Implementation challenges – the thyroid hormone example

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JCTLM Members' and Stakeholders' Meeting
Session V: New challenges for traceability in laboratory medicine

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

UNIVERSITEIT GENT

Faculty of Pharmaceutical Sciences
Department of Pharmaceutical Analysis
Ref4U *- Laboratory of Toxicology*

Standardization/harmonization of FT4/TSH

Approach

- **Method comparison study with a clinical panel reasonably covering the assays' measurement range**
- **Standardization of FT4 assays by recalibration against the conventional reference measurement procedure (RMP) based on equilibrium dialysis (ED) ID-LC/tandem MS#**
- **Harmonization of TSH assays by recalibration against a surrogate RMP, i.e., the All-Procedure-Trimmed Mean (APTM) by robust factor analysis**

#Van Uytfanghe K et al. Clin Chem 2006;52:1817-21.
Van Houcke SK et al. Clin Chem Lab Med 2011;49:1275-81.
$Van Houcke et al. Clin Chem Lab Med 2013;51:e103-5.
Stöckl et al. Clin Chem Lab Med 2014;52:965-72.

References

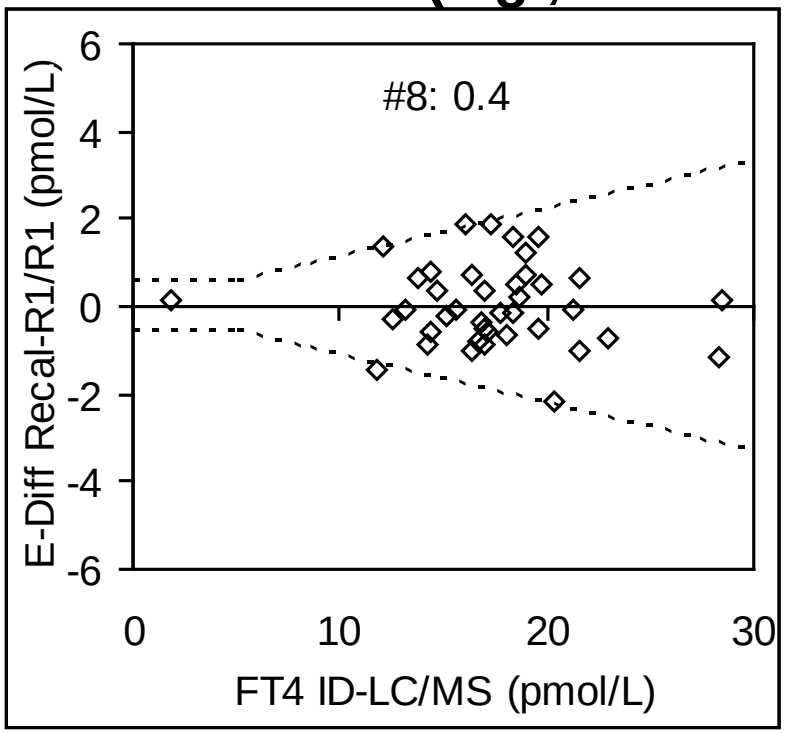
- Thienpont LM, Van Uytfanghe K, Beastall G, Faix JD, Ieiri T, Miller WG et al. Report of the IFCC working group for standardization of thyroid function tests
  - Part 1: Thyroid-stimulating hormone. Clin Chem 2010;56:902-11.
  - Part 2: Free thyroxine and free triiodothyronine. Clin Chem 2010;56:912-20.
  - Part 3: Total Thyroxine and Total Triiodothyronine. Clin Chem 2010;56:921-29.
- Thienpont LM, Van Uytfanghe K, Van Houcke S; IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). Standardization activities in the field of thyroid function tests: a status report. Clin Chem Lab Med 2010;48:1577-83.
- Thienpont LM, Van Uytfanghe K, Van Houcke S, Das B, Faix JD, MacKenzie F et al. A Progress report of the IFCC Committee for Standardization of Thyroid Function Tests. Eur Thyroid J 2014;3:109-16.

