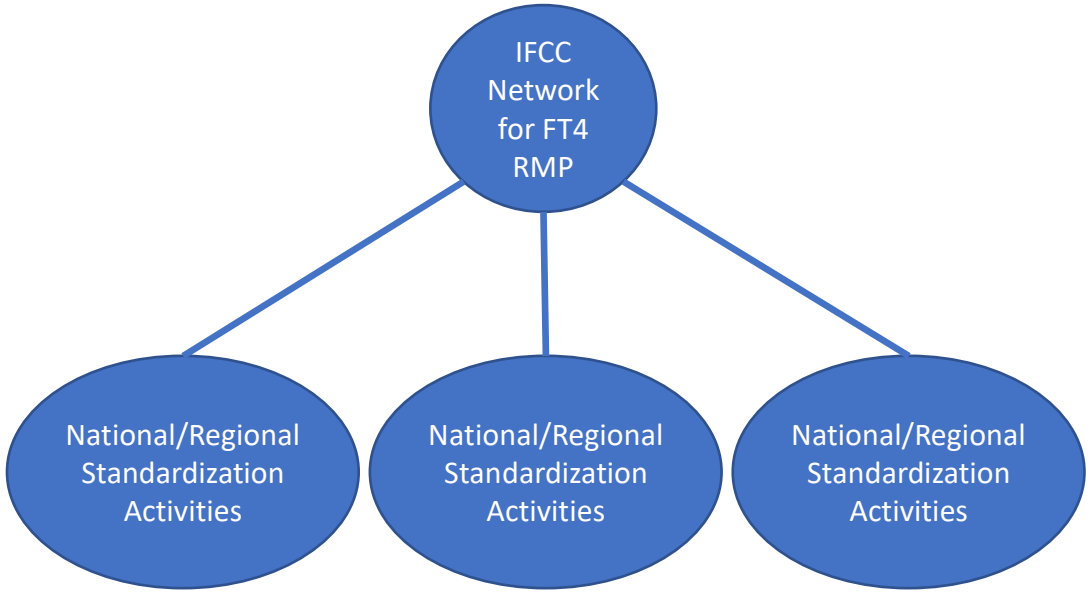


Calibration traceable to SI
Patient result traceable to FT4 RMP



- IFCC Network ensures consistent calibration internationally
- National/Regional standardization activities can address additional aspects as needed

➢ This allows for national/regional stakeholders to customize activities to their needs, while ensuring consistent calibration globally

The same basic approach used for FT4 is applied for TSH
More information on traceability provided in presentation on Preparations for 3rd TSH Harmonization Panel

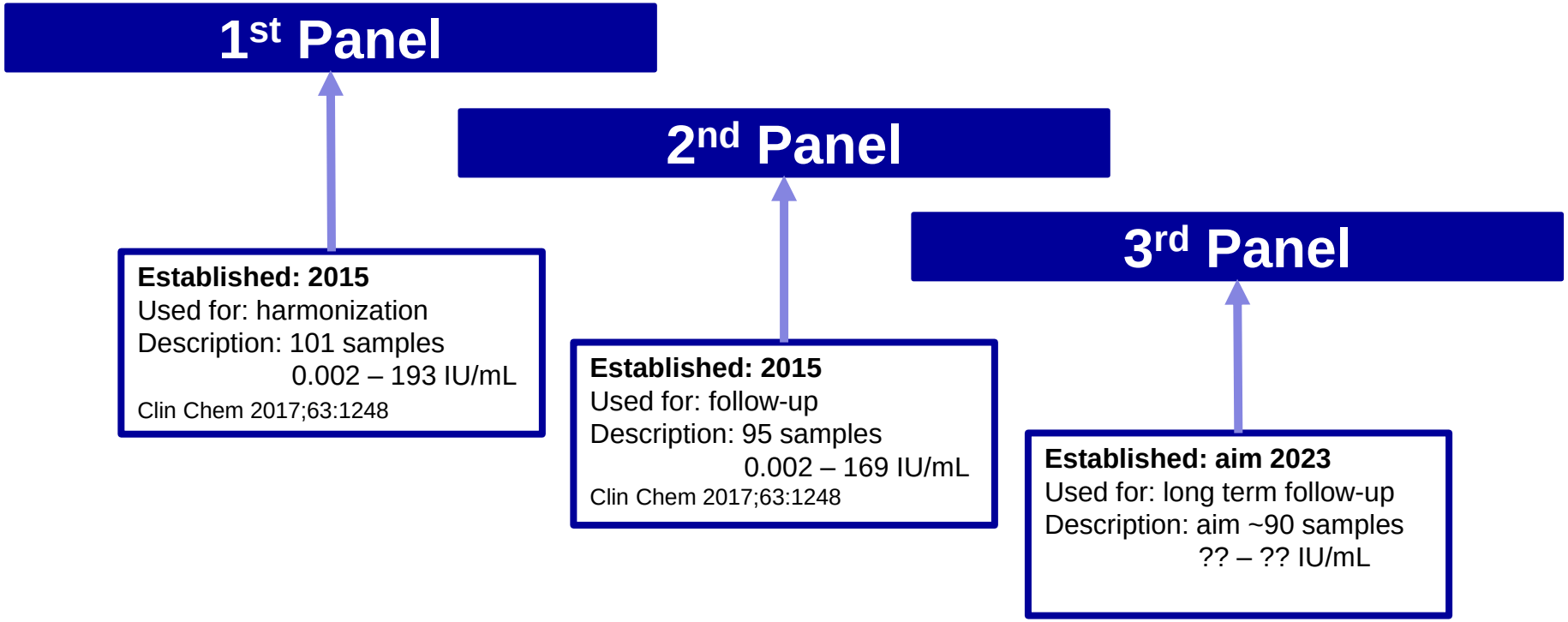
3. Preparations for 3rd TSH Harmonization Panel

Overview

- Reminder on the objective
- Proposal for the measurement protocol
- Tentative timelines
- Status update on the sample collection
- Preliminary results

Objective

Ensure continuity of established calibration set-point using a third harmonization panel and linking third panel to second panel through overlapping measurements.



Objective

- Same protocol and requirements as 2nd Panel
- Samples covering the entire measurement range
- More samples close to the assays LLoQ

Proposed protocol

1. **First phase**

   The measurement of the TSH follow-up panel should allow you to recalibrate against its targets.
   The WHO materials are measured to enable evaluation and value-assignment of the candidate 4th WHO IS.

   a) Samples from the TSH follow-up panel
   (certified along with the initial TSH harmonization panel (see DOI: 10.1373/clinchem.2016.269456)).

   b) 3rd WHO International Standard for human TSH (81/565) and the candidate 4th WHO International Standard for human TSH (81/615)

2. **Second phase**

   The certification of the 3rd TSH harmonization panel

First Phase – logistics and samples

Logistics

- Initiated September 2022
- Samples shipped November 2022

Samples

- Samples from the TSH follow-up panel

  86 – 91 0.5 mL aliquots, concentration range between 0.002 and 168 mIU/L

- 3rd WHO International Standard for human TSH (81/565) and the candidate 4th WHO International Standard for human TSH (81/615)

  1 ampule each

First Phase – measurement protocol

- **Duplicate analysis of each sample within the same run.**
- **Inclusion of a dilution series pf bothe the 4th WHO International Standard for human TSH (81/615) and the current 3rd WHO IS (81/565).**

→ Include your TSH “master calibrators” in the method comparison study.

→ Apply a randomized order of the samples for measurement (proposed by us in the report template).

→ If you have more than one system: identify one system to measure the samples with, and then apply an in-house transfer protocol for your other systems.

→ Store all raw data. We do not necessarily need them, but in case of doubt, it might be useful for both parties to have them.

→ Apply your own QC-protocol

First Phase – Instructions and report

Instructions

- Separate instructions for the follow-up panel and the WHO material

Report

- **Report the results as measured with your current calibration, and after recalibration against the targets provided with the panel.**
- An excel template will be provided
- This includes the proposed measurement sequence
- Please also provide the used QC protocol
- Please also provide the details of the dilutions made for the WHO material
- Please also provide details on the recalibration protocol used

First Phase – Preliminary data

Target – as certified in the previous method comparison study

See also Clin Chem 2017;63:1248

IFCC HARMONIZATION OF TSH MEASUREMENTS –

1st FOLLOW-UP REFERENCE SERUM PANEL

Certified by value assignment with a robust factor analysis model from a method comparison study

Name and e-mail address of the chair of the IFCC Committee for Standardization of Thyroid Function Tests: Linda Thienpont, PhD, Prof. Emeritus Ghent University.
E-mail: linda.thienpont@ugent.be

First Phase – Preliminary data

Target

THYROID STIMULATING HORMONE (TSH) IN HUMAN SERUM					
Serum ID	Assigned value[1,2] (mIU/L)	Serum ID	Assigned value (mIU/L)	Serum ID	Assigned value (mIU/L)
TSH Phase IV P155	0.002	11157S-733-052	0.418	11157S-733-086	3.181
11157S-1875-017	0.002	TSH Phase IV P038	0.695	11157S-733-026	3.375
11157S-733-072	0.002	TSH Phase IV P049	0.696	11157S-733-045	3.512
11157S-1874-039	0.003	TSH Phase IV P050	0.814	TSH Phase IV P031	3.765
211404	0.003	TSH Phase IV P058	0.823	11157S-733-049	4.467
225088	0.004	TSH Phase IV P039	0.847	11157S-1874-037	5.430
211009	0.004	TSH Phase IV P053	1.102	212273	6.330
11157S-1874-019	0.005	TSH Phase IV P042	1.109	11157S-1874-009	6.419
11157S-1874-045	0.006	TSH Phase IV P043	1.194	TSH Phase IV P207	6.708
11157S-1874-031	0.007	TSH Phase IV P054	1.259	TSH Phase IV P208	7.006
11157S-733-074	0.007	TSH Phase IV P037	1.328	TSH Phase IV P209	8.926
11157S-733-107	0.009	TSH Phase IV P036	1.374	11157S-733-054	10.24
11157S-1875-020	0.009	TSH Phase IV P032	1.486	11157S-733-022	17.06
11157S-733-001	0.009	TSH Phase IV P051	1.556	11157S-1874-041	19.15
11157S-733-021	0.012	TSH Phase IV P033	1.613	TSH Phase IV P200	19.24
11157S-733-005	0.018	11157S-733-012	1.727	11157S-733-032	20.37
11157S-733-009	0.018	TSH Phase IV P060	1.732	TSH Phase IV P199	24.19
11157S-733-051	0.026	TSH Phase IV P061	1.823	11157S-1876-008	40.76
11157S-733-014	0.034	TSH Phase IV P055	1.881	11157S-1876-015	41.77
TSH Phase IV P179	0.038	TSH Phase IV P045	1.928	TSH Phase IV P203	47.81
TSH Phase IV P187	0.044	TSH Phase IV P046	1.973	11157S-1876-017	47.82
TSH Phase IV P188	0.065	TSH Phase IV P059	2.018	233515	58.53
TSH Phase IV P204	0.073	TSH Phase IV P044	2.201	11157S-1876-013	69.83
11157S-733-016	0.093	TSH Phase IV P048	2.230	11157S-1874-043	70.31
11157S-1874-023	0.129	TSH Phase IV P034	2.271	11157S-1876-010	72.35
11157S-733-090	0.140	TSH Phase IV P056	2.325	11157S-1876-007	75.80
211243	0.144	11157S-733-010	2.458	TSH Phase IV P185	86.49
226102	0.189	TSH Phase IV P035	2.545	11157S-1876-011	92.82
TSH Phase IV P191	0.244	TSH Phase IV P040	2.555	11157S-1874-024	120.1
TSH Phase IV P158	0.266	TSH Phase IV P052	2.755	TSH Phase IV P210	149.7
11157S-733-060	0.333	TSH Phase IV P047	2.858	232317	168.6
TSH Phase IV P193	0.409	TSH Phase IV P057	3.133		

The product must be handled with appropriate care such as any potentially infectious material of human origin. It is intended for in-vitro analysis only.

