APPENDIX M3 – DETAILED CIMA-Q PROJECT PROTOCOL

ABBREVIATIONS

Aβ: Bêta-Amyloide

AD: Alzheimer's Disease

ADL: Activities of Daily Living

ADCS-PI: Alzheimer's disease cooperative study – Prevention Instrument

AI: Apathy Inventory

ALP: Alkaline Phosphatase

AST: Alanine Transaminase

BDNF: Brain-Derived Neurotrophic Factor

bFGF: Basic Fibroblast Growth Factor

BORB: Birmingham Object Recognition Battery

BUN: Blood Urea Nitrogen

CCI: Cognitive Change Index

CCNA: Canadian Consortium on Neurogeneration in Aging

CDR: Clinical Dementia Rating

CERAD: Consortium to Establish a Registry for Alzheimer's Disease

CH: Cognitively Healthy

CHUQ: Centre Hospitalier Universitaire de Québec

CIHR: Canadian Institutes of Health Research

CIMA-Q: Consortium for the Early Identification of Alzheimer's Disease - Québec

CPT: Cell Preparation Tube

CRIUGM: Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (IUGM Research center)

CRP: C-Reactive Protein

CSF: Cerebrospinal Fluid

DNA: Deoxyribonucleic Acid

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, version IV

EDTA: Ethylene Diamine Tetraacetic Acid

eMCI: early Mild Cognitive Impairment

FDG: Fluorodeoxyglucose.

FLT: Fms-like Tyrosine Kinase

FRQS: Fonds de Recherche en Santé - Québec

GAI: Geriatric Anxiety Inventory

GDS-30: Geriatric Depression Scale

HbA1c: Glycated Hemoglobin

ICAM: InterCellular Adhesion Molecule

ICAO: International Civil Aviation Organization

IFN: Interferon

IL: Interleukine

INR: International Normalized Ratio

IP: Interferon gamma-induced Protein

ISI: Insomnia Severity Index

IUGM: Institut Universitaire de Gériatrie de Montréal

IUSMQ: Institut Universtaire en Santé Mentale de Québec

lMCI: late Mild Cognitive Impairment

LP: Lumbar Puncture

MCI: Mild Cognitive Impairment

MCI-AD: Mild cognitive impairment – Alzheimer disease

MCP: Monocyte Chemoattractant Protein

MDC: Macrophage-Derived Chemokine

MIP: Macrophage Inflammatory protein

ML: Millilitre

MNA® SF: Mini Nutritional Assessment Short form

MoCA: Montreal Cognitive Assessment

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

MSSS: Ministère de la Santé et des Services Sociaux

mSv: Millisievert

NIA-AA: National Institute of Aging – Alzheimer's Association

NPI-Q: Neuropsychiatric Inventory

PET: Positron Emission Tomography

PHQ-9: Patient Health Questionnaire

PLGF: Placenta Growth Factor

QAM: Questionnaire auto-évaluation de la mémoire (Memory self-evaluation questionnaire)

RAVLT: Rey Auditory Verbal Learning Task

REM: Rapid Eye Movement

RNA: Ribonucleic Acid

SAA: Serum Amyloid A

SCI: Subjective Cognitive Impairment

SST: Serum Separator Tube

T0: Initial CIMA-Q assessment visits

T1: Interim clinical telephone assessment time: 1 year after the initial assessment visits

T2: Complete follow-up Time, 2 years after the initial assessment visits

T3: Interim clinical telephone assessment time: 3 years after the initial assessment visits

T4: Complete follow-up Time, 4 years after the initial assessment visits

T5: Interim clinical telephone assessment time: 5 years after the initial assessment visits

T6: Complete follow-up Time, 6 years after the initial assessment visits

T7: Interim clinical telephone assessment time: 7 years after the initial assessment visits

T8: Complete follow-up Time, 8 years after the initial assessment visits

TARC: Thymus and Activation-Regulated Chemokine

TICS: Telephone Interview for Cognitive Status

Tie: Tyrosine kinase with Immunoglobulin and EGF homology domains

T-MMSE: Telephone Mini-Mental State Examination

TNF: Tumor Necrosis Factor

TSH: Thyroid-Stimulating Hormone

VCAM: Vascular Cell Adhesion Protein

VEGF: Vascular Epidermal Growth Factor

WAIS-III: Wechsler Adult Intelligence Scale-III (Third Edition)

WMS-III: Wechsler Memory Scale-III (Third Edition)

TABLE OF CONTENTS

1. INTRODUCTION

People 65 years of age and older currently account for 16% of the population in Quebec; they are now more numerous than individuals under the age of 15. This spectacular transformation of the demographic landscape is a demanding challenge and calls for significant research efforts in order to reduce the considerable impact of age-related diseases on autonomy and quality of life among this significant segment of the population. Alzheimer's disease (AD) is a condition that should be prioritized. Indeed, in addition to being devastating and incurable, it is also the most common neurological disease among elderly people. AD and related diseases affect 10% of individuals after the age of 65 and this percentage increases to 35% after the age of 85. Coordinated efforts are necessary to reduce the psychological, social and economic burden that the disease places on patients, their families and society as a whole. Two principal challenges of this project are: **(1)** To develop new methods enabling earlier diagnosis. Presently speaking, AD is diagnosed at the dementia stage, once the symptoms have had a considerable impact on quality of life and autonomy and the brain has sustained serious damage. **(2)** To acquire a better understanding of the etiology of AD in order to develop more effective treatments.

2. STUDY OBJECTIVES

The specific objectives are:

(1) Identify sensitive and specific tests for diagnosing AD early at prodromal (MCI) and preclinical (SCI) stages;

(2) Develop new neuroimaging markers;

(3) Identify new biological and genetic markers;

(4) Develop an effective "toolbox" combining cognitive, neuroimaging and biomarker data;

(5) Identify early molecular mechanisms contributing to evolution towards MCI, SCI, and AD stages;

(6) Identify lifestyles that predispose one to developing the disease and preventative factors;

(7) Implement structured clinical procedures for diagnosing and biomarker analyses in memory clinics.

3. RESEARCH PLAN

3.1 LONGITUDINAL STUDY PLAN

3.2 TARGET POPULATION

The principal aim of this project is to recruit participants who are representative of the different Alzheimer's disease stages (pre-symptomatic and symptomatic) and clinical situations (comorbidity, etc.). Moreover, we invite cognitively healthy elderly volunteers and healthy young volunteers to participate in order to obtain comparison values (targeted cognitive and biological measures). The participants will be recruited from the following settings: **(1)** the NuAge cohort, **(2)** participating memory clinics **(3)** the community (advertisements and participant banks at participating sites) and **(4)** the CCNA project.

3.3 SAMPLE SIZE

3.3.1 Participants 65 years of age and older

In this study, approximately 350 elderly participants (65 years and older) will be recruited to form groups comprised of the following proportions:

I. 50 participants classified as CH (Cognitively Healthy)
II. 150 participants classified as SCD (Subjective Cognitive Decline
III. 100 participants classified as MCI (Mild Cognitive Impairment), early or late
IV. 50 participants classified as mild AD (Alzheimer's Dementia)

In order to obtain 350 study admissible participants, we plan to screen approximately 650 potential participants. All participants included in the study (350) will be assessed in neuropsychology and neuropsychiatry, and will provide blood samples and undergo a basic clinical assessment (clinical questionnaires, neurological and physical examination, blood tests). Imaging assessments (MRI) will be conducted (62) among the greatest number of participants possible (approximately 16.7% of CH, 50% of SCI, 16.7% of MCI, 16.7% of AD). Our objective is to collect cerebrospinal fluid (CSF) from 80 participants (approximately 20 per Dx group) for analysis of known biomarkers such as Aβ1-42, Tau and phospho-Tau, or future biomarkers associated with aging (59, 60, 61). We plan on conducting FDG-PET among around 35 participants according to the following approximate proportions: 20 SCI, 12 MCI and 3 mild AD. Finally, for those who consent, their brain will be collected upon death and sent to the Brain Bank, in compliance with Brain Bank procedures and rules.

3.3.2 Participants 20 to 45 years of age

In addition to the targeted cohort of 350 elderly people 65 years and older, we plan on recruiting 20 young participants (20-45 years old) who will act as controls for biomarker analyses (YCH). We plan on using CSF samples of young patients for whom a CSF sample (10 to 15 mL) has already been collected within the scope of usual care (for example, to rule out a clinical diagnosis). The unused portion of these samples is usually destroyed, and it is this unused portion we plan to use. This strategy will be put into place at the CHU de Quebec-Université Laval. To do so, a member of the CHU de Quebec-Université Laval clinical team will contact patients aged 20 to 45 years who have already undergone a lumbar puncture to inform them of the CIMA-Q project and to obtain their permission to forward their name and contact information to the CIMA-Q team. Consenting patients will be contacted by a CIMA-Q team member. These potential participants will answer a screening questionnaire to determine their eligibility. This form is similar to the screening questionnaire for elderly patients. Once the patient's eligibility is confirmed, a consent form will be sent to the potential participant who must then sign and return it by email or mail, in order to obtain their permission to use the unused CSF for the CIMA-Q project. Once the signed form received, the CIMA-Q research team can ask for the CSF sample to be transferred.

These samples will be preserved according to the procedures described in this protocol for CSF samples at the Quebec BioBank site.

3.4 INCLUSION CRITERIA FOR THE COGNITIVELY HEALTHY (CH) OR NORMAL ELDERLY GROUP

3.4.1 Answers (**a**) or (**b**) to this question about cognitive complaints (1)

"Do you think that your memory is getting worse?"

- **a.** No
- **b.** Yes, but I'm not worried about it
- **c.** Yes, and it worries me

3.4.2 Has a deferred recall score on Logical memory (Wechsler Memory Scale, max score of 25) (2)

- **I.** ≥9 for 16 years of education and more
- **II.** ≥5 for 8-15 years of education
- **III.** ≥3 for 0-7 years of education.

3.4.3 Has a score of 26 or more (≥26/30) on the Montreal Cognitive Assessment (MoCA) (3).

3.4.4 Has a CDR (Clinical Dementia Rating) (4, 5) score of 0.

3.5 INCLUSION CRITERIA FOR THE SUBJECTIVE COGNITIVE IMPAIRMENT (SCI) GROUP

3.5.1 Answers (**c**) to this question about cognitive complaints

"Do you think that your memory is getting worse?"

