THE COUNCIL OF RESEARCH ETHICS BOARD (COREB): COMMON REB APPLICATION FORM

INSTRUCTIONS:

1) Please refer to the **COREB: Common REB Application Guidelines** when completing this application. All sections of this application must be completed before it will be considered for an ethical review by the Research Ethics Board (REB) at the facility where the research will take place (i.e. the research site facility). If a section is not applicable, please indicate "Not Applicable" and provide a brief explanation in the space provided. **Unless specifically indicated, do not refer to or attach other documents as a means to complete a section of the REB application.**

2) A complete application and supporting documents (e.g. original study protocol, investigator's brochures) must be submitted to the primary site for REB review and each site where this research will take place. When selecting the primary site for REB review, please refer to the COREB Common REB Application Form Guidelines for directions. It is the responsibility of the applicant to contact each research site REB (see Appendix A for contact information) for instructions regarding; a) the number of copies to be submitted, b) submission deadlines, etc.

ETHICS REVIEW AND APPROVAL STATUS:

COREB Research Site Facilities in the Ottawa Region

Application submitted to: (check all that apply):		***Ethics Review and Approval Status:** (Check all that apply and indicate date where applicable)				
		Date of Application Submission:	Primary Site for REB Review	Review Pending	Conditional Approval Received	Date of Final REB Approval
☐	University of Ottawa – Social Sciences and Humanities		☐	☐	☐	
☐	University of Ottawa – Health Sciences and Sciences		☐	☐	☐	
☐	University of Ottawa – Heart Institute		☐	☐	☐	
☐	The Ottawa Hospital		☐	☐	☐	
☐	Children's Hospital of Eastern Ontario		☐	☐	☐	
☐	Royal Ottawa Health Care Group		☐	☐	☐	
☒	**Bruyère Continuing Care**	June 13th 2017	☒	☐	☐	September 11, 2017
☐	The Rehabilitation Centre		☐	☐	☐	
☐	Montfort Hospital		☐	☐	☐	
☒	Other (specify): Carleton University	September 28th, 2017	☐	☐	☐	September 30, 2017

*Please include all relevant correspondence related to ethics review of the research study by COREB REBs (e.g. REB review letter, replies, approval form). If applying to more than one site,

please indicate which site will be the primary site for ethics review – see Guidelines for the selection of the primary site for REB review.

RESEARCH ETHICS APPLICATION

Please Use the Guidelines when Completing this Application

1. PROTOCOL TITLE: Longitudinal validation of computerized technologies in the detection of mild cognitive impairment and Alzheimer's disease.

2. STUDY DURATION: Expected Start Date: 01/05/2018

Expected End Date: 31/12/2021

3. ORIGIN OF STUDY (check one)**:**

☒ **a) Investigator Driven**

☐ **b) Corporate Sponsor**

i) Provide name and contact information for corporate sponsor:

_____

ii) Country

_____

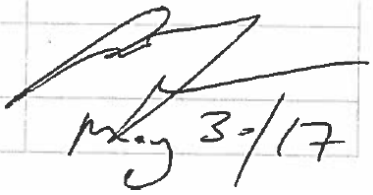
4. PRINCIPAL INVESTIGATOR (See Guidelines)

This individual has the overall responsibility for the project at all research sites.

Last Name	Frank	First Name	Andrew
Title/Position	Physician, Memory Program Director	Tel.	(613) 562-6322 ext. 1078
		Fax	(613) 562-6013
Dept/Unit & Location	Bruyère Memory Program	Email	afrank@bruyere.org
Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	May 3/17

5. RESPONSIBLE SITE INVESTIGATOR (For multiple COREB site projects, cut and paste copies of this section to identify the Responsible Site Investigator for each research site facility)

Do you have an affiliation with Bruyere Memory Program (enter the name of the Research Site Facility) and will you serve as the study's contact person for the facility's Research Ethics Board? ☒ Yes ☐ No If No, have a delegate complete Section 6a.

Last Name	Frank	First Name	Andrew
Title/Position	Physician, Memory Program Director	Tel.	(613) 562-6322 ext. 1078
		Fax	(613) 562-6013
Dept/Unit & Location	Bruyère Memory Program	Email	afrank@bruyere.org
Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	May 3-/17

***Responsible Site Investigator Agreement – By signing above**, I assume full responsibility for the scientific and ethical conduct of the study at my research site as described in this REB application and supporting documentation (e.g. protocol) and agree to conduct this study in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Subjects and any other relevant regulations or guidelines endorsed by the research site facility. I certify that all researchers and other personnel involved in this project at this institution are appropriately qualified and experienced or will undergo appropriate training and supervision to fulfill their role in this project.

AF By initialing here, I certify that I meet the requirements of a "Qualified Investigator" as defined by Health Canada. ☐ Not Applicable

6. CO-INVESTIGATORS (See Guidelines)

If the Responsible Site Investigator does not have an affiliation with the research site facility, or has an affiliation, but is not available to be the contact person for the REB of the research site, the responsibility for reporting to the REB should be assigned to a Co-Investigator who is listed immediately below in Section 6a.

If this is not the case, check off "Not applicable" and begin listing Co-investigators in 6b.

☒ Not applicable

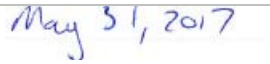
a) Last Name		First Name	
Title/Position		Tel.	( ) - ext.
		Fax	( ) -
Dept/Unit & Location		Email	
Division/ Portfolio		Signature:	
		Date:	

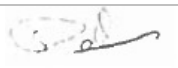
I have an affiliation with (enter the name of the Research Site Facility) and will serve as the study's contact person for facility's Research Ethics Board.

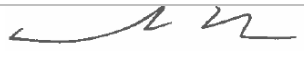
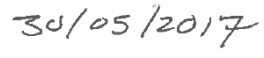
☐ Yes ☐ No

6. CO-INVESTIGATORS (cont'd)

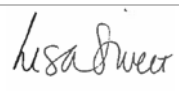
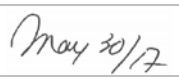
b) Last Name	Knoefel	First Name	Frank
Title/Position	Physician, Clinical Scientist	Tel.	(613) 562-6262 ext.1357
		Fax	
Dept/Unit & Locatio	Bruyère Memory Program	Email	fknoefel@bruyere.org
Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	08/06/2017

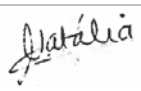
c) Last Name	Wallace	First Name	Bruce
Title/Position	Post Doctoral Fellow	Tel.	(613) 520-2600 ext. 1943
		Fax	(613) 520-5727
Dept/Unit & Location	Department of Systems and Computer Engineering	Email	wally@sce.carleton.ca
Division/ Portfolio	Carleton University	Signature:	
		Date:	

d) Last Name	Goubran	First Name	Rafik
Title/Position	Vice-president (Research and International)	Tel.	(613) 520-5745
		Fax	(613) 520-5727
Dept/Unit & Location	Faculty of Engineering and Design	Email	goubran@sce.carleton.ca
Division/ Portfolio	Carleton University	Signature:	
		Date:	08/06/2017

e) Last Name	Breau	First Name	Michael
Title/Position	Psychological Associate	Tel.	(613) 562-6262 ext. 1629
		Fax	
Dept/Unit & Location	Bruyère Memory Program	Email	mbreau@bruyere.org
Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	

f) Last Name	Sweet	First Name	Lisa
Title/Position	Clinical Neurpsychologist	Tel.	(613) 562-6262 ext. 1368
		Fax	
Dept/Unit & Location	Bruyère Memory Program	Email	lsweet@bruyere.org

Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	

g) Last Name	Valech	First Name	Natalia
Title/Position	PhD student	Tel.	(613) 402 4531
		Fax	
Dept/Unit & Location	Bruyère Research Institute	Email	nvalech@bruyere.org
Division/ Portfolio	Bruyère Continuing Care	Signature:	
		Date:	30/05/2017

As needed, cut and paste additions to this section in order to list all co-investigators.

7. REVIEW TYPE (See Guidelines)

Please indicate whether you are requesting a full or an expedited review. (Please contact each research site for more information on the criteria for each type of review)

☒	Full Review **(FULL REVIEWS MUST BE SUBMITTED IN ENGLISH)**
☐	Expedited Review

8. STUDY TYPE AND DESIGN (See Guidelines)

(Describe the Research Project by checking as many of the following as apply)

a) Type of Study:	
☐	Experimental Research/Clinical Trial
☐	Drug Study (Check one): Phase I ☐ Phase II ☐, Phase III ☐, Phase IV ☐
☒	**Observational Research**
☐	Pilot Study
☐	Sequel to previously approved project (Protocol # or title: _____)
☐	Genetic Research (Genetic Addendum must be included with completed application)
☐	Program Evaluation
☐	Chart Review
☐	Qualitative Research (e.g. Case Study, etc.)
☐	Study involves the secondary use of personal health information or other confidential information

☐	Survey					
☐	Other (describe):					
b) Study Design:						
☐	Controlled Experimental Study (e.g. Randomized Controlled Trial)					
☐	Experimental Study Employing	☐	Single-Blind or	☐	Double-Blind (or more) methodology.	
☐	Case-Control study					
☐	Cohort study					
☐	Cross-sectional Study					
☒	**Longitudinal Study**					
☐	Case Study					
☐	Quality Assurance Study	☐ within a single facility		☐ across multiple facilities		
☐	Other (describe):					

9. RESEARCH PROJECTS REQUIRING HEALTH CANADA APPROVAL (See Guidelines)

☐ Not Applicable

☒	**Medical Device Research** Please indicate the status of the Health Canada application/approval: ITA has been submitted by the manufacturer on March 19th 2018. Reference number: 281621. The protocol is under review. The answer from Health Canada will be re-submitted to the REB at the earliest opportunity, once received. .	
	☒	**Health Canada Application/Approval** is attached (insert as next page) Application and Approval attached
	☐	**The investigator will require a conditional approval letter from the REB in order to obtain a "No Objection Letter" from Health Canada. Conditional approval letters will be provided if the REB approval is the only impediment to the issuing of a Health Canada license.** **Please forward the "No Objection Letter" to the REB office as soon as it is available.** This is mandatory prior to final REB approval.
☐	**Drug Trial** Please attach a letter from sponsor indicating Health Canada application/approval. This is mandatory prior to final REB approval.	
	☐	**Health Canada Application/Approval** is attached (insert as next page)

Health Canada Santé Canada

APPLICATION FOR INVESTIGATIONAL TESTING AUTHORIZATION

(disponible en francais)

1. DEVICE CLASSIFICATION

☑ Class II Class III Class IV

2. DEVICE NAME (as it appears on label)

[Note: this is the device name for which the Authorization will be issued]

NeuroCatch™ Platform

3. PROTOCOL IDENTIFICATION:

Include the type of diagnosis or treatment for which the device will be sold.

Study no.: AWSIPA-Apr17-030

Study title: Predicting conversion to dementia in subjects with mild cognitive impairment using event-related potentials.

Study Objectives:

Primary:

To explore event-related potential (ERP) variabilities in subjects with Mild Cognitive Impairment (MCI) using the NeuroCatch™ Platform (NCP), and assess its capacity to predict conversion todementia in this population.

Secondary:

a) To discriminate changes in ERP related to neural damage from normal variations in cognitively normal older adults (CN)
b) To compare the sensitivities of ERP and MoCA test for detecting cognitive decline in MCI
c) To compare the predictive powers of ERP and MoCA test for conversion to dementia in MCI
d) To evaluate the safety and tolerability of NCP

4. NAME AND ADDRESS OF MANUFACTURER (as it appears on the label)

[Note: this is the name and address to which the Authorization will be issued]

Company Name	NeuroCatch Inc.
Street Address/P.O. Box: 13737 96 Avenue, Unit 201 City: Surrey Province/State: British Columbia Postal/Zip Code: V3V 0C6 Country: Canada	
Contact Name and Title:	Pamela Tannouri, MSc., MEng. Technology Development Manager
Telephone No.: 604-639-9057	Fax No.: 1-888-597-8564
E-Mail Address:	pamelatannouri@neurocatch.com

Health Canada Santé Canada

(disponible en francais)

5. MAILING ADDRESS FOR REGULATORY CORRESPONDENCE (if different from 4)

Note: (i) The Authorization will be **issued** to Company named in Item 4 but will be **sent** to the Company shown below if different. (ii) The Company named below must be authorized by the manufacturer named in Item 4 to submit an authorization application on their behalf.