[1]The value assignment has been done with a robust factor analysis model from a method comparison study, as described in Refs. 1 and 2.
[2]The mean uncertainty amounted to 0.7% (upper limit) and 1.0% (lower limit), see also Ref. 1.

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First Phase – Preliminary data

Data presented at today's meeting

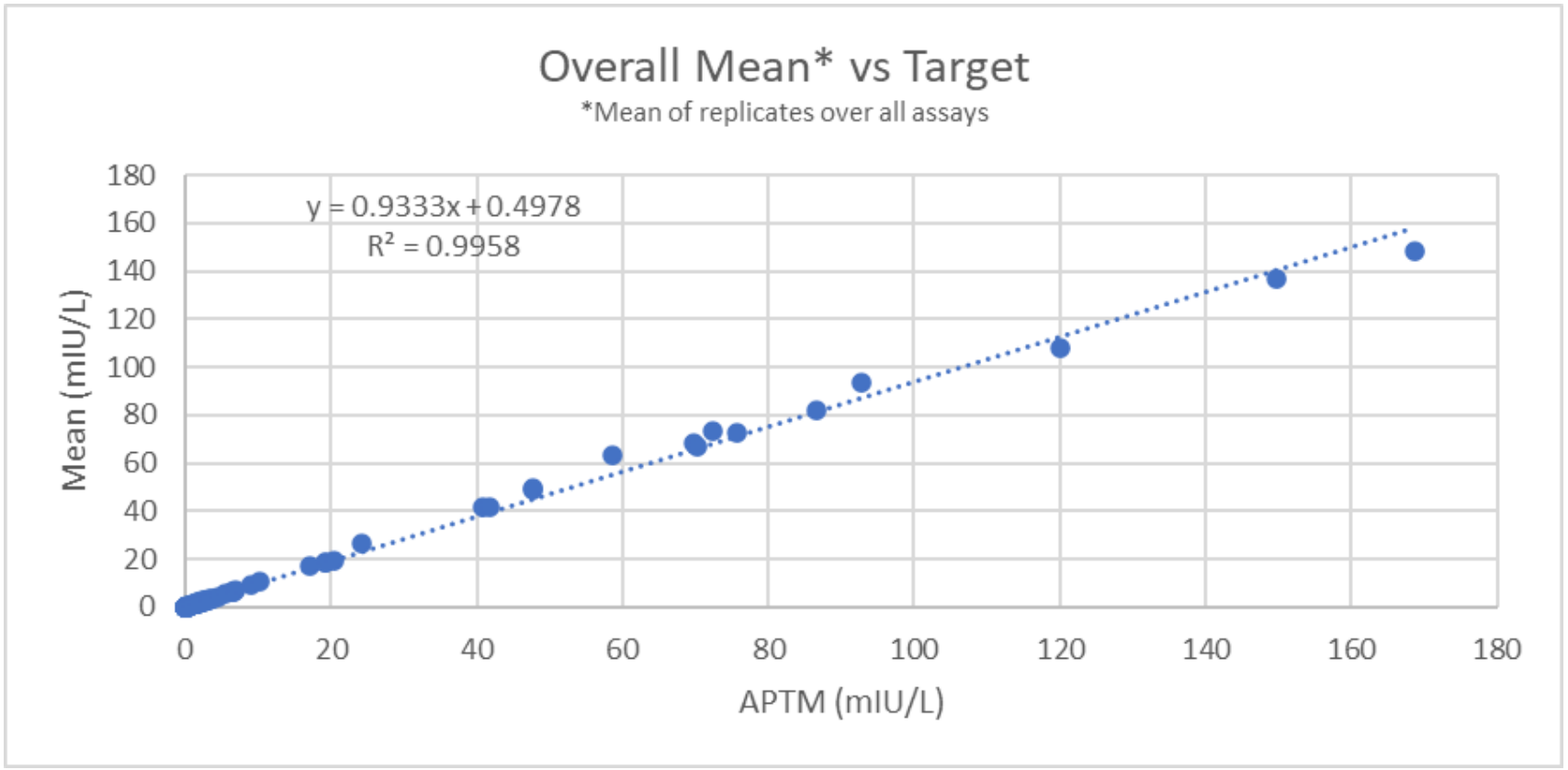
- **Focused on native samples**
- **NIBSC is independently evaluating the data for the WHO materials**
  - **Direct contact with manufacturers in case of questions.**
- **Data-analysis**
  - **Based on raw data, no outliers removed at this point**
  - **APTM based on current data**
    - **Script runs fine with the data set from the previous study**
    - **Incompatibility with recent excel-version/new PC for data-analysis**
      Step by step getting there, but painstaking and time consuming
      Just used the mean for now.

First Phase – Preliminary data

Data presented at today's meeting

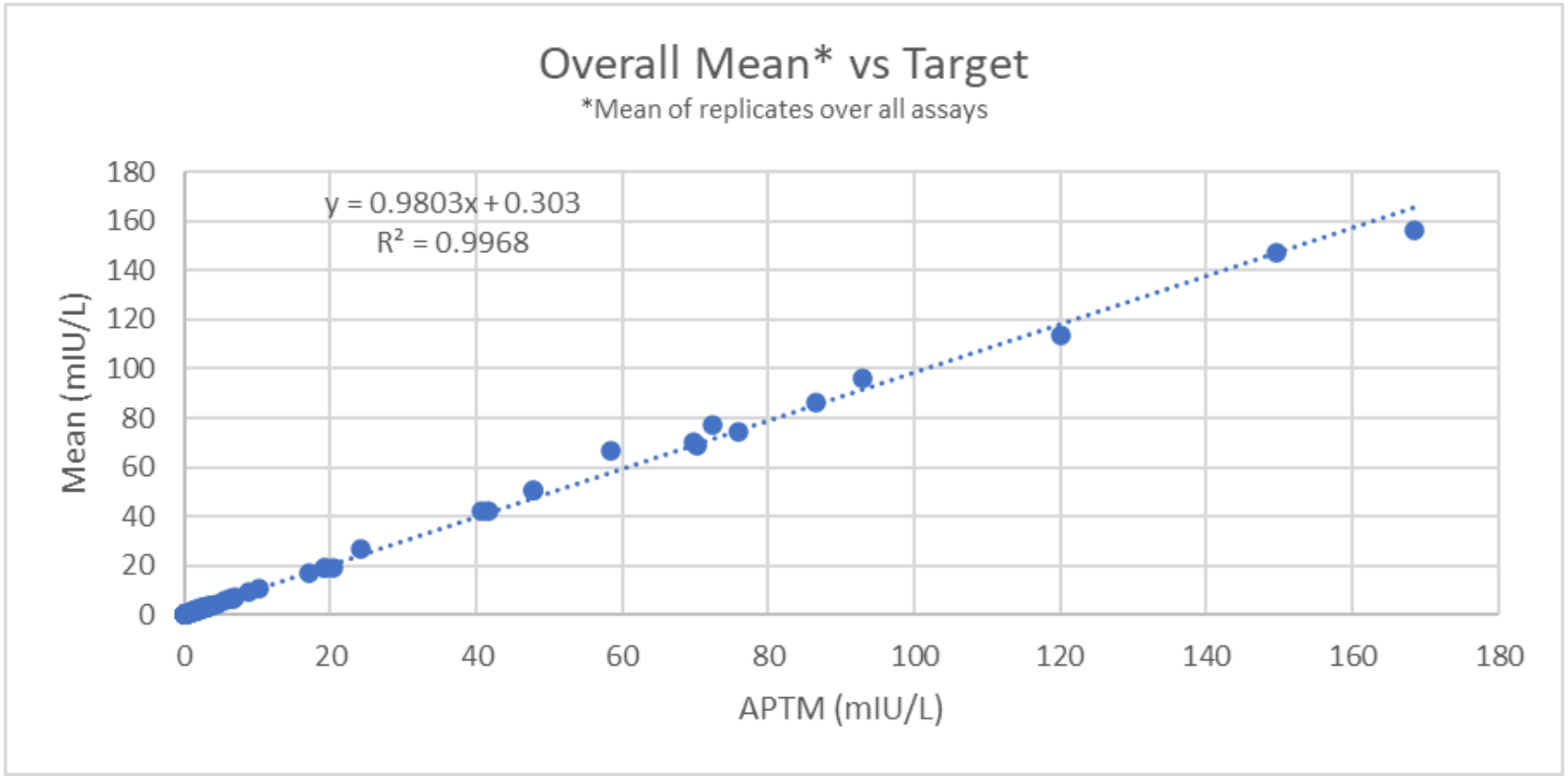
- **Anonimized**
  - **Some questions popped-up, will contact individual manufacturers in the upcoming weeks**
  - **Possibility to report numerical values for samples outside the measurement range?**
- **Data after recalibration**
  - **Without one assay**