- **a.** No
- **b.** Yes, but I'm not worried about it
- **c.** Yes, and it worries me

3.5.2 Has a deferred recall score on Logical memory (Wechsler Memory Scale, max score of 25)

- **I.** ≥9 for 16 years of education and more
- **II.** ≥5 for 8-15 years of education
- **III.** ≥3 for 0-7 years of education

3.5.3 Has a score of 26 or more (≥26/30) on the (MoCA)

3.5.4 Has a CDR (Clinical Dementia Rating) score of 0.

3.6 INCLUSION CRITERIA FOR THE EARLY MILD COGNITIVE IMPAIRMENT (eMCI) GROUP

3.6.1 Answers (**b**) or (**c**) to this question about cognitive complaints

"Do you think that your memory is getting worse?"

- **a.** No
- **b.** Yes, but I'm not worried about it***
- **c.** Yes, and it worries me

*** Certain participants are not worried, but the informant is.

3.6.2 Has a deferred recall score on Logical memory (Wechsler Memory Scale, max score of 25)

- **I.** 9-11 for 16 years of education and more
- **II.** 5-9 for 8-15 years of education
- **III.** 3-6 for 0-7 years of education

3.6.3 Has a score of 20 to 26 (inclusively) on the MoCA

3.6.4 Has a CDR (Clinical Dementia Rating) score of 0.5

3.6.5 Meets NIA-AA clinical criteria for MCI-AD (6)

3.7 INCLUSION CRITERIA FOR THE LATE MILD COGNITIVE IMPAIRMENT (lMCI) GROUP

3 7.1 Answers (**b**) or (**c**) to this question about cognitive complaints

"Do you think that your memory is getting worse?"

- **a.** No
- **b.** Yes, but I'm not worried about it***
- **c.** Yes, and it worries me

*** Certain participants are not worried, but the informant is.

3.7.2 Has a deferred recall score on Logical memory (Wechsler Memory Scale, max score of 25)

- **I.** ≤ 8 for 16 years of education and more
- **II.** ≤ 4 for 8-15 years of education
- **III.** ≤ 2 for 0-7 years of education.

3.7.3 Has a score of 20 to 25 (inclusively) on the MoCA

3.7.4 Has a CDR (Clinical Dementia Rating) score of 0.5

3.7.5 Meets NIA-AA clinical criteria for MCI-AD

3.8 INCLUSION CRITERIA FOR MILD AD (ALZHEIMER'S DISEASE) PATIENTS

3.8.1 Has a deferred recall score for the logical story (Wechsler Memory Scale, max score of 25)

I. ≤ 8 for 16 years of education and more
II. ≤ 4 for 8-15 years of education
III. ≤ 2 for 0-7 years of education.

3.8.2 Has a score of 13 to 24 (inclusively) on the MoCA

3.8.3 Has a CDR (Clinical Dementia Rating) score of 1.0

3.8.4 Meets NIA-AA clinical criteria for probable Alzheimer's.

3.9 INCLUSION CRITERIA FOR ALL ELDERLY PARTICIPANT GROUPS

- Be 65 years of age and older
- Live in the community or an independent living residence (or an equivalent living environment)
- T-MMSE score of 17 or more (≥17/26) (7)
- Understand, read and write in French or English
- Possess sufficient vision and hearing to complete the neuropsychological tests
- For participants with mild Alzheimer's disease (AD), they must be accompanied during clinical visits. For other participants, they must have a close relation who can answer some questions (in person, by phone, or in writing).
- Consent to respond to questionnaires on health status; undergo a physical examination and complete a neuropsychological assessment; take a blood test.

3.10 EXCLUSION CRITERIA FOR ALL ELDERLY PARTICIPANT GROUPS

- Plan on moving from Quebec province within the next three years
- Score of 20 or more (≥20/27) on the PHQ-9 (8)
- CDR score greater than 1 (>1)
- Have a disease affecting or an impairment to the central nervous system:
  - I. A subdural hematoma (active or past)
  - II. A subarachnoid haemorrhage (active or past)
  - III. A primary or metastatic cerebral cancer
  - IV. Epilepsy (active)
  - V. Dementia other than mild Alzheimer's or another neurodegenerative disease
- Have undergone intracranial surgery
- Alcohol, drug or narcotic dependency
- Regularly consume benzodiazepines, at an equivalence of 1 mg per day of lorazepam taken orally
- Have a disease/condition that, in the opinion of the specialist, is related to cognitive deficits and could disrupt the subject's participation in the project.

NOTE: All assessment visits must be planned to take place more than 2 months after a hospitalization lasting more than or as long as 72 hours (≥72 hours) or more than 2 months after having undergone general anaesthesia.

3.11 POSSIBLE EXCLUSION CRITERIA FOR MORE SPECIFIC INTERVENTIONS

3.11.1 For magnetic resonance imaging (MRI / MRS)

- Pregnancy
- Pacemaker
- Defibrillator (an apparatus for cardiac rhythm)
- A prosthetic heart valve (heart prosthesis)
- A Swan-Ganz catheter (a tube in the pulmonary artery on the thorax)
- A subdural insulin or metallic chemotherapy pump
- A neurostimulator, a cerebral neurostimulator, a clip on a cerebral aneurysm (a clip on a blood vessel within the brain)
- A metallic prosthesis or rod (following surgery)
- A metallic strapping (metal support on a bone)
- A cochlear and ocular implant (an implant in an ear or an eye)
- A penial implant
- An intraocular metallic fragment (metallic debris in the eye)
- A patch on the skin for administering a medication

Other situations that could cause an **impediment to or cessation of the MRI exam**

- The presence of piercings, tattoos, permanent makeup
- Dental braces
- Acute claustrophobia (unpleasant sensation when in closed spaces).

3.11.2 Lumbar puncture

- Take anticoagulants such as warfarin, Dabigatran or heparin.
- Allergy/hypersensitivity to local anaesthetics

3.11.3 PET

- Women who are not sterile (surgically or more than 2 years postmenopause)
- Women who are breastfeeding.

3.12 INCLUSION / EXCLUSION CRITERIA FOR THE YOUNG PARTICIPANTS

3.12.1 Inclusion criteria for the young participants

- Men or women between the ages of 20 and 45
- Living in the community
- Have consented to the collection of cerebrospinal fluid by LP

3.12.2 Exclusion criteria for the young participants

- In the past 2 months, have been hospitalized for a period greater or equal to 72 hours (≥72 hours) or have undergone general anaesthesia.
- Have a disease affecting or an impairment to the central nervous system:
  - ***I.*** Subdural hematoma
  - ***II.*** Subarachnoid haemorrhage
  - ***III.*** Cerebral tumour or metastasis

IV. Infectious or inflammatory cerebral disease
V. Epilepsy
VI. Neurodegenerative disease
VII. Dementia

- Have parents or grandparents who had or have neurodegenerative diseases.
- Presence of antecedents of repeated minor traumatic brain injuries or people who participate or participated in contact sports (ex. hockey, football, soccer) where brain injuries were likely
- Have undergone intracranial surgery
- Have a chronic psychiatric disease
- Be treated for depression
- Have a disease/condition requiring medication, or have undergone or are undergoing radiotherapy or chemotherapy
- Have had an alcohol or any other drug dependency at some point over the last 2 years
- Use narcotics or benzodiazepines on a regular basis
- For women, pregnancy

3.13 PARTICIPANT WITHDRAWAL

For any participant who decides to withdraw from the project, a short telephone follow-up will be conducted. If the participant does not object, a few questions will be asked regarding the reason for withdrawing from the project.

3.14 REPLACEMENT OF WITHDRAWN OR DECEASED PARTICIPANTS

Every participant who withdraws from the study before the first complete follow-up visit will be replaced by a participant from the same Dx group in order to maintain a total of 350 study participants.

4. STUDY PROCEDURES

4.1 SCREENING PROCEDURES

Participants are recruited from four sources:

1) NuAge cohort participants**,**

2) Participants referred by private or public memory clinics,

3) Participants from the community.

4) Participants of the CCNA project

All of the participants recruited for the study will be pre-screened by phone in order to minimize the number of volunteers who will be excluded during on-site screening. Participants must respond to a telephone version of the Mini-Mental State Examination (T-MMSE) to exclude participants with T-MMSE scores lower than 17. This telephone interview should last 15 to 20 minutes. If the volunteer is admissible, contact information is gathered and the screening visit (Visit 01) is planned a maximum of 180 days after the telephone interview (see study course). After a brief introduction to the project, volunteers are questioned about their interest in participating and answer questions regarding their eligibility to participate. These volunteers are informed that their responses are noted. Questions about memory are asked to help classify the potential participants within the Dx groups: one regarding self-perceived memory (and a question regarding the perception of close friends and family as to the participant's memory). For participants who wish for more information on the optional techniques, information brochures on lumbar puncture, stem cells, neuroimaging and organ (brain) donation will be available.

4.1.1 Participants from the NuAge study

The NuAge cohort is comprised of 1212 elderly people who were assessed as having no cognitive impairment between 2004 and 2005. They were then re-evaluated in 2008-2009 in order to determine if they developed dementia since their prior assessment. Participants from this cohort were contacted by the NuAge team who administered the screening battery mentioned above. In addition to the T-MMSE, these participants answered memory questions adapted from the TICS. Participants who responded (b) or (c) to the Jessen et al., 2014 question, with a score of 17 or more (≥17/26) on the T-MMSE were admissible to the CIMA-Q study. The CIMA-Q team contacted the admissible participants who agreed to be contacted.

4.1.2 Participants from memory clinics

CIMA-Q study information was provided to clinicians from participating memory clinics. With permission of potential participants, memory clinic clinicians will forward their contact information to a CIMA-Q team member who will then reach out to them. The clinician of patients who show interest in the study will give them a brochure with the CIMA-Q team contact numbers. These patients will be contacted to respond to the pre-screening questionnaire (described in section 4.1).