Company Name	Elisabeth Bruyère Hospital
Street Address/P.O. Box: 43 Bruyère St , Suite #369Y City: Ottawa Province/State: Ontario Postal/Zip Code: K1N 5C8 Country: Canada	
Contact Name and Title:	Natalia Valech, Research Coordinator
Telephone No.: 613-402-4531	Fax No.: 613-569-6734
E-Mail Address:	NValech@bruyere.org

6. DEVICE TYPE (check one only)

Single Device	
Medical Device Group	
Medical Device Family	
Medical Device Group Family	
Test Kit	
System	X

7. PREFERRED NAME CODE: (xxAAA) optional

n/a

8. IS THIS DEVICE A NEAR PATIENT *IN VITRO* DIAGNOSTIC (IVDD)? Yes No ☑

IS THIS DEVICE INTENDED TO BE SOLD FOR HOME USE? Yes No ☑

Health Canada Santé Canada

APPLICATION FOR INVESTIGATIONAL TESTING AUTHORIZATION

(disponible en francais)

9. DEVICE USAGE CATEGORY

(73) Anaesthesiology	
(74) Cardiovascular	
(76) Dental	
(77) Ear, Nose & Throat	
(78) Gastroenterology & Urology	
(79) General & Plastic Surgery	
(80) General Hospital	

(84) Neurology	X
(85) Obstetrics & Gynaecology	
(86) Ophthalmology	
(87) Orthopaedics	
(89) Physical Medicine	
(90) Radiology/Imaging	

FOR IVDDs ONLY

(75) Chemistry	
(81) Haematology	
(82) Immunology	

(83) Microbiology	
(88) Pathology	
(91) Clinical Toxicology	

10. DOES THIS DEVICE CONTAIN A DRUG? Yes No ☑

(Note: this question does not apply to IVDDs)

If yes

Brand /Trade Name of Drug:
Active Ingredient:
Drug Manufacturer:
Applicable Drug Identification Number (if any):

Health Canada Santé Canada

APPLICATION FOR INVESTIGATIONAL TESTING AUTHORIZATION

(disponible en francais)

11. DEVICE DETAIL

Please provide the following information, where applicable for each component device, part or accessory.

Name of Device, Components, Parts and/or Accessories as per product label	Device Identification Number if previously assigned	Model or Catalogue number
NeuroCatch™ Platform	NCP 02	Model no. NCP 02

Health Canada Santé Canada

APPLICATION FOR INVESTIGATIONAL TESTING AUTHORIZATION

(disponible en francais)

12. ATTACHMENTS

In addition to items 1 to 11, of the Application for investigational testing, please indicate ( ) which of the relevant information requirements listed below, are included as attachments to this application, or will be provided at a later date. For details regarding content and format, please refer to the guidance documents "Preparation of an Application for Investigational Testing - Medical Devices" and "Preparation of an Application for Investigational Testing - in Vitro Diagnostic Devices"

	Attached	To Come
Background Information	n/a (Class II application)	
Risk Assessment	n/a (Class II application)	
Ethics Committee or IRB Approval(s)		On request
Protocol	X	
Device Label	X	
Investigator Agreements	n/a (Class II application)	

13. If this Device contains a drug and it does **not** have a Drug Identification Number, **I the Manufacturer of this device attest** that the (**drug meets**) (**drug does not meet**) acceptable standards of safety, efficacy and quality.

N/A; Device does not contain a drug

I hereby certify that the information provided on this application and in any attached documentation is correct, complete and in accordance with all relevant sections of the *Medical Devices Regulations*.

Name of Signing Official: Pamela Tannouri, Technology Development Manager P.T.

Signed: Tannouri **Date:** 13-Mar-2018

Health Canada Santé Canada

Therapeutic Products Directorate
11 Holland Ave, 2nd Floor
Address Locator: 3002A
Ottawa, ON K1A 0K9

DATE: 29 May 2018

Application No. 281621

Natalia Valech
Research Coordinator
Elisabeth Bruyere Hospital
43 Bruyere Street, Suite #369y
Ottawa ON K1N 5C8

Investigational Testing Authorization - Class II

Dear Natalia Valech:

This is in reference to your application for Authorization to conduct Investigational Testing in Canada, received on 15 March 2018, and submitted pursuant to Part 3 of the *Medical Devices Regulations*. This pertains to the following:

Protocol: Predicting conversion to dementia in subjects with mild cognitive impairment using event-related potentials.

Number: AWSIPA-Apr17-030 **Date:** Version 1.0, 07Feb2018

Objectives: The primary objective is to explore event-related potential (ERP) variabilities in subjects with Mild Cognitive Impairment (MCI) using the NeuroCatch Platform (NCP), and assess its capacity to predict conversion to dementia in this population. Secondary objectives: a) To discriminate changes in ERP related to neural damage from normal variations in cognitively normal older adults (CN); b) To compare the sensitivities of ERP and MoCA test for detecting cognitive decline in MCI; c) To compare the predictive powers of ERP and MoCA test for conversion to dementia in MCI; and, d) To evaluate the safety and tolerability of NCP.

Informed Consent: Participant: Version 1.0, 20Feb2018
Substitute Decision Maker: Version 1.0, 20Feb2018
Study Partner: Version 1.0, 20Feb2018

Device: NeuroCatch Platform

No. of Devices: One (1)

No. of Patients: Sixty (60)

The information has been reviewed and NEUROCATCH INC. is hereby authorized under Section 83 of the *Medical Devices Regulations* to sell the subject device for investigational testing to the investigators as listed in the attached Appendix 1.

Please note that authorization of this Investigational Testing should not be construed as agreement by Health Canada that the data obtained from the testing will be considered sufficient to meet licensing requirements.

Sections 86, 87 and 88 of the *Medical Devices Regulations* impose additional requirements regarding the advertisement, record keeping and labelling of devices involved in investigational testing. Please advise the Bureau of any changes to the device, protocol or list of investigators. Any changes to the device or protocol that fall outside the scope of the risk assessment of this protocol will require a new application.

Consistent with Health Canada's 2007 Notice concerning registration and disclosure of clinical trial information for therapeutic products (including drugs and devices), sponsors of investigational testing of medical devices are reminded to register their investigational testing within 21 days of the start of the investigation, using a publicly available registry that conforms to international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

You are also requested to submit a copy of the final study report upon completion of the study.

Yours sincerely,

David Boudreau, ing.
Director
Medical Devices Bureau

DB/cd
Attach.

Health Canada Santé Canada

Appendix 1 - List of Investigators and Institutions **Application No. 281621**

Date: 29 May 2018

Investigators; **Names and addresses of Institutions**
Dr. Frank Knoefel, Principal Investigator Elisabeth Bruyère Hospital Suite #369Y, 43 Bruyère St Ottawa, ON, K1N 5C8

10. STUDY SUMMARY/ABSTRACT (See Guidelines)

This summary must be suitable for lay audience (approximately 200 words). Please note that this is not a substitute for the full protocol, and do not refer the reader to sections of an attached protocol.

This research project will test two new computerized technologies in the detection of brain changes related to Mild Cognitive Impairment (MCI) and dementia due to Alzheimer's disease. These technologies are:

1) Computerized cognitive battery: Cognigram (CG) (*Appendix 1: Cognigram*)
Computerized assessments have multiple advantages for the early detection of subtle changes in cognition in older adults. One of their main advantages is their higher precision when measuring accuracy and speed of responses, compared to pencil-and-paper tests. They also allow a greater reliability in measures, as tests are given in a standardized format without the interference of an evaluator [1]. Finally, by including automatized instructions and reports, they are suitable for off-site or long-distance use.

The present study aims to validate the Cognigram™ (CG) [2] computerized cognitive tool **(*Appendix 1: Cognigram)***, in a prospective and longitudinal fashion, determining if changes in the CG scores over 3, 6, 9, and 12 months, can predict progression to dementia at 1-year, 2-years, and 3-years, for patients with Mild Cognitive Impairment (MCI).

For the purpose of this project, a total sample of 30 MCI and their study partners, and 30 cognitively normal subjects (CN), will be recruited. Study partners of MCI subjects will answer the functional questionnaire and the cognitive questionnaire required for defining the clinical status of participants. It is mandatory for MCI participants to have a study partner available in order to participate in this study.

The participants will undergo CG and Montreal Cognitive Assessment (MoCA) ***(Appendix 2: MoCA*)** testing sessions at baseline, 3-months, 6-months, 9-months, and 12-months. The capacities for predicting clinical longitudinal outcomes (i.e., reversion to normal cognition, significant decline within MCI spectrum, or progression to dementia) of CG and MoCA will be compared. The clinical outcome will be assessed using a Neuropsychological battery, a functional assessment and a brief cognitive questionnaire at baseline, 12-months, 24-months and 36-months. It is expected that changes in CG scores will be sensitive to cognitive decline, allowing an early prediction of progression of the cognitive impairment.

2) The NeuroCatch™ Platform (NCP) *(Appendix 14: NCP)*

Event-related potentials (ERP) are non-invasive, low-cost, electrophysiological methods that allow recording of the electrical activity of the brain *in vivo* through an Electroencephalogram (EGG). They are free from cultural and educational influence and can provide insights into the cognitive processes (Jiang et al., 2015). ERP could enable us to detect brain changes and determine the prognosis of MCI subjects [16].

The NCP ***(Appendix 14: NCP)***, an investigational medical device system developed by NeuroCatch Inc., consists of an EEG software and hardware that captures brain health information. It offers a quick (i.e., 10 minutes for EEG preparation and 6 minutes for each task of EEG recording), simple (i.e., includes only 8 electrodes), and easy-to-use solution (i.e., includes a computerized software that automatically analyzes data and outputs graphs in less than 1 minute) for the acquisition of EEG and ERP.

For the purpose of this project, a total sample of 30 MCI and their study partners, and 30 cognitively normal (CN) subjects will be recruited. The participants will undergo NCP ***(Appendix 14: NCP)*** and MoCA ***(Appendix 2: MoCA)*** testing sessions at baseline, 6-months, 12-months, 24-months, and 36-months. The capacities for predicting clinical outcomes (i.e., reversion to normal cognition, significant decline within MCI spectrum, or progression to dementia) of the NCP and MoCA tests will be

compared. The clinical outcome will be assessed using a Neuropsychological battery, a functional assessment and a brief cognitive questionnaire at baseline, 12-months, 24-months, and 36-months. It is expected that changes in ERP will be sensitive to cognitive decline, allowing an early prediction of progression of the cognitive impairment.

11. PURPOSE AND OBJECTIVES (See Guidelines)

a) Based on the current literature, justify the need for this study. Clearly outline the rationale and hypothesis to be tested:

Rationale

Today's aging population brings an increase in the incidence of dementia. In Canada, there are approximately 564,000 persons diagnosed with dementia, with an expected two-fold increase in this number by the year 2031 [3]. In this context, the early detection and prediction of cognitive decline are both imperative for achieving the prevention and/or slowing of dementia.

Standard pencil-and-paper neuropsychological tests are pivotal for the detection and follow-up of cognitive impairment; however they are labor-intensive and require the presence of a trained neuropsychologist on-site. In this regard, computerized testing may be better suited for cognitive screening in large epidemiologic studies and for longitudinal monitoring by primary care providers, due to their higher efficiency for serial assessments and their suitability for off-site or long-distance use [4]. At the same time, computerized testing allows for higher precision in the recording of accuracy and speed of response, with a level of sensitivity not possible in standard administrations [1].

A number of computerized cognitive batteries have been recently developed, though intended as research tools [5]. There is a current demand for the validation of computerized cognitive batteries in the clinical setting. One such computerized battery is the Cognigram™ (CG), which measures processing speed, attention, working memory and learning [6]. Previous cross-sectional studies have demonstrated the validity of CG for detecting MCI and various types of dementia [6-7]. However, there is no current literature on the longitudinal validity of CG, and minimal longitudinal validation of other computerized cognitive batteries currently in existence [8].