First Phase – Preliminary data

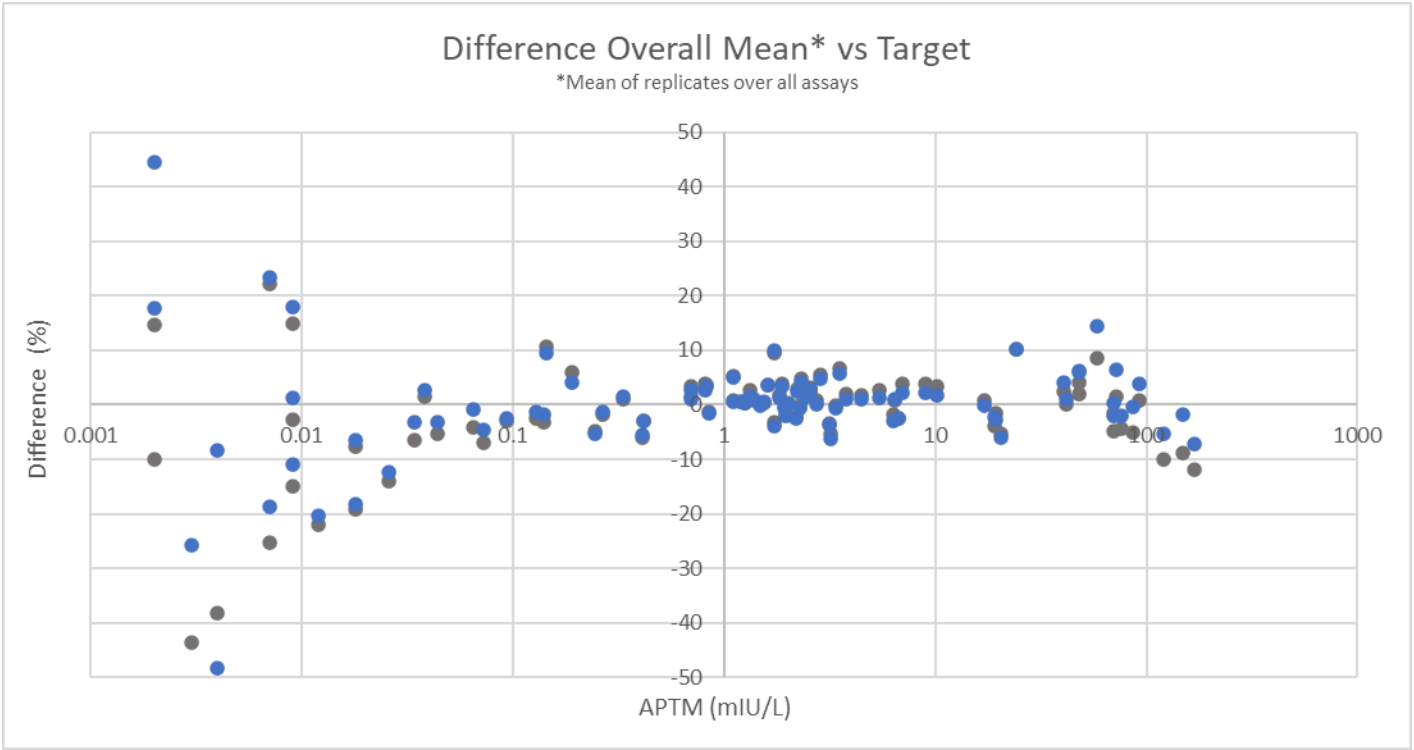


First Phase – Preliminary data

After Recal



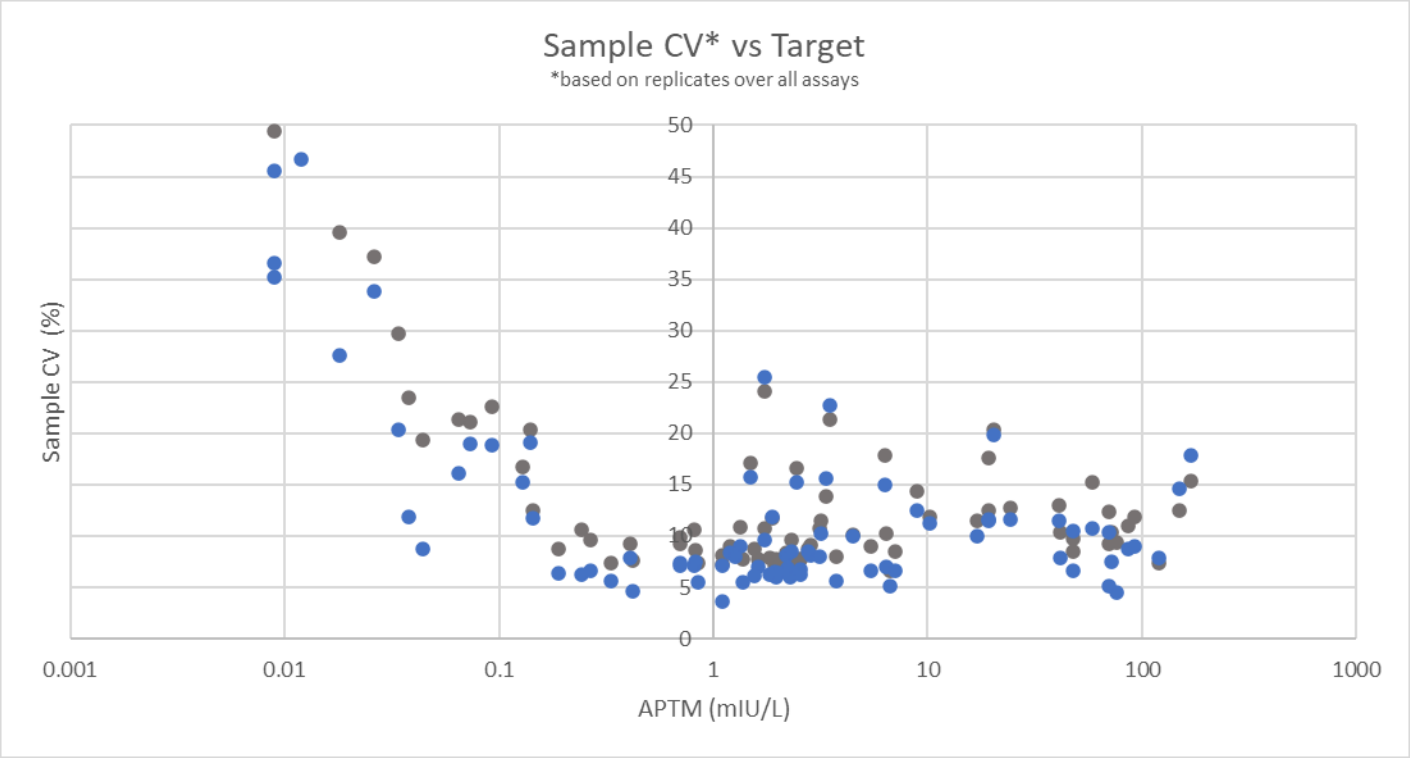
First Phase – Preliminary data



Grey before recal, blue after recal

Some samples < 0.01 mIU/L outside y-axis

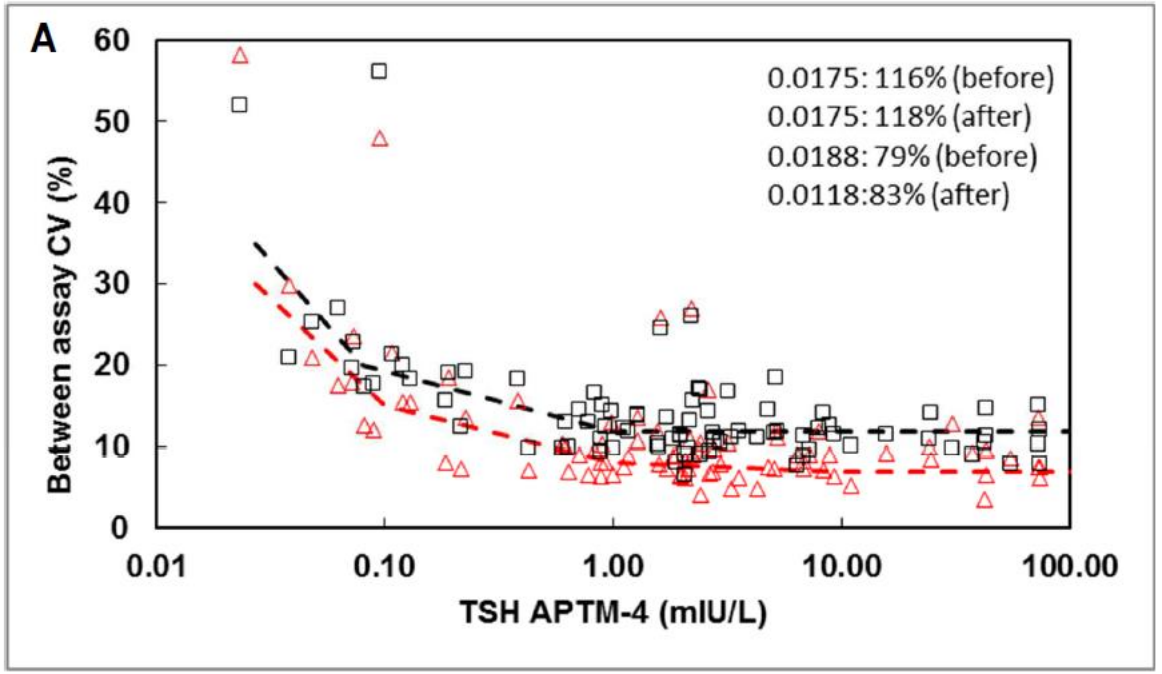
First Phase – Preliminary data

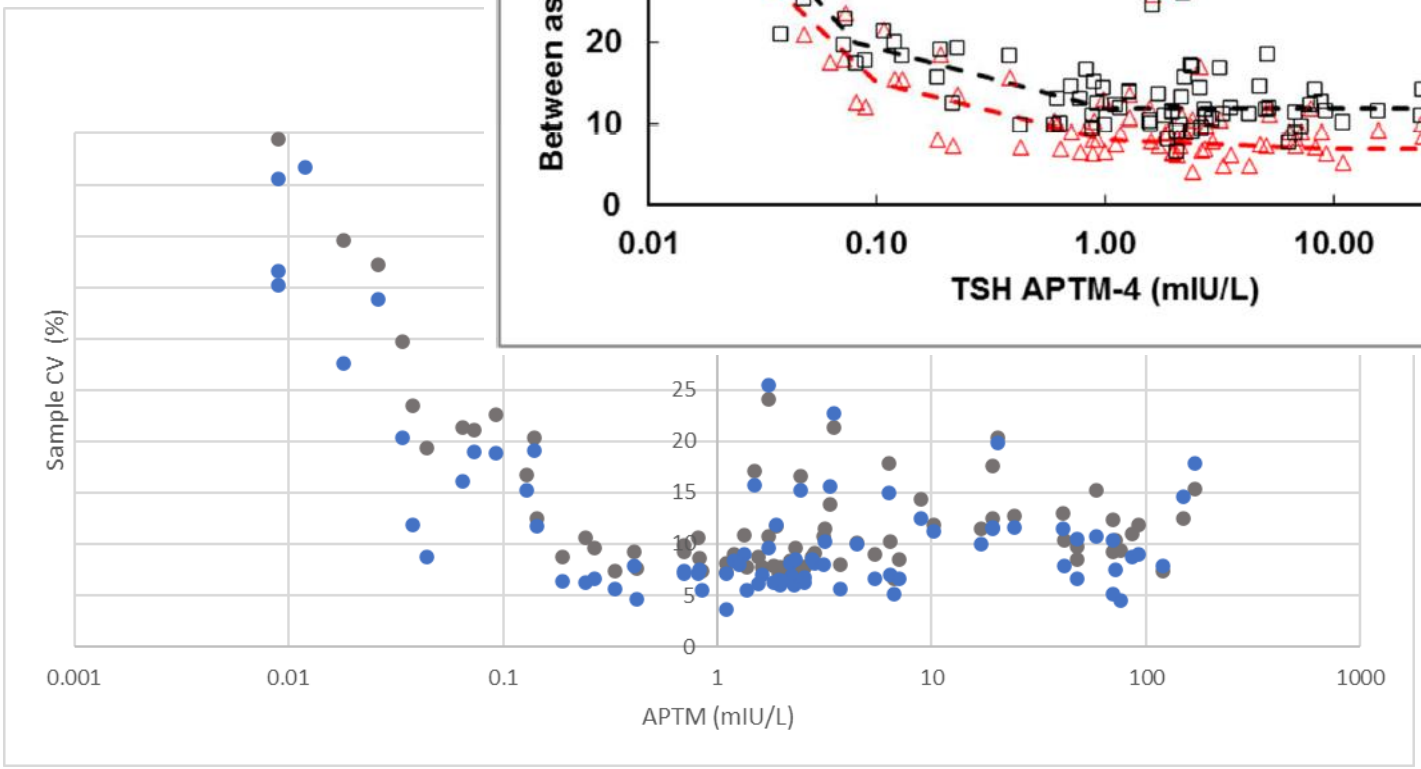


Grey before recal, blue after recal

Some samples < 0.01 mIU/L outside y-axis

First Pha

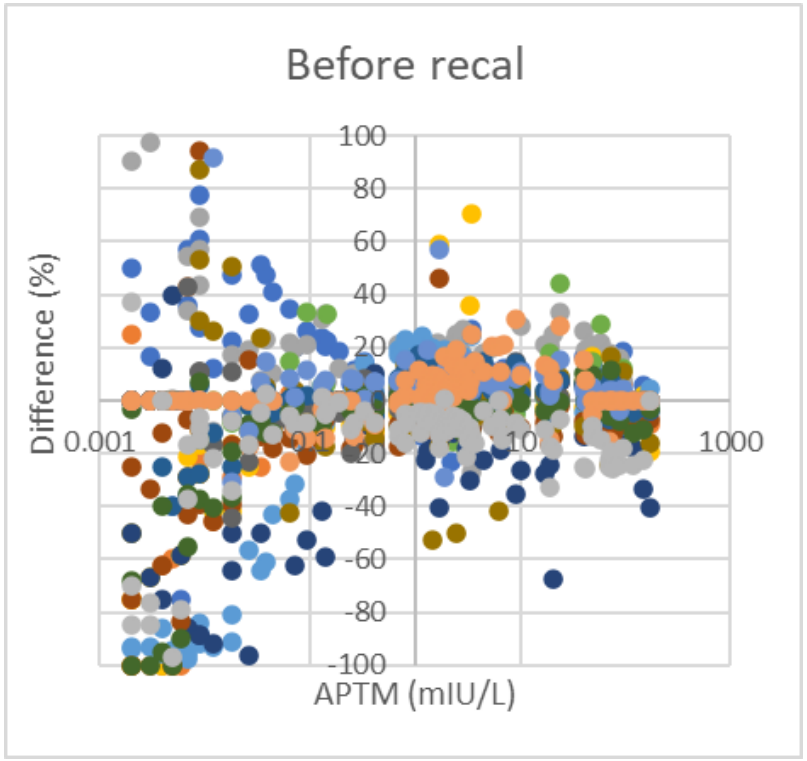


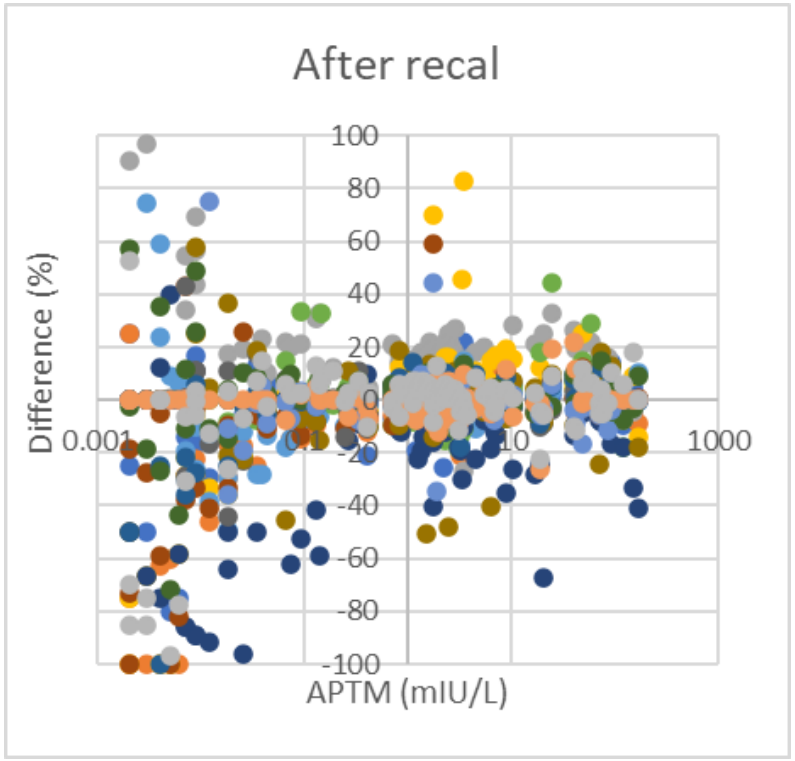


Same order of magnitude as in the previous study

First Phase – Preliminary data

Results for each individual sample, each color is a different manufacturer





First Phase – Preliminary data

Deviation per concentration range

Grey: not recalibrated

Before recal																
Average	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
<0.5	26	-29	60	-29	-58	5	-37	-25	51	73	-8	-30	18	8	-11	-23
0.5-5	2	1	14	5	13	-7	-10	-6	4	-4	6	-1	1	8	6	-9
>5	8	2	13	1	-2	6	-16	-8	3	-3	3	-1	-2	4	11	-18