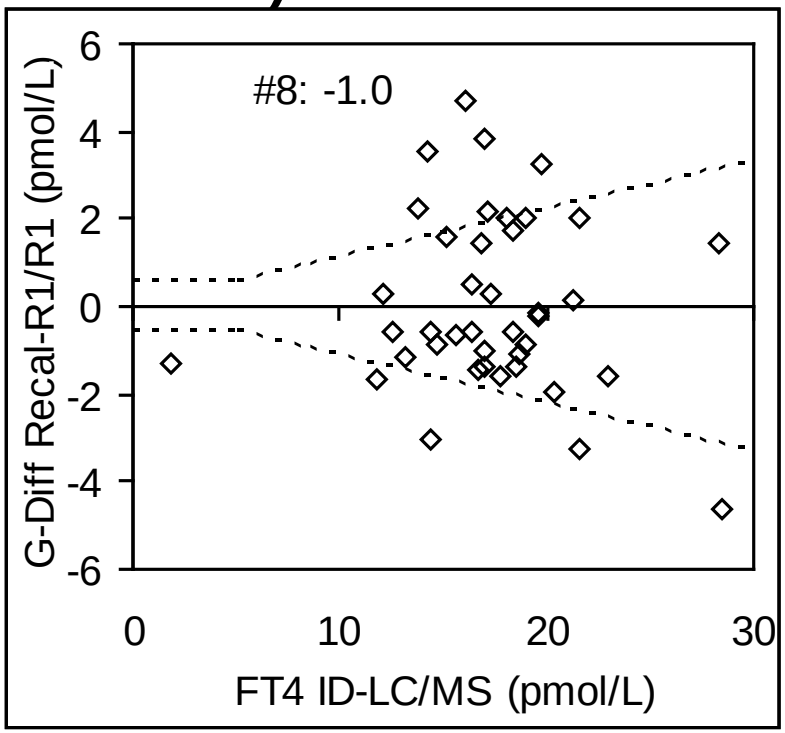
Requirements for successful standardization/harmonization

Sufficient intrinsic quality of performance

Common performance attributes inferred from measurement of native samples

Total error assessed *vs* biological limits to reflect sample-related effects (e.g., limit for FT4: 9.6%)#



