MEMENTO: Une cohorte de personnes consultant dans les centres mémoire de ressources et de recherche afin d'améliorer les connaissances sur la maladie d'Alzheimer et les maladies apparentées

MEMENTO: a cohort of outpatients from French research memory centers in order to improve knowledge on Alzheimer's disease and related disorders

BIOMEDICAL RESEARCH PROTOCOL

Version n°15.0 dated 08/03/2017
including modification #27

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HISTORY OF REVISIONS TO THE PROTOCOL

VERSION	DATE	REASON FOR THE REVISION
1.0	01/12/2010	CPP and AFSSAPS Submission
1.1	15/01/2011	Modifications following CPP's comments 15/12/2010
2.0	04/10/2011	CPP and AFSSAPS Submission including amendment #2
2.1	15/11/2011	Modifications following AFSSAPS' comments 14/11/2011
3.0	05/12/2012	Extension of inclusion period
4.0	06/02/2013	CPP and ANSM Submission including amendment #10
5.0	24/05/2013	Changes in source documents, clarification of definition of expected adverse effects, generalization of the quality of life questionnaire at all visits.
6.0	04/10/2013	Extension of inclusion period,
7.0	06/11/2013	- Additionnal exclusion criteria - Addition of questionnaires in order to detect signs of Lewy Body disease - Addition of a self-administered questionnaire for participants'spouses - Possibility for demented participants to have the usual follow-up at the discretion of local investigator - Addition of MEMENTO-AmyGing ancillary study protocol - Addition of MEMENTO-Vascod ancillary study protocol
7.1	14/02/2014	Modifications following ANSM' comments 30/01/2014
8.0	05/03/2014	CPP and ANSM Submission including amendment #16
9.0	10/04/2014	Modifications following ANSM' comments 10/04/2014 CPP and ANSM Submission including amendment #17
10.0	03/09/2014	CPP and ANSM Submission including amendment #19
11.0	05/11/2014	CPP and ANSM Submission including amendment #20
12.0	07/10/2015	CPP and ANSM Submission including amendment #23
13.0	04/05/2016	CPP and ANSM Submission including amendment #24
14.0	05/10/2016	CPP and ANSM Submission including amendment #25
15.0	08/03/2017	CPP and ANSM Submission including amendment #27

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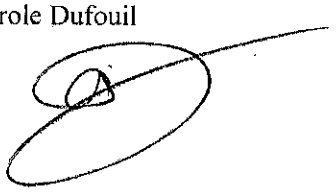

A. MAIN PROTOCOL: MEMENTO

LIST OF ABBREVIATIONS

18F	18'Fluoro
Aβ	Amyloid-β
ABPM	Ambulatory blood pressure monitoring
ACT	Activated Cephalin Time
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRD	Alzheimer's Disease and Related Disorders
AIx	Augmentation Index
ALT	Alanine Aminotransferase
ANSM	Agence Nationale de Sécurité des Médicaments
APP	Amyloid Precursor Protein
ASL	Arterial Spin Labeling
AST	Aspartate aminotransferase
AT	Applannation Tonometry
BMI	Body Mass Index
BNA	Banque Nationale Alzheimer
BP	Blood Pressure
CATI	Centre d'Acquisition et de Traitement d'Images Center for Image Acquisition and Processing
CBF	Cerebral blood flow
CDR	Clinical Dementia Rating scale
CERAD	Consortium for the Establishment of a Registry for Alzheimer's Disease
CFAS	The Cognitive Function and Ageing Studies
CHU	Centre Hospitalier Universitaire
CI	Confidence Interval
CMRR	Centre Mémoire de Ressources et de Recherches
CNRS	Centre National de la Recherche Scientifique
CPP	Comité de Protection des Personnes
CRF	Case Report Form
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography
DAT	Dementia of Alzheimer Type
DICOM	Digital Imaging and Communications in Medecine
DMS	Delayed Matching to Sample
DO	Denomination Objet
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighting MR Imaging
ECG	Electrocardiography
eCRF	Electronic Case Report Form
FAB	Frontal Assessment Battery
FDG	Fludeoxyglucose
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FOV	Field Of View
GM	Grey Matter
HDL	High Density Lipoprotein
IB	Investigator Brochure

