Publishable Summary for 18NET02 TraceLabMed
Support for a European Metrology Network on Traceability in Laboratory Medicine

Overview

Metrologically-based quality assessments (QA) of clinical laboratory testing for *in vitro* diagnostic devices (IVD) are now compulsory for meeting the new European In-Vitro Diagnostic Device Regulation (IVDR) 2017/746 which requires traceability of values assigned to calibrators and control materials. To support the needs of the IVDR, EURAMET has approved a European Metrology Network (EMN) on Traceability in Laboratory Medicine. The EMN brings together metrology institutes and key stakeholders in this field, such as proficiency testing (PT) providers, clinicians, and regulators. The main goals of the EMN are to identify and prioritise stakeholder needs, to coordinate the provision of services, and to foster the development of new standards in order to support the IVDR. The EMN to be established will be a central point of contact for calibration and reference laboratories as well as for IVD manufacturers to ensure the traceability of their procedures and IVDs to metrological reference points according to the requirements of the IVDR. This project aims to support the associated EMN by developing plans and strategies for a joint European metrology infrastructure for traceability in laboratory medicine, including processes for initiating and promoting dialogue amongst NMIs/DIs and stakeholders and by developing a coherent strategy for a Pan-European response to the legal requirements of the IVDR on a sustainable basis.

Need

The reliability of measurement results in laboratory medicine has a major impact on decision making for the health of the European citizen. The end goal for such reliable measurements is to produce equivalent results for a stated measurand within medically relevant limits, irrespective of the measurement procedure used or the laboratory performing the measurement. A large proportion of the measurands relevant to disease diagnostics and health monitoring are determined by using diagnostic test kits (i.e. IVDs). The results generated from these test kits should be comparable, reliable, and independent of the hospital, country, or time in which they are made, to ensure that patients receive the correct diagnosis and treatment. However, further work is needed to ensure this. Linking up working level results obtained in clinical laboratories with the international reference framework is currently making a substantial contribution to maintaining a consistent level of safety and performance for users (clinical laboratories) and end users (patients) but more is needed.

To meet the requirements of the new IVDR, metrologically based QA of clinical laboratory testing for IVDs is needed. According to the IVDR, metrological traceability of values assigned to calibrators and control materials must be assured to certified reference materials (CRM) or reference measurement procedures (RMP). European NMIs and DIs are very active in this field and already provide traceability for a range of clinical markers. However, several additional measurands currently being considered as high priority are not yet linked to the SI via CRMs or RMPs. In addition to this, a common priority list has not been established and agreed in view of the new IVDR on a Pan-European basis.

Regardless of whether current or potential future priority lists will be considered, no NMI or DI of a single European member state has the capacity and the technological capabilities to provide the full scope of primary standards needed for laboratory medicine. Furthermore, the capabilities to provide the services required for disseminating the measurements are currently insufficient.

Objectives

The overall aims of this project are to formally integrate existing PT schemes for reference laboratories into the associated EMN infrastructure and to develop a joint strategy to identify and prioritise measurands for laboratory medicine for which SI-traceability needs to be provided. The project addresses the following objectives:

1. To develop a plan for a joint sustainable European metrology infrastructure for traceability in laboratory medicine by stimulating smart specialisation of European NMI facilities and services. This should include processes to promote a constructive dialogue between NMIs/DIs and stakeholders such as clinicians, national medical associations, External Quality Assurance (EQA) providers, regulators and IVD manufacturers.
2. To create a coherent strategy for a joint European response to the need for traceability in laboratory medicine and IVD producers in this field, in accordance with the IVD Regulation (EU) 2017/746. This response should accommodate the need for sufficient redundancy while avoiding unnecessary duplication of work. A web portal serving as a single access point should direct customers' requests for specific calibration services and reference materials to the service providers.
3. To develop a joint strategy with EQA providers for reference laboratories to identify and prioritise measurands for which SI traceability is required. Existing national priority lists should be utilised to identify a core set of measurands to start with. Reference points in proficiency testing schemes for SI-traceable measurements should be provided. With input from clinical research and national medical associations, the strategy should also propose additional candidate measurands for future EQA schemes.
4. To set up a roadmap addressing the further development of the EMN both regarding timing and content of the activities and services offered. Broadening the scope of the activities may include but is not limited to engagement with (a) clinicians, to support the identification and quantification of novel biomarkers and the definition of more reliable clinical thresholds, (b) IVD manufacturers, to provide tools for the metrological validation of new assays in accordance with the new IVD Regulation (EU) 2017/746, (c) emerging European NMIs/DIs or even non-EU countries, to organise knowledge transfer by provision of support and training such as staff exchange and the organisation of interlaboratory tests.