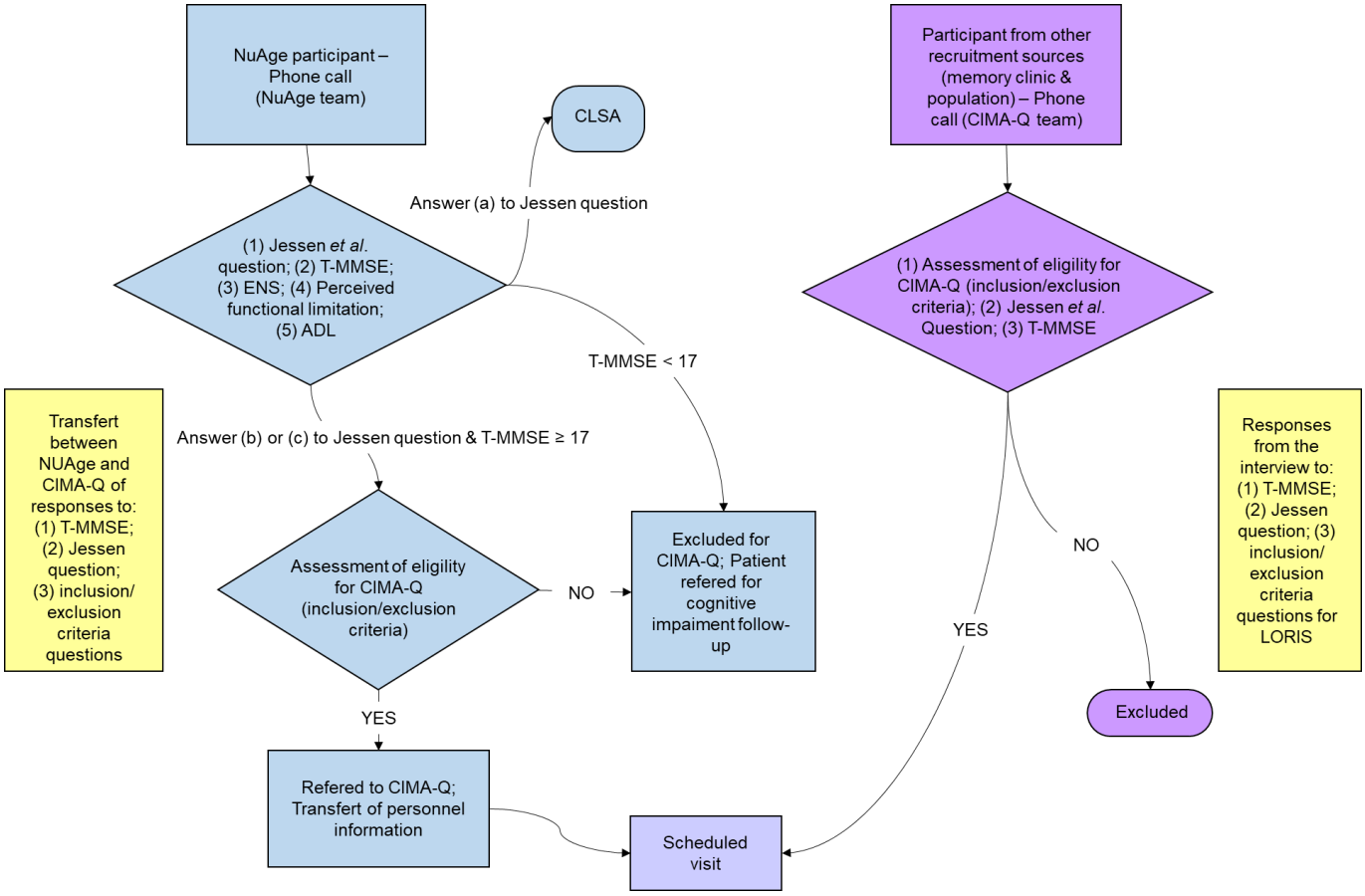
4.1.3 Participants recruited from the community (recruited through advertisements)

A portion of the elderly participants who are cognitively healthy and the young participants will be recruited through potential participant banks held by the Institut universitaire de gériatrie de Montréal (IUGM) and the Institut universitaire en santé mentale de Québec (IUSMQ). These banks contain the names and contact information of people who are interested and consented to participate in projects conducted at the IUGM or the IUSMQ. Eligible people will be contacted by phone to confirm their interest and verify their eligibility (see section 4.1). A portion of the CH and the SCI participants will be recruited from the community through advertisements posted and published in the media (ex. local newspapers). A CIMA-Q team member contacts potential participants who respond to the ads, and conducts the telephone screening (section 4.1).

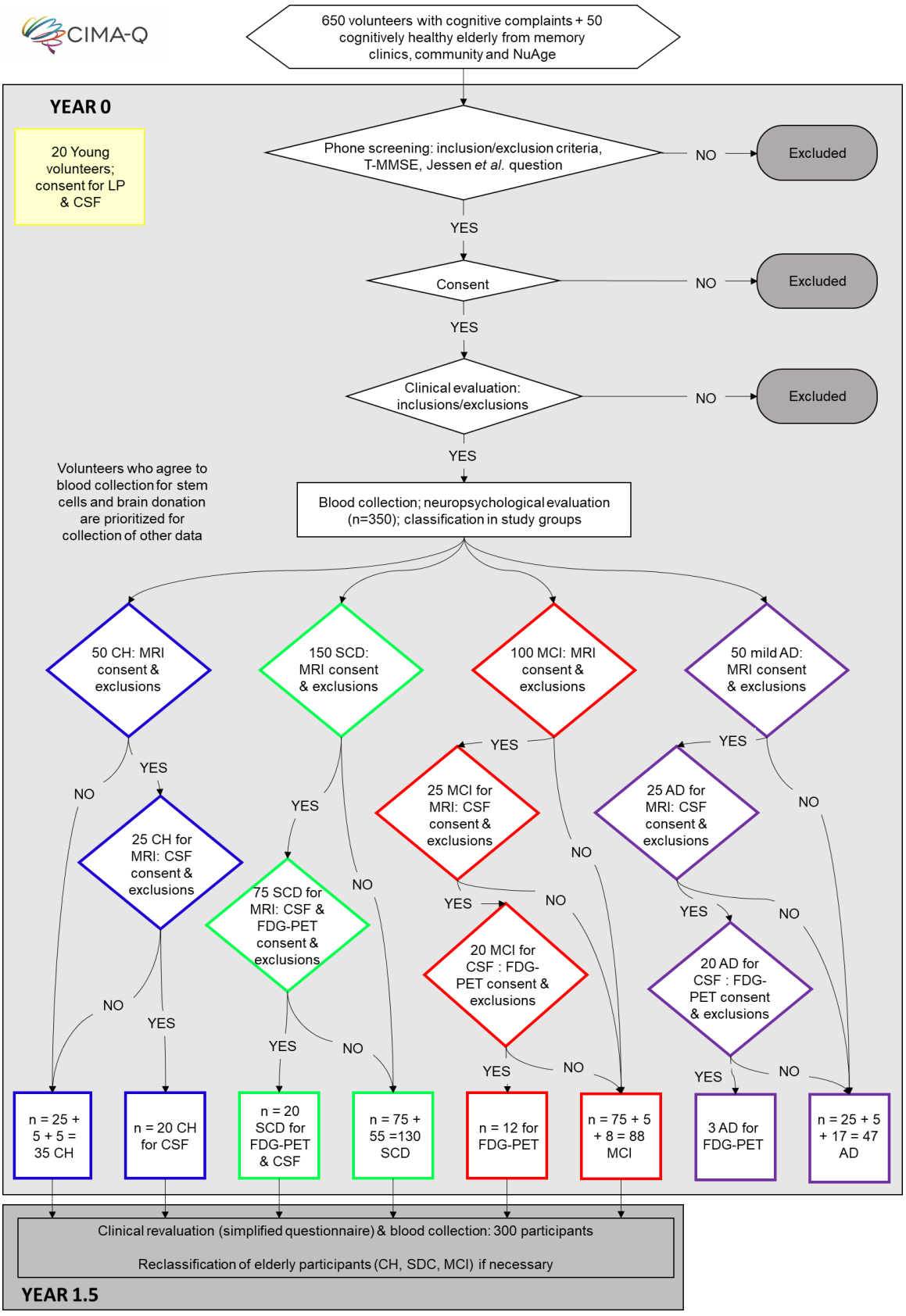
4.1.4 Participants of CCNA project

CIMA-Q collaborates with a Canadian Consortium on Neurogeneration in Aging (CCNA) study whose goal is to study people with neurodegenerative problems associated with aging. It will be possible for CIMA-Q cohort participants to join the CCNA's COMPASS-ND study. Participation in this project will only be proposed to candidates with certain cognitive profiles who consented to be contacted for other research projects. Participants who accept to participate in the COMPASS-ND project or any other research project associated with the CCNA must sign information and consent forms associated with each of these projects. Inversely, some of the participants recruited for the CCNA's COMPASS-ND study may be invited to participate in the CIMA-Q project. Information and consent forms for both the CIMA-Q and CCNA must be signed by participants who agree to participate in both projects.

4.2 DIAGRAM ILLUSTRATING THE INITIAL COHORT RECRUITMENT PROCEDURES



4.3 DIAGRAM ILLUSTRATING THE INITIAL COHORT PLANNING



5. ASSESSMENT / VISITS

Abbreviations for the project follow-up times

T0: CIMA-Q initial assessment visits

T1: Interim clinical telephone assessment: 1 year after the initial assessment visits

T2: Complete follow-up, 2 years after the initial assessment visits

T3: Interim clinical telephone assessment: 3 years after the initial assessment visits

T4: Complete follow-up: 4 years after the initial assessment visits

T5: Interim clinical telephone assessment: 5 years after the initial assessment visits

T6: Complete follow-up: 6 years after the initial assessment visits

T7: Interim clinical telephone assessment: 7 years after the initial assessment visits

T8: Complete follow-up: 8 years after the initial assessment visits

5.1 BLOCKS

Each series of tests or procedures are grouped within a unit called a “Block”. An assessment visit can comprise one or several Blocks. The following Blocks are planned:

I. Consent Block
II. Clinical Block
III. Neuropsychology Block
IV. Blood test Block
V. MRI-Neuroimaging Block
VI. MRS-Neuroimaging Block
VII. PET-Neuroimaging Block
VIII. Lumbar puncture Block

5.1.1 Consent Block

The study is explained to the potential participants. They are free to ask questions before signing the information and consent form. Participants will have the choice to consent or not to certain optional procedures/samplings. However, to be included in the study, the participant must agree to procedures that are considered to be obligatory.

Obligatory assessments/samplings for study inclusion:

I. Initial clinical assessment (T0)
II. Initial neuropsychological assessment (T0)
III. Blood test for blood panel; and for biomarker search analyses (T0)

Optional assessments/samplings:

I. Lumbar puncture: for collecting cerebrospinal liquid and biomarker analyses
II. MRI and MRS imaging
III. PET imaging
IV. The eventual creation of stem cells
V. Brain donation

Describing the study and signing the information and consent form can take up to one hour, depending on the participant's questions. Participants will be informed of their right to withdraw consent at any time during the study and for any procedure whether obligatory or not. Participants interested in undergoing the MRI, MRS, PET and lumbar puncture will complete screening questionnaires during the Consent Block in order to immediately exclude those who do not meet inclusion criteria for each of these optional procedures.

