Long-term follow-up of cognitive and functional evolutions of persons with isolated cognitive complaints or mild cognitive deficits
The Memento-Plus Cohort

Suivi à long terme des évolutions cognitives et fonctionnelles de personnes avec plaintes cognitives isolées ou déficits cognitifs
La cohorte Memento-Plus

Sponsor code: CHUBX 2019/16

NON-INTERVENTIONAL RESEARCH PROTOCOL INVOLVING THE HUMAN PERSON (*category 3 - research on prospective data*)

PROTOCOL version no.3.0 of 08/11/2021

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This protocol was designed and drafted by Carole Dufouil and Geneviève Chêne based on version 3.0 of 01/02/2017 of the template protocol of GIRCI SOHO

HISTORY OF REVISIONS TO THE PROTOCOL

VERSION	DATE	REASON FOR UPDATE
1.0	13/03/2019	CPP Submission
2.0	16/10/2020	- Update of coordination team at clinical epidemiology unit - Update table summarising participant's follow-up and follow-up visits - Add the possibility to inform participants by phone - Clarification on optional procedures - Add the possibility to perform full neuropsychological battery test, CDR and NPI at a different date from the clinical examination - Add the possibility to perform neuropsychological evaluation by phone with the COGTEL battery - Add the possibility that the partner, companion, the family physician or a family member, could answer to any questions for the participant during the interview by phone. - Add of the Patient Dignity Inventory scale
2.1	05/02/2021	- Modifications following CPP comments 15/12/2020 - Suppression of the Patient Dignity Inventory scale
3.0	08/11/2021	- Update of coordination team at clinical epidemiology unit - Extension of inclusion period - Add the possibility to inform by phone participants unable to express non objection

PROTOCOL SIGNATURE PAGE

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in Bordeaux, on 08 NOV. 2021

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADRD	Alzheimer's Disease and Related Disorders
ANSM	Agence Nationale de Sécurité des Médicaments
CDC	Cahier des charges
CDISC/CDASH	Clinical Data Interchange Standards Consortium / Clinical Data Acquisition Standards Harmonization
CDR	Clinical Dementia Rating scale
CHU	Centre Hospitalier Universitaire
CMRR	Centre Mémoire de Ressources et de Recherches
COGTEL	Cognitive Telephone Screening Instrument
CPP	Comité de Protection des Personnes
CRA	Clinical Reaserch associate
CRF	Case Report Form
CSF	Cerebro-Spinal Fluid
DAT	Dementia of Alzheimer Type
DMS	Delayed Matching to Sample
DO	Denomination Objet
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	Electronic Case Report Form
FAB	Frontal Assessment Battery
GCP	Good Clinical Practices
ICH	International Conference on Harmonisation
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
PET	Positron Emission Tomography
QOL	Quality Of Life
SCC	Subjective Cognitive Complaint
TMT	Trail Making Test

SUMMARY OF THE STUDY

SPONSOR	CHU de Bordeaux
COORDINATING INVESTIGATOR	Pr Geneviève CHÊNE
SCIENTIFIC DIRECTOR, CO-COORDINATOR	Carole DUFOUIL
ACRONYM AND TITLE	Memento-Plus: Long-term follow-up of cognitive and functional evolutions of persons with isolated cognitive complaints or mild cognitive deficits
SHORT TITLE	Memento-Plus
JUSTIFICATION / CONTEXT	Dementia is a clinical syndrome that is the result of distinct underlying pathologies including Alzheimer's disease (AD). Despite more than two decades of research on prevention and treatment of dementia and aging-related cognitive decline, highly effective preventive and therapeutic strategies remain elusive. Many features of dementia render it especially challenging. Indeed development of disease occurs insidiously over the course of years or decade. In addition, the causes of dementia and determinants of its severity are likely multi-factorial. To overcome these challenges and better understand the causes and course of AD and related disorders, long term follow-up studies of persons at high risk of dementia are required including multidimensional and harmonized assessment of risk factors, phenotypes (cognition, neuropsychiatric symptoms, physical health, self rated health) and endophenotypes (blood markers, genetic markers, neuroimaging markers). This project proposes an extension of the follow-up of Memento participants over 5 to 10 years with of focus on cognitive outcomes and comorbities.
PRIMARY OBJECTIVES	To study the long term evolution of a variety of potentially early preclinical signs of AD and related disorders and to estimate the prognostic value of a comprehensive number of markers (neuropsychological, vascular damage indicators, psycho-behavioral, socio-economic, genetic, blood, neuroimaging) on progression from early signs to clinical dementia or severe cognitive deterioration stages, and then to death.
SECONDARY OBJECTIVES	The secondary objectives will aim at studying the long term evolution of participants in order: - To assess the validity of an operational set of criteria to help identifying the transition from pre-clinical dementia stages,

	- To study how vascular risk factors or damage markers are associated with the risk of progression to clinical dementia stage, - To study prevalence and incidence of prodromal AD or symptomatic pre-dementia according to different definitions, - To assess factors explaining the variability in time of clinical diagnosis of Alzheimer's Disease and Related Disorders (ADRD), - To study the relationships between neuropsychiatric symptoms and AD or associated dementia progression, - To assess factors predicting • Mortality • Loss of autonomy • Institutionalization • Rate of cognitive decline in different areas of cognition • Cardiovascular events during follow-up • Change in quality of life
STUDY DESIGN	A multicentre national prospective cohort study will follow participants previously recruited in the Memento cohort who agree to have extended follow-up through the Memento-Plus protocol
INCLUSION CRITERIA	- Participants aged over 18 year-old - Being included in Memento cohort - Affiliated person or beneficiary of a social security scheme. - Participants capable of expressing non objection - Non objection expressed by the tutor for participants under tutorship - Non objection expressed by the participant assisted by their guardian for participants under guardianship - Non objection expressed by the trusted person (in accordance with art. L1111-6 of Code de la Santé Publique) for participants without the capacity to express non-objection and who are not under legal protection measure
NON-INCLUSION CRITERIA	- Expressing opposition to participate in Memento-Plus
ENDPOINTS/OUTCOME MEASURES	The primary endpoint is the progression to clinical dementia stage according to standardized classifications (DSM-IV for dementia and NINCDS-ADRDA for AD). (appendix I, appendix II). These classifications have evolved over time, but the primary endpoint will use the same definitions as in Memento Cohort for the sake of consistency in the analyses. Secondary endpoints are: - Mortality - Loss of autonomy based on functional activity assessment - Institutionalization - Rate of cognitive decline based on change in

