EMPIR Call 2015 – Health, SI, Normative and Research Potential

Selected Research Topic number: **SRT-h13**
Version: 1.0

Title: Innovative measurements for improved diagnosis and management of neurodegenerative diseases

Abstract

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are incurable debilitating mental disorders that represent an increasing global challenge due to the ageing of the population. Although the molecular mechanisms behind such neurodegenerative diseases are different, many processes such as neuronal dysfunction and ultimately neuronal death are characteristic of the diseases in general. Therefore, in order to combat neurodegenerative diseases identification and accurate quantification of relevant biomarkers needs to be established. In addition to this, validated and non-invasive measurement protocols are needed that support; early stage diagnosis; tracking of disease progression and new therapeutic developments, in order to promote improved patient care and quality of life.

Keywords

Neurodegenerative disease, biomarkers, non-invasive, Alzheimer's disease, Parkinson's disease, early diagnosis, magnetic resonance imaging

Background to the Metrological Challenges

Early diagnosis of neurodegenerative diseases, such AD and PD, is essential as their development begins 10 to 20 years prior to clinical manifestation. This has been demonstrated by the failure of anti-AD therapies to work in late-stage clinical trials. Currently, clinical diagnosis of neurodegenerative diseases is challenging during the early stages of disease as the presentation of symptoms is both subtle and gradual. Instead, it is only during the later stages of the disease, that a clinical diagnosis is possible with 70-90 % certainty, when all known symptoms of dementia are present and all other possible causes have been excluded. However, this stage is then too late for any measures against AD, other than patient care.

Quantitative structural magnetic resonance imaging (MRI) is sensitive to neurodegeneration in mild and preclinical AD and can be semi-predictive of the decline into dementia in individuals with mild cognitive impairment. However, even when combined with neuropsychological and cognitive testing, disease diagnosis specificity is still <80 % and therefore quantitative volume evaluation of MR images is required. Currently image analysis methods exist for quantitative volume evaluation of MR images however uncertainties for the measurement of the total volume and thickness have yet to be established.

Many potential cerebrospinal fluid (CSF) and blood biomarkers have been identified for neurodegenerative diseases however none have been validated for use in early diagnosis. To date, most validation studies have focussed on CSF biomarkers Abeta1-40, tTau and pTau, which have proven value in the diagnosis of AD, and can be used to predictive progression to AD in subjects with MCI. However, there is a need for biomarkers for less invasive diagnostic methods and therefore to avoid the use of CSF. Studies using animal and human AD brain tissue have demonstrated the potential use of specific miRNAs as AD biomarkers. The studies indicate a correlation between expression levels of these specific miRNAs found in blood serum/plasma samples (and CSF) of AD patients and the expression of tissue-specific miRNAs in the AD brain. This suggests that miRNAs could be used as non-invasive blood biomarkers for early diagnosis of AD however this needs to be validated.

As part of neurodegenerative diseases patient care, new person-centred indicators such as satisfaction and anxiety should be considered alongside traditional metrics, such as blood pressure, body temperature and biomarkers. Although person-centred indicators are considered subjective, they have support from the World Health Organisation Person-Centred Care (WHO PCC) and the Federal Drug Administration Patient Reported Outcomes (FDA PRO), and are particularly appropriate for monitoring progressive deterioration such as behavioural and psychological symptoms. However, the robustness of person-centred indicators is

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limited by the patient's (or carer's) ability to respond, and therefore an accurate and validated point-of-care (POC) assay for the detection of biomarkers of stress, would be hugely beneficial.

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 traceable measurements for improved diagnosis and management of neurodegenerative diseases, and on establishing validated and non-invasive protocols.

The specific objectives are

1. To develop validated high- and ultrahigh-field MRI methods for the *in vivo* characterisation of the brains of an established patient cohort representative of the stages of neurodegenerative disease and healthy matched control subjects.
2. To develop minimally invasive methods for the early diagnosis of neurodegenerative diseases and for neurodegenerative therapeutic monitoring.
3. To develop accurate methods with low uncertainty for the quantification of key biomarkers for neurodegenerative diseases.
4. To determine and characterise person-reported indicators for neurodegenerative diseases. In addition, to develop a validated POC device for the measurement of biomarkers of stress.
5. To facilitate the uptake of the technology and measurement infrastructure developed by the project by establishing a Network of Excellence in Europe for neurodegenerative disease diagnosis and disease progression monitoring between National Measurement Institutes, clinical laboratories and other stakeholder organisations.

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.

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 to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded 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 medical 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.