Publishable Summary for 18HLT09 NeuroMET2
Metrology and innovation for early diagnosis and accurate stratification of patients with neurodegenerative diseases

Overview

Neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD), are a group of chronic, progressive disorders, which lead to deficits in specific brain functions including cognition and movement. NDDs can affect people of all ages and are one of the most pressing medical issues of the modern time. The NeuroMET2 project addressed the challenges associated with diagnosis of AD by building upon the results of the preceding EMPIR 15HLT04 NeuroMET project and its unique patient cohort to apply metrological principles of ADdiagnosis. The most promising NeuroMET minimally invasive methods for early diagnosis of AD were advanced through longitudinal studies and transferred to clinical settings. The project also developed novel approaches and reference measurement procedures (RMP) to address the current measurement challenges of early NDD diagnostics and therapies.

Need

There are over 9.9 million new cases of dementia each year worldwide, with one new case every 3.2 seconds and a desperate need for treatments. NDDs are one of the leading medical and societal challenges faced by European society with costs for care currently around €130 billion per annum**.**

Research suggests that the brain changes associated with AD (as with many other NDDs) begin fifteen or more years before symptoms appear, and that treatment of NDDs is typically most effective when started at the early stages. Translational research is however needed to fine-tune the methods developed and define their measurement uncertainty and accuracy before they can become fit for clinical use.

The 15HLT04 NeuroMET project was the first metrological project to combine the diverse expertise of NMI/DIs together with that of clinicians and academics to build the infrastructure required to translate research into clinical or pharmaceutical settings and overcome specific metrological barriers in NDD diagnosis and treatment. In the 15HLT04 NeuroMET project, person-centred outcome measures (PCOMs) were, for the first time, metrologically validated using clinical laboratory data, RMP for protein biomarkers and ultra-high field magnetic resonance imaging (MRI) and spectroscopy (MRS) protocols. All these have high potential for use in early diagnosis or to facilitate the uptake into clinics and industry of novel assays. However longitudinal studies were required to determine their prognostic value. The fully characterised 15HLT04 NeuroMET patient cohort (90 individuals) and data associated to it constituted an invaluable European and international resource to carry out longitudinal studies and validate methods and biomarkers developed elsewhere. It was therefore important that the cohort was maintained in order to address the most up to date NDD measurement issues and validate new assays.

This project addressed needs for: (i) screening programs for early NDD diagnosis; (ii) RMPs and protocols to facilitate implementation of new assays into clinics and improve differentiation by reducing measurement uncertainty; and (iii) improved specificity of drugs by developing new methods for monitoring NDD protein aggregation.

Objectives

This project aimed to consolidate and further develop the 15HLT04 NeuroMET metrological infrastructure and validate biomarkers and procedures for early NDD diagnosis and accurate patient stratification, leading to new patient screening programs and increased rate of success in clinical trials. The specific objectives were:

1. To maintain the already established and stratified 15HLT04 NeuroMET patient cohort and enrol new patients to cover the defined stages of neurodegeneration and account for patient drop-out. Patients will be clinically assessed, and blood as well as cerebrospinal fluid (CSF) samples will be collected and distributed to partners for longitudinal studies in Objective 2, 3 and 4.
2. To advance the 15HLT04 NeuroMET PCOMs for cognition and early diagnosis. This will lead to the validation of a 'NeuroMET Memory Score' and the development of an app (software application downloadable onto mobile devices) for clinicians and patients to deliver validated cognitive tests.
3. To refine ultra-high field MRI and MRS protocols from 15HLT04 NeuroMET through longitudinal studies for application into clinics. Additionally, new *in vivo* approaches will be developed to monitor supplemental biomarkers in the project cohort.
4. To advance biomarker measurements for early and accurate diagnosis through the validation and implementation into clinics of the 15HLT04 NeuroMET methods and other methods. Biomarkers such as Aβ1-42, Aβ 1-40, neurofilament light chain (NFL), total-tau (t-tau) and α-synuclein will be monitored in the NeuroMET cohort and new RMP for NFL and *p*-tau will be developed. Methods for monitoring aggregation of NDD proteins will be also developed and validated to improve specificity of therapeutic targets and as potential diagnostic tools.
5. To enhance Causal Rasch mathematical models to define prototype metrological references for cognition expressed as "construct specification equations (CSE)". This will provide an extensive explanation of how able a human can act as an "instrument" when measuring the difficulty of a task such as a cognitive test. Those models will be applied to the PCOMs, MRI and MRS, biomarker data to define and improve the prognostic values of the methods developed.
6. To transfer the project's results to the measurement supply chain, standards developing organisations (ISO/TC212, the International Federation of Clinical Chemistry (IFCC), and the Joint Committee for Traceability in Laboratory Medicine (JCTLM)), instrument manufactures and end users (e.g., clinical laboratories and pharma) and promote the 15HLT04 NeuroMET multidisciplinary infrastructure to become the ideal space for NDD translational research.