	cognitive performances - Neurovascular and cardiovascular events (Stroke and Coronary events) - Quality of life - Prodromal AD (Pre-symptomatic dementia)
SAMPLE SIZE	Up to 2000 participants (among the 2323 included in Memento Cohort)
STUDY DURATION	- Duration of the inclusion period : 30 months - Maximum duration of follow-up for each participant: 5 years and 6 months +/- 3 months - Total duration of the research project : 5 years and 6 months +/- 3 months - End of study: June 2025
STATISTICAL ANALYSIS	Primary outcome: time to event methods (i.e. Kaplan Meier plots, Cox regression models with delayed entry) Trajectories over time (autonomy, cognition, quality of life): random effects models Occurrence of at least one secondary endpoint (death, institutionalisation, cardiovascular events): Kaplan Meier plots and Cox regression with delayed entry models.
EXPECTED IMPACTS	Findings from Memento-Plus could lead to identify biomarkers, alone or in combination, that allow stratification of patients based on phenotypes of interest, e.g. disease subtypes, prognosis and response to future therapy.
CONDITIONS	Alzheimer's disease
KEYWORDS	Dementia, Alzheimer's disease, phenotypes, endophenotypes, risk factors, prognosis, cohort, prediction, causality

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

1.1. CURRENT STATE OF KNOWLEDGE

Maintaining brain health is a challenge for ageing societies as the burden of late life brain disorders is expected to increase exponentially in the coming years.[1] ADRD are the most frequent and feared of these brain disorders with a prevalence of cases of dementia of Alzheimer's type (DAT) above 5 percent after the age of 65 years. The number of DAT cases worldwide, estimated to be almost 27 million in 2007, is expected to quadruple by 2050, with one in every 85 people having DAT at that time if interventions are not implemented.[2] Early diagnosis and intervention are therefore a priority target to defeat late-onset ADRD, while the causes remain disputed and no curative treatment is available. Despite continuous search and recent huge progress in the identification of new biomarkers or new genes associated with brain disorders, including ADRD [3-5], the disease natural history, the surrogate biology markers of ADRD as well as the correlates of healthy brain ageing remain largely unknown. Therefore, we are not able to fully explain the discrepancies between observations at brain level (through neuropathological or brain imaging features) and observations at the clinical level (mainly through neuropsychological and functional performances)[6]. This uncertainty between underlying causes and clinical consequences is well illustrated by recent clinical trials results that showed the efficacy of a variety of immunotherapy strategies in stopping amyloid accumulation (thought to initiate AD pathology by destroying synapses) but had no significant impact on the clinical course compared to placebo [7,8].

Improving knowledge on the natural history of ADRD involves long-term follow-up of individuals from early symptoms, known to be compatible with further progress to ADRD, until clinical dementia with an integrative phenotyping approach that combines standardized, repeated clinical investigations and cutting edge biomarkers measurements [9,10].

Early and accurate identification of individuals at high risk of AD has therefore become a priority.[11,12] Over the last years, research has focused on the concept of "Mild Cognitive Impairment" which happens to be a heterogeneous condition and the exploration of potentially earlier stages i.e. subjective cognitive complaints (SCC) and pre-clinical stages are becoming of interest. A study of the full range of stages of evolution until the clinical dementia or death is therefore of utmost importance to improve knowledge on AD and trigger the development of new treatments, especially when transition between stages can be related to neuroimaging markers, blood, genetic or Cerebrospinal Fluid (CSF) biomarkers, vascular damages markers, lifestyle characteristics, neurobehavioral characteristics either alone or in combination. However, if all types of above markers have been individually associated with worsening of cognitive status, very

few studies have simultaneously explored the association of a large panel of risk factors and markers with the progression through cognitive impairment until AD in a large sample of study participants. In parallel, to improve the knowledge on ADRD, it is also important to better estimate the social and economic burden of AD and their consequences on the individual and its environment.

The Memento cohort (NCT01926249) is a large clinical based cohort of participants consulting in French memory clinics ("Centres de Mémoire, de Ressources et de Recherche", CMRR) and presenting with either isolated cognitive complaints or recently diagnosed mild cognitive impairment at enrolment.[13] Between October 2011 and June 2014, 2323 participants were included in the cohort, and the study protocol initially aimed at following participants at least annually during 5 years. Investigations included regular standardized clinical, brain neuroimaging and biological workups from cohort's inception, using standardized and highly reproducible techniques. The rationale and the full protocol of Memento have been described elsewhere[13].

Compared to other clinical studies worldwide, the Memento cohort does not focus only on memory deficits[14] as first symptoms, as almost a third of the participants has exclusive non memory deficits, and this offers the opportunity to study the evolution of patients with a comprehensive spectrum of cognitive deficits. In Memento, 370 participants had isolated SCC at inclusion [13]. Their baseline neuroimaging or genetic biomarkers do not suggest major differences from Mild Cognitive Impairment (MCI) participants as expected, moreover they are an interesting group to follow on a longer term as they also represent the target of most recent intervention studies such as the A4 trial [15]. Therefore, Memento represents a powerful resource to complement investigations on the natural history of ADRD in participants whose first symptoms are not memory specific [16,17].

The Memento study has been enriched through the addition of biomarkers: Lumbar puncture was proposed to participants at each visit and repeated at least every two years, the Amyging ("AMYloid imaGING") sub-study enrolled 448 participants who had PET amyloid imaging (using either18F-Florbetapir or 18F-Flutemetamol radioligands)[18-21].

