Northumbria Healthcare NHS
NHS Foundation Trust

Title: Evaluation of Neuromotor Pen in early identification of dementia and differential of dementias subtypes: A feasibility study

Short Title: Dementia Pen Study

Sponsored by: Northumbria Healthcare NHS Foundation Trust

Funded by Manus Neurodynamica Ltd.

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2. Protocol Signatures Page

Protocol Authorisation Signatories

I confirm that I have read and understood protocol version 1.3 11th July 2023. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature……. Date ……..

Dr Christopher Davison, Chief Investigator

3. Protocol Summary

The study sets out to evaluate the feasibility of using the Neuromotor Pen™ (NMP) in memory clinic setting to support diagnosis and differentiation of dementia subtypes. The NMP has been evaluated as safe and of potential diagnostic benefit in Parkinsons clinics. There is potential use of the pen in dementia clinic setting however no studies have been completed to see if the pen would be practical and whether results would support diagnosis. We are therefore completing a feasibility study to evaluate use of pen in memory clinic settings.

If proved to be useable in memory clinic setting with potential diagnostic benefit then further case control study will look at further evaluating the diagnostic capability of the NMP.

4. Background

The Neuromotor Pen ™ (NMP) is a novel sensor system that has been evaluated for differential diagnosis of PD that allows an objective assessment of handwriting. The subject performs writing and drawing tasks. Pressure and motion sensors and advanced analysis techniques assess the dynamic pen motion and pen-hand interaction.

There are potential benefits in using NMP to aid identification of potential dementia in primary and secondary care. There is also potential to aid diagnosis of dementia subtypes. Tests involving NMP have found it to be safely and effectively incorporated into Parkinsons disease clinics.

5. Main hypothesis

We will test a novel, user-friendly and inexpensive system to aid in the differential diagnosis of dementia It is hypothesized that the system can be developed to differentiate between dementia, MCI and normal subjects as well as potentially differentiating dementia subtype.

6. Objectives

The overall objective of this project is to assess the usefulness of the system for identification and differential diagnosis of dementia and dementia subtypes. Initially however we are looking to evaluate proof of concept and acceptability in a cohort of patient accessing memory clinics to evaluate potential cognitive impairment and dementia.

An initial sample size of more than 101 referrals to NHS memory clinic services will be required. Healthy age-matched controls will be included as comparison.

If the study proves successful, the system may find application in clinics to aid in diagnosis of dementia and differentiating between dementia subtypes as well as a tool to identify those requiring referral to memory services and help differentiate dementia and MCI as a low-cost screening and diagnostic tool.

Following initial evaluation further cohorts of patients with confirmed diagnosis of MCI, dementia and controls will be compared to evaluate ability to differentiate diagnosis. Design of the later study will be dependent on the initial evaluation of results.

7. Study Design

The study follows up a local study investigating use of the NMP in a Parkinsons disease clinic.

The aim is to replicate use of NMP in a memory clinic population to evaluate the feasibility to incorporate it into clinical practice and to assess the possible usefulness in the diagnosis of dementia

The study will assess the ability of drawing tasks preformed with NMP analysis platform to diagnose dementia compared to current best practice. It will assess for usability of NMP tasks and allow these to be adjusted to aid diagnostic ability and performance in real world memory clinics. The overall longer-term objective is to assess the usefulness of the platform in diagnostics by determining the ability to detect presence of disease (sensitivity) and absence of disease (specificity).

7.1 Setting and timing

The study will be open for a maximum of two years after opening to recruitment.

7.2 Data Collection and Recruitment

Subjects will be recruited from:

i. Referrals to the Northumbria Healthcare NHS Foundation Trust (NHCT) memory clinics. Consecutive referrals to the service will be approached and asked to participate, with those who consent being recruited.

ii. . To act as comparator age-matched control subjects will also be assessed. Controls will be approached from local research databases / registers / local community groups where people have provided previous consent to be contacted about taking part in research.

Referrals to NHCT memory clinic service

All people referred to the NHCT memory service are assessed by a local specialist memory clinic based at NTGH. Assessments are completed in clinic or at patient home address. Assessment using the Manus platform will be carried out by a trained clinician at the clinic. The assessor will be blinded to results of the NMP tests. A research nurse will review clinical records and record results of relevant cognitive and functional tests. Clinical diagnosis and other tests result will be recorded for analysis.

ii. **Controls**

Age matched controls will be approached and asked if they wish to be assessed using the Manus Platform. Only those who consent will be assessed. A brief cognitive test (Montreal Cognitive Assessment - MoCA) will be carried out for screening. Controls scoring less than 26/30 on the MoCA will be excluded and advised to consult their GP if they have any concern.

7.3 Inclusion / Exclusion Criteria

Inclusion criteria

- See source of referral criteria above
- Only participants with capacity to consent to trial will be recruited

Exclusion criteria

- Unable to give fully informed consent for any reason.
- Unable to hold the assessment pen for any reason.
- Significant visual problem affecting use of pen.
- Scoring less than 26/30 on MoCA (Controls Only)

7.4 Consent and Ethical considerations

All people who express an initial interest in participating will receive an information sheet explaining the reasons for the study and their role in it. Only people who provide fully-informed consent will be recruited to the study and recruited subjects will be free to withdraw at any point without needing to provide a reason. Any person, who is unable to provide consent due to severity of cognitive impairment, or any other condition, will not be considered for inclusion.