On the other hand, research and medicine is moving away from behavioral responses to assess brain health (e.g. verbal responses, reaction time, etc.) and are moving toward more neuroimaging focused measures. Biological tests could enable us to detect pre-dementia and determine the prognosis of MCI subjects [16].A promising biological test is EEG/ERP. Our group has previously shown group differences in ERPs for patients with MCI and CN [17, 18]. Other studies have reported promising ERP markers of pre-dementia [15,19, 20,] and progression of MCI to dementia [21]. However, ERP can be complex to process and labor-intensive, limiting its value in the clinical setting [22]. For example, the usual time for an ERP series measuring multiple cognitive domains typically lasts 1 hour, another 25 minutes for applying the EEG cap and ensuring all electrodes are connected, and some 30 minutes per paradigm (x2-3 paradigms).

The NeuroCatch™ Platform (NCP) offers key competitive advantages compared to other EEG platforms, having a rapid test time with automated processing, analysis and results display – benefitting patients and clinicians being significantly easier to use than current EEG systems, and it alleviates training and ramp up costs amongst EEG users. In this study, we will use the NPC to explore for ERPs that could predict progression to dementia in patients with MCI. The present study will make an initial assessment of the capacity of the NCP to detect cognitive decline and predict conversion to dementia in patients with MCI.

Hypotheses:

In Cognigram, we hypothesize that the following will occur:

i. Significant differences in the CG scores at baseline will be found between MCI and CN groups
ii. MCI subjects will show greater longitudinal changes than the CN subjects
iii. Intra-individual Significant longitudinal changes in the CG performances at 3 and/or 6 months and/or 9 months and/or 12 months, will relate to the prospective clinical outcome at 12-months, and/or 24-months, and/or 36-months.
iv. The CG will show a higher sensitivity in detecting cognitive changes, and a higher predictive power of longitudinal clinical outcome than the pencil-and-paper MoCA test.

In NeuroCatch, we hypothesize that the following will occur:

I. Significant differences in the ERP parameters (amplitude and latency of ERPs such as N100, N400, P300) at baseline will be found between MCI and CN groups
II. MCI subjects will show greater longitudinal changes in ERP parameters than the CN subjects
III. Intra-individual significant longitudinal changes in ERP parameters at 6 months and/or 12 months and/or 24 months, will relate to the prospective clinical outcome at 12-months, and/or 24-months, and/or 36-months.
IV. The NCP will show a higher sensitivity in detecting cognitive changes, and a higher predictive power of longitudinal clinical outcome than the pencil-and-paper MoCA test.

b) Objectives of the project:

The objectives of the project are as follows:

i. To discriminate CG longitudinal changes related to neural damage from normal variations in cognitively normal (CN) older adults
ii. To determine if CG baseline score is related to the clinical outcome at 12-months, 24-months, and 36-months
iii. To determine if intra-individual CG changes at 3, 6, 9, and 12 months, are related to the clinical outcome at 12-months, 24-months, and 36-months.
iv. To compare the powers of CG and MoCA for predicting longitudinal clinical outcomes.
v. To discriminate ERP longitudinal changes (e.g., changes in N100, N400, P300 amplitudes and latencies) related to neural damage from normal variations in cognitively normal (CN) older adults.
vi. To determine if ERP baseline parameters (e.g. amplitude of N100, N400, P300) is related to the clinical outcome at 12-months, 24-months, and 36-months
vii. To determine if intra-individual changes in ERP parameters at 6, 12, and 24 months, are related to the clinical outcome at 12-months, 24-months, and 36-months.
viii. To compare the powers of NCP and MoCA for predicting longitudinal clinical outcomes.

c) Clinical relevance of the project:

Prospective longitudinal validation, if demonstrated, would greatly increase confidence in using CG and NCP in a clinical setting for the assessment of MCI patients and would allow early prediction of future clinical outcomes. This could help to develop preventive therapeutic strategies, while providing additional time for patients and their families to prepare for the future (e.g., financial arrangements, treatment options, and community services). CG and NCP would be of greatest use in primary care, where multiple constraints make cognitive assessments problematic (e.g., lack of time to perform cognitive testing, and lack of access to expensive neuropsychological testing not covered by OHIP) and EEG/ERP assessments prohibitive (e.g., lack of time to perform EEG, lack of access to trained experts for analyzing and interpreting the results of the EEG/ERP).

12. DESCRIPTION OF METHODS AND PROCEDURES (See Guidelines)

a) Study Design and Methodology:

The Study will have a longitudinal design, with a total duration of 3 years. For a summary scheme of the study design, please see ***Appendix 3: Project's Workflow***. All processes involved in the study will be performed at the Bruyère Memory Program. The research team will cover parking costs, if required.

- Participants

Both projects (CG and NCP) will include 30 participants with MCI and their Study partners and 30 CN subjects.

The projects will be offered as parallel studies, meaning that we will invite potential participants to participate in the CG and/or NCP studies. By merging both projects, we will reduce the load (e.g., testing sessions and visits to the clinic) to individuals interested in participating in both studies. Merging is possible given that the same populations (i.e. MCI and CN), neuropsychological battery, functional questionnaire, and brief cognitive complaints questionnaire are needed in both projects. The main objective of both studies is the same: testing computerized technologies in the prediction of the longitudinal outcomes of MCI subjects.

Potential participants will be recruited from The Recruitment Database Project REB M16-15-050 ***(Appendix 15: Bruyère Memory Study Procedure).*** The Recruitment Database is an independent project of the Bruyère Memory Program that aims to introduce a more manageable and robust research recruitment system that: 1) streamlines the research recruitment process, 2) increases the research awareness of patients in the Bruyère Memory Program, and 3) provides patients with memory research opportunities if they are interested. By increasing the number of consenting patients for screening and research participation, investigators will have an opportunity to improve study enrollment. The project's objective is to develop a Research Database and a corresponding standardized recruitment process, to acquire and securely store health and demographic information of potential patients. The database will collect basic health information from consenting participants i.e. age, gender, diagnosis and a brief medical history. The patients must give their consent to be contacted for research to be in the Recruitment Database Project. The Recruitment Database includes patients that were found to be cognitively normal, have MCI, or dementia. It also includes participants that have been identified through community services. In case the Recruitment Database does not provide us with enough participants, we will proceed with the "dot" system for identifying potential participants: the Bruyère Memory Program keeps a record of patients who are interested in being contacted to possibly participate in future research studies. Patients who have indicated they do want to be contacted have their patient chart marked with a green sticker; those who do not want to be reached are identified with a red dot sticker in their chart. Additionally, study partners will be invited to participate as CN subjects.

Potential participants approached through these systems will be invited to participate in the CG study and/or the NCP study.

Each MCI participant must have a Study Partner available, for answering the Functional Activities Questionnaire (5 minutes) ***(Appendix 4: FAQ*)** and the General Practitioner assessment of Cognition tool (5 minutes) ***(Appendix 5: GPCOG).*** For the NCP, Study Partners are also going to be asked to report the list of medications that the participants are taking at the time of each EEG session. Having a Study Partner is required for determining the clinical status of participants, as significant functional impairments and decline from previous levels are core criteria for diagnosing dementia [10]. Given that cognitive impairment progressively impairs the patient's insight and cognitive abilities, having an informant-report is necessary. The type of information that the study partner will be asked to give about the participant is included in the main participant´s consent form.

- Design

The design will depend on whether participants choose to participate in the CG, or NCP, or both:

A) When choosing to participate in the CG study only:

	Visit 1 (baseline)	Visit 2 (3 months)	Visit 3 (6 months)	Visit 4 (9 months)	Visit 5 (12 months)	Visit 6 (24 months)	Visit 7 (36 months)
Tests	1. MoCA *(10')* 2. CG *(15')* *Break (5')* 3. NPS battery *(60') with a 10' break in-between* 4. Questionnaires *(5')*	1. MoCA *(10')* 2. CG *(15')* 3. Questionnaires *(5')*	1. MoCA *(10')* 2. CG *(15')* 3. Questionnaires *(5')*	1. MoCA *(10')* 2. CG *(15')* 3. Questionnaires *(5')*	1. MoCA *(10')* 2. CG *(15')* *Break (5')* 3. NPS battery *(60') with a 10' break in between* 4. Questionnaires *(5')*	1. Questionnaires (5') 2. NPS battery *(60') with a 10' break in-between*	1. Questionnaires (5') 2. NPS battery *(60') with a 10' break in-between*
Time (approx.)	90 minutes *(105 with breaks)*	30 minutes	30 minutes	30 minutes	90 minutes *(105 with breaks)*	65 minutes *(75 with breaks)*	65 minutes *(75 with breaks)*

-Baseline session: At the beginning of the session, RA nº1 will administer the MoCA test (10 minutes) and then the CG battery (10-15 minutes) to participants in a private office at BRI. At the same time, for the MCI subjects, the RA nº2 will administer the FAQ and GPCOG (detailed below) to the study partner in a separated private office. If the Study Partner does not attend the session, questionnaires will be administered by phone

When finishing the CG, participants will then be given a 5 minutes break after which the RA nº2 will administer a Neuropsychological battery (NPS) (described below, 50-60 minutes) and the GPCOC participant form (5 minutes) in a private office. Midway through the NPS battery, after 30 minutes have passed, participants are going to be given an additional 10 minutes break, after which the testing will be resumed. The MCI and CM participants will undergo the assessments simultaneously; thus they will be switched between RA nº1 and nº2 depending on the assessment being performed.

The RA nº2 will be blind to the results of CG and MoCA (dependent variables), while the RA nº1 will be blind to the results of the NPS battery and questionnaires results (gold standards). This has been decided to allow a blind assessment of the clinical status of the participants, avoiding biases when administering and scoring the tests that will be used for defining the clinical status of the participants. The NPS and questionnaires results will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to the CG and MoCA results.

-Follow-up MoCA and CG: Four additional MoCA and CG testing sessions will be performed. Specifically, testing will be performed at: 3-months, 6-months, 9-months, and 12-months. Alternate forms of the MoCA test will be used in the longitudinal setting to avoid learning effects. Also, the CG battery provides a large number of equivalent alternative forms, with the system randomly selecting an exemplar for a large stimulus set each time an individual takes the test, limiting the learning-effects of serial testing. Every session will start with the MoCA, followed by the CG. The same RA nº1 will administer all CG and MoCA tests, when possible, to enhance consistency. On the meanwhile, for MCI subjects, the RA nº2 will be administering the FAQ and GPCOG to the study partner in a different private room, if the study partner is available, or by the phone. After the participant finishes the CG, the RA nª2 will administer the GPCOG to her/him in a private room.

-Follow-up Clinical Outcomes: The clinical outcomes of participants will be determined at the 12-months, 24-months, and 36-months. For this, participants will undergo the NPS battery (50-60 minutes) and answer the GPCOG (5 minutes). Participants will be given a 10 minutes break halfway through the NPS assessment, after which testing will be resumed. The FAQ and GPCOG will also be administered to the Study Partners of MCI subjects preferably in person but if not, by phone. In the case of the 12-months session, the NPS battery will be administered to the participants after finishing the CG testing

session, leaving a 10 minute break in between. The same RA (if possible) will perform all longitudinal assessments, to ensure consistency. The Neuropsychological battery, FAQ, and GPCOG outputs will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to CG and MoCA results. The following clinical outcomes will be considered:
a) Stable normal cognition (for CN subjects)
b) Reversion to normal cognition (for MCI subjects)
b) Conversion to MCI (for CN subjects)
b) Stable MCI (for MCI subjects)
c) Cognitive decline inside the MCI spectrum (for MCI subjects)
d) Conversion to dementia

**For the longer sessions, in the case of intense fatigue in participant and incapacity to continue with the testing, we will interrupt the testing and ask them to return another day to complete the session.*

- Material

1. **Cognigram™ (CG):** is a validated, computerized battery of cognitive tasks based on card games, developed by Cogstate Ltd. This technology includes four tasks, with a total duration of 10-15 minutes. The subject is asked to answer each task by pressing either 'D' or 'K' keyboard buttons. The technology supports the measurement of attention/vigilance, processing speed, concentration, visual working memory and visual recognition memory. The software will run on a computer supplied by the Bruyère Research Institute, in a private test room. The RA will be present during the testing session, reading out loud the batteries standardized instructions and doing the practice trials with the participants. After the practice trials, the RA will not give any feedback or support. For more information see ***Appendix 1: Cognigram***.