1.2. STUDY HYPOTHESES

We hypothesise that an extension of 5 years of follow-up of participants initially included in the Memento cohort may reveal novel associations between level of biomarkers or types of abnormal imaging and the time from early signs of cognitive impairment to the diagnosis of AD. This extended follow-up through Memento-Plus would maximise the initial huge investment in the set up of this world-class cohort, increase its scientific value and would allow more external researchers to access to data through a secured platform and according to European union regulation on personal data protection.

1.3. JUSTIFICATION OF DESIGN

The design (cohort study) and the main outcome (time to dementia, including of Alzheimer's type) in Memento-Plus remain similar as in Memento cohort. The follow-up visits will be simplified so that their content mimic the usual care management of participants attending memory clinics.
It is of utmost importance that the quality of follow-up is maximised. To achieve this, attempts will be made to get information about the participants' vital status and dementia status by contacting their general practitioner and/or an informant.

1.4. EXPECTED IMPACTS

The study design of the Memento-Plus cohort as well as the variety of the data collected are a powerful resource for the discovery and validation of disease mechanisms, as well as candidate biomarkers that are needed for earlier diagnosis of AD cases and identification of efficient preventive or early interventions. Findings from Memento-Plus could lead to identify biomarkers, alone or in combination, that allow stratification of patients based on phenotypes of interest, e.g. disease subtypes, prognosis and response to future therapy.

2. OBJECTIVES

2.1. MAIN OBJECTIVE

To study the long term evolution of a variety of potentially early preclinical signs of AD and related disorders and to estimate the prognostic value of several markers (neuropsychological, vascular damage indicators, psycho-behavioral, socio-economic, genetic, blood, neuroimaging) on progression from early signs to clinical dementia or severe cognitive deterioration stages, and then to death.

2.2. SECONDARY OBJECTIVES

The secondary objectives will aim at studying the long term evolution of participants in order:

- To assess the validity of an operational set of criteria to help identifying the transition from pre-clinical dementia stages,
- To study how vascular risk factors or damage markers are associated with the risk of progression to clinical dementia stage,
- To study prevalence and incidence of prodromal AD or symptomatic pre-dementia according to different definitions,
- To assess factors explaining the variability in time of clinical diagnosis of ADRD

- To study the relationships between neuropsychiatric symptoms and AD or associated dementia progression,
- To assess factors predicting
  - Mortality
  - Loss of autonomy
  - Institutionalisation
  - Rate of cognitive decline in different areas of cognition
  - Cardiovascular events during follow-up
  - Change in quality of life

3. STUDY DESIGN

A multicentre national prospective cohort study will follow participants, previously recruited in the Memento cohort, who agree to have extended follow-up through the Memento-Plus protocol.

4. ELIGIBILITY CRITERIA

In this study, all participants previously recruited in the Memento cohort are eligible if they are still alive at the calendar date of authorization of this protocol. Co-inclusion in other research will be possible but the information would need to be recorded.

4.1. INCLUSION CRITERIA

- Participants aged over 18 year-old
- Being included in Memento cohort
- Affiliated person or beneficiary of a social security scheme.
- Participants capable of expressing non objection
- Non objection expressed by the tutor for participants under tutorship
- Non objection expressed by the participant assisted by their guardian for participants under guardianship
- Non objection expressed by the trusted person (in accordance with art. L1111-6 of Code de la Santé Publique) for participants without the capacity to express non-objection and who are not under legal protection measure

4.2. NON-INCLUSION CRITERIA

- Expressing opposition to participate in Memento-Plus

4.3. JUSTIFICATION FOR INCLUDING PROTECTED PERSONS

Given the lack of risk and the minimal contraints in this study and in order not to restrict recruitment, it is not excluded to include :

- Participants subjected to a legal protection measure (tutorship or guardianship)
- Participants without the capacity to express non-objection and who are not under legal protection measure (participants included in Memento cohort and become demented during their follow-up)

4.4. FEASABILITY AND RECRUITMENT PROCEDURES

Participants will be recruited from the "Centres de Mémoire de Ressources et Recherches" (CMRR). These clinical research platforms are clinical sites located at French hospitals, mainly university hospitals, with dedicated resources to conduct clinical research on Alzheimer and other neurodegenerative diseases. Data collection and procedures of participants in the cohort will essentially conform to the current standard of care, while aiming at optimising standardisation of data collection whenever needed.

Eligible memory clinics are those which included participants in the Memento cohort.

5. PROCEDURE(S) OF THE RESEARCH

- Full neuropsychological battery tests
  - *Global cognition*: Mini-Mental State Examination

    The MMSE consists of a set of standardized questions and tests to assess a participant's mental status and identifies the participant's global level of impairment.
  - *Short term memory*:
    - Digit span (forward and backward)

      The test consists repeating dictated series of digits (e.g., 4 1 7 9) forwards and other series backwards. Series begin with two digits and keep increasing in length, with two trials at each length.
  - *Long term memory:*
    - Free and Cued selective reminding Test

The test gives a measure of memory under conditions that control encoding and cognitive processing in order to obtain an assessment of memory unconfounded by normal age related changes in cognition.

- Delayed Matching to Sample 48 (DMS48)

The test consists in a visual recognition memory task.

- *Language and semantic Memory*
  - Verbal Fluency

    The test consists in producing as many words as possible within two categories in two minutes. One category is semantic (animals), the other one is phonemic (begin with letter p).
  - Image Naming (DO 80)

    The test consists in a set of 80 black and white line drawings pictures presented to the participant who is asked to name them.
- *Praxis*

  The test gives an assessment of gestural ideational and ideomotor praxis. It consists in asking to participants to repeat a series of gestures with or without significance.
- *Visuo Spatial abilities*

  Rey-Osterrieth Complex Figure Test is a neuropsychological assessment in which examinees are asked to reproduce a complex line drawing, first by copying and then from memory at 3 minutes.
- *Attention and executive functions :*
  - Trail Making Test (TMT) Part A and B

    The test consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the participant should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The time in seconds to complete the task is recorded.
  - Frontal Assessment Battery (FAB)

    The test has been designed to assess frontal lobe functions. It consists in six subtests exploring the following: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.