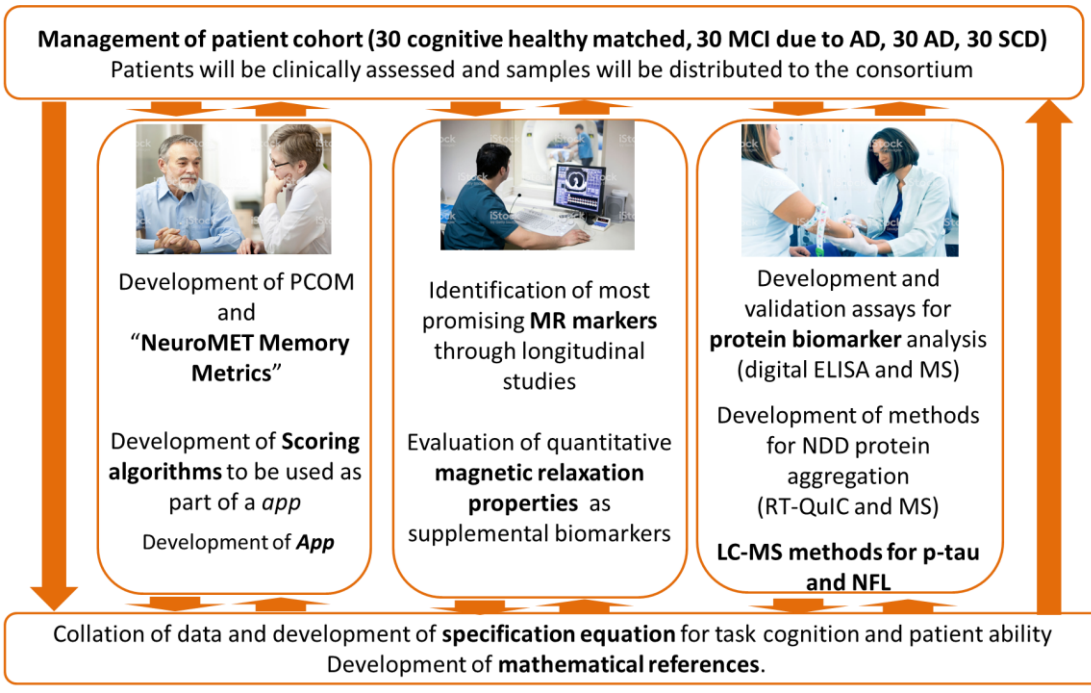

Figure 1. Schematic representation of the project

Progress beyond the state of the art

While significant progress has been made over the past decade towards early NDD diagnosis across different fields, no reference methods are currently available for clinical use. This project built upon on the success of 15HLT04 NeuroMET by contributing to the uptake and validation of new assays for NDD diagnosis through i) the development of new multidisciplinary RMPs; ii) the use of the unique NeuroMET patient cohort and iii) the application and implementation of the RMPs into clinical use. Specifically, the project's:

- PCOMs, validated by clinical laboratory data, were refined for early diagnosis through the additional data acquired on the patient cohort from the follow up visits and the inclusion of new patient groups. The results were used to validate a 'NeuroMET memory metric' (NMM), and to design and implement an app to deliver cognitive tests. This is, to our knowledge, the first attempt to develop such an app for use by clinicians and patients.
- 7T and 3T MRI and MRS protocols were refined and the main components contributing to the calculation of measurement uncertainties were identified and optimised. Furthermore, approaches were developed to increase measurement accuracy for diagnostic purposes (e.g. to define measurement variability from real changes due to the disease). The 15HLT04 NeuroMET 3T protocol was implemented into a clinical setting and clinical staff were trained to facilitate its uptake into clinical use. Ultra-high field strength MRS with its reduced measurement uncertainty was applied to define the prognostic value of a number of metabolites in brain tissues, including myo-inositol, glutamate and GABA, which are promising MRS NDD biomarkers.
- biomarker blood assays were advanced through correlation with the MR and PCOM data from the project's cohort. New liquid chromatography mass spectrometry (LC-MS) methods for NFL and phosphorylated-tau (p-tau) were developed which complement the current international effort to promote these markers as powerful diagnostic and stratification tools. Reference methods for these analytes will also facilitate the uptake of new assays for their measurement. RMPs for α-synuclein and t-tau developed during 15HLT04 NeuroMET were validated to facilitate measurement standardisation and validation of new assays. This represents the first time an MS-based approach for quantification of α-β and γ synucleins with routes to SI traceability has been developed and applied to patient samples in order to define and improve the diagnostic value of this important synaptic marker.
- causal Rasch models of cognitive constructs (articulated through specification equations) were, for the first time, validated and proposed as metrological references for PCOMs in order to define and decrease measurement uncertainty and enable standardisation of results. Specifically, significant progress was made towards understanding the role of entropy when formulating CSEs for memory task difficulty, leading in turn to improved reliability, validity, and efficiency of the NMM.

Results

1. *To maintain the already established and stratified 15HLT04 NeuroMET patient cohort and enrol new patients to cover the defined stages of neurodegeneration and account for patient drop-out. Patients will be clinically assessed, and blood as well as CSF samples will be collected and distributed to partners for longitudinal studies.*

The COVID-19 pandemic presented a significant challenge to patient recruitment for the NeuroMET cohort, as the class of targeted patients was one of the most vulnerable groups. However, the significant efforts of the project partners ultimately enabled the recruitment, follow up visits, and collection of samples from 82 participants. From the 90 participants recruited in 15HLT04 NeuroMET, 42 participants were followed up in this project, NeuroMET2. Combining the NeuroMET and NeuroMET2 cohorts, the final dataset comprises of 129 participants with a total of 315 visits.

Additional samples and data sets from the Charité SmartAge cohort from were added to provide further relevant data. (https://alzres.biomedcentral.com/articles/10.1186/s13195-019-0484-1).

The collected blood, CSF, and saliva samples were distributed to partners for use in RMP and clinical method development (Objective 3) and to generate biomarker data to feed into mathematical models (Objective 4).

It should be noted that the NeuroMET patient cohort represents a unique resource, as it is the first ever metrologically characterised cohort in the field of AD research.

2. *To advance the 15HLT04 NeuroMET PCOMs for cognition and early diagnosis. This will lead to the validation of a 'NMM' and the development of an app (software application downloadable onto mobile devices) for clinicians and patients to deliver validated cognitive tests.*

The data obtained in Objective 1 facilitated the development and validation of a novel measurement of cognitive ability known as the 'NeuroMET Memory Metric' (NMM). Under the preceding EMPIR 15HLT04 NeuroMET project, a prototype metric based on legacy cognitive PCOMs was developed. The 18HLT09 NeuroMET2 project further developed and validated this metric and developed an app which could be used to roll the new metric out to the clinical community.

The new app was transferred to the project's clinical partners for testing. Eighteen healthcare professionals from the NeuroMET2 partners, including those from Charité (n=11) and Uni Greifswald (n=6), as well as from the external collaborators Fachklinik Briese (n=1), and Immanuel Klinik Rüdersdorf (n=1) were recruited to test the app. The testers were from a variety of roles, including neuroscientists (n=11), neurologists (n=4), psychologists (n=2), project managers (n=1) and study assistants (n=1). Updates and further testing of the app (after the end of the project) will be carried out following feedback from clinicians.

The NMM and its associated app represent a novel and more accurate measurement system for cognitive testing. They are also an important and new method for cognitive testing through an app for use by clinicians and patients.