5.1.2 Initial clinical assessment Block (T0) – Obligatory to participate

The Clinical Block assessment lasts around 3 to 4 hours. This Block is comprised of the following elements:

A. Clinical assessment questionnaires for participants aged 65 or older

1. Personal information
2. Socio-demographic information
3. Logical Memory test from the Wechsler Memory Scale (immediate recall)
4. Cognitive reserve questionnaire (Bartres score)
5. Self-perception of health and smoking
6. Health status – measurements (vital signs)
7. Walking speed
8. Grip strength
9. MNA® SF
10. Allergies
11. List of current medications
12. Questions relating to sleep disorders
13. Alzheimer's disease cooperative study (ADCS) - Activities of Daily Living questionnaire
14. Logical Memory test from the Wechsler Memory Scale (delayed recall)
15. PHQ-9
16. MoCA
17. Medical history
18. Physical examination
19. Neurological examination
20. Score – Clinical Dementia Rating (CDR)
21. Hachinski Ischemic Scale
22. Clinical diagnosis
23. Review of clinical inclusion/exclusion criteria

Since 2020

24. Mild Behavioral Impairment Checklist (MBI-C)
25. Gender identity

Since 2022

26. Smell identification test (UPSIT)

B. Questionnaires to be completed at home
(to be returned at the time of the following assessment or by mail) – Around 1.5 hours

1. Geriatric Depression Scale (GDS-30)
2. Cognitive Change Index (CCI)
3. Short form of the Memory Self-Evaluation Questionnaire (QAM, short form)
4. Geriatric Anxiety Inventory (GAI)
5. Epworth Sleepiness Scale (Epworth)
6. Insomnia Severity Index (ISI)
7. Questions on bilingualism

Since 2020

8. Pain Self-Assessment Questionnaire
9. Technology experience profile
10. Mobile Device Proficiency Questionnaire
11. Short Form health and well-being survey (SF-36)
12. Perception Regarding Investigational Screening for Memory in Primary Care questionnaire
13. Dementia Attitudes Scale (DAS)
14. Knowledge about Alzheimer's disease
15. Siegrist's Questionnaire (effort-reward imbalance)
16. Karasek Questionnaire (Work and professional relationships)

C. Questionnaires for the loved one/study partner (informant)

1. Neuropsychiatric Inventory Questionnaire (NPI-Q),
2. Apathy Inventory (AI) and
3. Questionnaire relating to activities of daily living completed by an informant (ADCS-PI) and not by the participant.

The participant must consent for a loved one (the study partner) to answer certain questions about him/her. These questionnaires will be administered over the phone, in person (if the partner accompanies the participant during the Clinical Assessment Block visit) or in writing (questionnaire forwarded to the partner by mail or email). Information regarding the study partner will also be gathered (age, gender, level of education, relationship to the participant, etc.). The questionnaires must be completed between 0 and 30 days (maximum) after the Clinical Assessment Block. NOTE: The participation of a research partner is an obligatory study inclusion criterion. However, if over the course of longitudinal monitoring, the participant loses their study partner, the participant will remain within the cohort.

5.1.3 Clinical Assessment Block (Interim telephone follow-up) – Brief clinical assessment

NOT PART OF THE INITIAL ASSESSMENT (T0)

One year after the initial complete assessment, the participant will be contacted by phone for a brief clinical assessment, which will also be conducted **every year during which there is no complete follow-up** until the end or the cessation of his/her longitudinal monitoring. The interim clinical assessment (T1-T3-T5-T7-…) includes the following items:

For participants aged 65 or older

1. Personal information - Verification
2. Socio-demographic information – Changes since prior clinical assessment
3. MNA® SF
4. Current list of medication
5. Questions on sleep disorders
6. Alzheimer's disease cooperative study - Activities of Daily Living questionnaire
7. PHQ-9
8. Medical history – Changes since prior clinical assessment

5.1.4 Neuropsychology Block (T0) – Obligatory to be recruited

This Block takes 2 to 3 hours to complete and includes the following tests:

1. Verbal fluency (categorical - animals)
2. Stroop-D-KEFS
3. Word list test of episodic memory (Rey Auditory Verbal Learning Task, RAVLT)
4. Envelope Task (prospective memory)
5. Trail making test A and B
6. Object Decision test from the Birmingham Object Recognition Battery (BORB)
7. Visual Perception test (BORB line orientation)
8. Questions on sleep habits
9. Face-Name memory test (associative episodic memory)
10. Computerized Hayling task
11. Digit Symbol test from the WAIS-III
12. Boston Naming Test
13. Cued recall from Memoria (episodic memory)
14. Alpha-span (short version)
15. Vocabulary test from the WAIS-III
16. Apathy Inventory (participant version)

5.1.5 Blood Test Block – Obligatory to be recruited

Blood samples (on an empty stomach, early morning) will be used for clinical analyses as well as for fundamental research analyses. Several blood components can be used for these analyses, such as the serum, plasma, red blood cells, RNA and DNA. Fundamental research samples will be stored in the CIMA-Q Biobank (see section 7.2.2) for future analyses. Consent for venipuncture for the aims mentioned above is an obligatory inclusion criterion for study participation. Participants can consent or not for their blood to be used for the eventual production of pluripotent stem cells. The refusal of the use of one's blood for the production of pluripotent stem cells is not a participant exclusion criterion.

5.1.6 MRI-Neuroimaging Block – Optional

The MRI-Neuroimaging Block will apply to those who consent to an MRI and who meet the inclusion criteria specific to this procedure. The MRI involves an imaging protocol lasting 60 to 75 minutes. The complete visit takes 90 to 165 minutes.

The MRI session is comprised of anatomic and functional sequences during which the participant lies down in the scanner. An activation sequence while carrying out a memory task is also planned. This activation sequence lasts around 15 minutes and takes place at the end of the neuroimaging session. During this sequence, images of known objects placed in one of four positions within a quadrant (upper-lower-right-left, of a screen divided into four) are presented at a rate of one image per 3 seconds with an inter-stimulus interval varying between 2 and 8 seconds. Non-objects (grey squares) are interspersed between the images (control condition). The image recall test is administered once outside of the scanner, on a laptop computer, in a quiet room. During the test, all of the images presented in the scanner, as well as 39 new images are presented in a random order on the screen. Participants must identify all the images that had been presented to them during the memory task within the scanner and indicate, for each of the images recognized, its position within the quadrant. **NOTE:** No substance is injected or otherwise administered during this visit.

The following table presents the 6 CIMA-Q validated MRI sites.

MRI platforms with a CIMA-Q validated protocol

SITE	PI	SCANNER	CITY
MNI	S. Baillet	Siemens 3T	Montreal (McGill)
UNF	P Bellec	Siemens 3T	Montreal (U. de Montréal) * MRS
CINQ	S. Duchesne	Philips 3T	Quebec City (U. Laval)
Douglas	M. Rajah	Siemens 3T	Montreal (McGill)
CHUM	A. Leblond	Philips 3T	Montreal (U. de Montréal)
CRC LeBel	M. Lepage	3T (Uns.)	Sherbrooke (U. de Sherbrooke) *MRS

5.1.7 Neuroimaging-MRS Block – Optional

Magnetic resonance spectroscopy (MRS) is a technique that is complementary to magnetic resonance imaging (MRI). It is an imaging method that makes it possible to visualise the metabolic activity of an organ such as the brain. It enables identification of certain molecular constituents (metabolites) involved in physiological or pathological processes. This technique allows for measuring glutamate concentration, and thus to quantify the biochemical modifications of certain regions of the brain involved in memory.

During the MRS, the participant lies on a mattress in a tube, like for the MRI session. The participant wears a headset and protective ear plugs in order to reduce discomfort relating to the loud noises emitted by the scan. Small cushions are placed around the head in order to ensure its immobility. The participant does not have to do anything during the session and no substance will be injected.

5.1.8 Neuroimaging-PET Block – Optional

The Neuroimaging-PET Block will apply to participants who consent to PET and who meet the inclusion criteria specific to this technique. The PET visit (PET using FDG tracers) lasts approximately 90 minutes. The participant must have an empty stomach for a period of 4 hours prior to the visit (with the exception of drinking limited quantities of water). The participant intravenously receives a standard dose of FDG (between 185 and 370 MBq) and is then placed in a calm environment for a period of 30 minutes. PET consists of a 3D scan lasting 20 minutes, followed by a transmission study lasting 5 minutes maximum. Participants will be informed of the procedures to follow in case of adverse reaction(s)/events when presented the information and consent form. In case of adverse reaction(s)/events, the participant is advised to go to the closest emergency room with all the relevant information for medical personnel. **NOTE:** In the information and consent form, it is mentioned that if the participant must go to the emergency room in case of adverse effects, he/she or a member of his/her family/friends must advise the CIMA-Q team within 24 hours so that the adverse effects of the PET are submitted to the appropriate authorities.

PET platforms with a CIMA-Q validated protocol

#	SITE	PI	SCANNER	VILLE
1	MNI	J.P. Soucy	Siemens HRRT	Montreal (McGill)
2	CRC LeBel	N. Paquet	Philips Gemini	Sherbrooke (U.de Sherbrooke)
3	CHUQ	J.M. Villemaire	Siemens Biograph	Quebec City (U. Laval)
4	CHUM	A. Leblond	Philips Gemini	Montreal (U. de Montréal)

5.1.9 Lumbar Puncture Block - Optional

One of the objectives of CIMA-Q project is to identify new markers in CSF well before AD manifests. Meaning, biomarkers that are predictive of AD may be found specifically in the CSF of people at risk for developing the disease, or biomarkers may be found in different proportions of those who will not develop the disease. The new biomarkers we seek must have a predictive value for detecting the disease in its early stages. The LP Block will apply to participants who consent to this procedure and who meet inclusion criteria specific to this intervention. CSF collection is conducted according to standard medical procedures by a specialist (neurologist) (58). During the LP visit, a volume of 10 to 15 ml of CSF is gathered through puncture, under local anaesthesia, by the neurologist using a fine needle inserted between two lumbar vertebrae. Following this intervention, the participant remains under observation for one hour with a member of the CIMA-Q medical team. The LP Block takes place in the afternoon for all participants in order to minimize inter-participant variables caused by the circadian cycle. This block lasts around 90 minutes (including the observation period following the puncture). Participants will be informed of the procedures to follow in case of adverse reaction(s)/events when presented the information and consent form. In case of an adverse reaction/event, the participant is advised to go to the closest emergency room with all the relevant information for the medical personnel.

Note: In the information and consent form, it is mentioned that if the participant must go to the emergency room following an adverse reaction, he/she or a member of their family or friends must advise the CIMA-Q team within 24 hours so that a report regarding the adverse effect of the LP are submitted to the appropriate authorities.

5.2 COURSE OF THE STUDY

INITIAL ASSESSMENTS: T0: V00 / V01 / V02/ V03 / V04 / V05 and V04LP

5.2.1 Screening (V00) and Initial clinical assessment (V01)

The assessment visit V01 will take place 180 days at the latest after the telephone screening call (assessment visit V00). The objective of this assessment visit is to obtain baseline clinical measures that will be compared to values gathered during subsequent assessment follow-ups. This assessment visit is typically comprised of the Consent Block followed by the Clinical Block. During this visit, no data is gathered until the potential participant has signed the information and consent form.