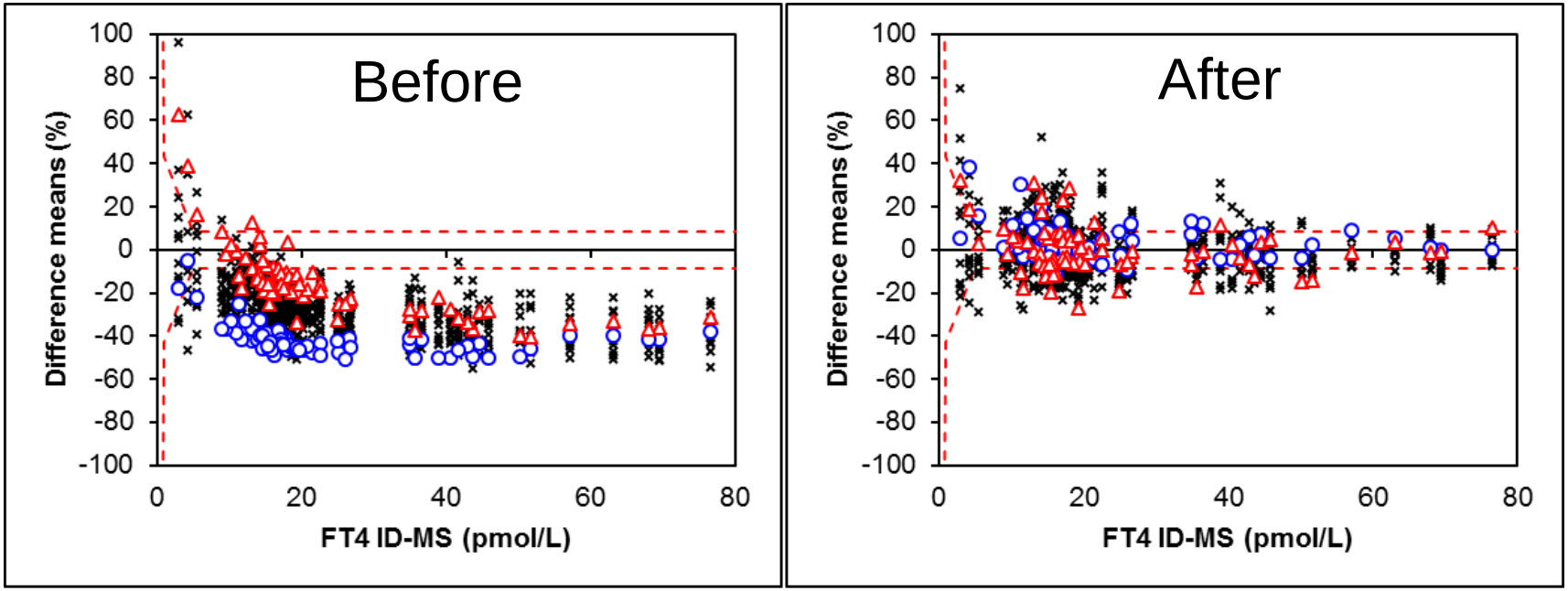


#Thienpont LM, et al. Clin Chem 2010;56:912-20.

Feasibility of standardization/harmonization

Feasibility of standardization/recalibration

FT4#



➔Bias to ED ID-LC/tandem MS removed

➔Residual dispersion nearly entirely due to within-assay effects

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Current status

Step-up to standardization/harmonization

Phase IV method comparison study

- New clinically relevant panels were collected to be measured in parallel with master calibrators:
  - FT4: 4.5 – 164 pmol/L (by ED ID/MS), n = 91
  - TSH: ~0.002 to 75 mIU/L (APTM), n = 101
- Measurements were done last May
- Preliminary report was discussed with the IVD manufacturers
- Recalibration by manufacturers is currently on-going
- Final data treatment and manuscript will follow

Preparation of follow-up panels

- TSH panel is ready (and targeted)
- FT4 panel is almost collected (will be targeted)

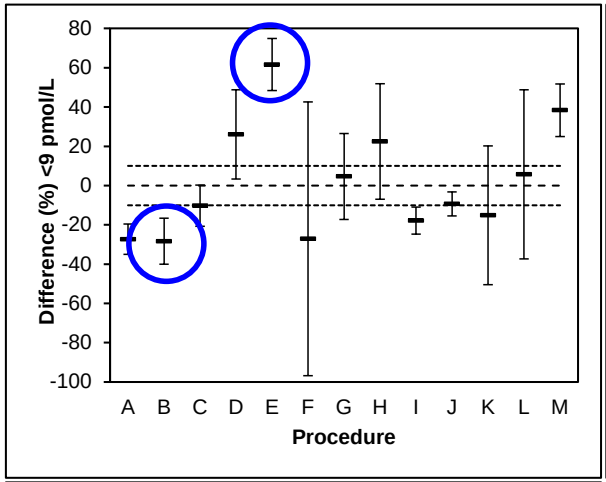
Standardization status – FT4

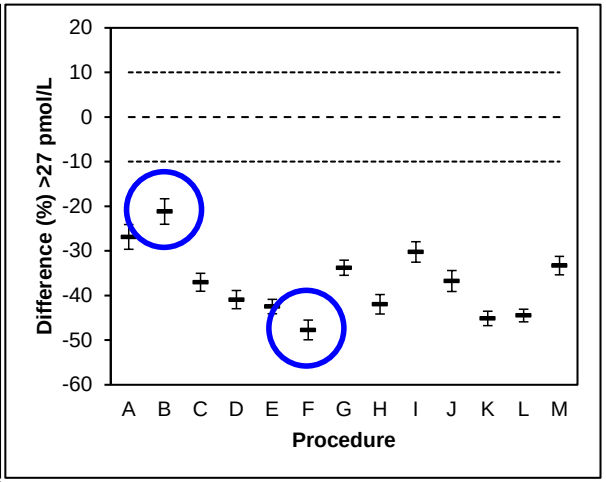
Bias to ED ID-MS#
(from Phase III)