3. *To refine ultra-high field MRI and MRS protocols from 15HLT04 NeuroMET through longitudinal studies for application into clinics and develop new in-vivo approaches. Additionally, new in vivo approaches will be developed to monitor supplemental biomarkers in the project cohort.*

The NeuroMET 2 project continued the work of 15HLT04 NeuroMET by characterising patients using the high accuracy of a 7T MR system. Each in-vivo MR measurement on the patients from the NeuroMET cohort (Objective 1) consisted of three major sections:

- structural or "morphometric" measurements, to assess structural information on each individual participant's brain structure and anatomy
- MRS measurements, to measure concentrations of neurometabolites within the brain tissue of participants
- resting-state functional MRI (rs-fMRI), to extract information on functional connectivity within the participant's brains

After analysis, the obtained results were included in PCOMs (including the NMM, Objective 2) and in mathematical models of cognition (see Objective 4).

Significant advances were also made in fundamental metrological aspects of MRS, including data analysis and measurement uncertainty. A statistical framework was also developed to estimate the measurement uncertainty of in-vivo MRS. The data set associated with this work including the raw data were published open access to allow their uptake in the examination of newly developed MRS modelling, postprocessing, and quantification pipelines and of their influence on the measurement uncertainty.

Workshops and hands-on training courses on MRS data acquisition and MRS data analysis were undertaken by the consortium as part of work to transfer the high accuracy 7T scanning protocols developed under the project to 3T clinical settings. The first 7T system received FDA and CE approval in 2019, and 7T scanners are now starting to enter clinical routine environments, however there are still many more 3T systems (than 7T systems) being used for clinical examinations and research.

Currently, 3T systems are not able to obtain the same detail and reduced measurement uncertainty as a 7T system. Thus, implementing into a clinical setting 3T protocols which are mapped to metrologically validated 7T protocols is a very important step for disseminating the project's results.

4. *To advance biomarker measurements for early and accurate diagnosis through validation and implementation into clinics of the 15HLT04 NeuroMET methods and other methods. Biomarkers such as Aβ1-42, Aβ 1-40, NFL, t-tau and α-synuclein will be monitored in the NeuroMET cohort and new RMP for NFL and p-tau will be developed. Methods for monitoring aggregation of NDD proteins will be developed and validated to improve specificity of therapeutic targets and as potential diagnostic tools.*

The NeuroMET 2 project continued the work of 15HLT04 NeuroMET by characterising the patient NeuroMET cohort (Objective 1) for key NDD biomarkers and to input this data into PCOMs (including the NMM, Objective 2) and in mathematical models of cognition (Objective 4).

Key AD biomarkers were measured in plasma (Aβ 1-40, Aβ 1-42, p-tau, NfL, GFAP) and in CSF (Aβ 1-40, Aβ 1-42, t-tau, p-tau, NfL). The analysis included patients recruited under both 15HLT04 NeuroMET and NeuroMET2, and across multiple time points in order to provide longitudinal data in relation to disease progression.

In parallel, a number of SI-traceable RMPs were developed and validated for key NDD protein biomarkers. This was achieved by characterisation and quantification of primary calibrators, followed by the development of mass spectrometry method(s) for quantification of the protein of interest.

- A LC-MS method for p-tau in CSF was developed and validated using pooled samples and was compared to immunoassay measurements in order to understand differences between the RMP and methods commonly used in clinical settings.
- A candidate LC-MS method for monitoring NfL in CSF was developed, encompassing novel antibody-free and immuno precipitation-based strategies which are required in order to reach the required sensitivity for the detection of NfL in clinical CSF samples (see Figure 2, below)
- A reference method for α-synuclein in CSF developed in the 15HLT04 NeuroMET project was validated during and used for comparison with orthogonal techniques including a clinical MS method developed during this project and an RT-QuIC assay.