5.2.2 Neuropsychological cognitive assessment (V02) and Blood test (V04)

The second visit consists of the neuropsychological assessment (V02) and a venipuncture (blood sample V04). This visit begins with the Blood test Block (on an empty stomach, always scheduled in the morning), followed by a breakfast, and ending with the Neuropsychology Block. This visit is planned a maximum of 30 days after the initial clinical visit.

5.2.3 MRI-Neuroimaging Block (V03)

This block will take place no later than 90 days after Visit V01 (clinical assessment visit).

5.2.4 MRS-Neuroimaging Block (V03S)

This Block is planned within 2 weeks maximum following the MRI visit (V03).

5.2.5 PET-Neuroimaging Block (V05)

This block will take place no later than 90 days after Visit V01 (clinical visit).

5.2.6 Lumbar Puncture-LP Block (V04 LP)

This Block will take place no later than 90 days after Visit (V01) (clinical assessment). This visit must take place after the Neuroimaging Block.

For the next follow-ups (2 years, 4 years, 6 years and 8 years), the same assessment visits will be repeated but these new assessment visits are attributed different visit numbers. See section 5.3.1.

5.3 CIMA-Q LONGITUDINAL FOLLOW-UP PERIODS AND FOLLOW-UP ASSESSMENT VISITS 2- to 8-year post (T2 to T8)

5.3.1 List of (possible) assessment visits planned for the longitudinal follow-up

The CIMA-Q obtained financing enabling it to pursue its longitudinal monitoring activities over a period of 8 years. Here (below) is a complete list of planned longitudinal monitoring visits. *The details of the tests included in each of these visits are described in **Appendix M2**.

Names of the longitudinal follow-up assessment visits

(Refers to the CIMA-Q LORIS data Bank)

T2:

V07 Clinical visit (2 years post-: T2)

V08 Neuropsychology visit (2 years post-: T2)

V09 Blood test (2 years post-: T2)

V10 MRI (2 years post-: T2)

V10S MRS (2 years post-: T2)

V11 PET (T2) – Not administered / V12 LP (T2) – Not administered

T3:

V13 Brief telephone clinical assessment (3 years post-: T3)

T4:

V14 Clinical follow-up (4 years post-: T4)

V15 Neuropsychology visit (4 years post-: T4)

V16 Blood test (4 years post-: T4)

V17 MRI (4 years post-: T4)

V17S MRS (4 years post-: T4)

V18 LP (T4) (Not planned on the schedule) / V19 PET (T4) (Not planned on the schedule)

T5:

V20 Brief telephone clinical assessment (5 years post-: T5)

T6:

V21 Clinical follow-up (6 years post-: T6)

V22 Neuropsychology visit (6 years post-: T6)

V23 Blood test (6 years post-: T6)

V24 MRI (6 years post-: T6)

V24S MRS (6 years post-: T6)

V25 LP (T6) Not planned on the schedule / V26 PET (T6) Not planned on the schedule

T7:

V27 Brief telephone clinical assessment (7 years post-: T7)

T8:

V28 Clinical follow-up (8 years post-: T8)

V29 Neuropsychology visit (8 years post-: T8)

V30 Blood test (8 years post-: T8)

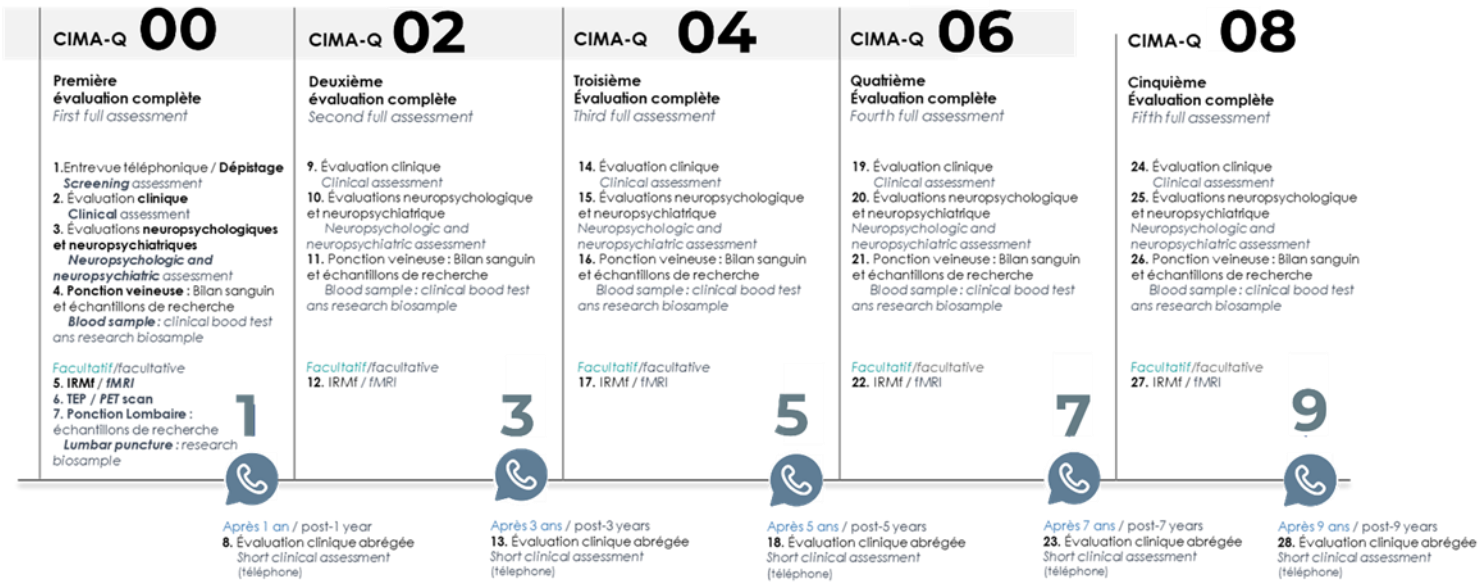
V31 MRI (8 years post-: T8)

V31S MRS (8 years post-: T8)

V32 LP (8 years post-: T8)

V33 PET (Not planned on the schedule)

5.3.2 Planned schedule of CIMA-Q longitudinal monitoring



6. ASSESSMENT METHODS

6.1 OVERALL, COGNITIVE, BEHAVIOURAL AND FUNCTIONAL ASSESSMENTS

6.1.1 Blood samples for clinical analyses

The participant must have an empty stomach at the time of venipuncture (at least 8 hours).

Analyses conducted on the samples:

1. TSH
2. Sodium, potassium, calcium
3. Fasting blood glucose + HbA1c, blood urea nitrogen (BUN), Creatinine
4. Vitamin B12
5. Alkaline phosphatase (ALP), Aspartate transaminase (AST or SGOT), Alanine transaminase (ALT or SGPT)
6. C-reactive Protein
7. Lipid panel
8. Full blood count
9. International Normalized Ratio (INR)

6.1.2 Vital signs and physical measures

I. Participants' resting (5 min) blood pressure and pulse while sitting or lying down.
II. Orthostatic change is measured one and three minutes after standing up from a sitting or lying down position.
III. Weight, height, waist and neck size measures.
IV. Assessment of grip strength and walking speed.

6.1.3 Medication

A full list of medications/products used (prescribed or not) is compiled by

(1) obtaining the list of prescribed medication from the pharmacy (with the participant's consent),

(2) an inventory of the contents of products used by the participant and

(3) an interview with the participant.

6.1.4 Medical history

The following information is gathered:

I. Medical, surgical, psychiatric and family history of certain conditions.
II. Family history of dementia within the biological family.
III. Habits related to alcohol and other drugs (exclusion criteria for participants with drug or alcohol problems).
IV. History and evolution of complaints and symptoms (except for the CH group).

6.1.5 Physical and neurological examinations

The physical examination, as well as the neurological examination is administered by a CIMA-Q clinical team medical doctor during the Clinical Block.

The neurological examination includes assessment of the following parameters:

I. Level of consciousness
II. Cranial nerves
III. Sensory system
IV. Cerebellar functions
V. Gait

6.1.6 Assessment scales

6.1.6.1 CLINICAL assessments

The baseline questionnaire groups together several questionnaires evaluating various themes:

A. LOGICAL MEMORY TEST FROM THE WECHSLER MEMORY SCALE-III (IMMEDIATE AND DELAYED RECALL) (2):

This test assesses memory. A short story is read to the participant who must then recount the story immediately after having heard it (immediate recall), reporting as many details as possible and using the same words. Thirty to forty minutes later, the participant must recall the story with as many details as possible and using the same words (delayed recall). Scores are calculated for both immediate and delayed recall, as well as the retention rate (delayed recall/immediate recall x 100%).

B. BARTRES COGNITIVE RESERVE (9):

This questionnaire evaluates several themes/factors associated with cognitive reserve: education, language, occupation, reading, musical instrument learning, leisure activities, physical activities and social life.

C. NUTRITION (10-13):

The Mini Nutritional Assessment (MNA®) is a questionnaire used to screen for nutritional problems.

D. FRIED FRAILTY INDEX (14):

This index measures different physical parameters, such as unintentional weight loss (10 lbs or more in the last year), grip strength, walking speed, continuous fatigue and physical activity.

E. SLEEP:

This questionnaire is comprised of ten questions exploring three different sleep disorders: chronic insomnia (15), sleep apnea (the STOP-BANG questionnaire (16-19)) and REM sleep behaviour disorders (20).

F. PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9; (8)):

This tool, based on DSM-IV diagnostic criteria, assesses the presence or absence of depression signs. This questionnaire has nine questions and each question is scored 0 to 3 according to the frequency of the problems stated over the course of the past two weeks.

G. MoCA (Montreal Cognitive Assessment) (3):

This cognitive test evaluates several cognitive spheres: visuospatial/executive (5 points); naming (3 points); memory of five words (5 points); attention (6 points); language (3 points); abstraction (2 points); orientation (6 points).

H. ALZHEIMER'S DISEASE COOPERATIVE STUDY - ACTIVITIES OF DAILY LIVING (21-23):

This questionnaire assesses the participant's ability to carry out complex domestic tasks such as managing money, using transportation, using household appliances, doing laundry, shopping, preparing meals or snacks, remembering important dates, finding personal objects, writing, watching television or reading/talking about the news, making phone calls, taking one's medication, planning activities, as well as leisure activities and pastimes. This questionnaire also includes 5 questions regarding sight, hearing, and mobility. The same questions regarding the participant's domestic living are also asked to a close friend/family member in a complementary independent questionnaire.