Results

Objective 1: To develop a plan for a joint sustainable European metrology infrastructure for traceability in laboratory medicine by stimulating smart specialisation of European NMI facilities and services.

Promotion of a constructive dialogue between NMIs/DIs and stakeholders such as clinicians, national medical associations, EQA providers, regulators and IVD manufacturers was pursued by regularly interacting with these key stakeholders. Strategic communication and dissemination of the goals of this network project and its associated EMN is an important aspect to establish broad acceptance amongst stakeholders. The consortium has developed a communications plan to facilitate stakeholder engagement and has undertaken stakeholder analysis which has been used to identify priority stakeholders for the project and EMN to contact.

In a communication workshop with members of the EMN, clear common goals for further communication activities were agreed upon such as with relevant European Partnerships and Notified Bodies. So far, the EMN has successfully engaged with stakeholders such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the Joint Committee for Traceability in Laboratory Medicine (JCTLM), and the European organisation for external Quality Assurance providers in Laboratory Medicine (EQALM).

The consortium has also prioritised those European Partnerships in Horizon Europe that have a health-related focus such as the partnerships for Innovative Health, Pandemic Preparedness, Personalised Medicine, and Rare Diseases.

A multi-functional web portal will further facilitate communication with stakeholders. The EMN website is available at https://www.euramet.org/new-laboratory-medicine and currently provides stakeholders with access to member contacts and ongoing and past projects.

A database of the services offered by EMN members, and a collection of training resources provided by stakeholders such as IFCC and JCTLM will also be added to the EMN website.

Objective 2: To develop a coherent strategy plan in compliance with IVD producers and other stakeholders to address ways to implement sustainable services for delivering metrological traceability as required by the IVDR.

The consortium and EMN have agreed to demonstrate the utility of metrological traceability in support of IVD manufacturers through (i) the use of reference laboratory samples for small inter-laboratory comparisons where NMI capabilities have been demonstrated (ii) the participation of NMI partners in schemes such as the IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine (RELA), and (iii) the analysis of on-going CCQM comparisons and their long-term impact for clinical measurements.

Together with calibration laboratories, the consortium agreed on regular participation of the EMN members to RELA comparisons and information about the participation of NMIs/DIs in 2023 RELA comparisons was submitted to the Reference Institute for Bioanalytics (RfB), one of the two German proficiency testing organisations, officially charged by the German Medical Association with the external quality control of proficiency tests.

Further to this, RELA data for creatinine and steroids acquired over several years was processed and the data analysis showed the benefits of metrological traceability when applied. The benefits of organising a small scale interlaboratory comparison vs expanding this historical data analysis over a longer period of time and by including data from other EQA and reference laboratories is being further discussed.

The practical benefits of a co-ordinated EMN on Traceability in Laboratory Medicine to underpin the IVDR will also be shown via demonstration exercises. As part of these demonstrations a CCQM study on the quantification of amino acids in plasma was successfully organised with input from LGC and the UK National Health Service (NHS). Participation in the demonstration study included European NMIs/DIs, and project partners PTB, and TUBITAK. The results of the demonstration study showed good measurement comparability between the participating laboratories. Amino acids are important target analytes in new-born screening programs and biomarkers used for monitoring metabolic disorders, and the benefits of their metrological traceability has already been already demonstrated through a small-scale study in the UK.

An extension to the demonstration study by including EQA providers and approx. 80 clinical laboratories is currently on-going. The subsequent results will be discussed within the EMN and used to help defined training requirements (Objective 4), measurement uncertainty, additional comparisons (Objective 2) and engagement with local EQA and clinical laboratories (Objectives 1 & 3).

A survey of European NMIs and DIs has also been completed and the results provided useful insights into national strategies and current research activities. The survey was designed to obtain an overview of (i) existing national strategies and priorities and (ii) current and planned activities related to the development of reference systems for clinical measurands. The survey results were summarised and shared within the consortium and the EMN and will be used as a basis for a more coordinated approach to future traceability in laboratory medicine services.

In addition, calibration laboratories (RfB, INSTAND, WEQAS, and Ref4U) who are collaborating with the consortium have agreed to provide access to historical data from a variety of comparison schemes such as RELA and various local EQA programs. This data will be used (i) to demonstrate the benefits of metrological traceability and (ii) to identify potential gaps in current research strategies.

