Title: Metrology and innovation for early diagnosis and accurate stratification of patients with neurodegenerative diseases

Abstract

Neurodegenerative diseases (NDD) are one of the most pressing modern medical issues. There are over 9.9 million new cases of dementia each year worldwide, with 1 new case every 3.2 seconds. Many NDDs, in particular Alzheimer's (AD) and Parkinson's disease (PD), are irreversible and progressive, and besides their large socioeconomic costs, they severely affect the quality of life of patients and caregivers. Early diagnosis through the implementation of screening programs, the identification of risk factors and the development of disease-modifying therapies are key for improving the quality of life of NDD patients. The EMPIR project 15HLT04 NeuroMET project has used its unique NDD patient cohort to develop metrologically validated tools for early NDD diagnosis and accurate patient stratification. However further work is still needed to (i) advance the quantification of NDD biomarkers, in both biological fluids and using minimally invasive methods, (ii) develop validated person-centred outcome measures (PCOMs) focused on the decline of cognitive functions in NDD patients and (iii) define prototype metrological references for cognition.

Keywords

Neurodegenerative disease, Alzheimer's disease, Parkinson's disease, PCOMs, MRI, MRS, biomarkers, early diagnosis

Background to the Metrological Challenges

In 2018 Pfizer ended its efforts to develop new drugs for AD and PD following many clinical trials failures. As reported in the Washington Post "These setbacks pile on to an already depressing situation: more than 400 failed clinical trials since the last Alzheimer's drug was approved more than a decade ago". The failure of NDD clinical trials is most often attributed to a variety of factors, including a lack of accurate measurements, and poor target engagement in recruitment.

Evidence suggests that the changes in the brain associated with AD begin more than 20 years before symptoms appear and that treatment of AD is most effective when started early in the disease process. Whilst the tools and expertise to identify some of the early brain changes in AD currently exist, additional research is needed to fine-tune these tools and establish their accuracy, before they can be clinically used.

The Big Data for Better Outcome programme was launched in 2017 in Europe with the goal of using big data in the healthcare sector and to promote healthcare focused PCOMs. This is particularly important for NDD as multiple tests are often required and diagnosis predominantly relies on cognitive assessments. However, there is still a lack of PCOMs for the early diagnosis of NDD based on clinical and cognitive assessment data.

Over recent years significant progress has been made in the area of NDD biomarkers in biological fluids, with two biomarkers approved by the European Medical Agency for clinical trials and included in diagnostic guidelines. Guidelines on pre-analytical sampling have also been produced and the first certified NDD reference material was introduced in 2017. But despite all this, further development of reference measurement procedures is still needed for established NDD biomarkers, such as tau, as well as the definition of target clinical cut off levels for biomarker identification.

3 Tesla magnetic resonance imaging (MRI) is widely used in clinics to confirm NDD diagnosis and can provide valuable information on brain structure and changes due to NDD. The use of MRI and magnetic resonance spectroscopy (MRS) for stratifying NDD patients at the early stages of the disease has high potential, but until now, its implementation has been limited by the large measurement uncertainty and intrinsically poor signal amplitude (particularly for neurometabolites) in 3 T field strengths.

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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 traceable measurements for the early diagnosis and accurate stratification of patients with neurodegenerative diseases (NDD).

The specific objectives are

1. To develop novel and validated person-centred outcome measures (PCOMs) for the early diagnosis of NDD focused on the decline of cognitive functions in NDD patients. The potential use of such cognitive assessments in screening programs should also be evaluated.

2. To develop enhanced magnetic resonance imaging (MRI) and spectroscopy (MRS) protocols and reference measurement procedures using ultra high field MR techniques *in-vivo,* in order to identify and quantify biomarkers in NDD patients. In addition, to develop novel techniques (e.g. chemical exchange saturation transfer) to increase the specificity of MRI and MRS methods for NDD discrimination.

3. To develop validated methods and traceable calibrants for the accurate measurement of NDD biomarkers in biological fluids (target uncertainty < 10 %). This should include the development of new reference measurement procedures for established biomarkers such as neurofilament (early diagnosis), tau fragments and phosphorylated tau (disease progression) and the definition of target clinical cut off levels for biomarker identification.

4. To establish Causal Rasch mathematical models and apply them to data from NDD studies in order to define prototype metrological references for cognition, which can be expressed as 'construct specification equations'. This should include the correlation of (i) cognitive task difficulty with instrument parameter and (ii) patient health status with the biomarker and MRI.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain, standards developing organisations (ISO/TC 212, the International Federation of Clinical Chemistry (IFCC), and the Joint Committee for Traceability in Laboratory Medicine (JCTLM)) and end users (e.g. clinical laboratories, hospitals).

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, 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 project 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 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

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 medical and health 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 EMPIR 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.