2. **Montreal Cognitive Assessment test (MoCA):** is a validated, rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstruction, conceptual thinking, calculations and orientation. Time to administer is approximately 10 minutes. The total possible score is 30 points: a score of 26 or above is considered normal ***(Appendix 2: MoCA).***

3. **Functional Activities Questionnaire (FAQ):** is a brief questionnaire developed by Pfeffer et al. [9], which asks an informant to rate the patient's ability to perform instrumental activities of daily living. Patient's ability can be rated from normal to dependent. Time to administer is approximately 5-10 minutes **(*Appendix 4: FAQ).***

4. **General Practitioner assessment of Cognition tool (GPCOG):** is a screening tool for cognitive impairment. It has been designed for general practitioners, primary care physicians, and family doctors. It includes a testing part for the patient, and an interview part for the informant. In this study, only the interview section of the GPCOG will be administered to both the participant and the Study Partner. A specific question of the original interview was deleted ("*Does he/she need more assistance with transport?*") since it is already assessed in the FAQ, and replaced by (*Does he/she repeat the same statement or question within a conversation, not remembering it was just said?*"), which is a common complaint in dementia. Lastly, a scale for rating the perceived impact of the cognitive difficulties in daily life functions was included ***(Appendix 5: GPCOG).***

5. **Neuropsychological battery (NPS):** a Neuropsychological battery assessing episodic memory, executive functions and attention, language, and praxis will be administered for defining the clinical outcome at baseline, 1 year, 2-years, and 3-years. The RA will administer the battery, in a private office at BRI. Scores will be registered using Study ID, with no personal identifiers. The specific tests administered will be the following: Mini-mental state examination (MMSE), Hopkins Verbal Learning test, Rey-Osterrieth Complex Figure test (copy, immediate and delayed recall), Stroop Effect test, the Digit-symbol coding and symbol search subtests of the Wechsler Adult Intelligence Scale, Trail Making Tests A and B, and the Semantic Verbal Fluency test (animals). The total administration time is expected to be 50-60 minutes, depending on the participant's speed. Participants will be given a 10 minutes break in-between

the neuropsychological testing. The Neuropsychological testing will be performed by the RA nº2, which is a trained psychologist with experience in Neuropsychological assessments.

B) When choosing to participate in the NCP study only:

	Visit 1 (baseline)	Visit 2 (6 months)	Visit 3 (12 months)	Visit 3 (24 months)	Visit 4 (36 months)
Tests	1. MoCA *(10')* 2. NCP *(25')* *5' break* 3. NPS battery *(60') with a 10' break in-between* 4. Questionnaires *(5')*	1. MoCA (10') 2. NCP (25') 3. Questionnaires (5')	1. MoCA *(10')* 2. NCP *(25')* *5' break* 3. NPS battery *(60') with a 10' break in-between* 4. Questionnaires *(5')*	1. MoCA *(10')* 2. NCP *(25')* *5' break* 3. NPS battery *(60') with a 10' break in-between* 4. Questionnaires *(5')*	1. MoCA *(10')* 2. NCP *(25')* *5' break* 3. NPS battery *(60') with a 10' break in-between* 4. Questionnaires *(5')*
Time (approx.)	100 minutes (115 with breaks)	40 minutes	100 minutes (115 with breaks)	100 minutes (115 with breaks)	100 minutes (115 with breaks)

-Baseline session: At the beginning of the session, RA nº1 will administer the MoCA test (10 minutes) while the RA nº2 prepares the NCP in a different office. When finishing the MoCA, the RA nº1 will administer two NCP auditory scans to the participant (10 minutes for setup + 13 minutes for recording). At the same time, for MCI subjects, the RA nº2 will administer the FAQ (5 minutes) and GPCOG (5 minutes) to the study partner in a different private office. If the study partner does not attend the session, the questionnaires will be administered over the phone. The participant and the study partner will be asked to list the medications that the participant is currently taking. This information will be recorded on a paper sheet using study ID. The medications will be asked at every NCP testing session. At every NCP testing session, the RA will have a case report form ***(Appendix 16: CRF)***, completed using study ID, in which s/he will record the occurrence of any adverse event, adverse device reaction, or device malfunction. An adverse event (AE) is any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the study's intervention. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational study intervention, whether or not related to the investigational study intervention. Worsening of a pre-existing condition is also considered an AE. During each visit, information on AEs will be gathered and documented accordingly. AEs will be graded by the Qualified Investigator as mild, moderate, severe or life threatening and assessed by causality as probably related, possibly related, unlikely to be related, or not related to the device. An adverse device reaction (ADR) is defined as an adverse event related to the use of an investigational device. A device malfunction is a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions. A device malfunction will be categorized as inadequacy of the investigational device with respect to its identity, quality, durability, reliability, safety or performance. When any AE or ADR happens, the RA will share the case report form with the Principal Investigator, who would decide the severity and causality of the event. The Principal Investigator will determine the need to withdraw the participant from the study. All AE or ADR encountered, and the decision taken by the Principal Investigator, will be shared with the participant, study partner, SDM (if corresponds), Manufacturer (NeuroCatch Inc.), and Ethics Board at the earliest opportunity (within a maximum of 72 hours of discovery).

When finishing the NCP, participants will then be given a 5 minute break after which the RA nº2 will administer a Neuropsychological battery (same as in CG study) and the GPCOC participant form (5 minutes) in a private office. Halfway through the neuropsychological battery, participants will be given an additional 10 minutes break. The MCI and CM participants will undergo the assessments simultaneously; thus they will be switched between RA nº1 and nº2 depending on the assessment being performed.

The RA nº2 will be blind to the results of NCP and MoCA (dependent variables), while the RA nº1 will be blind to the results of the Neuropsychological tests and questionnaires (gold standards). This has been decided to allow a blind assessment of the clinical status of the participants, avoiding biases when

administering and scoring the tests that will be used for defining the clinical status of the participants. The Neuropsychological battery, FAQ, and GPCOG results will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to the NCP and MoCA results.

-Follow-up MoCA and NCP: Four additional MoCA and NCP testing sessions will be performed. Specifically, testing will be performed at: 6-months, 12-months, 24-months and 36-months. Alternate forms of the MoCA test will be used in the longitudinal setting to avoid learning effects. Every session will start with the MoCA, followed by the NCP. The same RA nº1 will administer all NCP and MoCA tests to enhance consistency. Meanwhile, the RA nº2 will be administering the FAQ and GPCOG to the study partner of MCI subjects in a different private room, if the study partner is available, or by phone. After the participant finishes the CG, the RA nª2 will administer the GPCOG to him/her in a private room.

-Follow-up Clinical Outcomes: The clinical outcomes of participants will be determined at the 12-months, 24-months, and 36-months. For this, participants will undergo a NPS battery (50-60 minutes) and answer the GPCOG questionnaire (5 minutes). These tests will be administered by the RA nº2 in a private office at BRI. The RA nº2 will be blind to the results of CG and MoCA. The FAQ and GPCOG will also be administered to the Study Partners of MCI subjects at these endpoints preferably in person but if not, by phone. The order of administration of each test will be identical to that of the baseline session. A 5 minutes break will be given to participants after the NCP, and 10 minutes break halfway through the NPS assessment. The same RA nº2 will perform all longitudinal assessments, when possible, to ensure consistency. The NPS battery, FAQ, and GPCOG outputs will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to the NCP and MoCA results. The following clinical outcomes will be considered:
a) Stable normal cognition (for CN subjects)
b) Reversion to normal cognition (for MCI subjects)
b) Conversion to MCI (for CN subjects)
b) Stable MCI (for MCI subjects)
c) Cognitive decline inside the MCI spectrum (for MCI subjects)
d) Conversion to dementia

**For the longer sessions, in the case of intense fatigue in participant and incapacity to continue with the testing, we will interrupt the testing and ask them to return another day to complete the session.*

- Material

1. NeuroCatch™ (NCP) ***(Appendix 14: NCP):*** the NCP includes 6 stimulus sequences specifically designed to elicit desired brain responses (N100, N400, P300). Each sequence contains both the oddball task and semantic word-pair task, and lasts 6 minutes. For more detail on the NCP, see ***Appendix 14: NCP.*** In our protocol, two sequences will be used. For the setup, EEG electrodes are placed on the participant's scalp, and the EEG signal quality is ensured by gently abrading the skin beneath each of the electrodes. Skin abrasion is sometimes necessary to ensure a good electrical connection between the skin and electrode. In these cases, the skin is gently rubbed using a wooden dowel (like a cotton swab without the cotton). No item is used to puncture the skin. A conductive gel is then placed between the skin and the electrode. Most electrodes are contained in an elastic cap, which is worn by the participants, but some electrodes are attached to the skin with adhesive. This part of the session takes around 10 minutes. Any adverse events (AE) experienced by the participant will be recorded, and any device malfunctions will be captured. Concomitant medications or procedures will also be recorded. Because EEG recordings are sensitive to other factors (e.g. low blood sugar, caffeine, certain medications), where possible, experimental sessions will be scheduled at approximately the same time of day. Participants will be encouraged to have a snack prior to completing each experimental session. EEG scan will commence once the setup is completed. Two auditory scans of 6 minutes each, separated by a one-minute break, will be administered. The total time of EEG testing for participants, including setup, will be of ≈25 minutes.
2. MoCA (described before)
3. FAQ (described before)
4. GPCOG (described before)

5. NPS (described before; idem of CG)

C) When choosing to participate in both CG and NC studies:

	Visit 1 (baseline)	Visit 2 (3 months)	Visit 3 (6 months)	Visit 4 (9 months)	Visit 5 (12 months)	Visit 6 (24 months)	Visit 7 (36 months)
Tests	1. MoCA (10') 2. CG (15') *5' break* 3. NCP (25') *5' break* 4. NPS battery (60') *10' break in-between* 5. Questionnaires (5')	1. MoCA(10') 2. CG(15') 3. Questionnaires (5')	1. MoCA(10') 2. CG(15') *5' break* 3. NCP(25') 4. Questionnaires(5')	1. MoCA(10') 2. CG(15') 3. Questionnaires(5')	1. MoCA (10') 2. CG (15') *5' break* 3. NCP (25') *5' break* 4. NPS battery (60') *10' break in-between* 5. Questionnaires (5')	1. MoCA (10') 2. NCP (25') *5' break* 3. NPS battery (60') *10' break in-between* 4. Questionnaires (5')	1. MoCA (10') 2. NCP (25') *5' break* 3. NPS battery (60') *10' break in-between* 4. Questionnaires (5')
Time (approx.)	115 minutes (135 with breaks)	30 minutes	55 minutes (60 with break)	30 minutes	115 minutes (135 with breaks)	100 minutes (115 with breaks)	100 minutes (115 with breaks)

-*Baseline session*: At the beginning of the session, RA nº1 will administer the MoCA test (10 minutes) and the CG (10-15 minutes) while the RA nº2 prepares the NCP in a different office and administers FAQ (5 minutes) and GPCOG (5 minutes) to the study partner of MCI subjects. The study partner will also be asked to list the medications currently taken by the participant. When finishing the CG, the participant will be given a 5 minutes break, after which the RA nº1 will administer the NCP auditory tasks (10 minutes for setup + 13 minutes for recording). Before completing the NCP tasks, the RA nº1 will ask the participant the list of medications that s/he is currently taking. During the NCP, the RA nº1 will write down any AE or ADR that may occur during the session.

When finishing the NCP, participants will then be given a 5 minutes break after which the RA nº2 will administer the NPS battery (60 minutes) and the GPCOC participant form (5 minutes) in a private office. A 10 minutes break will be given to the participant in-between the NPS assessment. The MCI and CM participants will undergo the assessments simultaneously; thus they will be switched between RA nº1 and nº2 depending on the assessment being performed.

The RA nº2 will be blind to the results of NCP, CG, and MoCA (dependent variables), while the RA nº1 will be blind to the results of the NPS tests and questionnaires (gold standards). This has been decided to allow a blind assessment of the clinical status of the participants, avoiding biases when administering and scoring the tests that will be used for defining the clinical status of the participants. The NPS, FAQ, and GPCOG results will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to the NCP, CG, and MoCA results.