Furthermore, the new multi-functional EMN web portal (Objective 1) is now accessible to stakeholders and will be used to direct stakeholders' requests for specific calibration services and reference materials to NMIs and DIs offering these services. Work is on-going to add this function to the EMN website.

Objective 3: To develop a joint strategy with EQA providers for reference laboratories to identify and prioritise measurands for which SI traceability is required.

A strategy is being developed which will include a process for the identification and prioritisation of measurands for which metrological traceability needs to be provided. The consortium has successfully conducted a "gap analysis" to identify a core set of measurands for which reference points in proficiency testing schemes for SI-

traceable measurements are currently unavailable. To do this, existing priority lists were evaluated and compared with the currently available reference measurement procedures and reference materials that are listed in the publicly accessible databases of the BIPM and the JCTLM. The list was then complemented by information from the results of the project's survey among EQA providers (see below).

A workflow to establish the priority list of clinical measurands was also presented in an online workshop together with the Greek Society of Clinical Chemistry - Clinical Biochemistry (GSCC-CB) and EQALM. The first version of the prioritisation was reported to BIPM's Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) and this resulted in the selection of a relevant measurand for an upcoming CCQM comparison.

The identified gaps are now being assessed and prioritised regarding the necessity and feasibility of metrological traceability. Furthermore, a strategy is being developed that should enable the widespread and efficient uptake and exploitation of research results from completed and ongoing projects and/or studies. The stakeholder support for this strategy includes contributions by EQA providers, clinical researchers and both national and international medical associations, such as the IFCC, EQALM, JCTLM and the International Consortium for Harmonisation of Clinical Laboratory Results (ICHCLR).

Using the project's links with EQALM the project has been able to significantly increase the success of its online survey among EQA providers. With the help of EQALM, the survey was distributed to its 39 European member organisations, of which 29 responded (74 %). The survey dedicated to EQA providers and calibration laboratories was designed to identify measurands for which reference systems are urgently needed to improve harmonisation of clinical measurement results (i.e. the identification and prioritisation of measurands for which metrological traceability needs to be provided). In addition, the survey included questions related to the IVDR (Objective 2) so as to be more efficient and to not have to contact the same stakeholders twice. Prior to sending out the survey, it was reviewed by collaborators WEQAS (a global provider of quality in diagnostic medicine), RfB and Instand (a society for promoting quality assurance in medical laboratories) and stakeholders KBUDEK (the National External Quality Control Program for Turkey) and EQALM.

Preparation of a similar survey dedicated to IVD manufacturers has been initiated and the principal agreement of the IFCC Scientific Division has been obtained to circulate the survey to all (> 100) IFCC corporate members. The survey will be used to (i) obtain agreement on the priority list of measurands for which metrological traceability needs to be provided and (ii) ask for additional analytes and the preferred kind of services needed to meet IVDR requirements.

Objective 4: To set up a roadmap addressing the further development of the EMN both regarding timing and content of the activities and services offered once the key tasks are addressed and after the core services have been implemented.

The project is developing a roadmap to encourage the participation of more European NMI/DIs in the field of clinical chemistry and laboratory medicine in the EMN. To support this the consortium has developed a close collaboration with the EURAMET Technical Committee for Metrology in Chemistry (TC-MC) and regularly participates in the annual TC-MC meetings. The consortium has also used the results of a survey of TC-MC members (Objective 2) for identifying and contacting potential candidates to join the EMN.

As a result of these promotional activities, the Slovenian National Institute of Biology (NIB) was accepted as a new member of the EMN. Furthermore, negotiations are currently underway with the JRC to join the EMN (i.e an amended MoU has been agreed and is expected to be signed shortly).

To attract further European NMIs and DIs, the consortium is now considering extending its scope beyond the traditional clinical chemistry and laboratory medicine field to include genomics and molecular diagnostics. When contacting and identifying such stakeholders the project will use its communications plan and identified priority stakeholders from Objective 1.