After recal	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
<0.5	-13	-29	60	-25	3	5	-37	-19	56	61	-7	6		-1	-2	-15
0.5-5	-2	1	14	13	1	-7	-10	2	2	0	3	1		-1	-2	2
>5	3	2	13	8	0	6	-16	0	-2	-2	2	0		-4	2	1

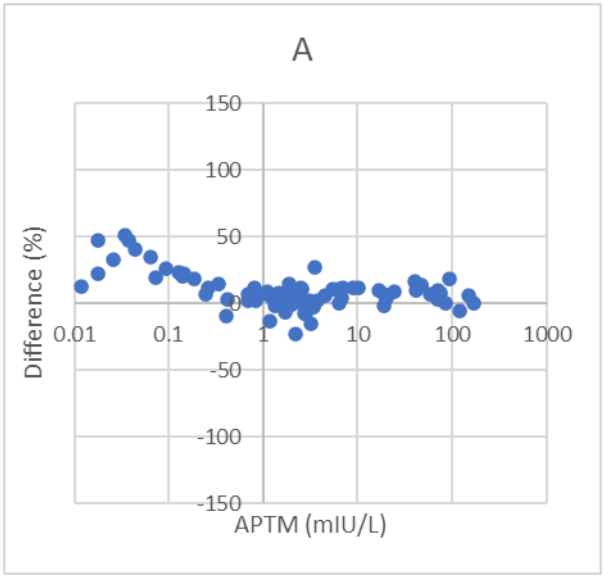
Table 3S: Median deviations (%) of each of the immunoassays to the APTM-4 before and after recalibration in distinct concentration intervals.

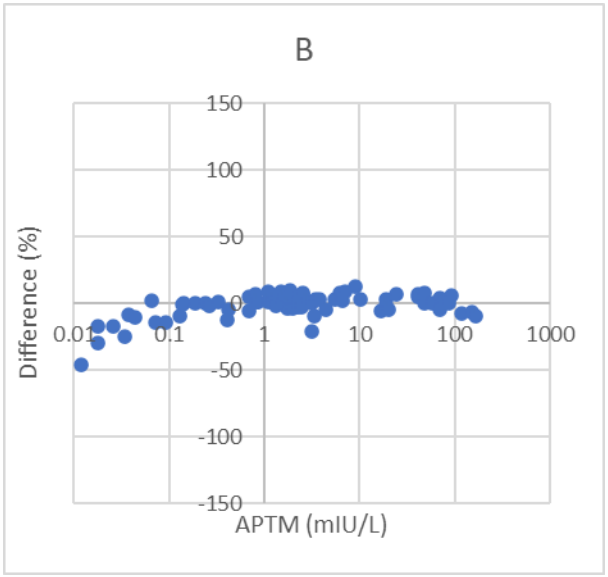
Assays	Before recalibration			After recalibration		
	<0.5 mIU/L	≥0.5 <5 mIU/L	≥5 mIU/L	<0.5 mIU/L	≥0.5 <5 mIU/L	≥5 mIU/L
A	-0.6	-1.6	0.0	-0.6	-1.6	0.0
B	-9.4	-7.0	-14.0	1.8	4.5	-3.4
C	23.0	19.4	8.3	6.6	2.6	-6.9
D	-41.4	1.0	1.0	-0.3	1.5	-0.2
E	-23.4	7.2	6.7	-9.5	-1.5	-2.3
F	-11.3	-9.5	-6.8	-5.9	-6.5	-1.9
G	-3.6	-4.3	-3.3	4.3	0.5	-1.8
H	-10.7	-11.8	1.0	-6.2	-8.4	1.8
I	9.1	3.1	4.7	15.9	2.0	-2.9
J	3.0	4.5	3.0	-1.1	0.4	-1.1
K	-19.4	-5.9	0.7	-20.7	-0.4	-0.8
L	-23.8	-15.4	-14.3	1.0	-0.5	2.5
N	-10.1	-14.9	-12.0	5.6	-5.4	3.1
O	-11.3	-5.4	-4.6	-0.1	7.1	6.3

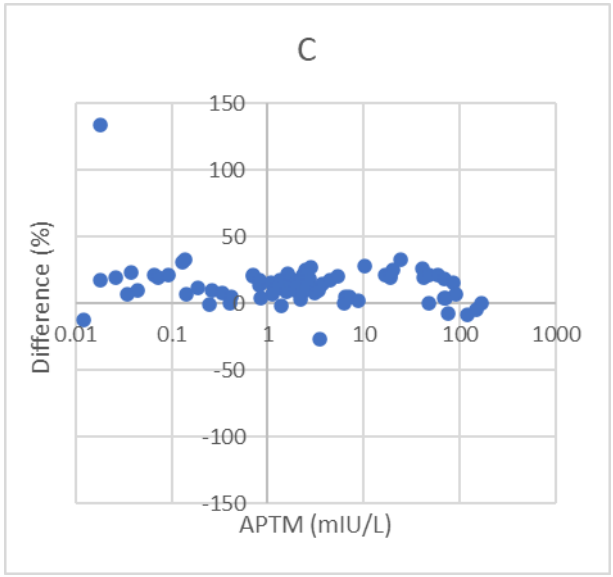
C - STFT ifcc International Federation of Clinical Chemistry and Laboratory Medicine