-*Follow-up CG, NCP, and MoCA*: CG will be re-administered at 3-6-9-12 months, and NC will be re-administered at 6 months, 12-months, 24-months, and 36-months. Alternate forms of the MoCA test will be used in the longitudinal setting to avoid learning effects.

-*Follow-up Clinical Outcomes*: The clinical outcomes of participants will be determined at the 12-months, 24-months, and 36-months. For this, participants will undergo the NPS Battery (50-60 minutes) and answer the GPCOG questionnaire (5 minutes). These tests will be administered by the RA nº2 in a private office at BRI. To reduce fatigue, 5 minutes breaks will be given to participants after each CG and NCP session, and a 10 minutes break will be given in-between each NPS assessment.

**For the longer sessions, in the case of intense fatigue in participant and incapacity to continue with the testing, we will interrupt the testing and ask them to return another day to complete the session.*

The RA nº2 will be blind to the results of CG, NCP, and MoCA. The FAQ and GPCOG will also be administered to the Study Partners of MCI subjects at these endpoints preferably in person but if not, by phone. The order of administration of each test will be identical to that of the baseline session. The same RA nº2 will perform all longitudinal assessments, when possible, to ensure consistency. The NPS, FAQ, and GPCOG outputs will be shared (using Study ID) with a Clinical Panel consisting of two physicians and two psychologists, for determining the Clinical Status of the participants. The panel will be blind to the NC and MoCA results. The following clinical outcomes will be considered:
a) Stable normal cognition (for CN subjects)
b) Reversion to normal cognition (for MCI subjects)
b) Conversion to MCI (for CN subjects)
b) Stable MCI (for MCI subjects)
c) Cognitive decline inside the MCI spectrum (for MCI subjects)
d) Conversion to dementia

b) Primary Outcome Measures:

-Baseline CG scores (accuracy and reaction speed)
-Baseline MoCA scores
-Baseline ERP´s amplitudes and latencies (e.g. N100, N400, P300) means and standard deviations.
-Longitudinal changes in CG scores
-Longitudinal changes in MoCA scores
-Longitudinal changes in ERP´s amplitudes and latencies
-Neuropsychological battery scores (at baseline and follow-up)
-FAQ and GPCOG scores (at baseline and follow-up)
-Clinical outcomes: stable normal cognition, reversion to normal cognition, conversion to MCI stable MCI, cognitive decline inside the MCI spectrum, conversion to dementia.

c) Plan for the Analyses of the Results:

Baseline CG, MoCA scores, and ERP components (mean amplitude +- standard deviation of N100, N400, P300 and others) will be correlated with the NPS battery, GPCOG and FAQ's score. Longitudinal within-subject and within-group differences in the CG, MoCA, and ERP components will be correlated with longitudinal within-subjects and within-group changes in the NPS battery, GPCOG and FAQ's scores. Regression analysis will also be performed at follow-up, to explore the CG, ERP, and MoCA's predictive capacities for cognitive and functional declines. Additionally, Receiver's Operative Characteristics curves will be performed for assessing the CG, ERP, and MoCA's discriminative powers for detecting longitudinal clinical outcomes, and discriminating CN/MCI/dementia cross-sectionally. Positive predictive and negative predictive values of CG, MoCA, and ERPs will be explored.

13. SAMPLE SIZE AND RESEARCH SITES (See Guidelines)

a) Total number of research participants being recruited at all centers globally: **CG**: 60 (30 MCI, 30 CN); **NCP**: 60 (30 MCI, 30 CN).
b) Total number of sites: **1** and list countries:**1**
c) Please indicate the number of research participants to be recruited at each COREB research site below:

University of Ottawa – Social Sciences and Humanities	
University of Ottawa – Health Sciences and Sciences	

University of Ottawa – Heart Institute	
Ottawa Hospital	
Children's Hospital of Eastern Ontario	
Montfort Hospital	
The Rehabilitation Centre	
Bruyère Continuing Care	**X**
Royal Ottawa Health Care Group	
Other (Specify)	

d) Is the enrollment of individuals into multiple studies likely to be an issue in this subject population?

☐ Yes ☒ No

e) How was the answer to 13d determined? If the answer was "yes", also indicate how this will be addressed.

Subjects already participating in clinical drug trials, or in multiple studies (≥2), will be excluded from the Study.

f) For quantitative studies, include sample size power calculations (see Appendix A in the Guidelines for details). For qualitative studies indicate approximate sample size and rationale. You may refer to the protocol for this information.

For CG study:
A sample size of 30 MCI subjects and their study partners, and 30 CN was chosen due to: a) feasibility of recruitment through BRI database, and b) literature evidence of sample size powers for detecting cognitive decline in MCI using the Cognigram battery. Previous studies have shown sufficient power for detecting significant cognitive decline in CG scores in samples of 15-20 MCI. Recruiting 3aMCI leaves us with a safe-space for attrition of up to 50%. For example, Maruff et al. [12] showed significant decline in the CG performance over 12 months in a sample of 15 MCI subjects, showing an effect size of d=1.03. The MCI sample included in the former study was recruited from the population; with our sample being recruited from a memory clinic, the magnitude of cognitive decline is expected to be even higher. Darby et al. [13] also showed that Cognigram multiple assessments detected cognitive impairment in a sample of 20 MCI. Finally, Darby et al. [14] also demonstrated that Cognigram is sensitive enough to detect intraindividual cognitive decline at 3, 6, 9 and 12 months, even in cognitively normal subjects.

For NCP study:
A sample size of 30 MCI subjects and their study partners, and 30 CN was chosen due to: a) feasibility of recruitment through BRI database, and b) literature evidence of sample size powers for detecting ERP components that differentiate MCI from normal cognition. In a recent meta-analysis [15], six studies with sample sizes ≤60 were described, showing significant differences in ERP signals in auditory paradigms between MCI and controls with a pooled effect size of 0.46.
Effect sizes are also going to be computed in our studies as standardized mean differences, expressed as the product of the difference in means of both groups (or both times, in intraindividual analyses) divided by their pooled standard deviation. An effect size is a robust measure of study variability as each study is given a standardized weight corresponding to their sample size, which may be used for future power analyses [21].

14. DESCRIPTION OF STUDY POPULATION (See Guidelines)

a) Inclusion criteria - Who is being recruited and what are the criteria for their selection?

The following inclusion criteria will be considered:

- Age ≥ 60
- Capable of giving consent, as stated by the University of California, San Diego Brief Assessment of Capacity to Consent ***(Appendix 9: UBACC)***
- Meeting the diagnostic criteria of MCI or CN (described below)
- **For MCI subjects: availability of a Study partner, defined as a person that knows the participant for at least 5 years, has frequent contact with them (≥2 days/week) and is knowledgeable of their functioning in activities of daily living

b) Exclusion criteria – Which research participants are excluded from participation?

The following exclusion criteria will be considered

- Significant visual, hearing, or hand-motor impairment that may interfere with the CG testing sessions or Neuropsychological Assessment
- Currently participating in Clinical Drug Trials
- Currently participating in multiple observational studies (≥2)
- Meeting the DSM-IV criteria for dementia at baseline
- Color blindness
- No consent to UBACC administration in MCI subjects
- Non-fluent in English
- Active Major depression, Stroke, Traumatic Brain Injury, substance abuse, any other neurological disease (with the exception of MCI in the MCI group).
- **For NCP project only**:
  In-ear hearing aid or cochlear implant, hearing device
  -Implanted pacemaker
  -Metal or plastic implants in skull
  -History of seizures
  -Allergy to rubbing alcohol or EEG gel
  -Unhealthy scalp (apparent open wounds and/or bruised or weakened skin)

c) Diagnostic criteria:

Mild Cognitive Impairment (MCI):

Diagnosis of MCI in recruitment database and corroborated at baseline by:
1) Objective cognitive impairment: expressed as ≥1.5 SD below the normative mean in at least one test of the NPS tests, AND
2) MMSE >19, AND
3) Subjective Cognitive Impairment, expressed by participant and/or study partner: defined by GPCOG, AND
4) Absence of significant functional impairment: score ≤5 in the FAQ.

Cognitively Normal (CN):

Diagnosis of CN in recruitment database –or absence of diagnosis of MCI or dementia- and corroborated at baseline by:

1) Normal score expressed as within 1 SD from the normative mean in every test of the NPS tests, AND
2) MMSE ≥ 27

** Results and associated data relating to testing for eligibility/inclusion will be destroyed for those persons found to be ineligible and not enrolled.

c) Which linguistic groups will be recruited?

French-speaking: ☐ **English-speaking:** ☒ Other ☐ (specify):

Please note that all documentation (e.g. advertisements, telephone scripts, information/consent forms, de-briefing summaries, etc) should be translated into the language of each linguistic group being recruited for the study and submitted for review after the primary version (English or French) is approved.

15. IDENTIFICATION AND RECRUITMENT OF RESEARCH PARTICIPANTS (See Guidelines)

a) Describe how the research study will be publicized for recruitment purposes. If the initial contact is by letter, telephone, e-mail, web-site and/or advertisement, attach applicable copies of the text to be used. For studies recruiting participants from different linguistic groups, please forward the translated texts after the primary versions (English or French) texts have been approved.

Not applicable. The study will not be publicized.

Texts are attached: ☐ Yes ☐ No ☒ Not applicable

Translated texts will follow: ☐ Yes ☐ No ☒ Not applicable

b) If the identification of prospective subjects will involve using information from their personal health information record, describe how the patient's agreement to be contacted by the researcher(s) will be obtained by members of his/her health care team or by the custodian of his/her health information record.

☒ Not applicable

c) Once identified, how will prospective research participants be recruited?

The RA will be provided with potential participants that have been identified by the Recruitment Database Team ***(Appendix 15: Bruyère Database Procedure)***, and call them by phone to give an overview of the study ***(Appendix 6: Overview Script)***. In the overview script, both CG and NCP projects will be summarized. If the subject shows interest in learning more about one study, or both of them, the RA will send by e-mail an informational package containing the Consent Forms **(*Appendix 7: Consent Form)***.Different Consent Forms have been prepared for the cases of: a) interest in CG ***(Appendix 7a: Consent Form for CG)***; b) interest in NCP ***(Appendix 7b: Consent Form for NCP)***; c) interest in CG and NCP ***(Appendix 7C: Consent form for CG and NCP)***. If the subject does not use e-mail, the following delivery alternatives will be offered: mail, fax, or meeting in person in the Bruyère Hospital. If the Consent is sent by e-mail, mail or fax, a subsequent teleconference will be scheduled to discuss the study details ***(Appendix 8: Consent review script)***. If during the consent review discussion, the recruit decides to participate in the study, the baseline session will be scheduled. During the baseline session, prior to initiating any testing, the research assistant will have a face-to-face consent discussion with the prospective participant for clarifying further questions. After all the questions have been resolved, and if the subject's decision to participate has not changed, the participant will be asked to sign the Consent Form ***(Appendix 7: Consent Form).*** The testing will proceed once the corresponding Consent Form has been signed.

d) How will the researcher ensure that there are no breaches of a prospective participant's privacy during the recruitment process?

The RA will keep record of the potential participants approached in a password-protected Excel file. This will allow avoiding re-approaching subjects. A master list will be created for those

subjects who decide to participate in the Study, linking the participants' names with a random Study ID. The master list will be kept in a password-protected Excel file. Regarding the signed Consent Forms, these will be printed at the earliest opportunity, storing the printed copies in a locked filing cabinet in the RA's office. Then the original email will be deleted. Results and associated data relating to testing for eligibility/inclusion will be destroyed for those persons found to be ineligible and not enrolled.

e) Does the study include subjects in a control group?

☒ Yes ☐ No

Although every participant will have to undergo the same testing procedure, meaning there are no control groups from an experimental point of view, a group of cognitively normal (CN) subjects have been included to differentiate the normal variations in the computerized technologies from variations that could be related to neuronal damage.

If yes, are the identification and/or recruitment consent processes different from those described above?

☒ Yes ☐ No

If yes, provide details.