I. PHYSICAL SELF-MAINTENANCE SCALE (PSMS) (23):

Participants indicate their ability to carry out tasks in 6 daily living categories, such as the ability to go to the bathroom, feed oneself, dress oneself, self-care, move around and wash oneself.

J. CLINICAL DEMENTIA RATING (CDR) (4-5):

This tool measures 5 levels of deterioration in performance in regards to 6 different categories: memory, orientation, judgment and problem-solving, activities in and outside of the home, pastimes and personal care.

K. HACHINSKI ISCHEMIC SCALE (24):

The Hachinski Ischemic Scale evaluates the presence of several symptoms in order to determine if the participant with cognitive impairment may suffer or not from vascular dementia.

L. NEUROPSYCHIATRY INVENTORY (NPI-Q); (25):

This scale addresses psychopathology in regards to Alzheimer's disease and on the basis of information gathered from a loved one who has frequent contact with the participant. Twelve different categories are evaluated: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, nocturnal agitation, and appetite/eating.

M. BRIEF PAIN INVENTORY (BPI) (26):

This assessment tool is one of the most commonly used to evaluate clinical pain. It is a self-assessment tool that evaluates the main dimensions of pain: intensity, functional disability, social and family repercussions, and level of psychological distress.

N. MILD BEHAVIORAL IMPAIRMENT CHECKLIST (MBI-C); (27):

The Mild Behavioral Impairment Checklist (MBI-C) is a scale that describes the emergence of neuropsychiatric symptoms that are precursors to cognitive decline and dementia among people 50 years of age and older. It describes symptoms of different severities that have been present for at least 6 months and occur before and in combination with mild cognitive impairment.

O. SEIGRIST EFFORT-REWARD IMBALANCE (ERI) (28.):

This tool aims to predict psychological distress and health problems that can occur when there is an imbalance between the efforts required by the activity and acknowledgement received. It evaluates 3 psychosocial dimensions: 1- intrinsic efforts or overinvestments corresponding to attitudes and behaviours associated with excessive commitment to work; 2- extrinsic efforts, which are the constraints and requirements related to work both psychologically and physically, and 3- the rewards.

P. KARASEK JOB CONTENT QUESTIONNAIRE (JCQ) (29):

This tool screens for work-related stress. It evaluates three spheres: 1- work psychological demand; 2- decision-making latitude, and 3 – social support.

Q. COMPUTER AND TECHNOLOGY EXPERIENCE (30):

To measure experience with computers and technology, two questionnaires are used. The first, called the Mobile Device Proficiency Questionnaire, has 16 items and aims to assess mastery of different tasks with the assistance of cellphones among elderly people. The second 36-item tool evaluates one's technological experience profile in different spheres: communications, health, daily life, leisure activities, and transportation.

R. SHORT FORM HEALTH AND WELL-BEING SURVEY (SF-36) (31):

This general tool comprised of 36 items aims to gather the point of view of participants regarding their state of health. It documents a functional health profile, a well-being profile, as well as a summary measure of physical and mental health.

S. PERCEPTIONS REGARDING INVESTIGATIONAL SCREENING FOR MEMORY IN PRIMARY CARE QUESTIONNAIRE (PRISM-PC) (32.):

This questionnaire aims to document the attitudes of participants regarding dementia screening in primary care. The tool is comprised of two distinct scales: acceptance of dementia screening by the participant and perceived inconveniences and advantages of dementia screening.

T. DEMENTIA ATTITUDES SCALE (DAS) (33):

This 20-item instrument measures attitudes towards dementia.

U. ALZHEIMER'S DISEASE KNOWLEDGE SCALE (ADKS) (34.):

The ADKS contains 30 true or false statements based on current scientific understanding of the disease and aims to evaluate knowledge about Alzheimer's disease. The scale takes around 5 to 10 minutes to complete and covers risk factors, evaluation, diagnosis, symptoms, evolution, impact on one's life, as well as care for, treatment and management of the disease.

V. SMELL IDENTIFICATION TEST ™ (64)

The University of Pennsylvania Smell Identification Test (UPSIT) measures smell identification, meaning the ability to recognize an odour and name it. The UPSIT is a "scratch and smell" type test and does not require any manipulation from assessment personnel members. During testing, participants are invited to scratch and smell 40 "smells" from an individual test booklet provided by the Sensonics company (UPSIT test) and then identify these smells from among four response choices. Test completion takes 10 minutes. The results regarding the standardization and validity of these tests are reported in the article by Doty et al. (64)

6.1.6.2 Neuropsychological assessment:

The neuropsychological assessment visit is a predictive cognitive evaluation (neuropsychological test battery and neuropsychiatric and functional scales). The tools selected have been identified as having strong predictive potential for Alzheimer's disease or MCI according to reviews and meta-analyses.

A. Episodic memory is assessed using:

- **I.** A pairing episodic memory test : the "Name-Face" pairing test (created by CIMA-Q (35)),
- **II.** A word memory test, the "Rey Auditory Verbal Learning Test" (36),
- **III.** A test measuring memory processes, the free and cued recall test of the Memoria battery (37-38).

B. Prospective memory is assessed using the envelope task (39).

C. Incidental learning is assessed using the digit symbol test from the WAIS-III (40) (pairing and free recall tasks).

D. Executive functions are assessed using:

- **I.** Computerized Hayling task (41)
- **II.** The alpha-span task (42)
- **III.** The code or digit symbol test from the WAIS-III ; (40)
- **IV.** Trail making test A and B (43, 44)
- **V.** STROOP test (D-KEFS) (45)

E. Semantic perception and visual discrimination are respectively assessed using the **(1)** object decision, and **(2)** line orientation subtests from the Birmingham Object Recognition Battery (BORB) (46),

F. Language is evaluated using:

- **I.** The Boston naming test (47) and
- **II.** Categorical Verbal Fluency test (animals)

A battery of **questionnaires** evaluating psychological and behavioural symptoms is used to assess **(1)** neuropsychiatric signs, **(2)** sleep, and **(3)** cognitive complaints. They are mostly self-administered. These questionnaires are completed by the participant either at home or at the beginning of the Neurocognition/neuropsychiatry Block visit (depending on the follow-up year / CIMA-Q 0, 2, 4, 6, 8).

Neuropsychiatric signs such as anxiety, depression and apathy are assessed with the following forms:

- **I.** Geriatric Anxiety Inventory (GAI, (48)) (self-administered).
- **II.** Geriatric Depression scale (GDS-30,(49-50)) (self-administered).
- **III.** Apathy Inventory, participant version (51) (administered during neurocognitive assessment).

Sleep is assessed using:

- **I.** Sleep questionnaire created by CIMA-Q (52)
- **II.** Epworth Sleepiness Scale (53)
- **III.** Insomnia Severity Index (ISI) (54)

NOTE: II and III are self-administered.

Memory complaints are evaluated using two self-administered questionnaires:

- **I.** The Cognitive Change Index (CCI) (55)
- **II.** A short version of the QAM (56, 57)

NOTE: The WAIS-III vocabulary test (40) is also administered and is used as a cognitive reserve marker in combination with the Bartres questionnaire that was completed at the clinical assessment. It is also used to estimate pre-morbid IQ.

The neurocognitive assessment session tests (predictive battery) are always administered before noon in the same order, following the same procedures to reduce clinician / tester biases. This visit lasts approximately 2.5 hours.

6.1.6.3 Validation procedures

All of the protocols and instructions for administering the predictive battery tests and questionnaires are available on the CIMA-Q Website, in a section devoted to procedure harmonization and psychometrician training. Psychometrician training is organized by the Neuropsychology coordinator. To obtain CIMA-Q certification, a psychometrician must successfully complete an online evaluation upon conclusion of the training (around 12 hours). In addition to evaluating their knowledge, the psychometrician is also evaluated with regard to performance when administering the tests. The psychometrician is evaluated during a CIMA-Q battery administration session in the presence of the Neurocognition team coordinator **(1)** 2 observations of full sessions by an experienced psychometrician **(2)** administration of tests to 1 false participant in the presence of the coordinator **(3)** first 2 CIMA-Q participants tested in the presence of the coordinator. Afterwards, test administration quality control audits are conducted on 10% of assessments carried out by each psychometrician. These procedures ensure continued assessment quality and guarantee harmonization of assessment across sites. **NOTE**: Clinical Block audits (for the nurses) are coordinated by the CIMA-Q Clinical coordinator and are conducted for 20% of participants seen. During these audits, an external nurse observes all of the steps conducted by the nurse during his/her clinical assessment visit and then provides a report describing his/her observations and elements to improve if applicable.

6.1.7 Blood sample

Blood will be collected and used for clinical biochemical lab analyses in order to assess the health status of participants, but will also be used for fundamental research. Around 21.5 mL of blood is required for fundamental research and we will request 4 tubes of blood. These tubes will be pre-identified and pre-prepared by the research personnel.

Each sample will be collected as follows (see following table):

- **I.** 6 ml of blood will be collected in 1 EDTA tube to isolate the plasma, red blood cells and the buffy coat in order to evaluate different biomarkers. Note that DNA is extracted from the buffy coat.
- **II.** 8 ml of blood will be collected in 1 “Cell preparation tube” (CPT) to isolate peripheral blood mononuclear cells (PBMC)
- **III.** 5 ml of blood must be gathered in 1 “Serum Separator Tube” (SST) which will be used to isolate and collect serum for later analyses of markers.
- **IV.** Two .5 ml of blood will be collected in 1 “PAXgene RNA” tube in order to extract RNA from blood cells for gene expression analyses.

TUBE	TYPE OF TUBES	MINIMAL QUANTITY OF BLOOD REQUIRED	AIM
1	1 EDTA tube	6 mL	Plasma, red blood cells, buffy coat

2	1 CPT tube	8 mL	PBMC
3	1 SST tube	5 mL	Serum
4	1 PAXgene Blood RNA tube	2.5 mL	RNA extraction

The level of several markers of interest can be analyzed, such as BDNF, cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNF-α, IL-1α, IL-5, IL-7, IL-12/IL-23p40, IL-15, IL-16, IL-17A, TNF-β, VEGF), and chemokines (Eotaxin, MIP-1β, Eotaxin-3, TARC, IP-10, MIP-1α, MCP-1, MDC, MCP-4), angiogenesis markers (VEGF-C, VEGF-D, Tie-2, Flt-1, PlGF, bFGF, SAA, CRP, VCAM-1, ICAM-1), stroke markers (SAA, CRP, VCAM-1, ICAM-1) or others. This list is not exhaustive and the analysis of additional markers justified by solid hypotheses could be conducted.

Moreover, a 3 ml of blood must be gathered in 1 “sodium citrate” tube which will be used for hemostasis analyses. ***Standard Operating Procedures (SOPs**) are available from the Clinical team (upon request Appendices N1 and N2).