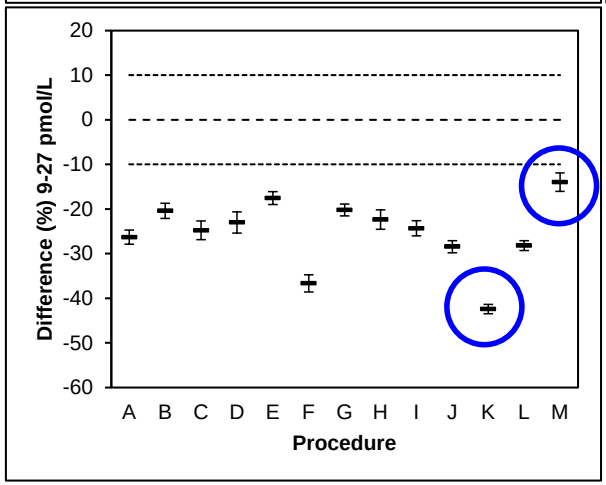
9–27 pmol/L:
-25% (mean)
Range: -14% to -42%

>27 pmol/L:
-37% (mean)
Range: -21% to -48%

<9 pmol/L:
2% (mean)
Range: -28% to 62%







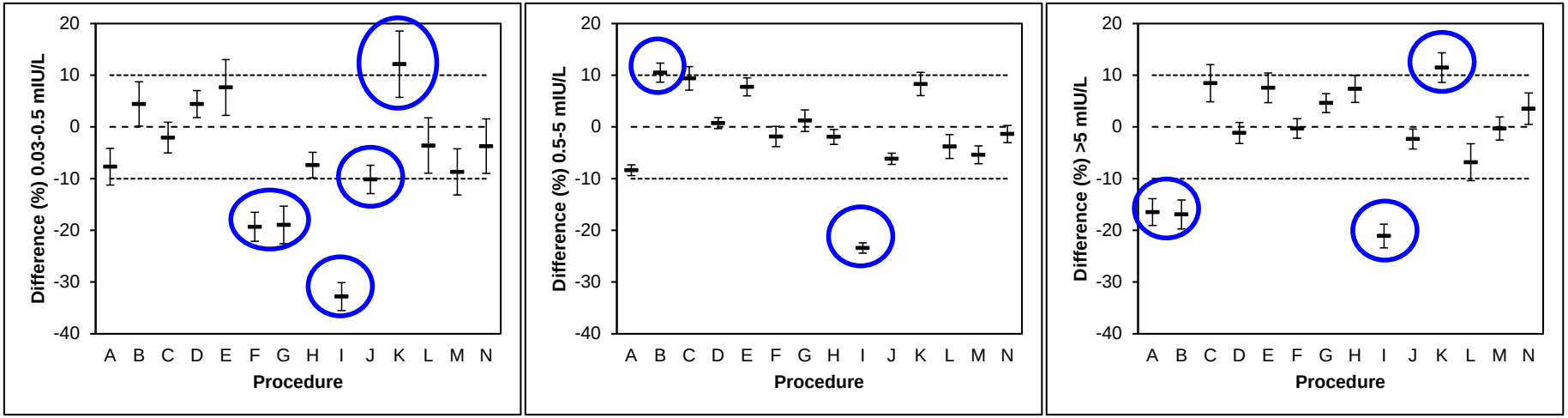
FT4 concentration range of the panel: 3 to 77 pmol/L

➔ All assays strongly negatively biased

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Standardization status – TSH

Bias to APTM# (from Phase III)



TSH concentration range of the panel: 0.04 – 80 mIU/L

- ➔ 0.5 – 5 mIU/L: comparability quite good; only 2 assays differ by >10% from APTM
- ➔ <0.5 mIU/L & >5 mIU/L: max 5 out of 14 assays outside the ±10% limit
- ➔ Max discrepancy between assays up to ~33% (whole range)

#Thienpont et al. Eur Thyroid J 2014;3:109-16.