- Neuropsychiatric Inventory (NPI) Questionnaires C and R

- Autonomy in daily life activities (Lawton IADL and Katz ADL scales)
- Clinical Dementia Rating Scale (CDR)
- Lewy Body disease signs assessment
    - Three tests of the Visual Object and Space Perception Battery (VOSP)[22] to assess a particular aspect of object or space perception, while minimizing the involvement of other cognitive skills : Position Discrimination, Number Location, Incomplete Letters
    - Rapid Eye Movement sleep disorders assessment
    - Parkinsonism assessment: adapted from Unified Parkinson's Disease Rating Scale (UPDRS)[23]
    - Hallucinations assessment, adapted from Parkinson's Disease-Associated Psychotic Symptoms Questionnaire[24]
    - Fluctuation assessment, adapted from "Clinician assessment of fluctuation"[25]
    - Neurovegetatives disorders exploration (orthostatic hypotension, hypersalivation, rhinorrhea, photophobia, constipation)
    - Depression assessment using Mini International Neuropsychiatric Interview (MINI)[26]
- Quality of life will be assessed using EQ-5D (EUROQOL) questionnaire. The instrument ranks a number of health states (mobility, self-care, usual activities, pain/disconfort, anxiety/depression).

For practical reasons, and when an onsite neuropsychologic evaluation is not feasible, this evaluation could be assessed using the Cognitive Telephone Screening Instrument (COGTEL)[27]. The COGTEL allows assessment of performance in 6 cognitive domains (prospective, short-term, long-term, and working memory, verbal fluency, and inductive reasoning – using tests adopted from well-established neuropsychological instruments such as the Wechsler scales), including an additional total score that is indicative of overall cognitive functioning. The expected duration of the evaluation range from 10 to 15 min.
In all cases, the COGTEL might not be considered part of the simplified follow-up by phone.

6. ENDPOINTS

6.1. PRIMARY ENDPOINT

The primary endpoint is the progression to clinical dementia stage according to standardized classifications (DSM-IV for dementia and NINCDS-ADRDA for AD). (appendix I, appendix II).

These classifications have evolved over time, but the primary endpoint will use the same definitions as in Memento Cohort for the sake of consistency in the analyses.

6.2. SECONDARY ENDPOINTS

Secondary endpoints are:

- Mortality
- Loss of autonomy based on functional activity assessment
- Institutionalization
- Rate of cognitive decline based on change in cognitive performances
- Neurovascular and cardiovascular events (Stroke and Coronary events)
- Quality of life

7. STUDY PROCEDURES

7.1. STUDY SCHEDULE

- Duration of the inclusion period : 30 months
- Maximum Duration of follow-up for each participant: 5 years and 6 months +/- 3 months
- Total duration of the research project : 5 years and 6 months +/- 3 months
- End of study: June 2025

7.2. TABLE SUMMARISING PARTICIPANTS' FOLLOW-UP

	Inclusion	*Visit 1*		Visit 2 ± 3 months		Visit 3 ± 3 months		Visit 4 ± 3 months		Visit 5 ± 3 months	
	Center or phone	center	phone	center	phone	center	phone	center	phone	center	phone
Explain study*	✓										
Obtain non-opposition*	✓										
Inclusion and Non Inclusion Criteria verification	✓										
Type of habitation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Major life events		✓		✓		✓		✓		✓	
Medical examiniations (including blood pressure measures)		✓		✓		✓		✓		✓	
Physical and neurological examinations		✓		✓		✓		✓		✓	
Medication at the time of the visit		✓		✓		✓		✓		✓	
Medical events since last visit		✓		✓		✓		✓		✓	
Results of paraclinical examination prescribed by investigators (such as.blood intake, lumbar puncture, neuroimaging markers)		✓		✓		✓		✓		✓	
Neuropsychological battery tests†		✓		✓		✓		✓		✓	
Autonomy in daily life activities (Lawton IADL and Katz ADL scales)		✓		✓		✓		✓		✓	
Dementia diagnosis		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical Dementia Rating Scale		✓		✓		✓		✓		✓	
Cognitive complaints (self rated)		✓		✓		✓		✓		✓	
Neuropsychiatric Symptoms (NPI)		✓		✓		✓		✓		✓	
Quality of Life (EQ-5D)		✓		✓		✓		✓		✓	
Lewy Body diseases assessment		✓		✓		✓		✓		✓	
Vital status, cause of death		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

***:** Under certain conditions (see § 7.3), the information may be given to the participant by phone.
†: When an onsite neuropsychological evaluation is not feasible this evaluation could be done by phone using COGTEL battery at a different date from the clinical examination (see §7.5.1)

7.3. INFORMATION OF THE PERSONS CONCERNED

The Investigator shall provide the eligible participants with information regarding:

- the objectives of the study,
- his/her right to refuse to participate
- his/her right to access, object to, or rectify the data.

The Investigator shall also ensure that the eligibility criteria are met. If the patient or his/her legal representative agrees to participate, he/ she shall give his/her consent orally. The date on which the information was given and the date on which the non-opposition was collected is recorded in his/her medical file.

For patients unable to go to the CMRR including those are under guardianship, tutorship nor without the capacity to express non-objection nor who are not under legal protection measure, the information may be given to the patient by phone.

- The investigator contacts the patient, or the tutorship, the trusted person if needed, by phone, informs him/her and records in patient's medical file;
- If the patient alone or assisted by his or her guardian agrees to participate to Memento Plus or if the tutorship, the trusted person agrees that the patient participates to Memento Plus, the investigator or his delegate sends the inform sheet by mail to the patient, the tutorship, the trusted person and records in patient's medical file in particular that the inclusion took place by phone;
- During the first visit in Memento Plus, the investigator ensures the participant, the tutorship, or the trusted person, has received the inform sheet by mail, then collects the non-opposition of the participant, the tutorship, the trusted person, and shall records in participant's medical file.

The participant may, at any moment, oppose the use of his/ her data as part of the research.

For participants under guardianship, the information is given to the participant assisted by his/her guardian and non-objection is given by the participant assisted by his/her guardian.

For participants under tutorship, the information is given to the participant and his/her tutor and non-objection is given by the tutorship.