For recruitment of CN subjects, besides using the Recruitment database (used for MCI) ***(Appendix 15: Bruyère Database Procedure)***, we will also invite study partners of MCI subjects to participate in the study. After consent has been given to act as a study partner, the RA will invite the study partner to participate as a CN subject in the study ***(Appendix 12: study partner consent review)***. If study partner is interested in this option, the RA will send him/her the informational package including the participant´s consent form ***(Appendix 7: Consent Form).*** The RA will call him/her in a subsequent appointment to review the study details, answer any questions they might have ***(Appendix 8: Consent Review script)***. If during the consent review discussion, the recruit decides to participate in the study, the baseline session will be scheduled. During the baseline session, prior to initiating any testing, the research assistant will have a face-to-face consent discussion with the prospective participant for clarifying further questions. After all the questions have been resolved, and if the subject's decision to participate has not changed, the participant will be asked to sign the Consent Form ***(Appendix 7: Consent Form).*** The testing will proceed once the corresponding Consent Form has been signed.

f) Will research participants receive financial compensation?

☒ Yes ☐ No

If yes, please explain the purpose of the compensation (e.g. reimbursement for expenses, gifts for participation, compensation for time, etc.).

The RA will ask participants if they require reimbursement for parking costs when scheduling each visit, and again when arriving to each session.

g) Commission fees that are to be paid to health professionals or research staff for the successful recruitment of research participants are prohibited (see Guidelines). Nonetheless, reimbursement for time spent recruiting is permitted. If fees are to be paid for the recruitment of subjects, please provide details below.

_____ ☒ Not applicable

16. PROCEDURES FOR SEEKING INFORMED CONSENT (See Guidelines)

a) Will informed consent be obtained from the study participants or their legal representatives?

☒ Yes ☐ No

If yes, complete Sections 16b to 16h. If no, answer "Not applicable" in Sections 16b to 16h and complete Section 16i.

b) What is the reading comprehension grade level of the information/consent form? Please include a description of the methodology used to make this determination.

For the CG study:
-Consent Form for MCI subjects ***(Appendix 7a1)***: 7.7
-Consent Form for CN subjects ***(Appendix 7a2)***: 7.6

For the NCP study:
-Consent Form for MCI subjects ***(Appendix 7b1)***: 8.1
-Consent Form for CN subjects ***(Appendix 7b2)***: 7.6

For interest in learning more about both CG and NCP studies:
In this case, both CG and NCP consent forms will be shared with the recruit. The consent forms will be preceded by a cover page ***(Appendix 7c1: cover page of consent form for participants interested in both studies)*** and followed by a schedule of visits ***(Appendix 7c2: Third Document for participants interested in both studies)*** with a reading comprehension level of 9.2.

For the study partners, the reading comprehension level is:
-Consent form for CG study ***(Appendix 11a):*** 8.6
-Consent form for NCP study ***(Appendix 11b):*** 8.8
-Consent form for CG and NCP studies ***(Appendix 11c):*** 8.7

For the Substitute Decision Makers (SDM), the reading comprehension level is:
-Consent form for CG study ***(Appendix 13a):*** 8.7
-Consent form for NCP study ***(Appendix 13b):*** 8.4
-Consent form for CG study ***(Appendix 13c):*** 8.7

The reading comprehension level was determined using the Flesch-Kincaid method of Microsoft Word.

c) Is the information/consent form written at the reading level of the population being sampled?

☐ Yes ☐ No ☒ Unknown ☐ Not applicable

If No or Unknown, describe the methodology to ensure that research subjects have a sufficient understanding to give "informed" consent (e.g. utilization of a reading level that is generally accepted as being appropriate for the population under study).

During the Consent review script, the RA will administer the University of California, San Diego Brief Assessment of Capacity to Consent questionnaire ***(see Appendix 9: UBACC)*** to MCI recruits. This is a validated instrument, and has shown to be reliable for assessing research participants' consent capacities [11]. The RA will have obtained the recruit's permission for administering the UBACC before, in the overview call ***(see appendix 6: Overview script).*** If the questionnaire results suggest that the MCI subject might not have the capacity to give consent, s/he will be excluded from the project. This means that all included participants will

give their personal consent at baseline, with no Substitute Decision Makers involved at the beginning of the study. The UBACC results will be destroyed using a shredder for those persons found to be ineligible. In the case of CN subjects and study partners, the capacity to consent will be assessed informally. Informal capacity assessment involves the RA's overall assessment that the subject understands the purpose and procedures of the study.

d) If the information consent form is written, attach a copy. If consent will be oral (in-person or via telephone), append a copy of the script to the application form that will be used during the consent process and given to the research participant for his/her information. For a description of elements that are required by the TCPS to be included in the consent form and consent process, please see Appendix C of the Guidelines.

The information/consent form or oral script is attached:

☒ Yes ☐ No ☐ Not applicable

e) Describe the consent process (e.g. who will obtain consent and how will the research staff ensure that "informed" consent has been obtained?). In the case of oral consent, include a description of how and where the oral consent for each subject will be documented.

The RA will be provided with potential participants that have been identified by the Recruitment Database Team (REB project M16-15-050) ***(Appendix 15: Bruyère Database Procedure)*** and will call them by phone to give an overview of the study ***(Appendix 6: Overview Script).*** In the overview script, both CG and NCP projects will be summarized. If the subject shows interest in learning more about one study, or both of them, the RA will send by Email an information package containing the Consent Form ***(Appendix 7: Consent Form).*** Different Consent Forms have been prepared for a) interest in CG ***(Appendix 7a)***; b) interest in NCP ***(Appendix 7b)***. If the recruit is interested in learning more about both, the consent forms will be preceded by a cover page ***(Appendix 7c1: cover page of consent form for participants interested in both studies)*** and followed by a schedule of visits ***(Appendix 7c2: Third Document for participants interested in both studies)***. If the subject does not use e-mail, the following delivery alternatives will be offered: mail, fax, or meeting in person at the Elisabeth Bruyère Hospital. If the Consent is sent by e-mail, mail or fax, a subsequent teleconference will be scheduled to discuss the study details ***(see Appendix 8: Consent review script).*** After reviewing the consent, if the MCI recruit is interested in participating the RA will administer the UBACC ***(Appendix 9: UBACC)*** to determine his/her capacity to give consent. The RA will have obtained the recruit's permission for administering the UBACC before, in the overview call ***(see appendix 6: Overview script).*** If the UBACC shows that the subject's capacity to consent is questionable, the subject will be excluded from the study. Exclusion is considered since the inability to consent reflects a cognitive impairment greater than MCI. The UBACC results will be destroyed with a shredder for those persons found to be ineligible. If the UBACC shows that the recruit has the capacity to give consent, then s/he will be included. In consequence, no SDMs will be approached at baseline. If during the consent review discussion, the recruit decides to participate in the study, the baseline session will be scheduled. During the baseline session, prior to initiating any testing, the research assistant will have a face-to-face consent discussion with the prospective participant for clarifying further questions. After all the questions have been resolved, and if the subject's decision to participate has not changed, the participant will be asked to sign the Consent Form ***(Appendix 7: Consent Form)***. The testing will proceed once the corresponding Consent Form has been signed.

For MCI participants: at the Consent Review ***(Appendix 8: Consent Review Script)*** the RA will ask the participant to look for a person who can act as his/her Study Partner and to discuss with him/her if s/he can be contacted by the RA. The RA will schedule a subsequent

teleconference with the participant, to obtain the potential study partner's contact. The RA will contact the potential study partner, to give an overview of the study ***(Appendix 10: Study Partner overview script).*** If the potential Study Partner is interested in learning more about the study, the RA will send him/her the consent form ***(Appendix 11: Study Partner Consent Form)*** and schedule a subsequent appointment to discuss the study details ***(Appendix 12: Study Partner Consent review script)***. If after reviewing the study details, the subject is interested in acting as the study partner, s/he will be asked to give written or verbal consent. If the recruit does not want to participate as study partner, the RA will call the participant and ask him/her to select another person who could act as such. If the recruit is unable to find a Study Partner, s/he will be withdrawn from the study. In the latter case, the UBACC results of the subject withdrawn will be destroyed using a shredder. After the consent process for the study partner has finished, the RA will also invite the study partners to participate as CN subjects in the study/s (***Appendix 12: Study Partner Consent review script)***. If they are interested in learning more, the RA will share with them the Consent Form of the study/s ***(Appendix 7: Consent Form)*** and schedule a subsequent appointment for discussing the study details ***(Appendix 8: Consent review script).*** If during the consent review discussion, the recruit decides to participate in the study, the baseline session will be scheduled. During the baseline session, prior to initiating any testing, the research assistant will have a face-to-face consent discussion with the prospective participant for clarifying further questions. After all the questions have been resolved, and if the subject's decision to participate has not changed, the participant will be asked to sign the Consent Form ***(Appendix 7: Consent Form)***. The testing will proceed once the corresponding Consent Form has been signed.

☐ Not applicable

f) Is there a relationship (e.g. physician-patient, employer-employee, professor-student) between the subjects and the person obtaining consent?

☐ Yes ☒ No ☐ Not applicable

If yes, explain the nature of the relationship and describe the steps that will be taken to minimize the potential of coercion, real or perceived.

_____

g) Will personal health information be accessed without first obtaining consent?

☐ Yes ☒ No ☐ Not applicable

The Recruitment Database Project M16-15-050 ***(Appendix 15: Bruyère Database procedure)*** will be used for recruiting includes the Memory Clinic's diagnoses of subjects. Consent to be included in this database has been obtained. If the potential participant is not included in the study, given that s/he did not consent to participate or any of the exclusion criteria was met, the health information will not be transferred from the charts, and charts will be returned to the Database Project at the earliest opportunity. If the recruit is included in the study, the diagnosis on the chart will be stored in a password-protected Excel File stored at the RA's assistant computer at Bruyère, using a study ID.
For NCP, the participants and the study partners of MCI subjects will be asked to list the medications that are currently taken by the participant at each testing session. This is stated in the consent form, and participants will have given their consent to share this information before initiating the study.

If yes, provide justification. As required by the Personal Health Information Protection Act, also attach a copy of the agreement between the health care custodian and the study's investigator(s) that outlines the terms and obligations imposed upon the

investigators when using personal health information for research purposes without obtaining the patient's consent.

_____

h) For studies that involve more than one contact with participants, describe the methodology that will be used to ensure that the participant's consent is current.

The UBACC will be re-administered every 6 months to the MCI subjects by the RA, to ensure that capacity to consent is current. If the participant has progressed to dementia and is no longer capable of giving consent, a Substitute Decision Maker (SDM) will be contacted to obtain consent for continuing the study ***(see Appendix 13: SDM consent form*)**. In such cases, the participant and their study partner will be asked to identify a SDM. The SDM could be the same as the study partner or a different person, according to the particular circumstances of each participant. This means that the two roles (study partner and SDM) may be played by different people depending upon the particular circumstances of the participant. This information is included at the Consent Forms ***(Appendix 7: Consent Forms).*** SDM will be contacted by the RA. If a cognitively healthy subject converts to MCI during the trial, the UBACC will be administered to him/her every 6-months until the end of the study. If at any moment the UBACC results suggest that the person might be loosing his/her capacity to consent, they will be asked to identify a SDM following the same procedure mentioned before.

☐ Not applicable

i) For studies where informed consent will not be obtained, please justify according to all of the requirements of Articles 2.1(c), 2.3 and 2.8 of the Tri-Council Policy Statement (see the Guidelines for the specific requirements that must be met).

_____ Not applicable.

17. COMPETENCY TO GIVE CONSENT (See Guidelines)

a) Does the research study include research participants who may not be capable of giving informed consent?

☐ Yes ☒ No

Participants who are not capable of giving consent at baseline- as defined by the UBACC- will be excluded from the study. Results from the UBACC will be destroyed with a shredder. The latter means that none SDM will be approached at the beginning of the study. However, participants may progress in their cognitive impairment during the study follow-up. Consent Capacity will then be re-assessed every 6 months, using the UBACC in the case of subjects with MCI diagnosis at baseline or at follow-up ***(Appendix 9: UBACC).***

If yes, please justify according to the conditions outlined in the Guidelines.

b) In studies where the research participants may not be capable of giving informed consent, please describe the methods that will be used to determine a participant's capacity to give consent.