Implementation

Benefit-risk analysis

Benefits of standardization/harmonization

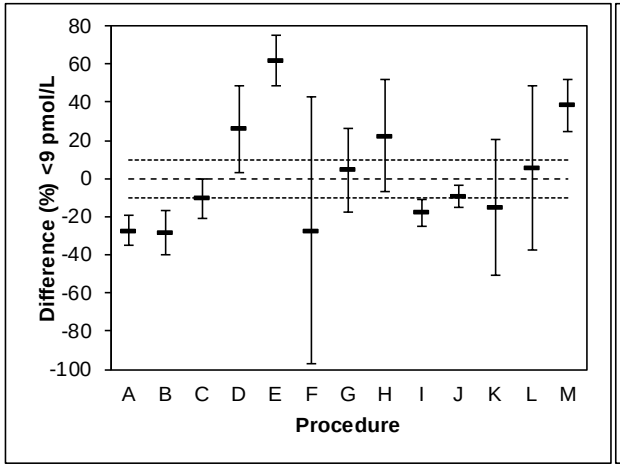
- Common reference intervals/clinical decision limits
- Evidence-based clinical practice guidelines
- Application of consistent standards of medical care
- Aggregation of results from several studies
- Translation of research into patient care & disease prevention activities
- Electronic patient records with inclusion of lab data

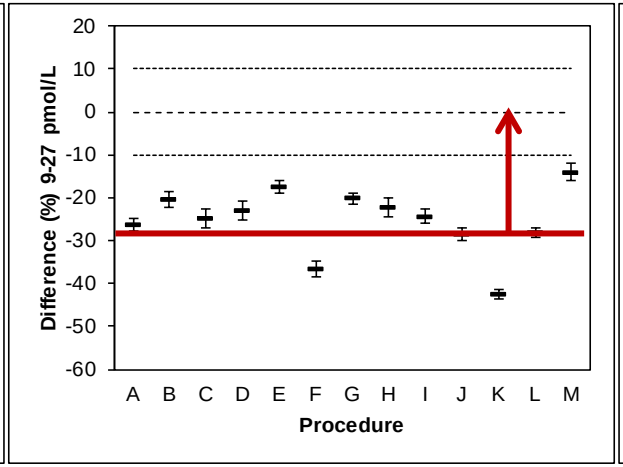
Risks

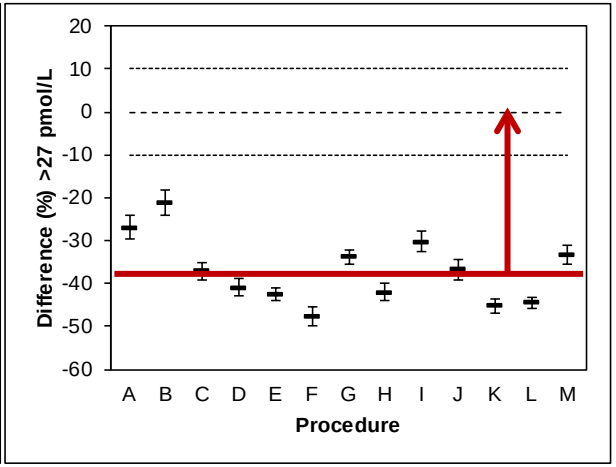
- Mainly related to impact of standardization/ harmonization

Impact of standardization

Most pronounced for FT4 testing (eu- & hyperthyroid)







➔Measurement values will increase in general by 30 – 50%

➔Reference intervals (RIs) will change

Potential risk for medical errors !!!