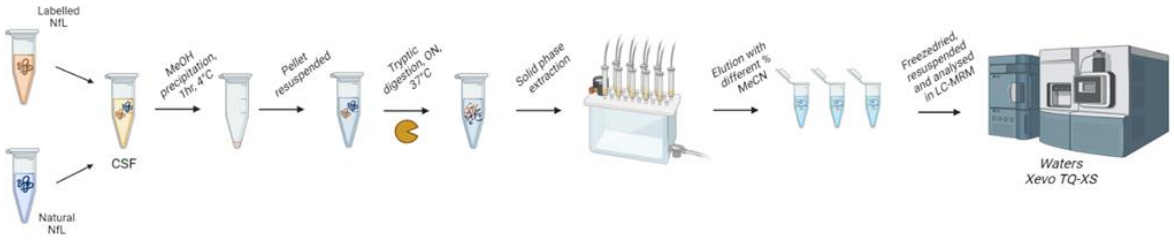

Figure 2 – Candidate NfL RMP workflow

5. *To enhance Causal Rasch mathematical models to define prototype metrological references for cognition expressed as "CSE". This will provide an extensive explanation of how able a human can act as an "instrument" when measuring the difficulty of a task such as a cognitive test. Those models will be applied to the PCOMs, MRI and MRS, biomarker data to define and improve the prognostic values of the methods developed.*

Building upon the results of 15HLT04 NeuroMET, work was undertaken to enhance the understanding of the role of entropy when formulating CSEs for memory task difficulty, leading in turn to the development of the NMM (Objective 2). While existing individual legacy neuropsychological tests have lacked both sufficient accuracies to distinguish disease stages and have not been quality-assured, the new NMM is based on modern measurement theory, metrological quality assurance, causal multivariate analyses and cross-walking between items carefully chosen from different legacy tests when composing the metric.

The new NMM shows an up to five-fold reduction in uncertainties for measurements of memory ability along the AD continuum without jeopardising validity which is a significant improvement. The new NMM should also be more efficient and specifically suitable for studies of, for example, early detection of disease onset or the effects of drug intervention.

The project also demonstrated that person memory ability can be explained in terms of causal models by bringing together results multidisciplinary measurements. Such causal models are CSEs, in which multimodal statistical approaches are used in order to explain the construct person memory ability as a function of a set of explanatory (independent) variables. The variables considered by the project were (i) brain volumes measured by MRI, (ii) metabolites measured by MRS, and (iii) blood-based biomarkers. Changes in biomarkers can cause a change in person memory ability and thus CSEs can provide a better understanding of what is causing variation in person memory ability.

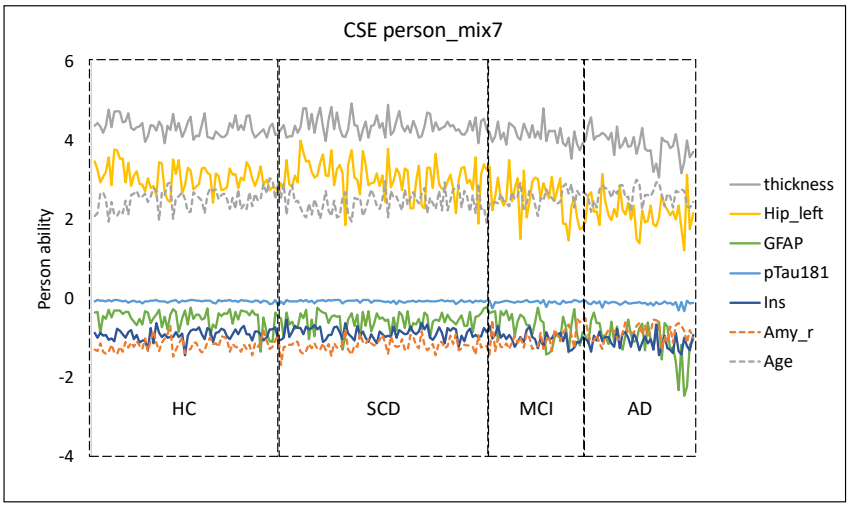

Figure 3 - Individual contributions to person ability (y-axis) from an optimal selection of 7 NeuroMET biomarkers (MRI, MRS and plasma-based). Measurements are ordered by decreasing person ability across the NeuroMET cohort (left to right along the x-axis) and approximate stratification into the sample groups (HC, SCD, MCI, AD) is shown in the figure. Abbreviations: AD = Alzheimer's disease, Amy_l = left amygdala GFAP = glial fibrillary acidic protein, HC = healthy control, Hip_l = left hippocampus, MCI = mild cognitive impairment, NfL = Neurofilament light, SCD = subjective cognitive decline.