The assessments are non-invasive and a safety certificate will be provided for the Manus platform; we do not envisage any risk to the patients. Patients will be allowed as much time as they need to decide if they wish to participate and to complete the assessments. Any findings that are relevant clinically will be fed back to the clinical team.

All experimental data gathered during this study will be associated with an anonymous subject identifier. The name and date of birth of the subjects will be kept only on the consent forms and recruitment log both of which will be stored securely within investigator site file. The participants name will only be available to the research team, and will not be used in any scientific reports.

All data will be handled anonymously. The data will not be shared with third parties. The consent forms and questionnaires will be stored in a locked cabinet, separate from any results of the study. Study results will be stored on a password-protected computer. The movement of pen and limb joints does not include any images that allow recognition of the subject and is considered an integral part of the data.

7.5 Assessment

Physician assessment

The primary outcome of interest is the level of agreement between the Manus dementia platform and current 'best practice' (clinical diagnosis) in the diagnosis of dementia and differential of subtypes. The assessment by a specialist clinician will be conducted as part of routine assessment of anyone referred with suspected dementia. Physician assessments may include physical exanimation, detailed history and appropriate cognitive and functional subscales. For the purposes of the study, we will extract data from this assessment relating to the final diagnostic decision of the physician. We will also extract data relating to the results of any specific assessments carried out.

Health screening

Basic demographic data (age, sex, etc.) will be collected. Additional clinical outcome measures used will be:

- The Addenbrooke's Cognitive Examination-III (ACE-III) assessment *(patients only)*
- The Hospital Anxiety and Depression Scale (HADS) *(patients only)*
- Functional assessment (BADLS) *(patients only)*
- Handedness *(all subjects)*
- Montreal Cognitive Assessment (MoCA) *(controls only)*

Motor performance outcome measurement using the Manus platform

A full description of the Manus platform is given in the pen task Standard Operating Procedure (SOP). Assessment involves the participant holding a specially designed digital pen with built in sensory and carrying out simple drawing tasks on an electronic screen.

The data from the platform are semi-automatically analysed by specially developed algorithms. Variables collected include:

- Fingertip pressure from the pen (Sampling frequency = 1000 Hz; Recorded from index finger, middle finger, thumb)
- Script x,y-coordinates recorded (sampling frequency ~100 Hz; X and Y coordinates of pen tip (Pen tip pressure)
- Gyroscope 3d rotation data from pen (sampling frequency ~200 Hz; resolution of orientation angles 0.5 °/s)
- Accelerometer 3d acceleration data from pen (sampling frequency ~200 Hz; resolution $1x10^{-3}$ g)

Differentiation between those with, and those without dementia will require the evaluation of two main groups of variables. The first group contains generic variables (time to complete the task, pen tip motion, pen tilt and 3D pen motion and derivatives, such as average pen speed etc). The second group contains more complex variables, derived from more advanced analysis methods and

additional features for identifying rest and kinetic tremor. Algorithms are implemented in Matlab. Performance is assessed by well-accepted measures such as sensitivity, specificity, accuracy and area under the ROC curve.

Blinding and timing of assessments

Patients: Patients will undergo Manus platform assessment after clinician assessment. We will conduct sub-group analyses to investigate the impact of Manus platform assessment after other assessments. The patients will not be informed of the results of the Manus platform assessment.

Study nurse: The person conducting the Manus platform assessment will be blinded to the results of the physician assessment in cases where the Manus platform assessment occurs after the physician assessment.

Physician: The physician (and patient) will not be aware of the results of the Manus platform assessment at the time of physician assessment.

Follow up

Patients and controls will not require follow up outside their normal routine clinical follow up. Data surrounding clinical test results and clinical diagnosis will be recorded for comparison.

7.6 Data analysis and sample size

If used in routine clinical practice we envisage that the system will be required to provide a score, relating to the probability of an individual having dementia, to be used in conjunction and to aid clinical diagnosis.

As first step the feasibility and tolerability of tests will be evaluated in patients presenting to dementia clinic. The test will be adjusted dependent on data to ensure it can be used in clinical practice and to improve diagnosis.

Once the above has been completed further assessment of test will be undertaken on future cohorts of patients with clinically confirmed dementias, MCI and controls to evaluate sensitivity and specificity in aiding diagnosis.

In order to gain meaningful insight into feasibility, it is anticipated a minimum sample size of over 100 would be required.

8. End of Study

The end of the study will be defined as when all data has been received and queries resolved.

Participants will be asked at the point of consent whether they wish to be informed about the results of the study. Results will be shared as a written summary and participants will be invited to a feedback session.

9. Study Management and Oversight

The study will be approved by the Research and Development Department, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, Rake Lane, North Shields, Tyne and Wear NE29 8NH before any data will be collected. As the sponsor, Northumbria Healthcare NHS Foundation Trust can conduct an audit of the study at any time to monitor the progress and ensure research governance standards are being maintained.

The study will conform to all overarching NHS governance requirements and will be conducted in line with the principles of GCP.

The study will be reviewed and agreed by Regional Ethics Committee before any participants are enrolled.