Consent Capacity will be re-assessed every 6 months in subjects with MCI diagnosis at baseline or follow-up, by the RA, using the UBACC ***(see Appendix 9: UBACC)***. If the capacity

to give consent is questionable at any point during follow-up, a SDM will be approached to give consent for continuing with the study **(*see Appendix 13: SDM Consent Form)*.** The study partner and the participant will be asked to identify a SDM. The SDM could be the same as the study partner or a different person, according to the particular circumstances of each participant. This means that the two roles (study partner and SDM) may be played by different people depending upon the particular circumstances of the participant. This information is included at the Consent Forms ***(Appendix 7: Consent Forms)***.If the SDM does not give consent; the participant will be withdrawn from the Study. All the information gathered until this point will still be used in the study analyses, unless the SDM requests otherwise.

☐ Not applicable

c) For those participants who are not capable of providing informed consent, describe how consent will be obtained and from whom. Also, outline your plans to ensure that the free and informed consent of an appropriately authorized third party remains current for the duration of the study, so long as the subject remains incompetent.

If the capacity to give consent is questionable at any point during follow-up, a SDM will be approached to give Consent for continuing with the Study **(*see Appendix 13: SDM Consent Form)***. The roles of Study Partner and SDM may be played by the same person or different people depending upon the particular circumstances of the participant. The right to withdraw the participant from the study at any point is explicit in the Consent Form.

☐ Not applicable

d) In studies where the research participants may not be capable of giving informed consent, describe the study's plans to regularly assess capacity and to obtain consent if the individual later becomes capable of providing consent.

If a participant who has lost the capacity to give consent shows significant improvements in the longitudinal NPS battery and FAQ's scores, the UBACC **(*Appendix 9: UBACC*)** will be re-administered to assess if they have regain their capacity of providing consent. If the capacity to consent is re-established, the participant's consent will be asked for continuing.

☐ Not applicable

e) In studies where the research participants may not be capable of giving informed consent, describe the methods that will be used to ensure that participants who display "dissent" behaviors will be precluded or withdrawn from participating in the study.

If participants show any dissent behavior during the testing session, the session will be suspended and a new session will be rescheduled. The research team will cover parking costs each time they need to return. If this is repeated three times, the PWD will be withdrawn from the study. SDMs will be informed of this decision.

☐ Not applicable

f) Does the research study include research participants who are below the age of 18 years?

☐ Yes ☒ No

If yes, explain how and from whom informed consent will be obtained.

g) Does the research project involve emergency situations where consent cannot be obtained?

☐ Yes ☒ No

If yes, please provide justification for proceeding without consent, and describe plans to seek consent to use the data if the individual later becomes able to provide consent or the individual's legal representative is found (see the Guidelines for all of the conditions that must be met).

18. RISKS, BENEFITS AND USUAL STANDARD OF CARE (See Guidelines)

a) For research studies involving the research site facility's patients, document the usual standard of care for this population in the research site facility and describe how the usual standard of care will be affected for patients participating in this study. If changes in the standard of care will vary according to the group to which patients are assigned, document the changes in the usual care for each group.

Participants with cognitive impairment are patients of the Bruyère Memory Clinic. Their standard care will not be compromised by their participation or non-participation in the study. To safeguard their level of care, the staff involved in their care will not be informed if they are participating or not in the study, and the RA will share study outputs with the panel of physicians and neuropsychologists using randomized ID without personal identifiers.

☐ Not applicable

b) For research studies that do not involve patients and where research participants will be recruited from other sources (e.g. general public), describe the frequency, duration and nature of contacts with research participants that are required by the study.

☒ Not applicable

c) Document the risks associated with the study. When the research participant is a patient, document the risks as compared to the usual care that the patient would receive. If the risks vary according to the group to which patients are assigned, document the risks for each group.

In CG study:
There are minimal risks to this study. Some participants may not enjoy CG or the neuropsychological testing. If so, he/she will be excused from participation. Participants will be reminded about their right to withdraw from the study at any point.

In NCP study:
The discomfort arising from auditory stimulation should not exceed that associated with playing a video game. Sound intensity will not exceed 80dB, which is well below the threshold of pain even under repetitive-stimulation conditions. Preparation of EEG recording sometimes requires skin abrasion and cleansing (with alcohol pads and scrubs) to ensure a good connection between the EEG electrode and the scalp. Participants may experience mild skin irritation and/or discomfort from this skin preparation. For example, hair can get tangled and pulled when

abrading the skin with a wooden dowel. Participants will be encouraged to tell the experimenter whether they are experiencing any discomfort. To minimize communication of viruses and bacteria, the elastic cap and electrodes are placed in an intermediate-level surface disinfectant that kills TB, HepB, HepC, HIV, fungi and other viruses and bacteria within 3 minutes. The risks are about the same as in hair salon. The risks of being connected to the EEG recording device are minimal. The cap contains a ground electrode to prevent the buildup of excessive static charge. The amplifier is battery powered and cannot be charged and attached to the participant at the same time. The cap can be easily removed should the need arise. The RA administering the NCP have been trained in proper application of the electrodes and the cap, this will reduce the likelihood of a pressure headache from an ill-fitting cap. She has also been trained din removal of loose electrodes to reduce the discomfort of removing adhesive material from the skin.

An adverse event (AE) is any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the study's intervention. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational study intervention, whether or not related to the investigational study intervention. Worsening of a pre-existing condition is also considered an AE. An adverse device reaction (ADR) is an event related to the use of the NCP. During each visit, information on AE and ADR will be gathered and documented accordingly ***(Appendix 16: Case Report Form)***. Whenever an AEs or ADR is registered, the research assistant will share this information with the Principal Investigator within 24-488 hours from the incident. The severity of the event will be graded by the Principal Investigator as mild, moderate, severe, or life threatening and its causality will be assessed as probably related, possibly related, unlikely to be related, or not related to the device. The Principal Investigator will decide if study disruption is required. All incidents and decisions taken will be notified to the Study Partner, SDM, and Ethics Board, at the earliest opportunity (within 72 hours from the incident).

d) Will participation in this study affect alternatives for the future care of the participant?

There is no direct impact to the future care of the participants.

e) Will the management of the participant's condition be prolonged or delayed as a result of the research?

☐ Yes ☒ No ☐ Not applicable

If yes, describe any risks associated with prolongation or delay (e.g. washout period, withholding of treatment or absence of treatment).

_____

f) Are there any standard therapies, diagnostic procedures or information to be withheld from participants for the purpose of the study?

☐ Yes ☒ No ☐ Not applicable

If yes, describe the risks and benefits to the participants. In the case of risks to the research participant that go beyond those of usual care, please provide the justification for exposing the research participants to these additional risks.

_____

g) Are there any restrictions being placed on the study's participants?

☐ Yes ☒ No

If yes, please explain

____

h) Are placebos being used?

☐ Yes ☒ No

If yes, please explain and provide justification according to the Tri-Council Policy Statement (see guidelines).

____

i) Does this study involve any deception of, or withholding information from study participants?

☐ Yes ☒ No

If yes, please explain the justification for employing these techniques (see guidelines for conditions under which these techniques may be used).

____

j) Outline the criteria for the early withdrawal of research participant(s).

Participants are free to withdraw at any point, without need for explanation. Consent will be reassessed every 6 months. Additionally, if any dissent behavior is observed during the testing session, the session will be suspended and a new session will be rescheduled. The research team will cover parking costs each time they need to return. If this is repeated three times, the PWD will be withdrawn from the study. SDMs will be informed of this decision

k) Describe any possible benefits to the research participants as a result of their participation in the research study.

There are no direct benefits, though patients may enjoy the research process. The main benefit is to the scientific community by developing generalized knowledge of brain functioning. If during the trial, a participant progresses to MCI or dementia, the research coordinator will advise them and their study partners to notify their family doctor. A report including their scores in the cognitive tests will be shared with them, if requested. Additionally, participants may request a report of study results. This is included in the consent form and will be enhanced during the consent review process at the baseline session. Participants may request to the RA a report of study results at any moment. Requests can be done in person, over the phone, or by e-mail. Reports will include the results in the neuropsychological tests and total score in the FAQ, specifying that the data corresponds to a research project. It will not include any diagnostic interpretation. For a template of the report, please ***see Appendix 17: Results report template***. Study partners and SDMs may also ask for a report of the results. However, they will only be shared with them after confirming assent of the main participant for sharing their results with them ***(Appendix 18: assent for sharing results).*** Because the report will contain personal identifiers, they will only be given in-person at the Bruyère Hospital by the RA to the main participant and/or study partner and/or SDM.

19. CONFIDENTIALITY (See Guidelines)

a) List the types of records containing personal information that will be accessed in the course of this study. Please outline the health information custodian's requirements for access, and whether the requirements have been met and access has been approved.

The following records will contain personal information:

1. Consent forms: will be printed, and the email will be deleted at the earliest opportunity. The printed versions will be kept inside a filing cabinet in the RA's office located at BRI.
2. Master Code: will be safely kept under lock, in a cabinet in the RA's office at BRI (separated from the consent forms). A digital copy will also be kept in the BRI computer, using a password-protected Excel file.

Every other document (e.g., CG results, NCP outputs, Case Report Forms, MoCA, NPS battery, FAQ, and GPCOG results) will use Study ID and will have no personal identifiers. Every paper document will use Study ID and kept in a filing cabinet at the RA's BRI office. Every electronic document will use Study ID and will be shared between the team members using password-protected files. The Cognigram software automatically flows data to the Cogstate database. The data will be de-identified: Study ID, age, years of education and gender will be included. Cogstate standard research contracts allow Cogstate to use de-identified data for their own research. A research agreement with Cogstate will be signed and shared with the REB prior initiating the study. The Cogstate application is HTML web-based software with both authentication and authorization rules based off of NIST guidelines. Cogstate currently uses Microsoft Azure HIPAA compliant cloud based servers/services which include appropriate safeguards for data privacy. They have password protected access controls based on authorized user roles. Cogstate maintain the entire database with geo-redundant back-ups as they have not needed to archive any data at the moment, however, they are required to maintain the records for 6 years should they archive in the future.

Regarding the NeuroCatch software, the data captured is kept locally on the laptop used. This laptop will be property of our research team, will be password-protected, and will not leave the Bruyère Hospital. No one other than our research team will have access to this data. To further protect the participant´s privacy, the files will only include study ID and will not have any personal identifiers.

b) Describe the methods that will be employed to maintain confidentiality during the time that research data sets contain personal identifiers. If different data collection mediums are being used (e.g. paper forms, audiotapes, video tapes, local computer databases, web-based database), describe the security measures that will be used for each medium.

As mentioned before, only the Consent Forms and Master list will contain personal identifiers. All other study's data will use Study ID, without any personal identifier. However, to further ensure the participants' confidentiality, all data will be kept inside the RA's office located at BRI on in password-protected Excel files in the RA´s computer.

c) Describe how and when the data will be encoded to remove all personal identifiers from the data collected during the course of the study.

As soon as the Consent Form is received, and therefore the participant is confirmed as part of the study, the participant will be identified using a random ID. The RA will create a master code list, with the demographic information of each participant and the randomized ID given. This list will be kept separate from the study's outputs, and will be under lock in a BRI office. Throughout the study, the project's data will be collected using Study ID with no personal identifiers.

d) If data containing personal identifiers will not be encoded at the earliest opportunity, please justify.

_____ ☒ Not applicable

e) Please indicate where the code-list will be stored and when it will be destroyed. Please note that the Health Records Departments of some facilities offer a service to store code-lists over long periods of time (e.g. 25 years).
Master list will be stored in a password-protected Excel file in the RA's computer located at the BRI office, separate from the Study's data. It will be deleted after seven years after the completion of the study.

f) If data containing personal identifiers will be transferred to another facility, please justify. In addition, please provide documentation that ensures the confidentiality of this information at the receiving facility (see guidelines for specific requirements). The transfer of information to another facility should also be described in the information/consent form.

Not applicable. Electronic database with study's outputs will be shared with Carleton engineering team, for analysis. However, this database will be de-identified. File will be shared using encrypted files to further ensure participants confidentiality. Cognigram software also flows data to Cogstate, however the data does not contain personal identifiers. NCP outputs will be shared with Carleton engineering team for analysis. The data will be de-identified, and shared through encrypted files.

g) Will project research staff be required to sign a Pledge of Confidentiality to comply with the policy and procedures of the research site facility?