First Phase – Preliminary data

Restricted to >0.01 mIU/L for resolution

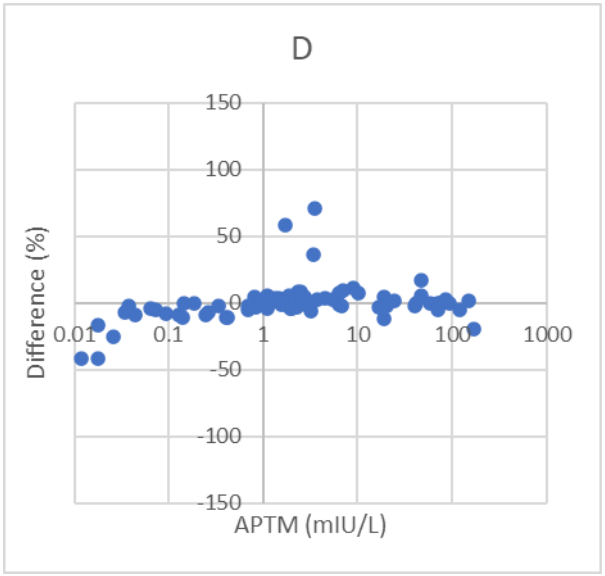


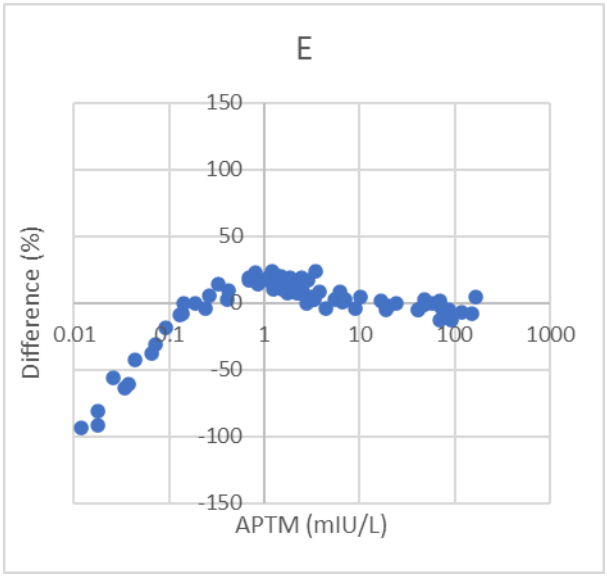


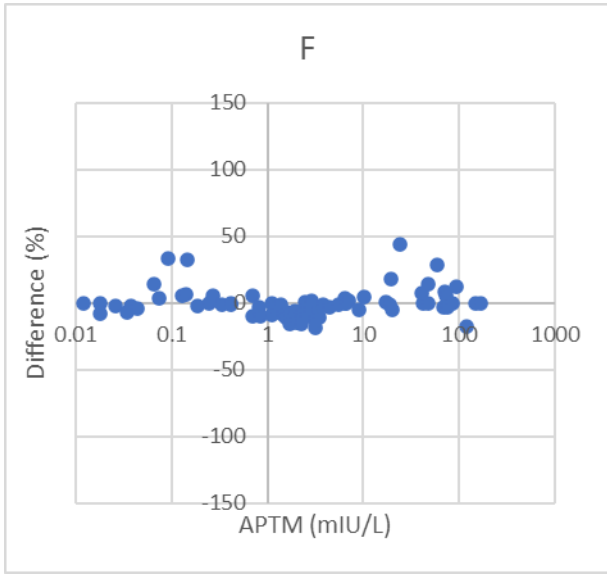


LOG-scale

First Phase – Preliminary data

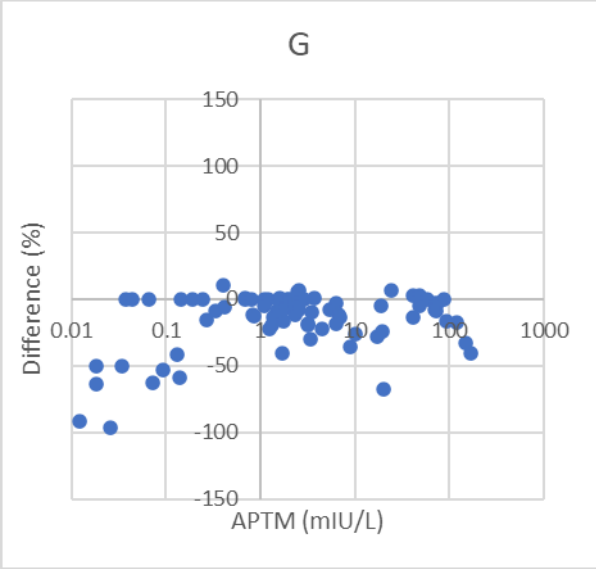


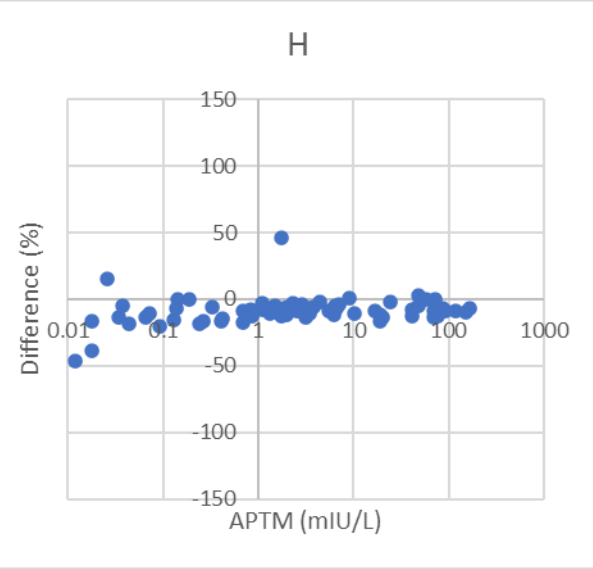


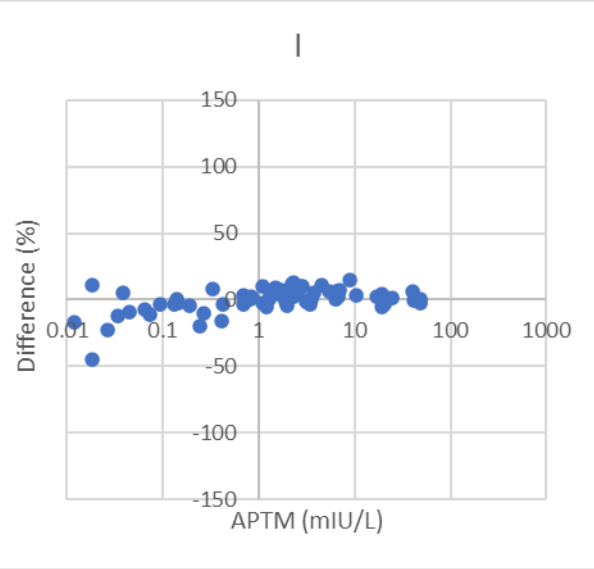


LOG-scale

First Phase – Preliminary data

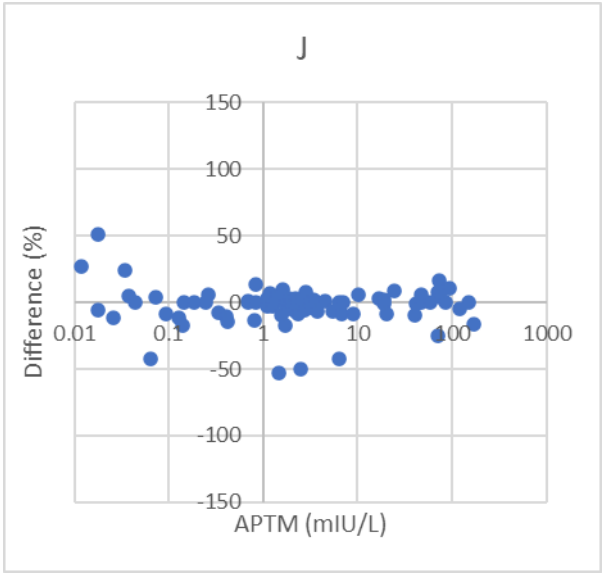


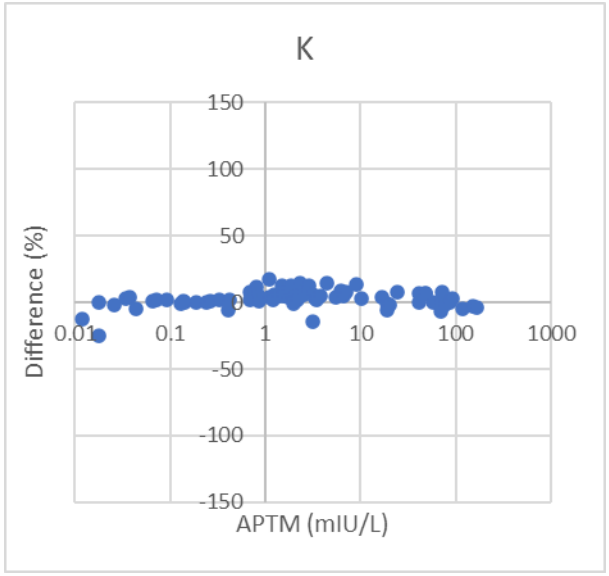


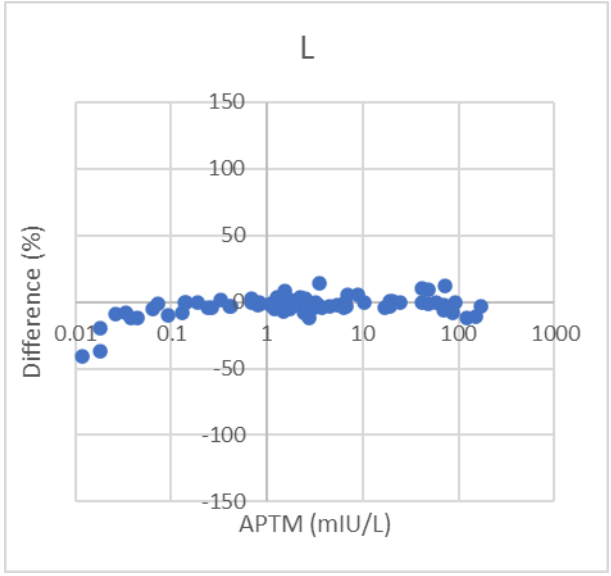


LOG-scale

First Phase – Preliminary data







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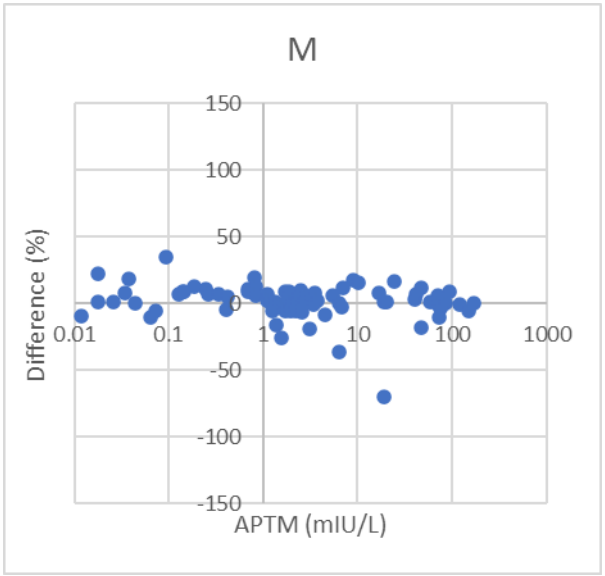
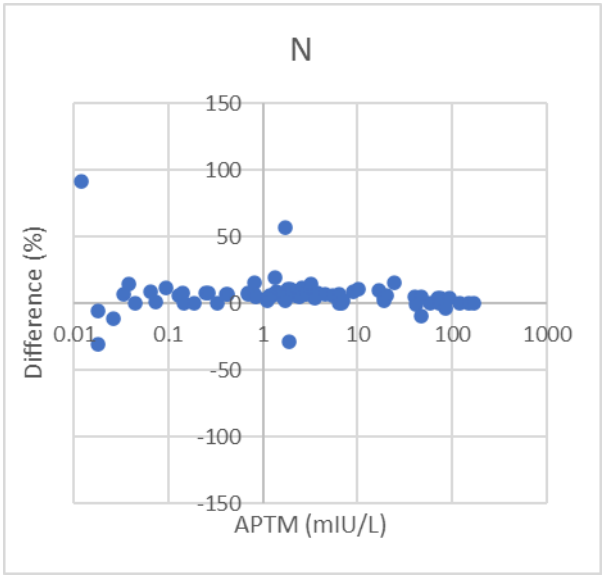
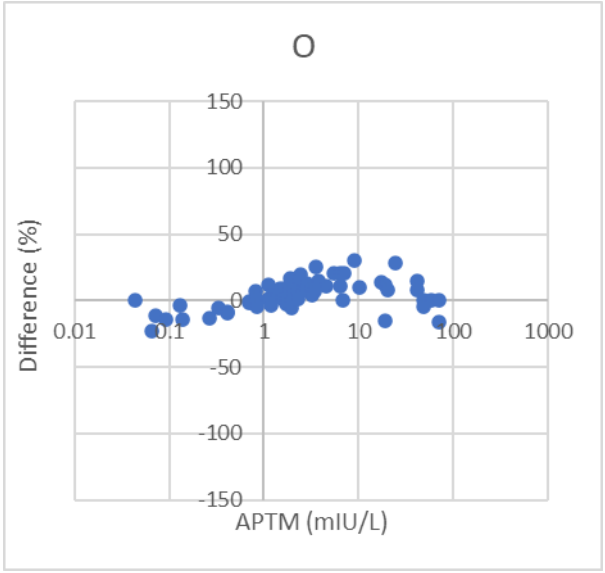
First Phase – Preliminary data