ICH	International Conference on Harmonisation
INSERM	Institut National de la Santé Et de la Recherche Médicale
IQ	Intellectual Quotient
IUD	Intrauterin Device
IV	IntraVenous
LDL	Low Density Lipoprotein
LFF	Low-Frequency Fluctuations
MAB	Microalbuminuria
MCI	Mild Cognitive Impairment
MCI-AD	Mild Cognitive Impairment-Alzheimer's Disease
MCI-LBD	Mild Cognitive Impairment-Lewy Body Disease
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NFT	NeuroFibrillary Tangles
NIA	National Institute of Aging
NIA-AA	National Institute of Aging-Alzheimer Association
NIH	National Institute of Health
OCT	Optical Coherence Tomography
OR	Odds Ratio
OTC	Over The Counter
PET	Positron Emission Tomography
PI	Principal Investigator
PIB	Pittsburgh Compound B
PT	Prothrombin Time
PWV	Pulse Wave Velocity
QOL	Quality Of Life
SBI	Silent Brain Infarcts
SD-OCT	Spectral Domain- Optical Coherence Tomography
SPC	Summary of Product Characteristics
SPM	Statistical Parametric Mapping
SUVR	Standardized Uptake Value Ratios
SV	Sedimentation Velocity
TMT	Trail Making Test
UAE	Urinary albumin excretion
VBM	Voxel Basel Morphometry
WM	White Matter
WMH	White Matter Hyperintensities
WML	White Matter Lesions

1. SUMMARY OF THE RESEARCH STUDY

SPONSOR	**Centre Hospitalier Universitaire de Bordeaux**
COORDINATING INVESTIGATOR	Pr Geneviève CHÊNE
SCIENTIFIC DIRECTOR, CO-COORDINATOR	Carole DUFOUIL
TITLE	MEMENTO: a cohort of outpatients from French research memory centers in order to improve knowledge on Alzheimer's disease and related disorders
BACKGROUND	The increasing incidence of Alzheimer's disease (AD) and related disorders with the change in the world age demographic is a source of major public health concern. Early and accurate identification of individuals at high risk of Alzheimer's Disease has become a priority. Over the last years, research has focused on the concept of "Mild Cognitive Impairment" which happens to be a heterogeneous condition as, depending on the studies, Mild Cognitive Impairment patients' conversion rates to dementia range from 2 to 15 percent per year. A study of the full range of stages of evolution, from preclinical stage, to clinical expression of dementia or death is therefore of utmost importance to improve our knowledge on AD and trigger the development of new treatments, especially if between stages transition can be related to neuroimaging (either structural or molecular), biological (Cerebro-Spinal Fluid, serum or plasma) or vascular damages markers. However, if all the above markers have been shown to be individually associated with worsening of cognitive status, no prior study has simultaneously explored the association of a large panel of risk factors and biomarkers with the progression through early signs of cognitive impairment until AD in a large sample of study participants. In parallel to improving the knowledge on AD, it is also important to better estimate the social and economic burden of AD and their consequences on the individuals and their circle and how they evolve from early phase (pre-clinical) of the disease to the most severe stages.
GUIDING PRINCIPLES OF THE COHORT	This cohort, solution to the item 29 of the Plan Alzheimer 2008-2012, has been developed according to the initial memorandum of understanding prepared by the "Comité Plan Cohortes" of the Fondation Plan Alzheimer, and taking on board comments provided by the Scientific Advisory Board (July 2010) of the Fondation Plan Alzheimer and the whole working groups constituted for the preparation of the pilot phase: clinicians, neuro-imaging specialists, biologists, social sciences researchers (from June 2010). The cohort is built to fulfil the guiding principles as follows:

	- It should be scientifically original and identify hypothesis-driven research, allowing a corpus of new or confirmatory knowledge of a high-level of evidence to be acquired. In addition, the infrastructure (standardised collection of socio-demographic, clinical, imaging, biological data) may allow to respond, in a timely manner, to additional questions that may emerge over time; - An interdisciplinary approach is set up as the condition of individuals affected by neurodegenerative dementias involves clinical and biological aspects but also environmental, social and economic components; - While pursuing its own original scientific objectives, the cohort should have the potential for a comparison with other equivalent cohorts around the world. This cohort will be including individuals at high risk of developing a neurodegenerative dementia. As such, the cohort is aiming at providing results with an expected impact for those individuals of the same profile, as well as their caregivers and their case management
PRIMARY OBJECTIVE	To study the 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.
SECONDARY OBJECTIVES	- To assess the validity of an operational set of criteria to help identifing 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 Alzheimer's disease or associated dementia progression, - To assess factors predicting o Mortality o Loss of autonomy o Institutionalisation o Rate of cognitive decline in different areas of cognition o Cardiovascular events during follow-up o Change in quality of life o Risk of developing prodromal AD (pre-symptomatic dementia) - To study factors associated with change in biomarkers