Further advances were also made towards provide an extensive explanation of how ably a human can act as an "instrument" when tackling a memory task of a certain difficulty by combining the CSEs to form a prototype certified reference procedure. In order to maintain the unique metrological properties of the Rasch model and improve estimates and understanding of person memory abilities on the path towards better targeted and more fit-for-purpose diagnostics, it is necessary to account for potential sources of model misfit. The Rasch transformation takes care of the basic ordinality arising from the counted-fraction character of raw psychometric data but may not account for additional effects of ordinal scaling such as response styles and patterns.

Based on work on this objective, a traceability pyramid for memory measurements based on ISO 17511:2003.30 was proposed. This is a novel approach which applies established metrological principles which are familiar in physics and chemistry into psychometric testing.

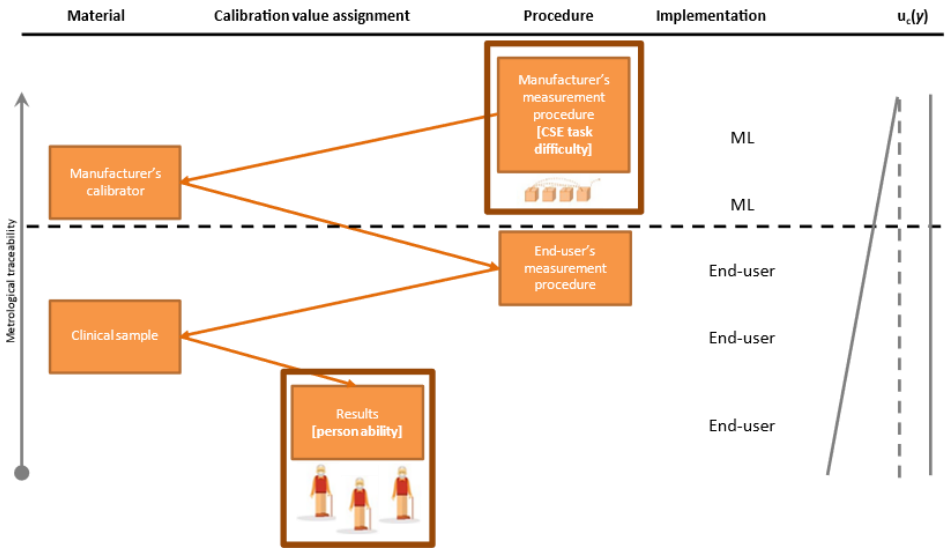

Figure 4 - A proposed traceability pyramid for memory measurements based on ISO 17511:2003.

Impact

A website for the project is available at https://www.lgcgroup.com/our-programmes/empir-neuromet/ . It contains information about both this project and the preceding 15HLT04 NeuroMET project. A LinkedIn page for the project was also created and it is updated regularly https://www.linkedin.com/company/neuromet.

Newsletters were circulated to stakeholders interested in the standardisation of liquid biomarkers, MRI/MRS, and PCOMs. Two leaflets on the NeuroMET projects and their results were also prepared and distributed to cohort volunteers and their families. These leaflets were made available in both English and German through the project website and LinkedIn page. Further to this, information events for study participants and their caregivers were held at Charité in July 2019 and November 2022.

The project was the subject of 35 conference presentations. Conferences attended included the Joint Conference of the Society for European Magnetic Resonance and the International Society for Magnetic Resonance EUROISMAR 2019, the Annual Meeting of the International Society of Magnetic Resonance in Medicine (ISMRM 2020, 2021, 2022), the Annual Scientific Symposiums on Ultrahigh Field Magnetic Resonance (2019), Alzheimer's Association International Conference (AAIC 2019, 2021, and 2022); the International Society for Magnetic Resonance in Medicine (2021, 2022), the International Metrology Congress (CIM) 2021, IMEKO 2021, and the International Lewy Body Dementia Conference 2022.

The project generated 13 open access peer-reviewed publications, of which 9 had international co-authorship between consortium partners.