6.2 COLLECTION OF CEREBROSPINAL FLUID THROUGH LUMBAR PUNCTURE

On a voluntary basis, ten (10) to fifteen (15) ml of cerebrospinal fluid (CSF) will be collected through puncture by a neurologist using a fine needle inserted between two lumbar vertebrae while under local anaesthesia (58). * **Standard Operating Procedures (SOPs**) are available from the Clinical team (Upon request, Appendices O1 and O2).

6.3 NEUROIMAGING

6.3.1 MRI (MRS):

Six centres will participate in acquiring MRI (MRS) data (see Table 5.1.6): These sites qualified on the basis of having conducted monthly studies of a geometry phantom, as well as an annual study of a control participant while complying with the Canadian dementia imaging protocol. All scans (qualification, quality control, study participants) will be centrally analyzed at the Institut universitaire en santé mentale de Québec.

6.3.2 PET:

Four centres will participate in the acquisition of PET data: (see Table 5.1.7). These sites qualified on the basis of an 18F study of a cerebral anthropomorphic phantom that was centrally analyzed at the Montreal Neurological Institute. The scans will be conducted according to the protocol described above. The data gathered will be deposited into the CIMA-Q LORIS database. Data analyses will be carried out locally and then centrally conducted at the Montreal Neurological Institute using the NeuroStat program.

6.3.3 Post-mortem brain collect and deposit in the Brain Bank

6.3.3.1 Brain donation

Upon the death of participants who specifically consented to brain donation, the loved one named by the deceased participant or the health professional present must contact the Douglas-Bell Canada Brain Bank as soon as possible. A Brain Bank representative can be contacted from Monday to Friday, between 9 a.m. and 5 p.m. Outside of these hours, a voice messaging system is available to transmit instructions to follow if death occurs in the evening, at night, on the weekend or during statuary holidays. The voice message is available outside of the opening hours by dialling (514) -761-6131, extension zero

(0) and by requesting Brain Bank emergency. The call will then be redirected to a voice message where different menus are proposed. As soon as advised of the death, the Brain Bank will take charge of the donation process and answer all of the deceased's loved ones' questions, and will ensure that the donation is treated respectfully and efficiently. In order to ensure optimal specimen preservation, the collection is conducted as soon as possible, less than 24 hours after death. The location of brain removal is chosen soon after death by the Brain Bank representative. The body is transported by a funeral services business to an autopsy room close to the place of death. Once the brain has been removed, the funeral service director is advised and the funeral process pursues according to the wishes of the donor or his/her family. Transportation of the brain towards the Brain Bank (Douglas Institute) is conducted quickly and the brain tissues are processed upon arrival at the Brain Bank to optimize specimen preservation for the purpose of neuropathological evaluation and future use of the tissue for research purposes.

6.3.3.2 Neuropathological evaluation

Each brain collected will be subjected to neuropathological evaluation by a pathologist collaborating with the Brain Bank according to the Bank rules. This brain autopsy makes it possible to establish or confirm the participant's clinical diagnosis. This evaluation is conducted according to the recommendations of the "National Institute on Aging - Alzheimer's Association". The neuropathological changes associated with Alzheimer's disease are classified according to three main criteria: **1)** Thal phase of Aβ deposits, **2)** Braak Stage of neurofibrillary degeneration, and the **3)** CERAD score for neuritic plaques, in order to determine an ABC Score for classifying cases into three levels of Alzheimer Disease neuropathological change: **(I)** none, **(II)** low, **(III)** intermediate or **(IV)** high. The study of each specimen also includes analyses of other pathological changes (such as Lewy bodies and vascular changes) with the objective of verifying whether other phenomena or diseases (comorbidities) may have contributed to the cognitive deficit. Upon completion of the evaluation, an analysis report is written and the brain tissue is returned to the Brain Bank.

Brain collection will be conducted according to the rules and procedures of the Douglas-Bell Canada Brain Bank. Upon receiving the brain, one hemisphere is conserved in 10% neutral buffered formalin and the other hemisphere is cut into coronal slices of around 1 cm thick, which are frozen at -40°C in 2-methylbutane before being stored at -80°C. First, **1)** a macroscopic assessment is conducted and the anomalies observed are logged if such is the case. **2)** The brain is photographed and **3)** its weight noted. **4)** The olfactory tubes and bulbs, as well as the pineal gland are dissected and frozen. **5)** The two hemispheres are then separated and weighed independently. **6)** The habenula is dissected from the two hemispheres and frozen. **7)** If such is the case, the hemisphere suspected of being most pathological is placed in formalin with the circle of Willis for an eventual neuropathological evaluation (the paraffin blocks and histological slides are all returned to the Brain Bank once this evaluation has been completed). If there is no notable macroscopic difference between the two hemispheres, one is paraffin-fixed as a whole (alternating left/right depending on the last case received). The formalin is changed three weeks after initial mounting. For the hemisphere that will be frozen, **i)** the leptomeninges are first withdrawn and frozen, then **ii)** the demi-brain stem and demi-cerebellum are separated. **iii)** The brain stem is frozen as a whole **iv)** The cerebellum is sliced into sagittal cuts. **v)** The hemisphere is cut into coronal slices, from the frontal lobe towards the occipital lobe, and **vi)** both sides of the slices are photographed. **vii)** Certain structures and nuclei are dissected from the entire specimen or slices and individually frozen. **viii)** The specimen's pH is measured directly from a fresh sample of the occipital pole. **ix)** A sample of the occipital cortex is also conserved for future genetic analyses.

7. SAMPLE MANAGEMENT

7.1 STORING OF SAMPLES

7.1.1 Fundamental Research samples

7.1.1.1 Storing of blood and CSF fundamental research samples

The biomaterial tubes will be stored at the Biobank at temperatures that are appropriate to each type of sample until the time at which they are used.

TYPE OF SAMPLE	CONSERVATION TEMPERATURE (°C)
Plasma	-80
Red blood cells	-80
Buffy coat	-80
Serum	-80
RNA	-80
DNA	-80
PBMC	-135 minimum
CSF	-80

The samples will be stored at the CIMA-Q biobank in Quebec City at the CHU de Québec-Université Laval Research Center located at the Centre Hospitalier de l'Université Laval (CHUL), under the supervision of the CIMA-Q biomarker committee. These samples will be kept locked and accessible only to the researcher and technicians responsible for the biobank. Samples can always be gathered at the different CIMA-Q affiliated sites (CHUM and CHUS) and can be repatriated to the central biobank (CHUL). Access to samples is not permitted until after access procedures have been completed for the UAC

CIMA-Q Biobank in Quebec City:

CHU de Québec-Université Laval Research Centre (CRCHUQ-UL)

Neurosciences Axis

Frédéric Calon, Ph.D. Laboratory

CIMA-Q (biomarker section) in Montreal:

Centre Hospitalier de l'Université de Montréal Research Center (CRCHUM)

Dr Pierrette Gaudreau Laboratory

CIMA-Q (biomarker section) in Sherbrooke:

Centre Hospitalier de l'Université de Sherbrooke Research Center (CR-CHUS)

Dr. Christian Bocti. Laboratory

7.1.1.2 Brains

Brain tissue storage complies with Douglas-Bell Canada Brain Bank rules and procedures. Frozen specimens (slices and blocks) will be stored at -80ºC. Each freezer has three independent temperature probes. Two of these are tied into an alarm system permanently connected to the Douglas Institute security personnel. If there is an equipment breakdown, a CO_2 safeguard system installed on each of the freezers ensures sample conservation until an on-call representative arrives and transfers all specimens into a functioning backup freezer (kept empty specifically for this reason). All of these security equipments are connected to independent electrical circuits. Moreover, active monitoring is conducted on the alarm system to ensure that communication between the unit within the Brain Bank and the Security's alarm system console is always operational. In regard to the formalin-fixed specimens, the paraffin-embedded brain blocks and the histological slides, they will be kept at room temperature. The room temperatures of the Brain Bank are controlled and monitored by the alarm system; in case of an air conditioning system breakdown, the on-call representative is advised and must ensure that adequate repairs and maintenance are conducted as soon as possible. Access to the Brain Bank rooms is controlled through the use of magnetic cards with limited access rights. The Douglas Institute security personnel conducts inspection rounds for all Brain Bank rooms and actively monitor the freezers and storage rooms.

7.2 SAMPLE TRANSPORTATION

7.2.1 Clinical samples

Clinical samples will be transferred from the sampling site to the analysis laboratory according to the standard procedures of each site.

7.2.2 Fundamental research samples

The blood samples intended for fundamental research will be transferred between the sampling site and the analysis laboratory, according to the standard procedures of each site. The different tubes obtained during blood sampling or the CSF must be transported to the analysis laboratory (CHUM, CHUS, or CHUL) within a certain amount of time and under certain conditions, according to the standard procedures of each site. The EDTA, CPT, and SST tubes must be processed within 2 hours following blood sampling. (See the SOP associated with the CPT, EDTA, SST tubes, as well as those of the PAXgene and CSF tubes). Once treated the samples will be transported according to appropriate conditions between affiliated labs and the central CIMA-Q biobank (CHUL).

7.2.3 Brains

Sample transportation follows Douglas-Bell Canada Brain Bank rules and procedures. Transportation of brains from the autopsy rooms to the Brain Bank, and those of the samples between the Brain Bank and the applicant researchers' laboratories, will be conducted via rapid specialized carriers and messaging services. Strict norms for packing, package identification and training are scrupulously followed, in compliance with local, national and international laws and regulations (Transport Canada, ICAO, IATA) and when appropriate, rules for the transportation of dangerous material (or other exempted material). The fresh brains will be transported on ice and the frozen samples are sent on dry ice. When the brain or samples are not taken from a person known to carry an infectious disease, the risk is considered minimal and they are transported as an "Exempt human specimen". When the brain or samples are removed from a donor with an infectious disease, the brain or samples are transported with the mention "Biological material Category B UN3373". Packaging is always the same regardless of the identification on the box,

and consists of a type 1B container that respects, at all times, the principle of triple packing (sealed primary and secondary recipients, absorbent material and an exterior shock-resistant container).

7.3 SAMPLE ANALYSES

7.3.1 Clinical samples

Clinical biochemical lab analyses will be conducted according to a standardized procedure to evaluate the full health status of volunteers.

7.3.2 Fundamental research sample analyses

Certain biomarker analyses could be conducted by participating research centre (CHUL, CHUM, CHUS) laboratories according to standardized procedures approved by the expert researcher. In order to optimize the quantity of sample used, the analysis of different biomarkers is strongly suggested for a sole sample.

All of the results from sample analyses of CIMA-Q participants must be shared with CIMA-Q users, regardless of who the researcher is. The LORIS platform was put into place to gather and store the results obtained.