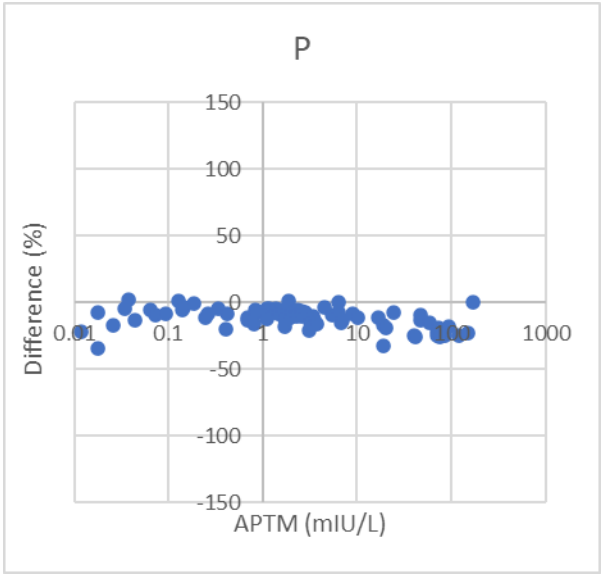






LOG-scale

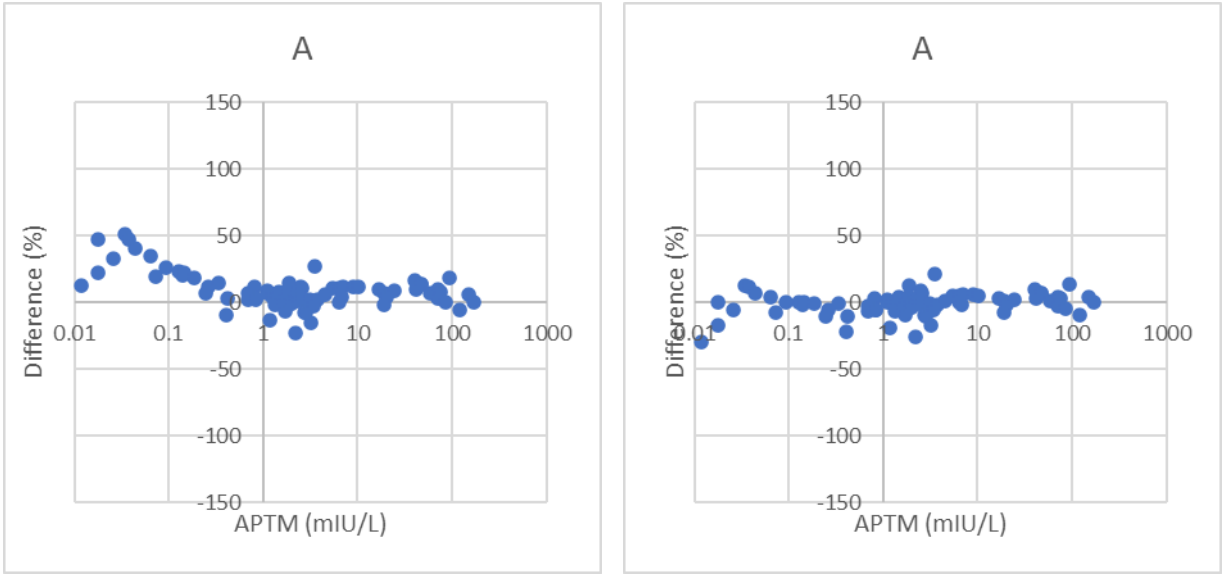
First Phase – Preliminary data



LOG-scale

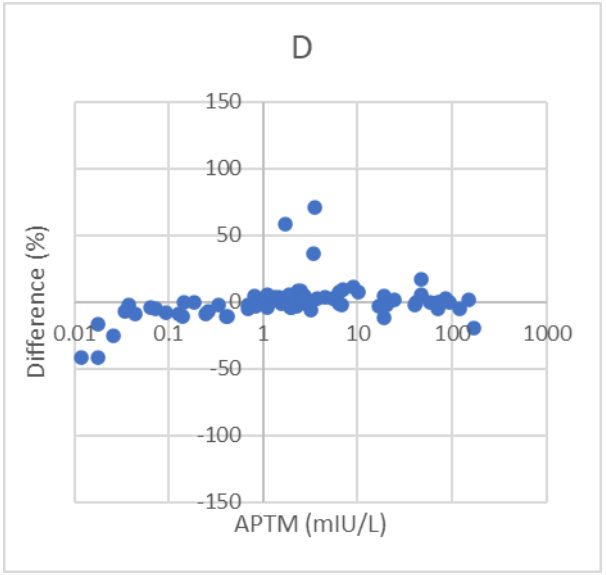
First Phase – Recall by MF

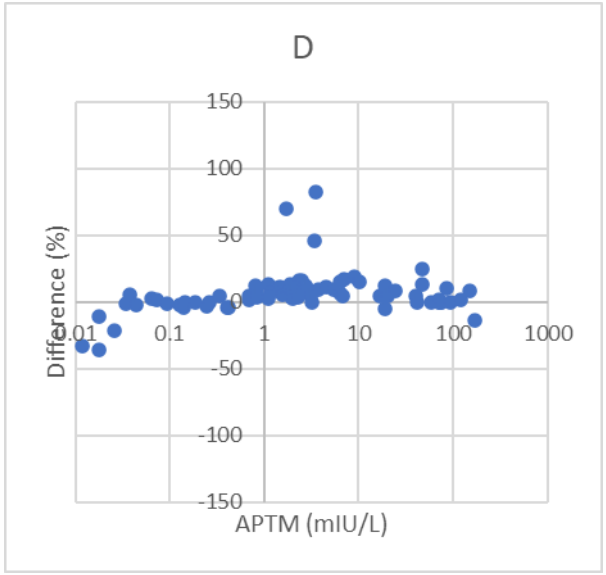
Before vs after recalibration



First Phase – Recall by MF

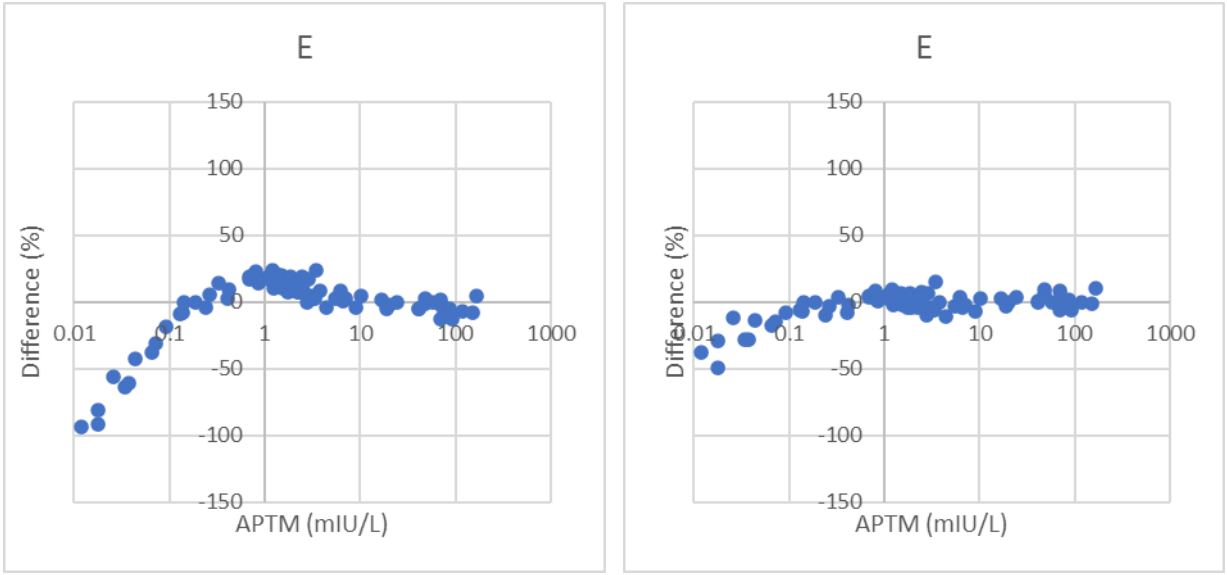
Before vs after recalibration





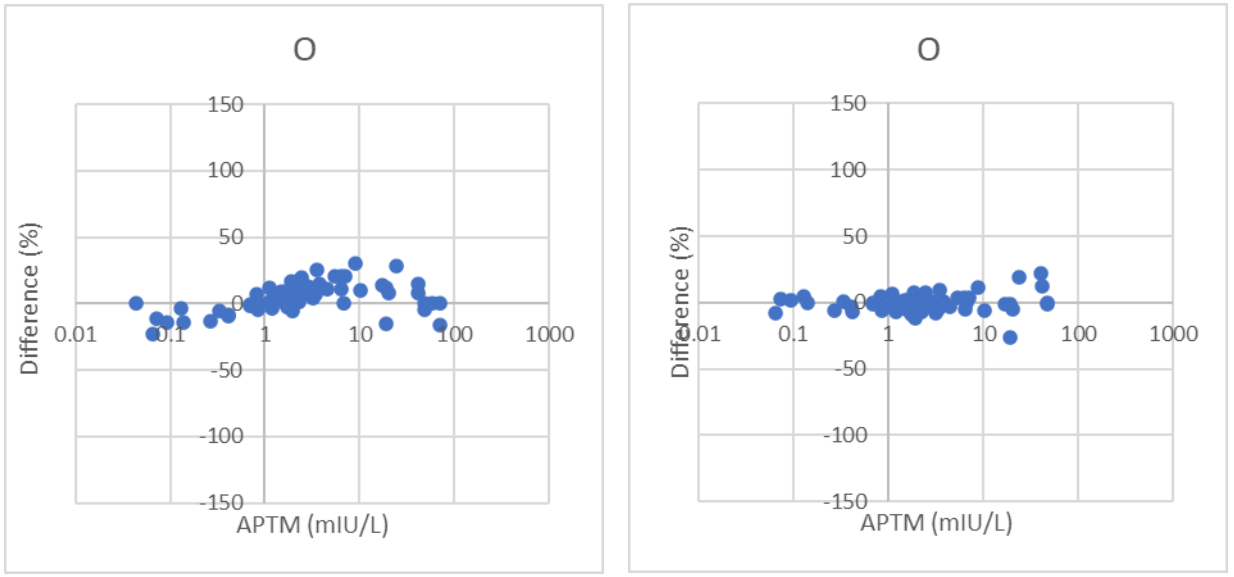
First Phase – Recall by MF

Before vs after recalibration



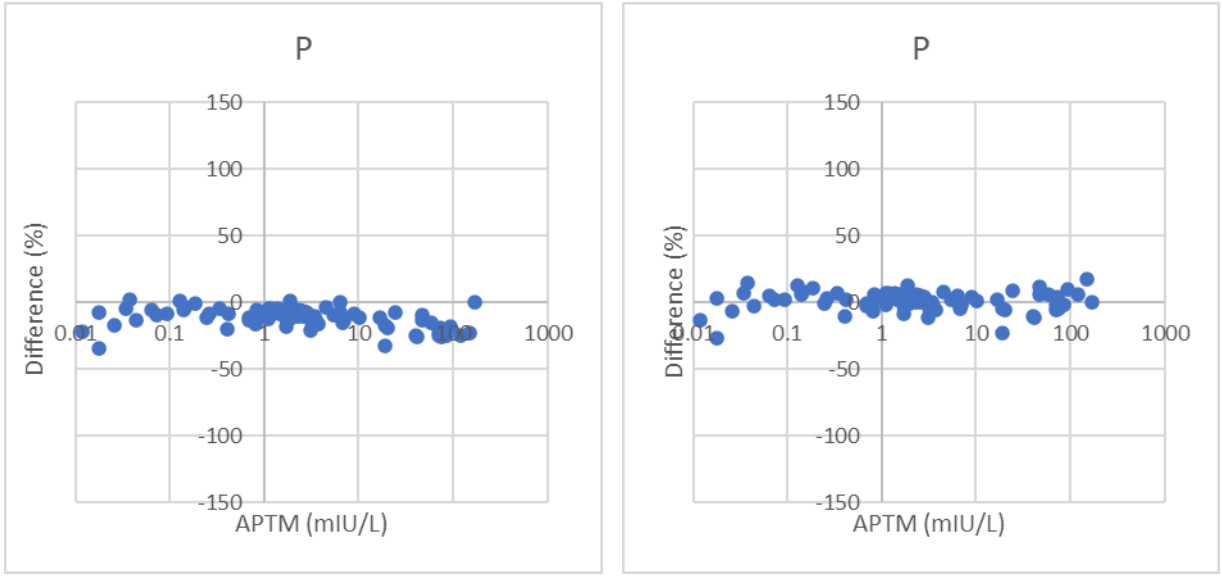
First Phase – Recall by MF

Before vs after recalibration



First Phase – Recall by MF

Before vs after recalibration



First Phase – Preliminary conclusions

- 0.5-5 mIU/L status before recalibration seems to be somewhat better than in the previous method comparison
- Recalibration brings further improvement, primarily at the level of the individual manufacturers
  ? Different/new assays compared to previous method comparison study
- No numerical data for 6 assays in the <0.5 mIU/L or lower concentration range
  No numerical data for 4 assays in the >50 mIU/L or higher concentration range
  Influence on selection of new samples, see further?

Second Phase – logistics and samples

Logistics

- Initiated: **To be determined** – after the results of the first phase are evaluated
- Shipment of samples: **To be determined** – collection of samples ongoing

Aim for the same time period and protocol as last year?

- **Update contact details: September 2023**
  If possible, use the same contacts, also within subcontracting couriers
- **Ship samples: November 2023**
- **Report: January 2024**
- **Reimbursement of costs via C-STFT**

Second Phase – measurement protocol

- **Duplicate analysis of each sample within the same run.**
- **Each manufacturer will measure a subset of the samples**
  - Randomized
  - Total of 5 results per sample
  - Goal: to have as much leftover samples as possible

Second Phase – Instructions and report

Instructions

- Similar to the first phase of this round of testing, details will be shared as we proceed.

Report

- **Report the results as measured after recalibration as performed in the first phase of this study**
- An excel template will be provided
- This includes the proposed measurement sequence
- Please also provide the used QC protocol

Requirements for sample collection

- **At least 20 mL of serum per donor (drawing at least 50 mL of whole blood)**
- **Only off-the-clot serum**
- **Sera must be from individual donors and must not be pooled**
- **Separated from clot and store immediately at -70 °C until shipment.**