Impact on industrial and other user communities

One of this project's goals was to bring benefits to the pharmaceutical and in vitro diagnostic industry, clinicians, and ultimately patients, by providing a set of metrologically validated methods to: (i) improve targeted NDD recruitment in clinical trials and to accurately monitor the efficacy of new therapeutics; (ii) facilitate the regulatory approval of new assays and their uptake into clinics; and (iii) enable accurate diagnosis of NDD patients, facilitate clinical decisions, and hence improve clinical outcomes. This project has achieved this goal through the deployment of the NMM and its associated app (Objective 2), and the provision of RMPs for key NDD biomarkers in both biological fluid testing and MIR/MRS (Objective 4) and their translation to clinical settings.

The project's metrologically validated app (Objective 2), is the first of its kind in the field of cognitive assessment and based data from the project's unique cohort (Objective 1) and is a significant project output and represents more accurate a robust route to memory testing. The phase one roll out of the app to clinicians at Charité and other institutes was completed during the project and a wider roll out will continue after the end of the project. The app will provide mobile NDD health information to clinicians with the potential for dynamic engagement with patients and health care providers, and a new means of improving health outcomes. The NMM and the app were disseminated to a wider group of users beyond the original testing group via a webinar in November 2022.

The validated RMPs developed for key NDD biomarker provide an SI-traceable reference against which performance of in-vitro diagnostics can be assessed (Objective 4). Roll out of these to clinical communities has included the development of a candidate MS clinical assay for monitoring α-synuclein in CSF, and the delivery of a commutability study on t-tau under the IFCC WG-CSF which has provided IVD manufacturers with insights into the performance of their products relative to a reference method.

Within MRI and MRS, direct links to clinical end users were maintained though the involvement of clinicians and industry as partners (i.e. partners Charité, Uni-Greif, Modus), and via transfer of the project's reference 7T MRI/MRS sequences to widely used scanners in a clinical setting at Uni-Greif. An agreement was made with Siemens (one of the leading manufacturers of MRI machines in Europe) to enable transfer of this project's 3T protocol (Objective 3) to the clinical environment at Uni-Greif. The 3T protocol was derived from the 7T NeuroMET protocol in the 15HLT04 NeuroMET project. Furthermore, hands on training on MRS data acquisition was provided by PTB to MR physicists at Uni-Greif in order to support MRS data acquisition uptake in clinical settings, and a webinar was organised to disseminate best practice to the clinical community more widely (Objective 3).

The outputs of the project were also presented to stakeholders at key clinical conferences including AAIC 2019, 2021, and 2022 which is the largest AD conference worldwide, and at International Lewy Body Dementia Conference 2022.

Longer term, the projects outputs will support pharmaceutical development with the PCOMs and blood tests (Objectives 2, 3, 4 & 5) developed and validated within the project contributing to identification of NDD patients before clinical on-set. This will support the recruitment of groups of patients to clinical trials for new therapeutics and hence increase their rate of success. The project's RMPs for CSF biomarkers, and the high-resolution MRI and MRS protocols (Objectives 3 & 4) will also increase confidence in the recruitment of targeted NDD patients for new drug trials.

Impact on the metrology and scientific communities

This project has built on the work of 15HLT04 NeuroMET to enhance the application of metrological concepts, which are commonplace in disciplines such as physical and chemical measurements, into the area of cognition and mathematical RMPs. The standardisation of the results from cognitive assessments and their application to develop a memory metric (the project's NMM) is the first example of standardisation of PCOMs (Objectives 2 & 5). This is a unique advancement for the metrological and scientific community, together with the development of mathematical models to be used as primary RMPs for cognition.

The application of the project's metrological concepts such as the measurement uncertainty of *in vivo* MRI and MRS results (Objective 3) should enable significant progress, not only in the definition of NDD diagnostic thresholds, but also in establishing novel RMPs for *in vivo* MRI and MRS. The data associated with this work has been made open access and freely available via the project's Zenodo community which will allow other researchers to replicate and enhance this novel uncertainty determination framework. The project also achieved pan-European impact in this area by close alignment and collaboration with the 18HLT05 QUIERO project in relation to T1-mapping examinations.

The project's RMPs for protein biomarkers (Objective 4) will help the scientific and metrological community address the challenges faced in standardising measurements of larger and more complex biomolecules. SI-traceable RMPs for protein biomarkers is still an emerging field relative to similar methods for small molecules, and work under this project (for example on tau) has demonstrated the feasibility and utility of such RMPs and their associated primary calibrators. LNE's validated RMP for t-tau reference measurement procedure was accepted for inclusion to the JCTLM database, which will further increase its impact on the laboratory medicine and IVD communities.