	- To study the frequency of Lewy Body Disease (LBD) symptoms at an early stage and to compare MCI-AD and MCI-LBD participants in term of clinical symptoms, cognition, cerebral imaging characteristics and outcomes - In the subsample of participants who will reach the clinical stage of dementia, specific objectives will consist in: o assessing the evolution of the social, behavioural and quality of life characteristics of the participants and their caregivers over time and their relation with clinical progression of the disease; o describing the efficiency of resources that are used over time
DESIGN OF THE STUDY	A Multicenter national prospective cohort study including at least 2300 individuals consecutively recruited from French memory clinics (CMRRs) and followed-up over 5 years. A pilot phase has been run in 5 memory clinics that have volunteered for that phase and were eligible for the cohort (Bordeaux, Lille, Marseille, Paris Pitié-Salpêtrière, Toulouse). Eligible memory clinics are those that may include at least 50 individuals during the inclusion period, have access to MRI (1.5 or 3T) and biobank facilities. As it is very important to understand why some individuals are not included (eligibility criteria, acceptance of the protocol), the CMRRs will be requested to carefully and timely complete the national Alzheimer database (BNA).Co-inclusion in other biomedical research will be possible on a case by case analysis and agreement, as far as respective principal investigators and legal sponsors agree.
INCLUSION CRITERIA	- Aged 18 years and above - Having at least a light cognitive deficit defined as performing worse than one standard deviation to the mean (compared to age and educational norms) in one or more cognitive domains (assessed from a neuropsychological tests battery exploring memory, language, praxis, vision, executive functions); this deviation being identified for the first time by tests performed less than 6 months preceding date of inclusion (i.e. signature of informed consent) Or Having isolated cognitive complaint regardless of its duration while being 60 years and older (i.e. without cognitive deficit as defined above)(maximum stratum size of 300 participants) ; - Clinical Dementia Rating scale ≤0.5 and not demented - Visual and auditory acuity adequate for neuropsychological testing - Having signed an informed consent - Being affiliated to health insurance

NON INCLUSION CRITERIA	- Being under guardianship - Residence in skilled nursing facility - Pregnant or breast feeding women - Alzheimer's disease caused by gene mutations - Meeting brain MRI exclusion criteria (pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin, or body) or refusing MRI - Having a history of intracranial surgery - Having a neurological disease such as: treated epilepsy, treated Parkinson's disease, Huntington disease, brain tumour, subdural haematoma, progressive supranuclear palsy, history of head trauma followed by persistent neurological deficits - Stroke that has occurred in the last three months - Schizophrenia history (DSM-IV criteria) - Illiteracy, is unable to count or to read
ENDPOINTS	- Progression to clinical dementia stage according to standardized classifications (DSM-IV for dementia and NINCDS-ADRDA for AD) - Other outcomes of interest • Mortality • Loss of autonomy based on functional activity assessment • Institutionalisation • Speed of cognitive decline based on change in cognitive performances • Cardiovascular event (Stroke and Coronary events) • Quality of life • Prodromal AD (Pre-symptomatic dementia) • Longitudinal evolution of biomarkers measured from blood, CSF, structural neuroimaging (MRI) and molecular neuroimaging (^{18}F-FDG PET). Ad hoc designated committees will validate dementia diagnosis (and aetiology), cardiovascular events, and mortality causes
SIZE OF THE STUDY	An initial sample of 2330 individuals maximum, recruited over 39 months (initial period of inclusion).
NUMBER OF STUDY SITES PLANNED	Up to 40
DURATION OF THE STUDY	– Start of inclusions: April 8th 2011 – Duration of the inclusion period: up to 39 months – End of inclusion period: June 30th 2014 – Duration of individual participation: 5 years±3 months – Total duration of the study: 10 years
STATISTICAL ANALYSIS OF THE DATA	Sample size was calculated under the assumption that the cumulative incidence of clinical dementia over 5-year follow-up will be 20%.

	Therefore an initial sample of 2300 individuals, recruited recruited over the period of inclusion, will provide a power of at least 83% to show a hazard ratio of clinical dementia of 1.2 for each unit increase in any exposition level (α=0.05, standard deviation of exposure =1, cumulative dropout rate=10%).
EXPECTED CONSEQUENCES	One expected impact is to increase knowledge on the progression from early signs of cognitive impairment to AD and estimate associations between these signs and level of biomarkers assessed through imaging or blood or CSF samples. Another major expected impact is to standardise and harmonise protocols in terms of clinical and neuro-psychological examinations, biological markers, neuroimaging markers, diagnosis of dementia, support to caregivers and informants.
ANCILLARY STUDIES	**Memento-Amyging** main objective is to investigate in a sample of 800 Memento participants the prospective association between PET amyloid load, measured twice two years apart, through either Florbetapir (^{18}F) or Flutemetamol (^{18}F) radioligands, and dementia incidence over up to 5 years of follow-up (Part B of protocol). **Memento-Vascod** main objective is to study in a sample of at least 350 Memento participants the consequences on cognitive decline course of several markers of vascular damages measured using sophisticated investigations (Part C of protocol)