For participants without the capacity to express non-objection and who are not under legal protection measure, an information which is adapted to their understanding ability is provided, and their personal non-objection is required. Non-objection is given by a trusted person (in accordance with art. L1111-6 of Code de la Santé Publique).

A unique identification code was assigned to Memento cohort participants at the screening visit. It is a 11 digits identification code, the first three corresponding to a study center number, the following four to the enrollment rank in the center, the last four to the first two initials of last name and the first two initials of first name . Memento Identification code will be kept and assigned to Memento-Plus participants in order to maximize the consistency between the two studies.

7.4. IINCLUSION VISIT

At inclusion visit, inclusion and non inclusion criteria are verified and non-opposition is collected.

7.5. FOLLOW-UP VISITS

Each participants is followed yearly until the end of 2024.

According to his/her date of inclusion in Memento Plus, a participant could have between 1 and 5 follow-up visits in Memento Plus. For convenience purpose, the initial visit in Memento Plus corresponds to visit 1 in the eCRF, the second visit to visit 2, etc… whatever the date of the visit. Annual visits should be performed 1 year ± 3 months following the previous visit.

7.5.1. INTERVIEW AT STUDY CENTER

Procedures at on site Visit 1 (V1), Visit 2 (V2), Visit 3 (V3), Visit 4 (V4), or Visit 5 (V5) include (procedures indicated with an asterisk (*) are optional):

- Social-demographic characteristics and major life event
- Subjective complaint assessment
- Full neuropsychological battery tests
    - *Global cognition*: Mini-Mental State Examination

      The MMSE consists of a set of standardized questions and tests to assess a participant's mental status and identifies the participant's global level of impairment.
    - *Short term memory*:
        - Digit span (forward and backward) (optional)*.

          The test consists repeating dictated series of digits (e.g., 4 1 7 9) forwards and other series backwards. Series begin with two digits and keep increasing in length, with two trials at each length.
    - *Long term memory:*
        - Free and Cued selective reminding Test

          The test gives a measure of memory under conditions that control encoding and cognitive processing in order to obtain an assessment of memory unconfounded by normal age related changes in cognition.
        - Delayed Matching to Sample 48 (DMS48) (optional)*.

      The test consists in a visual recognition memory task.
    - *Language and semantic Memory*
        - Verbal Fluency (optional)*.

          The test consists in producing as many words as possible within two categories in two minutes. One category is semantic (animals), the other one is phonemic (begin with letter p).
        - Image Naming (DO 80) (optional)*.

The test consists in a set of 80 black and white line drawings pictures presented to the participant who is asked to name them.

- *Praxis* (optional)*.

  The test gives an assessment of gestural ideational and ideomotor praxis. It consists in asking to participants to repeat a series of gestures with or without significance.

- *Visuo Spatial abilities* (optional)*.

  Rey-Osterrieth Complex Figure Test is a neuropsychological assessment in which examinees are asked to reproduce a complex line drawing, first by copying and then from memory at 3 minutes.

- *Attention and executive functions :*

  - Trail Making Test (TMT) Part A and B

  The test consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the participant should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The time in seconds to complete the task is recorded.

  - Frontal Assessment Battery (FAB)

  The test has been designed to assess frontal lobe functions. It consists in six subtests exploring the following: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.

- Neuropsychiatric Inventory (NPI) Questionnaires C and R
- Autonomy in daily life activities (Lawton IADL and Katz ADL scales)
- Clinical Dementia Rating Scale (CDR)
- Medical event
- Medication at the time of the visit
- Physical and neurological examinations
- Cognitive status
- Any paraclinical examination prescribed by the investigator
- Vital status
- Lewy Body disease signs assessment :

- Three tests of the Visual Object and Space Perception Battery (VOSP)22 to assess a particular aspect of object or space perception, while minimizing the involvement of other cognitive skills : Position Discrimination, Number Location, Incomplete Letters
- Rapid Eye Movement sleep disorders assessment
- Parkinsonism assessment: adapted from Unified Parkinson's Disease Rating Scale (UPDRS)23
- Hallucinations assessment, adapted from Parkinson's Disease-Associated Psychotic Symptoms Questionnaire24
- Fluctuation assessment, adapted from "Clinician assessment of fluctuation"25
- Neurovegetatives disorders exploration (orthostatic hypotension, hypersalivation, rhinorrhea, photophobia, constipation)
- Depression assessment using Mini International Neuropsychiatric Interview (MINI)26

- Quality of life will be assessed using EQ-5D (EUROQOL) questionnaire. The instrument ranks a number of health states (mobility, self-care, usual activities, pain/disconfort, anxiety/depression).

As long as possible, these procedures are performed on site, during the same visit.

However, the following alternatives can be considered:

- If necessary and according to the availability of the participant or the organization of the site, full neuropsychological battery test, CDR and NPI may be performed at a different date from the clinical examination. Then, interval between tests and clinical examination is left to the investigator's decision. Howeover, it should be consistent with the participant follow-up;
- Or If the participant is unable to go again to the CMRR for a visit for neuropsychological evaluation, it could be performed by phone. In this case, the COGTEL tool (specifically developed and validated for phone assessment) will be used.

7.5.2. INTERVIEW BY PHONE

For any of these follow-up examinations, it is advised that it takes place at the study center (CMRR), but in case the clinical investigator considers otherwise, it is allowed to organise a simplified follow-up by phone. If the participant is unable to answer, the partner, companion, the family physician or a family member could answer to any questions. The identity of the person (name and surname) as well as the relationship are recorded on the participant medical file.

Procedures at phone Visit 1 (V1), Visit 2 (V2), Visit 3 (V3), Visit 4 (V4), or Visit 5 (V5) include:

- Contact / relationship with the participant
- Vital status
- Institutionalization
- Cognitive status and etiology

7.6. DISCONTINUATION

Any participant who wishes to discontinue their participation in the study (as is their right at any moment) shall no longer be followed up within the framework of the protocol but must be provided with the best possible care, taking into account their health condition and current knowledge.

Discontinuation is a participant's decision to exercise his/her right to interrupt his/her participation in a study, at any moment during the follow-up, without suffering any prejudice for this reason and without having to justify his/her decision.