The project pursued close alignment with key European Metrology Networks (EMNs) on 'Traceability in Laboratory Medicine' (TraceLabMed) and MATHMET, in order to support their integration into international initiatives such as EFLM (European federation of Laboratory Medicine) and EUFIND (European Ultrahigh-Field Imaging Network for Neurodegenerative Diseases).

Work from the project was also presented at key metrology conferences including CIM 2021, IMEKO 2021, and MSMM 2021; and key technical conferences including the International Society for Magnetic Resonance in Medicine (2021, 2022), Joint Conference of the Society for European Magnetic Resonance (EUROMAR) and the International Society for Magnetic Resonance (ISMAR), EUROISMAR 2019, and the 3rd International Hydrogen Deuterium Exchange Mass Spectrometry conference.

Impact on relevant standards

The project maintained close alignment with a number of standardisation committees including ISO TC 12 Quantities and Units and ISO TC 212 Clinical laboratory testing and in vitro diagnostic test systems, ISO TC 215 on Health informatics. Many of the scientists involved in the delivery of the project sit on key standardisation committees.

The project also provided input to the IFCC WG-CSF, the Society of CSF analysis and clinical Neurochemistry, EUFIND, JCTLM and BIPM's Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) Working Groups. Standardisation activities to highlight include (i) a p-tau interlaboratory value assignment study and (ii) a t-tau commutability study, both organised in association with the IFCC WG-CSF, (iii) acceptance of the t-tau RMP to the JCTLM database, and (iv) presentation of the project's work at key standardisation conferences including JCTLM Accurate Results for Patient Care Workshop 2019.

Longer-term economic, social and environmental impacts

Many NDDs such as AD are irreversible and progressive. In addition to large socioeconomic costs, they severely affect the quality of life of patients and their caregivers. Early diagnosis through implementation of screening programs, the identification of people with risk factors, and the development of new therapeutics are vital for delaying the onset of symptoms and improving the quality of life of NDD patients. Thus, in the long term, this project will help to decrease the socioeconomic burden of NDD, reduce the resources spent by the pharmaceutical industry, and improve the quality of life of NDD patients and their caregivers.

List of publications

1. Melin, J., Cano., S.J. and Pendrill, L. The Role of Entropy in Construct Specification Equations (CSE) to Improve the Validity of Memory Tests. Entropy. Dec 2020. https://doi.org/10.3390/e23020212
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9. Pendrill, LR. et al, Assuring measurement quality in person-centred care, in Person-Centered Outcome Metrology: Principles and Applications for High Stakes Decision Making in Springer International Publishing, William P. Fisher Jr. & S. J. Cano (ed.) (s. 311-335), https://doi.org/10.1007/978-3-031-07465-3_11
10. Person-Centered Outcome Metrology: Principles and Applications for High Stakes Decision Making in Springer International Publishing, William P. Fisher Jr. & S. J. Cano (ed.), https://doi.org/10.1007/978-3-031-07465-3
11. Das, S.; Dewit, N.; Jacobs, D.; Pijnenburg, Y.A.L.; In 't Veld, S.G.J.G.; Coppens, S.; Quaglia, M.; Hirtz, C.; Teunissen, C.E.; Vanmechelen, E. A Novel Neurofilament Light Chain ELISA Validated in Patients with Alzheimer's Disease, Frontotemporal Dementia, and Subjective Cognitive Decline, and the Evaluation of Candidate Proteins for Immunoassay Calibration. Int. J. Mol. Sci. 2022, 23, 7221. https://doi.org/10.3390/ijms23137221
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This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

Project start date and duration:		July 2019, 42 months
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Internal Funded Partners: 1 LGC, United Kingdom 2 LNE, France 3 PTB, Germany 4 RISE, Sweden	External Funded Partners: 5 Charité, Germany 6 CHU Mpt, France 7 Modus, France 8 Uni-Greif, Germany 9 VUmc, Netherlands	Unfunded Partners: 10 HKR, Sweden
RMG: -		