- **Schedule of assessments**

Table 1. Schedule of assessments – MEMENTO cohort & ancillary studies

		Screening	Baseline (Month 0)	Month 6		Month 12	Month 18		Month 24	Month 30		Month 36	Month 42		Month 48	Month 54		Month 60
		Center	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center
COHORT	Explain Study	✓																
	Obtain Consent	✓																
	Inclusion and Non Inclusion Criteria[1]		✓															
	Socio-demographic characteristics		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
	Medical history or event		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
	Physical, neurological examinations		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
	Medication		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
	Clinical Dementia Rating scale	✓		✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
	Full neuropsychological battery[2]	✓		✓[3]		✓	✓		✓	✓		✓	✓		✓	✓		✓
	AD-8 dementia screening interview				x			x			x			x			x	
	Mini-Mental State Examination	✓		✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
	Subjective complaint assessment (Visual analogic Scale)		✓	x		✓	x		✓	x		✓	x		✓	x		✓
	Neuropsychiatric Inventory		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
	Neuropsychiatric Inventory Questionnaire				x			x			x			x			x	
	Lifestyle (Mini Nutritional Assessment, alcohol and smoking habits, International physical activity questionnaire)		✓			✓			✓			✓			✓			✓
	Autonomy in daily life activities (Lawton IADL and Katz ADL scales)		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
	Motricity (SPPB)		✓			✓			✓			✓			✓			✓
	Quality of life (EQ-5D)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Lewy Body disease signs assessment		✓			✓			✓			✓			✓			✓
	Human sciences and health economic component		✓			✓			✓			✓			✓			✓
	Blood sampling laboratory assessment[4]		✓			✓			✓			✓			✓			✓
	Biobank[5]		✓						✓						✓			
	DNA Sample collection[6]		✓						✓						✓			
	RNA collection		✓						✓						✓			
	Brain structural MRI		✓						✓						✓			
	Positron emission tomography – Scan (FDG)		✓	✓[7]		✓	✓		✓	✓		✓	✓		✓	✓		✓
	CSF collection by lumbar puncture		✓	✓[8]		✓	✓		✓	✓		✓	✓		✓	✓		✓

[1] HCG urine dipstick tests are performed for women of childbearing potential
[2] Digit span, visuo-sptatial span, Grober & Buschke test, DMS 48, Verbal Fluency, Praxis, DO 80, Rey figure, TMT A & B, BREF
[3] For participants not demented at previous examination but CDR≥1
[4] In case blood sampling is performed as part of usual care, the laboratory results will be recorded and can include part or all of the following: Complete blood count platelet, TP, TCA, VS, C-reactive protein, phosphate, calcium, creatinine, Sodium, potassium, chlore, AST, ALT, alkalin phosphatase , total bilirubin, Glucose, cholesterol (total, HDL, LDL), triglycerids, Thyroïd-stimulating, Folates, B12 Vitamins (Optional)
[5] At inclusion if a usual care blood sampling is planned after informed consent was signed, an additional maximum of 30 mL of blood will be collected and stored in the biobank. Otherwise, participants will have specific blood intake from which a maximul of 30 mL will be collected for biobank storage.
[6] Performed only if participant does not state to refuse genetic tests in informed consent
[7] Participants who refuse to have 18F PET FDG at baseline will be asked to reconsider at 6, 12, 18 month follow-up, those who refused to have 18F PET FDG at 24-month will be asked to reconsider at 30, 36, 42 month follow-up, and those who refused to have 18F PET FDG at 48-month follow-up will be asked to reconsider at 54, and 60 month follow-up
[8] Participants who refuse to have lumbar puncture at baseline will be asked to reconsider at 6, 12, 18 month follow-up, those who refused to have lumbar puncture at 24-month will be asked to reconsider at 30, 36, 42 month follow-up, and those who refused to have lumbar puncture at 48-month follow-up will be asked to reconsider at 54, and 60 month follow-up