- **The institution's standard protocol for blood collection can be used (sharing a copy or short description would be beneficial)**
- **If possible, send on a monthly basis donor information**

- **Suggested donor information needed to categorize samples:**
  Age category, gender, ethnicity, diagnoses (statement and thyroidal status, with an additional field to add a comment), thyroidectomy, thyroid and other medication, family history thyroidal dysfunction, smoking status, weight, height, BMI, date of blood collection, Anti-TPO*, TG AB*, TRAB*, AB assay, AB Cut-off, TSH conc*, TSH assay, TSH Reference range, FT4 conc*, FT4 assay, FT4 Reference range. *: when screening upon selection. **Local regulation on data sharing will be followed.**

Resources

- Current budgets on the C-STFT account are estimated to be sufficient to cover the costs of the current sample collection
- C-STFT will perform viral testing as needed and budget allows
- CDC will receive, aliquot and store samples

Collection sites

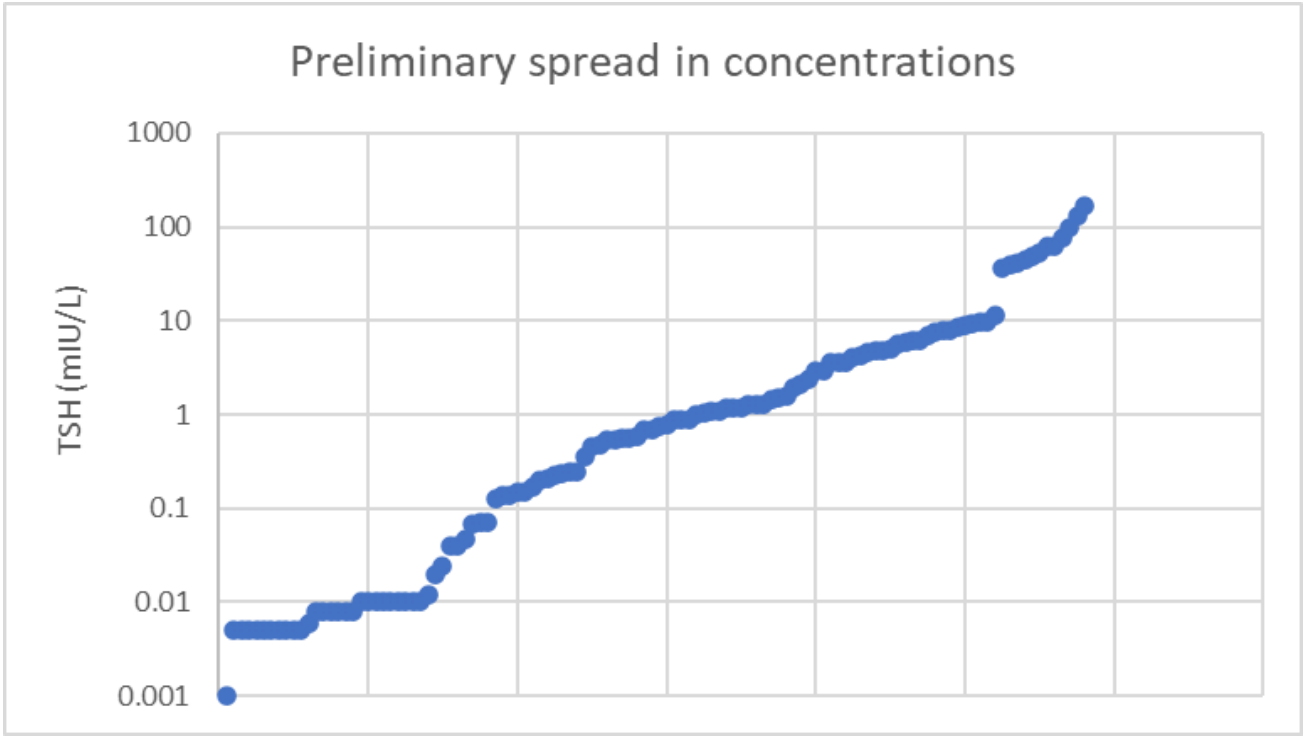
Active

- **University of Ghent (Dr. B. Lapauw)**
- **O.L. Vrouw Aalst (Dr. P. Van Crombrugge) (BE)**
- **Dokkyo Medical University, Department of Endocrinology (Dr. Kato) (JP)**
- **Hospices Civils de Lyon (Fr)**
- **CDC repository samples (euthyroid range only)**
- **General hospitals Sint-Jan Bruges (Dr. A. Van den Bruel)**

Pending

- **University of Sydney (Dr. P. Williams) (AU)**
- **Oslo University Hospital (No)**

Preliminary overview of samples



Preliminary overview of samples

Group	Description	2022	Harmonization panel 2017
GROUP A:	Hyperthyroid		
A1:	10 patients with suppressed TSH, around 0.01 mIU/L	**18**	**11**
A2:	10 patients with TSH values between 0.01 – 0.1 mIU/L	**18**	**13**
A3:	10 patients with TSH values between 0.1 – 0.5 mIU/L	**15**	**8**
GROUP B:	10 patients with TSH values between 0.5 – 5 mIU/L	**39**	**44**
GROUP C:	Hypothyroid		
C1:	20 patients with TSH values between 5 – 50 mIU/L	**19**	**19**
C2:	20 patients with TSH values > 50 up to 100 mIU/L	**7**	**6**
TOTAL	With preliminary values	**116**	**101**
	All	**123**	**101**

Aim → ~ 132 samples

Preliminary overview of samples

Group	Description	2022	Harmonization panel 2017
GROUP A:	Hyperthyroid		
A1:	10 patients with suppressed TSH, around 0.01 mIU/L	**18**	**11**
A2:	10 patients with TSH values between 0.01 – 0.1 mIU/L	**18**	**13**
A3:	10 patients with TSH values between 0.1 – 0.5 mIU/L	**15**	**8**
GROUP B:	10 patients with TSH values between 0.5 – 5 mIU/L	**39**	**44**
GROUP C:	Hypothyroid		
C1:	20 patients with TSH values between 5 – 50 mIU/L 1 with recTSH	**19**	**19**
C2:	20 patients with TSH values > 50 up to 100 mIU/L 4 with recTSH	**7**	**6**

Need to collect more?