Impact

The consortium has successfully promoted the network project and the EMN and has attracted more than 25 stakeholders including, standards development organisations, calibration laboratories, and EQA Providers. It has also undertaken the following dissemination activities:

- The consortium has promoted the project at 27 conferences (e.g., the 2021 JCTLM Workshop on "overcoming challenges to global standardization of clinical laboratory testing: reference materials and regulations") and at two national events i.e. a symposium of the Dutch Society of Clinical Chemistry and Laboratory Medicine and the 17th National Congress of The Greek Society of Clinical Chemistry and Clinical Biochemistry.
- The consortium presented the project to user communities such as the 93th Meeting of Verband der Diagnostica-Industrie (VDGH; Diagnostics Industry Association) committee for Science and Technology in Germany.
- The consortium presented the project at the 2019 JCTLM members and stakeholders' meeting to a wide audience interested in traceability and method standardisation or harmonisation including laboratory medicine specialists, EQA providers, IVD manufacturers, and national metrology institutes.
- The consortium organised a symposium on "standardisation and harmonisation in clinical chemistry" to exchange expert knowledge on the value of metrology for EQA and analyte prioritisation. Two stakeholder workshops related to (i) pandemics and (ii) current challenges in laboratory medicine were also organised to help identify research topics for the European Partnership on Metrology's Health Call 2022.
- The consortium used "World Metrology Day 2021" as an opportunity to promote the project to the general public through presentations and video contributions, available at https://www.euramet.org/european-metrology-networks/laboratory-medicine/tlm-world-metrology-day-2021/
- The EMN was invited by the JCTLM to contribute to a series of videos for broader perspectives on the importance of metrological traceability in laboratory medicine, available at https://www.bipm.org/en/committees/jc/jctlm/jctlm-wmd-2021

This project will support its associated EMN to implement a European quality infrastructure in accordance with the new IVDR by transferring the developed reference measurement procedures for important measurands to reference laboratories across Europe. This approach will promote European coherence by providing consistent services for clinical laboratory testing on a long-term basis and will enable a faster response to stakeholder needs by better directing research resources. In cooperation with the IFCC, the consortium appointed a member from the EMN as a representative within the IFCC Committee for Traceability in Laboratory Medicine (C-TLM). Members of the consortium have also participated in other IFCC Scientific Division working groups, such as the Working Groups on Commutability in Metrological Traceability (WG-CMT), CSF-Proteins (WG-CSF) and Standardisation of Procalcitonin assays (WG-PCT). In 2023, representatives from partner PTB also took over the leadership of the IFCC working groups on (i) the standardisation of Troponin I (WG-TNI) and (ii) Standardisation of Hemoglobin A2 (WG-HbA2).

The envisaged sustainable infrastructure that this project and the EMN will provide should help to ensure the long-term provision of services for clinical laboratory testing Considering the full scope of services needed, compared to the total resources available within the European metrology landscape, it is obvious that this cannot be achieved through a single institute or an individual country and that an EMN is vital.

The coordinated approach organised by the EMN, and supported by this project, should create a central contact point for NMIs and DIs seeking to enhance their clinical laboratory testing capabilities and enable individual sets of necessary reference points to be provided by at least one partner in the EMN. A first step towards improved coordination was achieved by the involvement of the consortium in the RELA ring trial for calibration laboratories (Objective 2). These comparisons are an efficient way of disseminating metrological traceability and the participation of NMIs/DIs is beneficial for accreditation purposes. The coordination among the NMIs by the EMN should ensure that at least one NMI/DI regularly takes part in relevant comparisons. To ensure the long-term cooperation of the consortium with European calibration laboratories, 4 European calibration laboratories (RfB, INSTAND, WEQAS, and Ref4U) have now become permanent partners in the EMN.

The successful implementation of the new IVDR has the potential for significantly improving safety and reliability in clinical diagnostics for the benefit of European healthcare systems. This should also lead to considerable cost savings and patient health benefits in the European healthcare systems through the (i) avoidance of duplicate measurements, (ii) improper medical treatments and (iii) unnecessary treatments based on false positive or false negative measurements results that might occasionally occur in routine laboratory medicine. In support of this, the EMN and project are striving to expand their stakeholder communication and use their extensive existing contacts to establish the implications of the IVDR. This information will then be used for decision-making by the EMN and to help guide the future strategic path of the metrological work for traceability in laboratory medicine.

Project start date and duration:	1 June 2019, 60 months	
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Internal Funded Partners: 1. PTB, Germany 2. MHRA, United Kingdom 3. INRIM, Italy 4. LGC, United Kingdom 5. LNE, France 6. NPL, United Kingdom 7. TUBITAK, Turkey	External Funded Partners:	Unfunded Partners: 8. BAM, Germany 9. METAS, Switzerland 10.UGent, Belgium