7.7. DEVIATIONS FROM THE PROTOCOL

Deviations may relate to all the aspects of a research protocol: inclusion process, follow-up, measurement of endpoints criteria, etc. Deviations will be discussed by coordinating center.

Even in the event of a protocol deviation, participant follow-up must be performed until the date scheduled in the protocol.

7.7.1. PARTICIPANTS LOST TO FOLLOW-UP

For participants who are lost to follow-up (i.e., those participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue), the investigator should show "due diligence" by documenting in the participant's medical records the steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. If no notice about the participant's status can be obtained the participant is considered lost to follow up.

7.7.2. SCREEN FAILURE

A participant will be considered as erroneously included when he or she has been included in the study but does not actually meet all the eligibility criteria. Participants erroneously included must be discussed by Memento-Plus executive committee. They must continue to be followed-up as foreseen by the protocol until Memento-Plus executive committee reaches a decision.

8. ASSESSMENT OF SAFETY

Adverse / incidental effects will have to be reported to the different circuits of health vigilance depending on the product or the procedure concerned (pharmacovigilance, material vigilance, haemovigilance ...).

No adverse effects / incidents are expected in this study.

9. STATISTICS

9.1. SAMPLE SIZE CALCULATION

The Memento-plus study will be proposed to all the 2323 participants included in the Memento Cohort who are still alive at the time of protocol implementation. Up to 2000 participants (among the 2323 included in the Memento Cohort) are expected to take part in MEMENTO-PLUS.

9.2. STATISTICAL METHODS FOR DATA ANALYSIS

Statistical methods are similar to those already used in the Memento Cohort.

The primary outcome is time to clinical dementia. It will be analysed using time to event methods i.e. Kaplan Meier plots and Cox regression with delayed entry models.

All multivariable analysis will be systematically adjusted for age, gender and a center effect will be accounted for.

In general, the recommendations to build adequate modelling for longitudinal analyses in dementia research will be applied.[28]

Recent work has pointed out the necessity of handling drop-outs and death separately in longitudinal studies in the elderly.[29]Although effort will be made to minimize dropouts rates in this cohort, adequate statistical methods will be applied in order to take into account missing participants in the analyses.

For secondary endpoint such as death, institutionalisation, cardiovascular events, Kaplan Meier plots and Cox regression with delayed entry models will be used.

To model the change in autonomy, trajectories of cognitive decline or change in Quality of life, random effects model will be computed.

Any other statistical method could be considered wether its use is relevant regarding the scientific question addressed (for instance competitive risks or latent class models).

10. SCIENTIFIC COORDINATION OF THE STUDY

Membership and specific roles and relationships of committees for the Memento-Plus are those of Memento and are described in the Memento/Memento-plus Committee Charter.

11. ACCES TO DATA AND SOURCE DOCUMENTS

11.1. ACCESS TO DATA

Agreement to participate in the protocol means that the investigators carrying out the research shall make documents and individual data that are strictly necessary for follow-up, quality control and audit available to the individuals who have a right to access these documents in accordance with applicable legal and regulatory provisions.

11.2. SOURCE DATA

This includes all information contained in the original documents, or in authenticated copies of these documents, relating to clinical examinations, findings or other activities carried out as part of the research and necessary to the reconstitution and evaluation of the research. The documents in which source data are recorded are called source documents.
All data collected in the Memento-Plus Cohort Follow-up Study should be available in the source medical records (see table summarizing participant's follow-up).

11.3. DATA CONFIDENTIALITY

In accordance with applicable legal provisions, individuals who have direct access to source data shall take all the necessary precautions to ensure the confidentiality of information relating to research, participants and particularly their identity, as well as the results obtained. These individuals, like the investigators, are subject to the conditions of professional secrecy.

During the research project or at the end of it, the collected data on participants and data transmitted to the sponsor by the investigators (or any other involved specialists) shall be made anonymous. The data must not, under any circumstances, clearly indicate the names of the participants or their address.

For the sake of consistency between Memento and Memento-Plus protocol, and to ensure integrity of the data, subjects' identification codes are those of the Memento cohort. Coding rules are: (i) a 4-letters code: the two first letter of the name and the two first letter of the first name of the subject, accompanied by (ii) a code number unique (generated at the inclusion in the Memento

Cohort) showing the center of inclusion (3 digits) and the order of inclusion of the subject (4 digits).

The sponsor shall ensure that each participant of the research project did not express his or her opposition for access to data relating to him or her and strictly necessary for quality control.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. INSTRUCTIONS FOR DATA COLLECTION

All the information required by the protocol must be entered in the electronic case report form (e-CRF) provided by the sponsor. The data must be collected as and when they are obtained, and transcribed into these forms in accordance with the guide for e-crf data entry . A guide for data recording will be provided by the coordinating center to clinical centers. An explanation must be provided for each piece of information which is missing.

12.2. RESEARCH FOLLOW-UP

A clinical research technician shall ensure research follow-up. The clinical research technician shall be responsible, under the Coordinating Investigator, for:

- logistics and monitoring of the research;
- providing reports on its progress and sharing them with the research stakeholders (sponsor, Methodology and Management Center, etc.);
- verifying the completeness of the electronic case report forms (request for additional information, corrections, etc.);

The clinical research technician shall work in accordance with standard operating procedures, in collaboration with the clinical research associate (CRA) delegated by the sponsor.

12.3. QUALITY CONTROL

A CRA appointed by the sponsor shall visit each center, during the implementation of the research, once or several times during the course of the research project, according to the monitoring plan defined for the research and the frequency of inclusions. The elements to be reviewed during these visits are defined by the monitoring plan. All visits will be subject to a written monitoring report.

12.4. DATA MANAGEMENT

12.4.1. DATA MANAGEMENT SOFTWARE

12.4.1.1. SOFTWARE USED

The sofware used for data management is Ennov Clinical, of the Ennov company, in version 8.0 and any subsequent versions. The software complies with the FDA requirements regarding IT systems used in clinical trial ("Guidance for Computerized systems Used in Clinical Trials") as well as electronic signature ("21CFR part 11") and various international norms (CDISC/CDASH, ICH, GCP 2001/20/CE).