7.3.3 Brains

Aside neuropathological assessment and pH determination mentioned in paragraphs 6.3.3.2, no other specimen analysis will be conducted at the Brain Bank. The samples will be dissected, prepared and preserved, according to the specific needs of applicant researchers, to the extent possible.

7.4 SAMPLE DISTRIBUTION

7.4.1 Fundamental research samples

The Brain Bank and the CIMA-Q Biobank were created with the goal of providing samples to the local, national and international scientific community. Samples use requests are reserved for Quebec researchers who must apply for access from the User Access Committee (UAC). Researchers must first provide a completed Appendix K and request ethical approval from a research ethics committee of the Réseau de la santé et des services sociaux du Québec or a Quebec university research ethics committee (See Appendix E). Once the project's relevance and the number of samples have been approved by the UAC, it is the researcher's responsibility to propose a plan for transporting samples in a way that ensures their integrity and safeguarding. This plan must also be submitted to and accepted by the UAC.

8. REPORTING ADVERSE EVENTS FOLLOWING AN INTERVENTION

8.1 DEFINITION OF AN ADVERSE EVENT

An adverse event is an unfavourable change in the participant's initial state, including clinical tests, or abnormalities that manifest themselves during the study after signing consent, following an intervention such as PET neuroimaging, lumbar puncture or blood tests.

8.2 MONITORING OF AN ADVERSE EVENT

The CIMA-Q clinician has the obligation to monitor the participant who suffers any adverse event and to do so until the participant's condition is considered to be medically stable. A participant who quits the study following an adverse event will be treated and cared for in conformity with good medical practices. These adverse events will be documented and serious* adverse events will be reported to the appropriate authorities (evaluating research ethics committee, etc…).

*A serious adverse event includes any event that is mortal, threatens one's life, causes significant or permanent disability, provokes a hospitalization, prolongs hospitalization or causes congenital anomalies.

8.3 REPORTING A SERIOUS* ADVERSE EVENT

Any serious adverse event that occurs during the study or up to 30 days after the end of the study, regardless of the reason that caused it, must be reported to the CIMA-Q Project Manager within 24 hours after a CIMA-Q clinical team becomes aware of the said event. A report will be distributed to all the sites and to the authorities concerned (evaluating research ethics committee, etc…).

9. ETHICS

9.1 HUMAN PARTICIPANTS: ETHICAL AND REGLEMANTARY CONSIDERATIONS

The CIMA-Q research activities comply with good clinical practice guides and the decisions and recommendations of the Aging and Neuroimaging Research Ethics Committee. The management of ethical issues related to the CIMA-Q Bank and the participants bank are subjected to continuous discussions between the CIMA-Q executive committee and the Aging and Neuroimaging Research Ethics Committee, such that ethical decisions are made as issues manifest. Members of the consortium act in compliance with Quebec's laws and regulations, as well as the Tri-Council policy statement: ethical conduct for research involving humans and the FRQS regulatory guidelines for good research practices. Because human participants and human biological material are involved, the project has obtained ethical approval from the Aging and Neuroimaging Research Ethics Committee. This committee is also responsible for evaluating all research projects that are conducted with CIMA-Q participants, data, and biomaterial. Moreover, ethical approval for a research project conducted using CIMA-Q participants, data or biomaterial may be provided by an ethics committee from the Réseau de la santé et des services sociaux du Québec or a Quebec university research ethics committee. The CIMA-Q team ensures that the participating institutions have standardized operating procedures coherent with their role within the consortium. All the laureates will have successfully completed levels 1 and 3 of the online MSSS ethics tutorial between now and the end of the year. Participant consent will be obtained in accordance with ethical rules and in compliance with the MSSS, FRSQ and CIHR guidelines. When signing the information and consent form, the participant will receive all of the detailed information regarding the study. The participant will be invited to sign the information and consent form for each of the project components. We do not foresee any direct risk to the medical security of participants.

9.2 INFORMED CONSENT FOR STUDY PARTICIPATION

During their first onsite visit, participants who volunteer for the study will sign the information and consent form. After being included in the study, participants must minimally accept to **1)** answer questionnaires regarding their state of health; **2)** undergo a physical and neurological examination; **3)** participate in a neuropsychological assessment; and **4)** undergo a venipuncture for blood testing (around 50 ml).

9.2.1 Informed consent for biomarkers, genetic material, stem cells and neuroimaging data

Participants can choose to agree or not to the following possibilities:

(1) the future production of immortalized stem cells;

(2) the MRI;

(3) the MRS;

(4) the collection of cerebrospinal fluid for biomarker analysis (10-15 ml);

(5) PET.

The participant will be informed that the cells gathered could be used for producing stem cells by academic laboratory researchers or by an industry laboratory possessing a particular technology or a

superior ability to produce stem cells and whose expertise is judged to be well established and approved by the CIMA-Q executive committee.

9.2.2 Consent to donate after death

The information and consent form specific to the Douglas-Bell Canada Brain Bank will be presented to recruited participants selected as potential candidates for brain donation.

9.3 PROCEDURES TO MAINTAIN PARTICIPANT CONFIDENTIALITY

The general, genetic, and medical imaging information gathered during the CIMA-Q study will be stored in the LORIS system (63) data bank, which is an adaptable modular application that works via a Web interface. LORIS makes it possible to gather and store heterogeneous information (medical imaging, clinical data, behavioural and genetic studies).

For the CIMA-Q study, the LORIS system will be installed on one of the CRIUGM servers and specific measures will be taken to ensure the confidentiality of the data gathered.

I. Access to the LORIS system is protected by a user name and password system. The password must qualify as strong (more than 8 characters including letters, numbers and special characters) and is kept in LORIS in an encrypted format.

II. Participants are identified in LORIS by a unique identifier. No personal information enabling participant identification is present within LORIS aside date of birth, ethnic background and postal code.

All of the measures described above ensure the confidentiality of project participants' personal information.

9.4 STORING OF GENERAL, GENETIC, BIOMARKER AND NEUROIMAGING INFORMATION AND BIOLOGICAL MATERIAL

9.4.1 Clinical samples and fundamental research samples

The clinical samples for research analyses will be identified with a participant code and other relevant information (specimen, sampling date, volume, etc.). Sample identification will provide no personal information.

9.4.2 Brains

The Brain Bank employs qualified personnel who have been trained to protect donor rights and to ensure that the Bank operates according to the best norms possible. Any information forwarded to the Bank regarding the donor is managed in a confidential manner. Upon receiving the brain, the donor's file is immediately opened. This file is nominally identified because correspondence must be sent to the deceased's family, the hospital, the nursing home or the treating medical doctor in order to obtain relevant medical information for **1)** making the most precise neuropathological diagnosis possible and **2)** provide adequate and precise samples to researchers. A specific code is attributed to each donor and this code will be placed on each of the donor's brain tissue samples. No nominative link will be displayed on the specimens or on the samples sent to researchers. The code is only accessible to restricted Brain Bank personnel. Within the scope of the CIMA-Q study, a second code must be used in order to link the tissue to the other data gathered on the participant during the study. The Brain Bank also has a database

regarding the donors and specimens. These databases are kept on the Douglas Institute computer network, a protected network whose access is minutely controlled and is a user name and password protected. The databases are protected with the assistance of an independent security system with passwords and a permission system giving access to certain types of information that are coded to give access to certain individuals while blocking access to confidential information. This system is administered by one person, the Brain Bank coordinator. Finally, paper files are situated in locked filing cabinets situated in the Brain Bank office whose access is protected by a system of locks, and access to the hallway in which it is located is protected by a magnetic card access system.

9.4.3 Neuroimaging (MRI and MRS)

All of the (denominalised) images gathered during the CIMA-Q study will be stored and available to access applicants in a section especially devoted to neuroimaging within the LORIS CIMA-Q data Bank. To obtain access, the applicant must make a request from the UAC and this request must be accepted and undergo all usual access request steps.

9.5 POTENTIAL RISKS

9.5.1 Blood sampling

Blood sampling may provoke ecchymosis (a bruise), discomfort or dizziness, pain where the prick takes place, and rarely infection or bleeding.

9.5.2 Lumbar puncture

The most common side effect associated with lumbar puncture is headache. There may be pain in the lower back where the puncture needle was introduced. This discomfort is minimal and should not last more than two days. Sometimes, a post-lumbar puncture syndrome may be observed with headaches when standing that fade when lying down. These symptoms spontaneously disappear after a few days. A “deafness effect” may occur during rapid changes in head position, giving one the impression that a liquid is obstructing the eardrum. Among the other possible side effects, but extremely rare, there are bleeding in the spinal canal (epidural hematoma which may require a surgical intervention), lesions to certain nerve roots, and reactions (allergies) to the local anaesthesia. The lumbar punctures are conducted in a sterile manner to minimize the risk of infections.

9.5.3 Neuroimaging

9.5.3.1 MRI and MRS

According to current knowledge, an MRI or MRS involves no medical risks if no contraindication is present. Indeed, because of the force of the magnetic field emitted by the machine, it is necessary to take certain precautions. A detailed screening questionnaire must be completed before the visit to detect any contraindication to undergoing this examination (see section 3.11.1). Finally, some discomfort could be associated with this examination due to **1)** having to remain still during the examination **2)** being exposed to the noise the machine makes when scanning.

9.5.3.2 PET

The risks associated with an 18FDG-PET study are related to the radiation emitted by the 18F atoms. No biological effect has been reported in relation to the quantity of diagnostic radiation that is used in the CIMA-Q project. Studies based on linear extrapolations based on observations of side effects following exposure to high doses of radiation (atomic bombs, thermal nuclear central catastrophes) suggest that the risk of long-term effects are very low for doses below 100 mSv. Health Canada allows for a dose of 50 mSv over the course of one year in PET research protocols. This protocol exposes participants to doses varying between 5.5 to 11mSv, thus very low doses, for which no biological effect is observed.

As for the FDG tracer doses used in the CIMA-Q protocol, pharmacological or allergic reactions are not usually observed.

9.6 INCIDENTAL FINDINGS

For a participant, much data in diverse spheres will be gathered during the study. Among others, a diagnosis will be determined within the scope of the cognitive assessment,. It is possible that certain results of these diverse evaluations suggest an anomaly that until then had been unknown to the participant and his/her family doctor. In cases of an incidental finding, the CIMA-Q team medical doctors will **(1)** send the details of the results judged to be abnormal and clinically significant to the treating physician, and/or **(2)** refer the participant to a specialist, and/or **(3)** ensure follow-up themselves if deemed necessary. New evaluations or assessments not described in this protocol may be necessary to confirm the incidental finding. When such discoveries occur, all medically relevant information is reviewed by a health professional within a reasonable delay.

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