European Partnership on Metrology
Call 2022 – Digital Transformation, Health, Integrated European Metrology, Normative and Research Potential

Selected Research Topic number: **SRT-s09**
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Title: Reference measurement systems for clinically relevant biomarkers to support the effective implementation of the *In Vitro* Diagnostic Regulation

Abstract

Medical laboratory test results influence clinical decisions. Consequently, it is vital to ensure their accuracy and equivalence. Regulation EU/2017/746, on *in vitro* diagnostic medical devices, requires the metrological traceability of values assigned to calibrators, or control materials, to be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. However, currently there are insufficient higher order reference measurement systems for many clinically relevant biomarkers (measurands). Therefore, to support the effective implementation of the *in vitro* diagnostic regulation, metrological capabilities need to be developed and new measurement services need to be provided.

Keywords

Analytical performance specification, biomarkers, commutability, external quality assessment, *in vitro* diagnostic medical devices regulation, measurement uncertainty, metrological traceability, purity, reference measurement systems

Background to the Metrological Challenges

Medical decisions often depend on accurate, informative and comparable biomarker measurement results. However, many biological measurements cannot be compared, which can hinder medical decision making and prohibit population based, preventative medicine approaches. The *in vitro* diagnostic medical devices regulation (EU) 2017/746 (IVDR) and ISO 17511:2020 state that the metrological traceability of values assigned to calibrators and/or control materials will be assured through suitable reference measurement procedures and/or suitable reference materials. Further mandates have been issued by the EC. Currently, there are insufficient higher order reference measurement systems (RMS) for many clinically relevant measurands. Essential components include i) the measurand definition being based on the clinical use, ii) consecutive levels of measurement procedures and calibrators in a calibration hierarchy and iii) internal and external quality control schemes. A number of international initiatives already aim(ed) to address this, including the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and a number of EMRP and EMPIR projects. This highlighted the difficulty in developing i) primary reference materials of well characterised purity, ii) reference measurement procedures (RMPs) with appropriate analytical performance specifications (APS) (e.g. SI-traceability, accuracy, selectivity, limit of quantification, measurement uncertainties) and iii) calibration and quality control materials of appropriate commutability. Therefore, RMS for clinically relevant biomarkers need to be selected based on current requirements including those of other initiatives.

The 'harmonisation of measurands in laboratory medicine through data aggregation' (HALMA) task force is aiming to collect and aggregate results from different External Quality Assessment (EQA) schemes in order to evaluate possibilities for the international harmonisation of measurement results. All EQA materials that are aggregated must be commutable. However, as evaluating the commutability of EQA materials is demanding, it is often unknown or assumed. To date, very little data is available on how well such processed materials mimic real patient samples. Therefore, a series of commutability studies needs to be organised for a panel of high priority clinical measurands including electrolytes, metabolites, proteins, cells, and genetic tests, which require improved harmonisation and/or accuracy. There is also a need to analyse aggregated EQA data using novel approaches (e.g. big data, AI and/or machine learning). Better predicting commutability will support the HALMA initiative and it will contribute to improving the availability of suitable EQA materials.

Although many analytical techniques have been developed, the metrologically sound purity assessment of all groups of measurands remains a challenge, including the reduction of the measurement uncertainty to meet clinical needs. For metabolites, qNMR needs to be improved as the measurement uncertainty of the primary calibrators has a critical impact on the final measurement uncertainty of the RMP and the certified reference materials (CRMs). For proteins, the size and high structural heterogeneity represent major difficulties. For nucleic acids, challenges include sequence purity and integrity, and the presence of interfering substances, which may inhibit PCR. Therefore, new orthogonal methods need to be developed. To be fit for purpose, RMPs need to meet appropriate APS. These include suitable limits of quantification, fit for purpose selectivity and SI traceability. At present, only some of the RMPs listed in the JCTLM database reach the APS required to meet the medical need. Therefore, suitable APS need to be defined and improved and efficient RMPs, primary reference materials with well-characterised purity, and matrixed-matched reference materials of appropriate commutability, need to be developed. In addition, the improved suitability and actual implementation of RMS requires the measurement uncertainty to be evaluated at each level of the calibration hierarchy as well as its impact on the quality of the laboratory tests.