Potential risks: involved stakeholders/actions

Manufacturers

Must duly communicate on recalibration

Laboratories

Must properly inform lab users (clinicians/patients) about changes in reports/RIs

Clinicians

Must accommodate for the changes in their diagnostic and patient monitoring strategies

Patients

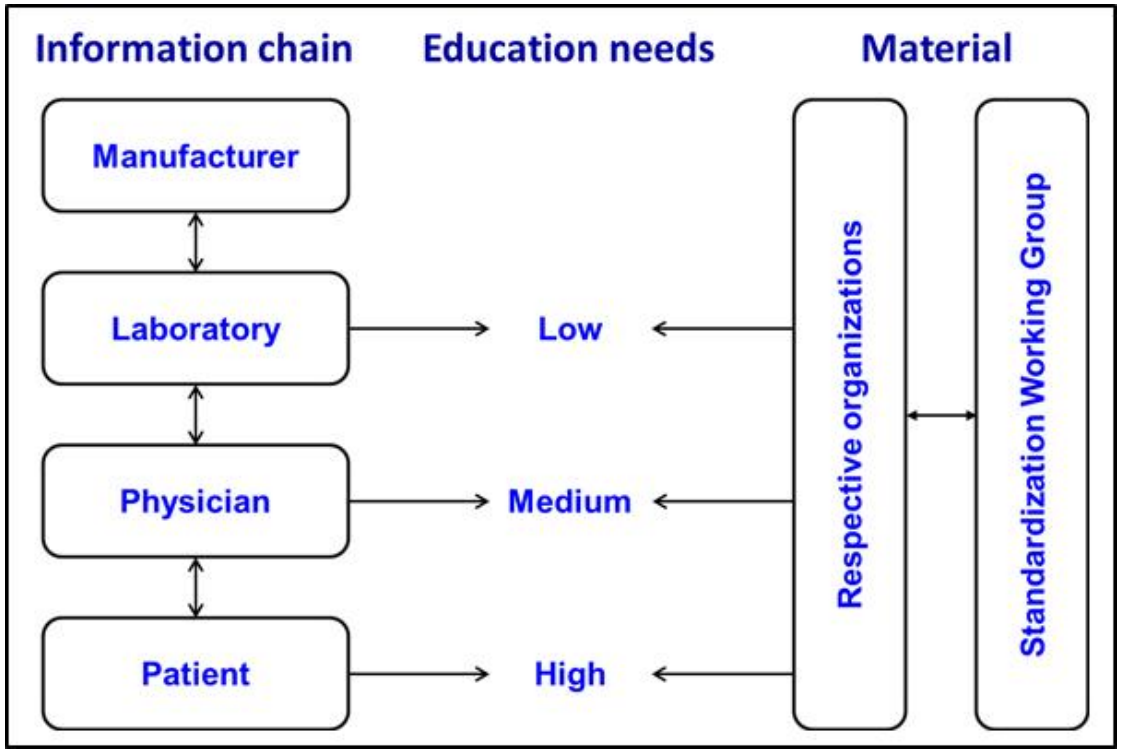
Should not be confused by the changed values for lab testing (non-compliance with the prescribed doses)

➔ Careful preparation of implementation is needed to waive the potential risks

Potential risks: possible actions

Establish a discussion platform with all involved stakeholders

- Look into the information chains used/needed
- Identify education needs
- Elaborate educational material



Potential risks: actions by C-STFT

Efforts done up to now to establish an interface between C-STFT and different stakeholders

Send questionnaires and evaluate outcome

Manufacturers

- **Communicate directly with the laboratories**
- **Via reviewed literature, bulletins/communications, meetings, intranet and electronic updates**

Big international laboratories

- **Often use different methodologies for the same test; clients are used that results may alter**
- **Use of different RIs is quite well accepted and understood**

➔ **Anticipate no or minimal risk for the patient**

Actions undertaken by C-STFT

Send questionnaires and evaluate outcome (cont.)