☒ Yes ☐ No ☐ Not applicable

If No or Not Applicable, please explain.

_____

h) Please indicate how long data will be kept, how it will before being destroyed and what measures are in place to ensure on-going confidentiality of the dataset.
Data will be kept for 7 years post-completion of the study, and will be destroyed after this time. The master list will be in a password-protected Excel file at the RA´s computer located in a BRI office, separate from the output database and study's outcomes.

☐ Not applicable

i) If your study involves collection of any biological specimens (e.g., blood, tissue, urine, etc), please indicate whether specimens are de-identified, where specimens will be stored, for how long and how they will be destroyed. * *If long term storage of specimens is planned, you must complete the "Genetic Addendum".*

_____ ☒ Not applicable

20. MONITORING (See Guidelines)

a) Is there a plan to monitor the study (e.g. internal audits or sponsor-initiated site visits)?

☐ Yes ☒ No

If yes, describe briefly and append the plan as an appendix.

_____

b) For sponsor-initiated research (e.g. drug trials, medical devices) is there a data safety monitoring board in place?

☐ Yes ☐ No ☒ Not applicable

If yes, describe the composition of the board's members. Are the board's members independent of the study and/or sponsor?

_____

c) Are there interim analyses planned?

☐ Yes ☒ No

If yes, describe briefly.

_____

d) Describe the stopping rules for the study.

Not applicable

21. PUBLICATION AND DISSEMINATION OF RESULTS (See Guidelines)

a) If this study is funded, will the investigator(s) require the approval of the sponsor(s) before publication or dissemination of the results? ☐ Yes ☒ No ☐ Not applicable

If yes, please explain

_____

b) Please describe the plan for publication and other dissemination of the study's results.

Presentations will be made at local and international conferences focused on dementia. Submissions to suitable clinical journals may also ensue.

c) Will a summary of the results be available in multiple languages?

English ☒ Yes ☐ No

French ☒ Yes ☐ No

Other ☐ Yes ☒ No If yes, specify _____

22. BUDGET (See Guidelines)

a) Has this research been funded?

☒ Yes ☐ No

The budget is for CG project. The cost of the NCP study will be covered through current research funding of the TAFETA project.

b) If yes, provide the:

Name of the Agency/Sponsor: Bruyère Academic Medical Organization (BAMO)
Name of the Contact Person for the Agency/Sponsor: Jo-Anne Dusseault
Address: 43 Bruyère St. Ottawa, ON K1N 5C8, room 735D
Telephone: 613 562 6262 ext 1087
E-mail Address: jdusseault@bruyere.org
Agency/Sponsor Protocol number (if applicable):not applicable
Amount of funding received: $19.325

c) If no, has funding been applied for?: ☐Yes ☐ No

If yes, please provide the name of the Agency/Sponsor: _____
Amount of funding applied for**:** _____
Date submitted: __/__/__
DD/MM/YYYY

d) A detailed budget is attached as an appendix. ☒ Yes ☐ No

e) If there is no funding or insufficient funding for this project, how will the cost of the study be financed?

_____

23. CONTRACTS (See Guidelines)

a) Please list and attach copies of all contracts/agreements with the corporate sponsor(s), public funding agencies or other parties (e.g. copyright holders) that are related to this study. These contracts/agreements may include but are not limited to clinical trial agreements, material transfer agreements involving human material and licensing agreements for the use of copyrighted materials.

Not applicable

All contracts have been forwarded to the relevant departments at the research site.

☐Yes ☐ No ☒ Not applicable

If No, please explain

b) Please indicate who will cover the costs of treatment not covered by the provincial health plan in case of injury directly resulting from participation in a research study (e.g. sponsor, research facility or university).

Injury directly resulting from participating in this study is not expected.

24. POTENTIAL CONFLICTS OF INTEREST (See Guidelines)

a) Please indicate whether the Principal Investigator, Responsible Site Investigator or any Co-Investigators or other research staff involved in this research study or any member of their immediate family:

i) function as an advisor, employee, officer, director or consultant for the study sponsor?

☐Yes ☒ No

ii) have direct or indirect financial interest in the sponsoring corporation (e.g. stocks) drug, device or technology employed (e.g. patents) in this research study?

☐Yes ☒ No

iii) receive an honorarium or other financial benefits from the sponsor (apart from fee for service or regular salary)?

☐Yes ☒ No

iv) are receiving incentives to recruit research participants for this study?

☐Yes ☒ No

If the answer is yes to any of the above questions, append a letter detailing these activities. Please include a description of all conflicts of interest (actual, apparent, perceived, or potential) relating to this project.

b) Does this study comply with the current “conflict of interest” policies of the research site facility?

☒Yes ☐ No ☐ Not applicable

If no or not applicable, please explain.

25. DIVISION/DEPARTMENT/PROGRAM APPROVAL

(THIS SHOULD NOT BE COMPLETED BY AN ADMINISTRATOR WHO IS LISTED AS THE STUDY’S PRINCIPAL INVESTIGATOR, RESPONSIBLE SITE INVESTIGATOR OR CO-INVESTIGATOR)

Hospital and university administrators share responsibility for research activities within their division, department or program. The purpose of this signature section is to ensure that administrators at research sites are aware of: a) the research activities undertaken in their division, department or program and b) the impact of these activities on the resources of their division, department or program and the patients and the communities they serve.

I have reviewed this application and by signing below, I certify that:

a) the study is consistent with hospital/faculty policies and mission
☒ Yes ☐ No ☐ Not applicable

b) the study resources (budget, space, and support staff) and/or the resources of my division, department or program are adequate to support the study,

☒ Yes ☐ No ☐ Not applicable

c) there are an adequate number of research participants suitable to be approached for enrolment for this study

☒ Yes ☐ No ☐ Not applicable

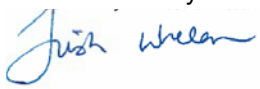
d) this population is not being excessively recruited for clinical research.
☒ Yes ☐ No ☐ Not applicable

Name: Trish Whelan

Contact Number: (613) 562-6262 ext. 2901

Title/Position: Senior Director of Operations

Dept/Unit & Location: Bruyère Research Institute

Signature: 

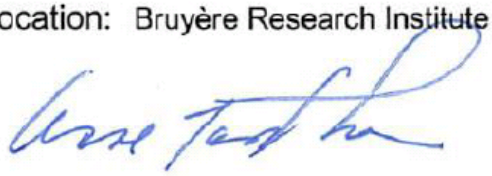
Date: 08/06/2017

Name: Anne Mantha

Contact Number: (613) 562-6262 ext. 1294

Title/Position: Care of the Elderly and Rehabilitation

Dept/Unit & Location: Bruyère Research Institute

Signature: 

Date: June 14th 2017

Please Note: ***In the case where a study will affect more than one financial cost centre within a facility, separate copies of Section 24 should be completed for each cost centre. Please contact each research site to identify the appropriate administrators.***

26. CONTINGENCY PLANNING (See Guidelines)

Outline the contingency plans for this project if the research hospital site becomes closed to all but essential personnel during an epidemic, pandemic or civil disaster. In the contingency plan, please describe the specific steps that will be taken to suspend the project at the hospital research site. If the health of the research subjects may be adversely affected by the suspension of the project, outline the steps that will be taken to protect the interests of the research subjects.

Not applicable.

References

[1] Wild K, Howieson D, Webbe F, Seelye A & Kaye J. (2008). Status of computerized cognitive testing in aging: A systematic review. *Alzheimer's & Dementia 4,* 428-437.

[2] www.cognigram.com

[3] Manuel D., Garner R., Fines P., Bancej C., Flanagan W., Tu K., Reimer K., Chambers L. and Bernier J. (2016). Alzhiemer's and other dementias in Canada, 2011 to 2031: a microsimulation population health modeling (POHEM) study of projected prevalence, health burden, health services, and caregiving use. *Population Health Metrics 14,* 1-10.

[4] Mielke M.M, Machulda M.M, Hagen C.E., Edwards K.K, Roberts R.O, Pankratz V.S, Knopman D.S, Jack Jr C.R. & Petersen R.C. (2015). Performance of the CogState computerized battery in the Mayo clinic Study on Aging. *Alzheimer's & Dementia 11,* 1367-1376.

[5] Gates N.J & Kochan N.A. (2015). Computerized and on-line neuropsychological testing for late-life cognition and neurocognitive disorders: are we there yet? *Curr Opin Psychiatry 28,* 165-172.

[6] Maruff, P., Lim, Y. Y., Ames, D., Ellis, K., Pietrzak, R., Savage, G., ... & Villemagne, V. (2013). Clinical utility of the cogstate brief battery in Alzheimer's disease–related memory impairment. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association 9*, 636-P637.

[7] Lim, Y. Y., Villemagne, V. L., Pietrzak, R. H., Snyder, P. J., Ames, D., Ellis, K. A., ... & Maruff, P. (2014). Utility of the Cognigram brief battery in assessing cognitive changes associated with AB and APOE genotype in preclinical Alzheimer's Disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(4), 429-430.

[8] Fowler K.S., Saling M.M., Conway E.L., Semple J.M. & Louis W.J. (2002). Paired associate performance in the early detectin of DAT. *Journal of the International Neuropsychological Society 8,* 58-71.

[9] Pfeffer RI, Kurosaki TT, Harra CH Jr, Chance JM & Filos S. (1982). Measurement of functional activities in older adults in the community. *J Gerontol 37(3),* 323-329.

[10] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC

[11] Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, Kim K, Meeks T, & Kraemer HC. (2007). A new brief instrument for assessing decisional capacity for clinical research. Arch Gen Psychiatry, 64, 966-974.

[12] Maruff, P., Collie, A., Darby, D., Weaver-Cargin, J., Masters C., Currie, J. (2004). Subtle memory decline over 12 months in Mild Cognitive Impairment. Dementia and Geriatric Cognitive Disorders, 18, 342-449.

[13] Darby D., Maruff P., Collie A., McStephen M. (2002). Mild Cognitive Impairment can be detected by multiple assessments in a single day. Neurology, 59, 1042-1046.

[14] Darby DG., Pietrzak RH., Fredrickson J., Woodward M., Moore L., Fredrickson A., Sach J., Maruff P. (2012). Intraindividual cognitive decline using a brief computerized cognitive screening test. Alzheimer's Dement, 8, 95-104.

[15] Howe AS, Bani-Fatemi A, De Luca V. (2014). The clinical utility of the auditory P300 latency subcomponent even-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. Brain and Cognition 86: 64-74.

[16] Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack Jr CR, …Hampel H. (2012). Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiology of Aging 33; 1203-1214.

[17] López Zunini R, Lord C, Dzuali F, Breau M, Sweet L, Goubran R, Knoefel F, Taler V. (2016a). Event-Related Potentials elicited during working memory are altered in Mild Cognitive Impairment. International Journal of Psychophysiology, 109, 1-8.

[18] López Zunini R, Knoefel F, Lord C, Breau M, Sweet L, Goubran R, Taler V. (2016b). P300 amplitude alternations during inhibitory control in people with Mild Cognitive Impairment. Brain Research, 1646(September), 241-248.

[19] Quiroz YT, Ally BA, Celone K, McKeever J, Ruiz-Rizzo AL, Lopera F, Stern CE, Budson AE. (2011). Event-related potential markers of brain changes in preclinical Alzheimer disease. Neurology 77:469-475.

[20] Rodriguez R, Lopera F, Alvarez A, Fernandez Y, Galan L, Quiroz Y, Bobes MA. (2014). Spectral Analysis of EEG in Familial Alzheimer's disease with E280A Presenilin-1 Mutation Gene. International Journal of Alzheimer's Disease, 2014: 1-10.

[21] Leiser SC, Dunlop J, Bowlby MR, Devilbiss DM. (2011). Aligning strategies for using EEG as a surrogate biomarker: A review of preclinical and clinical research. Biochemical Pharmacology 81: 1408-1421.

[22] Jackson CE, Snyder PJ (2008) Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. Alzheimers Dement 4: S137-S143.