12.4.1.2. DATA HOSTING

The Ennov company ensures the hosting and maintenance of the database in compliance with the specifications defined in detail in the CDC Fournisseur Ennov Clinical and the procedures of Ennov. The server is hosted in a Data Center of OVH company located in Roubaix (59).

12.4.1.3. DATA SECURITY

A local backup server for remote replication of the server is hosted in a different site localized in Strasbourg (67), and an external backup server is localized in Gravelines (59), France. Ennov Clinical software rights management shall be the responsibility of the Ennov Clinical Administrator of the coordinating center and the management of access to the eCRF for investigating physicians and their coworkers is the responsibility of the CRA of the study.

12.4.2. DATA ENTRY

Data entry into the eCRF shall be the responsibility of the investigator center. Any person who enters data into the eCRF must be trained and chosen by the investigator to do so. The eCRF is developed through the Ennov Clinical software by the data manager of the study. The Memento-Plus eCRF will be the continuation of the Memento cohort eCRF. Additional pages will be added after the Memento M60 visit.

12.4.3. DATA CODING

The prescribed treatments and clinical events are coded in the eCRF in order to carry out the testing and analysis of the data.

The following dictionaries are used for the coding of medical terms:

- *MedDRA (medical terms)*
- *WhoDrug, B format (treatments)*

12.4.4. DATA TESTING

Tests shall be programmed to check the consistency and completeness of the data entered in the eCRF. The list of tests to implement shall be set by data manager of the coordinating center.

Correction requests shall be managed by the data manager and CRA via the eCRF. The investigator makes the corrections necessary to resolve the correction requests.

12.4.5. FREEZING OF DATABASE

The freezing of the data shall be carried out in accordance with the procedure in force at the coordinating center.

12.4.6. DATA TRANSFER

Data transfers (sending, receiving) shall be carried out in accordance with procedures in place at the coordinating center. The data transfer arrangements must be defined in the Data Management Plan. For security reasons, the data files shall be anonymised and then transferred via the CIRRUS secure platform.

12.4.7. ARCHIVING THE DATABASE

The archiving of the database shall be the responsibility of the study sponsor. The data of the study shall remain stored in the Ennov company server and a physical copy (engraved CD Rom for example) is retained by the sponsor.

12.5. AUDIT AND INSPECTION

An audit may be conducted at any time by persons appointed by the sponsor and independent of the persons conducting the research. Its purpose is to verify the participants' safety and respect for their rights, compliance with applicable regulations and the reliability of data.

An inspection can also be carried out by a competent authority (ANSM for France or EMA in the context of a European study, for example).

The audit, as well as the inspection, can be applied at all stages of the research, from the development of the protocol to the publication of the results and the classification of the data used or produced as part of the research.

Investigators agree to comply with the sponsor's requirements as regards an audit and the competent authority for a research inspection.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. COMPLIANCE WITH REFERENCE TEXTS

The sponsor and the investigator(s) undertake to ensure that this research is carried out in accordance with law no. 2012-300 of 5 March 2012 on research involving the human person, as well as in agreement with Good Clinical Practices (ICH version 4 of 9 November 2016 and the

decision of 24 November 2006), the Declaration of Helsinki (which can be found in full at http://www.wma.net) and the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

Data recorded during the course of the study shall be subject to data processing at CIC-EC1401 in accordance with act No. 78-17 of 6 January 1978 on data processing, data files and individual liberties, amended by act No. 2018-801 of 20 June 2018.

This research project received the positive endorsement of the CPP (*Comité de protection de personnes* – Committee for the Protection of Persons – French equivalent of an Ethical Committee) and was reported to the ANSM (the French National Agency for the Safety of Health Products).

This research is part of the "Reference Methodology" (MR-003).

This research project shall stored in the European database ID-RCB.

This research has been registered on the site http://clinicaltrials.gov/

AMENDMENTS TO THE PROTOCOL

Any substantial amendment, i.e. any amendment that may have a significant impact on the protection of persons, on the validity conditions and on the results of the research, on the quality and safety of tested products, on the interpretation of scientific documents that support the conduct of the research or on its conduct methods, is subject to a written amendment submitted to the sponsor; the latter must obtain, prior to implementing the amendment, a positive endorsement by the CPP.

Non-substantial amendments, i.e. those that do not have a significant impact on any aspect of the research project, shall be reported to the CPP for information purposes only.

All amendments are validated by the sponsor. This validation may require calling a meeting of all the committees set up for the research project.

All amendments to the protocol must be reported to the individuals carrying out the research, who shall commit to respecting their content.

14. STORAGE OF DOCUMENTS AND DATA CONCERNING THE STUDY

The following documents relating to this study are archived in accordance with Good Clinical Practice:

- By the investigating doctors:

  - For a period of 15 years following the end of the study

  - The protocol and any amendments to the protocol
  - The case record forms
  - The source files of participants in Memento-Plus
  - All other documents and letters relating to the study

  The investigator is responsible for all these documents for the regulation period of archiving.

- By the sponsor:

  - For a period of 15 years following the end of the study

  - The protocol and any amendments to the protocol
  - The originals of the case record files
  - All other documents and letters relating to the study

  The sponsor is responsible for all these documents for the regulation period of archiving.

All of these documents shall be the responsibility of the investigator during the prescribed archiving period.

No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

15. RULES RELATING TO PUBLICATIONS

The rules of publications are described in “Access to Memento data and Publications Charter”.

15.1. SCIENTIFIC COMMUNICATION

Any written or oral communication of the results of the study must have been previously agreed by the coordinating investigators.

Publication of the main results should mention the name of the legal sponsor, the name of all funders and all the investigators who recruited or monitored participants in the study, the

methodologists, biostatisticians and data managers who took part in the study, the members of the committee or committees set up for the study. All publications should adhere to the international rules for writing and publication (*IMCJE's Uniform Requirements for Manuscripts, April 2010*).

15.2. COMMUNICATING OF THE RESULTS TO PARTICIPANTS

Participants shall be informed, at their request, of the overall results of the research.