→ **Which concentrations?**

Depending on concentration range?

→ **Inclusion of genuine euthyroid samples?**

4. FT4 RMP Network

Network Members

- Ref4U (Belgium)
- CDC Clinical Reference Laboratories (USA)
- Radboud University Medical Center of Nijmegen (The Netherlands)
- Reference Material Institute for Clinical Chemistry Standards (Japan)

Requests for joining/collaboration

- Autobio, China
- Government of Western Australia, Department of Health

More organizations have expressed their interest in implementing the cRMP

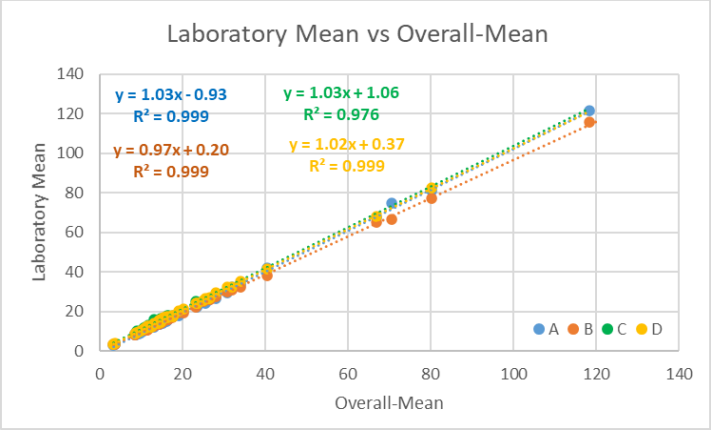
Second network method comparison

Goals

- Assess agreement among candidate reference laboratories over a broader concentration range
- Identify potential sources of bias
- Included characterization of reference materials from the U.S. National Institute for Standards and Technology (NIST).

Results

- Average difference to the overall mean A: -2.4%; B: -2.0%; C: 10.5%; D: 4.2%
- All laboratories performed calibration independently (no common calibrators)
- Report and publication in preparation



C - STFT ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Network Rules

- Operate the cRMP for FT4 based on the current version of the network approved SOP
- Participate in regular meetings/communications
- Participate in regular network studies to monitor the analytical performance of the member laboratory. To maintain membership, network members need to successfully pass two consecutive network studies.
- Meet analytical performance requirements for FT4 cRMP:
  - Imprecision: ≤5%,
  - Bias: ±2.5%,
  - Expanded measurement uncertainty: 7.6%,
  - LoQ: 1.3 pmol/L (0.10 ng/dL)
  - chromatographic separation of isomers

Network Rules

- Operate the cRMP for FT4 based on the current version of the network approved SOP

Heleen I. Jansen, Rob van der Steen, André Brandt, André J. Olthaar, Hubert W. Vesper, Eri Shimizu, Annemieke C. Heijboer, Katleen Van Uytfanghe and Antonius E. van Herwaarden*

Description and validation of an equilibrium dialysis ID-LC-MS/MS candidate reference measurement procedure for free thyroxine in human serum

Development of an equilibrium dialysis ID-UPLC-MS/MS candidate reference measurement procedure for free thyroxine in human serum

Ashley Ribera [a], Li Zhang [a,*], Amonae Dabbs-Brown [a], Otoe Sugahara [a], Krista Poynter [a], Katleen van Uytfanghe [b], Eri Shimizu [c], Antonius E. van Herwaarden [d], Julianne C. Botelho [a], Uliana Danilenko [a], Hubert W. Vesper [a]

[a] *Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Atlanta, GA, 30341, United States*
[b] *Ref4U—Laboratory of Toxicology, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium*
[c] *Reference Material Institute for Clinical Chemistry Standards, Yokohama, Kanagawa, Japan*
[d] *Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands*

Rules for new members

- Laboratories must provide in writing to the network coordinator their intent to join the network
- Candidate network laboratories must demonstrate that they correctly perform the latest version of the FT4 cRMP and meet analytical performance criteria
- Candidate laboratories must successfully participate in two consecutive network studies

Way forward

- **Refine RMP SOP based on feedback from network laboratories**
- **Formalize network**

  → **Manuscript describing the results, network rules, rules for new members under preparation.**

- **Count repository samples**
- **Set-up next round of testing, that would also allow candidate members to participate**
  Aim: end of 2023
- **TBD: need for additional samples? Funding?**

Sustainability of RMP

To ensure sustainability of the RMP, the network is conducting several studies to investigate the impact of different supplies on measurement accuracy:

- Different membranes
- ED cells and related hardware
- Primary calibrators

→ Initial data suggest that different membranes and ED designs provide equivalent results

→ A manuscript is under revision in Journal of Mass Spectrometry and Advances in the Clinical Lab

5. Educational activities and activities supportive of FT4 and TSH standardization/harmonization

Focus on Educational Activities

- Create awareness about the importance of having standardized/harmonized FT4 and TSH assays
- Prepare stakeholders about potential changes in values as a result of recalibration
- Inform stakeholders about the work of the IFCC C-STFT and national/regional organizations conducting standardization/harmonization

Education/Communication

- ATA Working Group, ATA is also putting together a panel reviewing thyroid function tests
  → manuscript under revision
- Partnership for the Accurate Testing of Hormones
- C-STFT Website
- Invited lectures for professional organizations

6. FT4 National/Regional Activities

Ref4U, UGent

- Chair activities of the C-STFT
- Continues to provide reference measurements to manufacturers, private laboratories and EQA providers
    - TT4
    - TT3
    - FT4

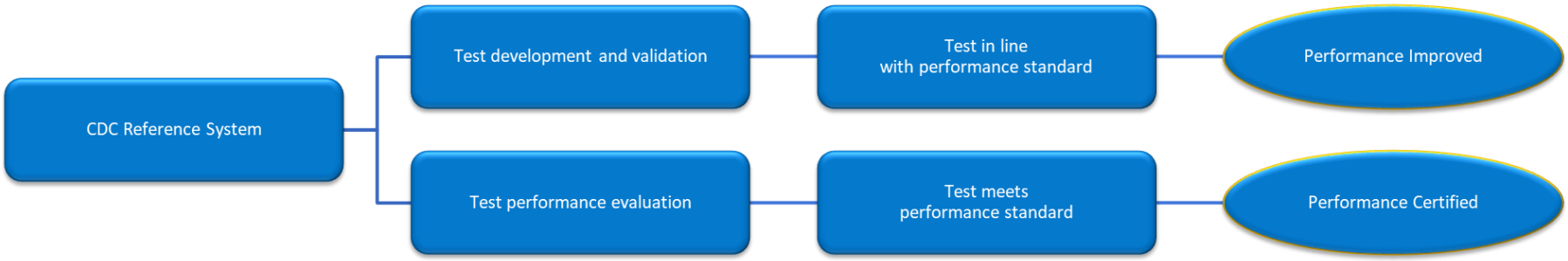
U.S. CDC Clinical Standardization Programs - FT4 Standardization Program -

- 2 manuscripts accepted/published:
  - Development of an equilibrium dialysis ID-UPLC-MS/MS candidate reference measurement procedure for free thyroxine in human serum. Ribera A., Zhang L., Dabbs-Brown A, Sugahara O., Poynter K., Van Uytfanghe K., Shimizu E., Van Herwaarden A.E., Botelho J.C., Danilenko U., Vesper H.W. *Clin. Biochem.* (2023), 116, 42 - 51
  - Practical considerations for accurate determination of free thyroxine by equilibrium dialysis. Ribera A., Zhang L., , Ribeiro C.M.B.,, Vazquez N., Thonkulpitak J., Botelho J.C., Danilenko U., Van Uytfanghe K. and Vesper H.W. *Accepted to JMSACL.*

U.S. CDC Clinical Standardization Programs - FT4 Standardization Program -

- Assisting assay manufacturers and laboratories operating LDTs with FT4 standardization
  - HoSt Phase 1 samples (serum samples with reference values assigned) are available. Please contact Standardization@cdc.gov to enroll
  - HoSt Phase 2 formal certification is set to start in 2024

Phase 1: "Preparation" for performance evaluation/certification (voluntary)



Phase 2: Performance evaluation/certification

Radboud University Medical Center of Nijmegen

Standardization/harmonization in Japan

- Dr. Hishinuma, president of the Japan Thyroid Association, organized a meeting including 10 in-vitro companies, ReCCs as well as scientific experts on how to establish TSH reference intervals in elderly, young, and pregnant people in Japan and how to standardize FT4 tests.
- ReCCS is establishing the IFCC FT4 RMP in its lab
- TSH RI for pregnancy, one infertility clinic will evaluate existing data
- FT4 standardization, ReCCs and 10 companies (members of JACRI: Japan Association of Clinical Reagents Industries) were asked to make serum panels for calibration. JACRI is now working on plans to develop such panels.

Member Updates and Other Items

Croatian Society of Medical Biochemistry and Laboratory Medicine
Update on reference ranges of thyroid functional tests

C - STFT ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Other agenda/discusion points

- For the future activities of the C-STFT
  - Focus on a better/more efficient/sustainable way to collect materials
  - Broaden the scope of our activities to other thyroid disease related analytes?

  → Input needed from all interested parties, liaise with other experts

- As a reminder, although not our focus, we should also keep promoting the existing reference measurement systems (TT4, TT3)

Next IFCC C-STFT ?
Dedicated meeting?

Fall 2023 – in preparation of the next round of testing?
Spring 2024 – after the next round of testing?