Advanced analytical methods need to be developed to unravel the structural heterogeneity of complex biomolecules at the molecular level. This should allow the definition of the measurand to be refined and permit metrological traceability early in the development of *in vitro* diagnostic (IVD) devices. This will ensure that the correct measurands are measured.

Achieving equivalent results in laboratory medicine is reliant on the development, and global availability, of secondary CRMs. The commutability of the reference materials, which are used as common calibrators, has emerged as a key requirement in establishing the metrological traceability of clinical measurement results and in effectively reducing inter-method variability. Although frameworks for evaluating the commutability of CRMs have been established, this work is cumbersome, and it cannot be done for all EQA materials. Consequently, most EQA schemes currently rely on materials with unknown commutability and consensus target values. Therefore, the ability to properly evaluate the accuracy and comparability of the results is compromised. A coordinated European metrology infrastructure, with the ability to assess the commutability of calibration and EQA materials, needs to be developed for a panel of high priority clinical measurands. This data will enable the commutability of materials to be better predicted. In addition, suitable manufacturing processes need to be identified which can consistently produce commutable quality control materials for electrolyte, metabolite, protein, cell and nucleic acid measurements. This will also enable the accuracy of IVD tests to be properly evaluated (post-market surveillance) through accuracy-based programs relying on commutable EQA materials with reference method target values.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the development of reference measurement systems for clinically relevant biomarkers regarding in-vitro diagnostic regulation.

The specific objectives are

1. To select reference measurement systems (RMS) for clinically relevant biomarkers based on current needs including those of other initiatives (e.g. International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), EMRP & EMPIR projects). This should include identifying a panel of high priority clinical measurands which require improved harmonisation and/or accuracy. In addition, to analyse aggregated External Quality Assessment (EQA) data using novel approaches (e.g. big data, AI and/or machine learning). This should be conducted in collaboration with the harmonisation of measurands in laboratory medicine through data aggregation (HALMA) task force.
2. To define analytical performance specifications for the RMS selected in objective 1. In addition, to develop improved and efficient reference measurement procedures, primary reference materials with well-characterised purity, and matrixed-matched reference materials of appropriate commutability, which are suitable for submission to the KCDB and/or JCTLM database. This should include an evaluation of the measurement uncertainty at each level of the calibration hierarchy and its impact on the quality of laboratory tests.
3. To develop advanced analytical methods to unravel the structural heterogeneity of complex biomolecules at the molecular level. This should allow the definition of the measurand to be refined and permit metrological traceability early in the development of *in vitro* diagnostic (IVD) devices.

4. To evaluate the commutability of clinical materials for the panel of high priority clinical measurands identified in objective 1. This should enable suitable manufacturing processes to be identified which can consistently produce commutable quality control materials for electrolyte, metabolite, protein, cell and nucleic acid measurements. In addition, to build a coordinated European metrology infrastructure to support the post-market surveillance of IVD tests.
5. To demonstrate the establishment of an integrated European metrology infrastructure and to facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (ISO TC212, CLSI) and end users (international organisations (IFCC, International Consortium for Harmonisation of Clinical Laboratory Results (ICHCLR)), assay manufacturers, medical associations, EQA providers, academia, regulators).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes. To enhance the impact of the research work, the involvement of the larger community of metrology R&D resources both within and outside Europe, plus engagement with existing European research infrastructures and European Partnerships is recommended. A strong industry involvement is expected in order to align the project with their needs and guarantee an efficient knowledge transfer into industry and end users.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this. In particular, proposers should outline the achievements of the EMRP projects SIB54 BioSITrace, HLT05 Metallomics, HLT08 INFECT-MET and the EMPIR projects 15HLT02 ReMIND, 15HLT04 NeuroMet, 15HLT07 AntiMicroResist, 18HLT03 SEPTIMET, 18HLT09 NeuroMET2, 18HLT10 CardioMet and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.9 M€ and has defined an upper limit of 2.6 M€ for this project.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 25 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the ’end user’ community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the ‘end user’ community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the healthcare sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of the Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Time-scale

The project should be of up to 3 years duration.