15.3. DATA SHARING

The collection and management of data will be carried out by CIC-EC1401.

This cohort is a high quality tool for researchers involved in its initial conception, as well as others that might be interested in developing new projects based on data already collected or additional information specifically collected for their project.

A formal document describing principles for access to data, the "Access to Memento data and Publications Charter", is developed separately and endorsed by the Executive Committee. CIC-EC1401 will systematically be involved in data collection, management and analysis.

The conditions for the transfer of all or part of the research database are decided by the research sponsor are the subject of a written contract.

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APPENDICES' LIST

APPENDIX I : DSM-IV-TR CRITERIA FOR DEMENTIA

A. Apparition de déficits cognitifs multiples, comme en témoignent à la fois :

1. Une altération de la mémoire (altération de la capacité à apprendre des informations nouvelles ou à se rappeler les informations apprises antérieurement) ;
2. **Une (ou plusieurs)** des perturbations cognitives suivantes :

a) aphasie (perturbation du langage)

b) apraxie (altération de la capacité à réaliser une activité motrice malgré des fonctions motrices intactes)

c) agnosie (impossibilité de reconnaître ou d'identifier des objets malgré des fonctions sensorielles intactes),

d) perturbation des fonctions exécutives (faire des projets, organiser ordonner dans le temps, avoir une pensée abstraite)

B. Les déficits cognitifs des critères A1 et A2 sont tous les deux à l'origine d'une altération significative du fonctionnement social ou professionnel et représentent un déclin significatif par rapport au niveau de fonctionnement antérieur.

C. L'évolution est caractérisée par un début progressif et un déclin cognitif continu

D. Les déficits cognitifs des critères A1 et A2 ne sont pas dus :

(1)à d'autres affections du système nerveux central qui peuvent entraîner des déficits progressifs de la mémoire et du fonctionnement cognitif (p. ex. maladie cérébro-vasculaire, maladie de Parkinson, maladie de Huntington, hématome sous-dural, hydrocéphalie à pression normale, tumeur cérébrale) ;

(2)à des affections générales pouvant entraîner une démence (p. ex. hypothyroïdie, carence en vitamine B12 ou en folates, pellagre, hypercalcémie, neurosyphilis, infection par HIV),

(3)à des affections induites par une substance.

E. Les déficits ne surviennent pas de façon exclusive au cours de l'évolution d'un délirium

F. La perturbation n'est pas mieux expliquée par une affection de l'axe I (p. ex., trouble dépressif majeur, schizophrénie)

Spécifier le sous-type:

- **A début précoce** si le début se situe à 65 ans ou avant
- **A début tardif** si le début se situe après 65 ans

APPENDIX II : NINCDS-ADRDA CRITERIA FOR ALZHEIMER'S DISEASE

(MCKHANN ET AL. 1984)

(National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association)

1. Les critères pour le diagnostic de maladie d'Alzheimer PROBABLE sont:

-Syndrome démentiel évoqué sur les données cliniques, objectivé par une échelle comme le Mini-Mental-State, l'échelle de Blessed ou un examen similaire et confirmé par des tests neuropsychologiques
-Présence d'altérations portant au moins sur 2 fonctions cognitives
-Aggravation progressive de la mémoire et d'autres fonctions cognitives
-Absence de troubles de la conscience
-Début entre l'âge de 40 et 90 ans: le plus souvent après 65 ans
-Absence de maladie systémique ou cérébrale qui pourrait rendre compte des altérations progressives de la mémoire ou de la cognition.

2. Le diagnostic de Maladie d'Alzheimer PROBABLE est étayé par:

- Détérioration progressive du langage (aphasie) de l'habileté motrice (apraxie) ou de la perception (agnosie) ;
- Diminution des activités quotidiennes et perturbations des schémas comportementaux ;
- Antécédents familiaux de troubles similaires surtout si une confirmation histologique a été apportée;
- Résultats des examens de laboratoire :
  - Absence d'anomalie du LCR étudié avec les méthodes usuelles ;
  - EEG normal ou présentant des anomalies non spécifiques comme une augmentation des rythmes lents ;
  - Signes d'atrophie cérébrale au scanner progressant lors d'examens répétés.

3. D'autres signes cliniques sont compatibles avec le diagnostic de maladie d'Alzheimer PROBABLE après élimination des autres causes de démence :

- Existence de plateaux dans l'évolution de la progression de la maladie
- Symptômes associés: dépression, insomnie, incontinence, délire, illusions, hallucinations, réactions de catastrophe (verbales, émotionnelles ou physiques), troubles sexuels, perte de poids
- Présence, chez quelques patients, surtout à un stade avancé, d'autres signes neurologiques: rigidité, myoclonies, troubles de la marche
- Crise d'épilepsie à un stade avancé de la maladie
- Scanner cérébral normal pour l'âge

4. Symptômes qui rendent le diagnostic de Maladie d'Alzheimer IMPROBABLE

- Début soudain, apoplectiforme
- Signes neurologiques focaux comme: hémiparésie, déficit de la sensibilité, du champ visuel, incoordination à une phase précoce de la maladie
- Crise d'épilepsie ou troubles de la marche au début de la maladie

5. Le diagnostic de "Maladie d'Alzheimer POSSIBLE" peut être porté :

Sur la base d'un syndrome démentiel, en l'absence d'autres étiologies reconnues de démence (affections neurologiques, psychiatriques ou maladie générale) et en présence de formes atypiques dans leur mode de début, leur présentation clinique ou leur évolution.
En présence d'une seconde affection générale ou neurologique, qui pourrait causer la démence mais qui n'est pas considérée comme actuellement et dans le cas considéré responsable de cette démence. Dans le cadre de la recherche clinique, ce diagnostic doit être retenu lorsqu'un déficit cognitif est isolé et s'aggrave progressivement en l'absence d'autre cause identifiable.

6. Les critères pour le diagnostic de "Maladie d'Alzheimer CERTAINE" sont :

- Les critères cliniques pour le diagnostic de Maladie d'Alzheimer probable.
- La mise en évidence d'altérations histopathologiques caractéristiques, obtenue par biopsie ou autopsie.