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

Selected Research Topic number: **SRT-h06**
Version: 1.0

Title: Standardisation of measurements of neurodegenerative disease biomarkers

Abstract

Neurodegenerative disorders (NDDs) affect over nine million Europeans, causing suffering to patients and their families, and creating a large economic problem to society. Furthermore, fluid biomarkers have transformed research by linking diseases to pathological processes and assisting drug development. NDD biomarkers have started to benefit patients by improving the accuracy of diagnosis and prognosis, but their implementation in clinical practise is currently hindered by a lack of standardisation. Therefore, this project aims to build on the knowledge and networks of the Horizon 2020 projects (e.g., 18HLT10 CardioMet, 15HLT04 NeuroMet) and the IFCC program to standardise measurements of neurodegenerative disease biomarkers, harmonise measurements between assay manufacturer and develop and implement new biomarkers.

Keywords

Neurodegenerative diseases, Alzheimer's disease (AD), biomarkers, standardisation, phospho-Tau

Background to the Metrological Challenges

The diseases of the nervous systems e.g. Alzheimer's and Parkinson disease, multiple sclerosis, epilepsy, brain tumours, paraplegia, etc., affect 1 in 8 people across Europe. Amongst these disorders, dementia is responsible for the greatest number of cases, with Alzheimer's disease. Early and accurate diagnosis of NDDs is crucial for effective management of disease and build an efficient infrastructure to rapidly implement new NDD biomarkers in clinical practice to decrease the impact of these diseases on patients and caregivers through planned and appropriate management. Furthermore, while research in NDDs have progressed significantly in the last few years through the discovery of new biomarkers and the development of sensitive assays implemented on automated platforms, large-scale implementation of these biomarkers in clinical routine settings needs standardisation of measurements through detailed molecular characterisation of the analytes, and development of reference method procedures (RMPs) and certified reference materials (CRMs).

Significant investment and progress made in the field of fluid and imaging biomarker research to enable objective diagnosis of specific NDD and targeted intervention. The development of ultrasensitive assays to measure pTau forms in plasma tau has led to a breakthrough, with the finding of increased levels of tau phosphorylated at Thr-181 in Alzheimers Disease (AD) plasma compared with control samples, and a good correlation with CSF pTau (Cerebrospinal Fluid**)** levels tau PET, and amyloid PET (positron emission tomography) indicating that plasma pTau is a good biomarker for brain AD pathology. Recent validation studies using slightly different assays shows very similar results corroborating plasma pTau as a robust blood biomarker for AD pathology that can be valuable to implement in clinical laboratory practice. Mass spectrometry-based methods for some pTau forms developed, providing a basis for developing RMPs. In addition, Recent studies have established NfL as a robust biomarker of neuroaxonal damage, in both acute neurological conditions, such as traumatic and vascular brain injury, infections as well as in neurodegenerative and neuroinflammatory conditions. With sensitive assays for pTau forms and NfL available from several manufacturers and a great foreseeable utility of these biomarkers, both in clinical practice and for drug development, thus the need for standardisation of measurement, and harmonisation of analysis results from different assay platforms.

Furthermore, supporting the implementation of those biomarkers into clinics, by providing the required traceability for calibrators, frameworks for measurement uncertainty and reference measurement systems to enable measurement standardisation and establishment of relevant clinical thresholds. This project aims to expand the work carried out on liquid biomarkers in the previous projects such as 18HLT10 CardioMet,

15HLT04 NeuroMet responding and supporting the international effort in the area by providing metrological solutions and underpinning the uptake of biomarkers and tests into clinic.

Moreover, enhancing the international metrological capabilities through the development of new approaches that address for the first time the development of reference measurement procedures targeting post-translational modified markers and protein conformational states can impact a number of standards and guidelines including from ISOTC12, ISO TC212, the IFCC, the Global Biomarker standardisation consortium of the Alzheimer Association, the Society of CSF analysis and clinical neurochemistry, JCTLM and BIPM's Consultative Committees for Amount of Substance: protein analysis working group providing tools for a better understanding of pathologies. In addition, the standardisation of measurement of NDDs biomarker can benefit assay manufacturers by facilitating the transfer of their assays from research to clinical practice. Pharmaceutical industry can also benefit by the availability of more accurate and reliable biomarker data in clinical trials. For patients and care providers, access to standardised fluid biomarkers enabling better treatments, improve the quality of life of patients and at the same time reduce health care costs. Therefore, supporting research into the early detection and diagnosis of AD and its implementation is not only a priority to ensure that the European healthcare system is prepared to embrace new therapeutics, but also plays an important role in upholding the right to dignity and combating stigma of patients with dementia.

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 metrology research necessary to support standardisation in biomarkers of neurodegenerative diseases (NDDs) including Alzheimer's disease, dementia with Lewi bodies, frontotemporal dementia, Parkinson's disease, and multiple sclerosis.

The specific objectives are

1. To standardise the measurement results of phospho-tau in plasma through the development of prototype reference materials and reference measurement procedures. This includes the development of new metrological strategies addressing multiple phosphorylation sites in biological matrices.
2. To standardise the measurement of neurofilament light chain in blood or serum by establishing reference measurement procedures and developing prototype reference materials. This requires defining the appropriate target analyte / measurand and establishing and validating traceability chain strategies to reach around 0.5 pg/mL in blood with target measurement uncertainty below 15 %.
3. To develop clinical measurement procedures for emerging biomarker candidates by ensuring fit for purpose metrological traceability is achieved early in the development of NDD biomarkers assays**.** These could include but not be limited to glial fibrillary acidic protein (GFAP), neurogranin, TAR DNA-binding protein 43 synucleins, synaptic proteins and lysosomal proteins.
4. To develop effective and fit-for-purpose metrological approaches to overcome the challenges in discovery and standardisation of NDD fluid biomarkers and implementation of new assays**.** This includes the development of new metrological strategies to address protein conformational states and post-translational modifications, and uncertainty frameworks and protocols for assay implementation to be used in objectives 1, 2 and 3. In addition, protocols and quality control materials should be developed to be applied in objective 3 to improve accuracy and robustness of the "omics" methods used to underpin NDD biomarker discovery and to understand pathophysiology of neurodegenerative diseases.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (EMN-TLM, JCTLM, ICHCLR), standards developing organisations (IFCC-CSF-WG, Diagnostic Devices Regulation 2017/746 (IVDR), ISOTC12, ISO TC212), and end users (e.g. clinical stakeholders, manufacturers of medical and healthcare products).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development.

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 EMPIR projects 18HLT10 CardioMet and 15HLT04 NeuroMet, 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 35 % 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.