Laboratories delegated by IFCC Member Societies

Changes of assays and effect on reporting/RIs are dealt with in general quality management guidelines

- **Newsletter/circulars are sent to all requestors of tests before implementation**
- **Information posted on intranet**
- **Dual reporting (pre- & post-change) and new RIs are shown with highlighting for several months**
- **Education, seminars and workshops are organized (in- and externally)**

➔ Consider it very unlikely that changes are not captured by doctors

Actions undertaken by C-STFT

Send questionnaires and evaluate outcome (cont.)

Endocrinologists and their respective societies (e.g., members of the Belgian Thyroid Club)

- **Welcome the benefits from the C-STFT work**
- **Laboratory-clinician interface well established**
- **Happy with the lab strategies to communicate on changes**
- **LIS used in hospital laboratories has a system to report "pre" and "post change" results, each with their resp. RIs**
- **Caveat: communication line from the lab to the clinician must also include changes in patient treatment protocols (of particular importance for laboratory testing in ICUs)**
- **Prefer dual reporting strategy (pre- / post change results)**

➔ Consider it very unlikely that they would miss the changes and misinterpret longitudinal reports

Actions undertaken by C-STFT

Send case studies and evaluate outcome (cont.)

Belgian general practitioners (GPs)

- **Interpret case studies with variability in RIs correctly, provided the lab data were accompanied by clinical data**
- **Caveat: apparently, GPs had difficulties with interpretation of laboratory data indicative for complicated thyroid dysfunction (= more a problem in the education of medical students?)**

➔ GPs know very well they should not interpret against absolute values but against the accompanying RIs

C-STFT calls upon candidates for extending the established contacts with endocrinologists/GPs in Belgium to the international scene!!!

Actions undertaken by C-STFT

Publish in journals from clinical societies/patient organizations

Call for input on benefit-risk analysis

- **Thienpont LM, Faix JD, Beastall G. Standardization of FT4 and harmonization of TSH measurements - a request for input from endocrinologists and other physicians/Thyroid Foundations.**
  - **Clin Endocrinol (Oxf) 2015 Jul 23. [Epub ahead of print].**
  - **Endocr J 2015 Jul 22.**
  - **Exp Clin Endocrinol Diabetes 2015 Sep 15.**
  - **Thyroid 2015 Sep 28.**
  - **Endocrine 2015 Oct 1.**
  - **Eur Thyroid J. DOI:10.1159/000440614.**
  - **ThyroWorld Newsletter 2015;18:13-4.**
  - **Sent by e-mail to relevant members from the ESE**

Actions undertaken by C-STFT

Make international publicity

C-STFT chair/members attend scientific meetings and make oral presentations

- **15th International Thyroid Congress (ITC) 2015 (Orlando, Florida) (J. Faix)**
- **Thyroid Foundation International annual meeting 2015 (Orlando, Florida) (G. Beastall)**
- **9e Symposium bioclinique de la SFMN 2015 "la Thyroïde dans tous ses états" (Paris) (L. Thienpont)**
- **COLABIOCLI Congress 2015 (Quito, Ecuador) (K. Van Uytfanghe)**
- **…**

➔ Interesting fora to have face-to-face contact with involved stakeholders

Future activities

Reference interval (RI) study

- **Panel of 120 samples from apparently healthy Americans to be measured by recalibrated FT4 and TSH assays**
- **FT4 target values assigned by ED ID-LC/tandem MS at UGent**

➔Proof-of-concept for standardization/ harmonization and feasibility to use a common RI

➔Basis for further establishment by manufacturers of new RIs after standardization/harmonization

Final implementation challenge

Coordination of implementation of standardized/harmonized assays by all manufacturers at the same point in time and worldwide

Timelines?

Only when all aspects have been tackled

After implementation

Monitor sustainability of standardization status

The “Percentiler” and the “Flagger”

- **Give real-time monitoring of patient medians from individual laboratories using different IVD test systems**
- **Build a global evidence base on IVD test stability across laboratories and peers/manufacturers**
- **Monitor flagging of results against RIs or decision limits used in the individual laboratory, but also at the peer group level**
- **Translate the effect of analytical instability on “flagging” frequency (“surrogate” medical decision).**

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Collaborating IVD manufacturers