		Screening	Baseline (Month 0)	Month 12	Month 24	Month 36
AMYGING[9]	Explain Study	❶❷❸ ❹❺❻❼	❶❷❸ ❹❺❻❼			
	Obtain Consent		❶❷❸ ❹❺❻❼			
	Inclusion and Non Inclusion Criteria[1]		❶❷❸ ❹❺❻❼			
	Baseline PET Amyloid scanning[1]		❶❷❸ ❹❺❻❼			
	Follow-up PET amyloid scanning[1]				❶❷❸ ❹❺❻❼	
VASCOD[10]	Explain Study	✓	✓			
	Obtain Consent		✓			
	Microalbuminuria		✓		✓	
	Pulse wave velocity		✓		✓	
	Neuropsychological, behavioral and mood scales		✓	✓	✓	✓
	Ocular assessment [10]		✓		✓	
	Cerebral MRI [10]		✓			

[10] Optional examinations

ABBREVIATIONS : AD=Alzheimer's Disease IADL=Instrumental Activities in Daily Living, ADL=Activities in Daily Living, FDG= [18F]-fluorodeoxyglucose, SPPB=Short Physical Performance Battery, MRI=Magnetic Resonance Imaging, DNA= DeoxyriboNucleicAcid, RNA= RiboNucleicAcid, EQ-5D=Euroqol

[9] For MEMENTO-Amyging, there are 7 scenarios (❶❷❸❹❺❻❼) of schedule of assessments depending on when informed consent is signed (M0 (❶), M6(❷), M12(❸), M18(❹), M24 (❺), M30 (❻) or M36 (❼) of Memento)

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. INTRODUCTION

A comprehensive plan to fight against Alzheimer's disease has been set up by the French Government in 2008 and is coordinated by the Fondation Plan Alzheimer. This plan includes the implementation of a cohort of patients identified at an early stage of Alzheimer's disease and related disorders to support research on the progression through different stages of the disease, with the expectation to better characterise populations of patients that might benefit from early diagnosis and intervention when available ("item 29" of the plan). The coordination of the constitution of the cohort was left to the Alzheimer Methodologies Group ("item 27" of the plan)[a].

It is estimated that 24 million people are affected by dementia in the world, with 4.6 million new cases annually.[1] Dementia resulting from Alzheimer's disease is the most common form, representing around two third of cases. It is a slowly progressive, neurodegenerative disorder that causes memory impairments and other cognitive dysfunctions and that affects social behaviours. Alzheimer's disease is a specific degenerative brain disease characterised by the presence of two abnormal structures, amyloid plaques and neurofibrillary tangles, which are prime suspects in damaging and killing nerve cells. Amyloid plaques are composed of amyloid-beta (Aβ) 42 and 40 peptides, derived from the proteolytic cleavage of amyloid precursor protein (APP), that builds up in the spaces between nerve cells. Tangles are twisted fibers of a protein called tau that builds up inside cells. The role of plaques and tangles in Alzheimer's disease is not fully resolved but they somehow play a critical role in blocking communication among nerve cells and disrupting processes that cells need to survive. [2]

While increasing research effort on Alzheimer's disease has occurred over the past decades, our understanding of the underlying pathogenesis is still incomplete. No cure is available to date and current treatment strategies are mostly symptomatic. Due to a rapidly aging population, if no major improvement in the treatment occurs, the number of cases is going to increase dramatically (Figure 1) in the next decades, as the incidence doubles each 5 years of age.[3,4]

[a] http://www.fondation-alzheimer.org/node/397

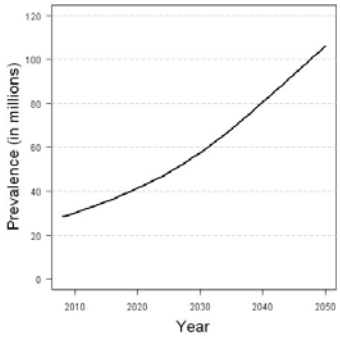

Figure 1. **Projections of Alzheimer's disease prevalence worldwide**
in millions for years 2010 to 2050
(Copyright 2008, Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health)

A major public health challenge is therefore to better understand the underlying pathobiology of the illness, by identifying modifiable risk factors and by an early and accurate screening of subjects at high risk, through biomarkers in case efficient cure for Alzheimer's disease becomes available.

2.2. RATIONALE

Biomarkers of Alzheimer's disease may play a central role in the reformulation of Alzheimer's disease criteria.[5-8] The tendency towards biomarkers is mainly based on the fact that reliable biomarkers could: allow identification of groups at high risk of developing AD, contribute to early diagnosis at pre-symptomatic or preclinical phase, improve differential etiology (such as AD vs Fronto-temporal), but also potentially allow monitoring of AD progression, or the response to therapy. (Figure 2)

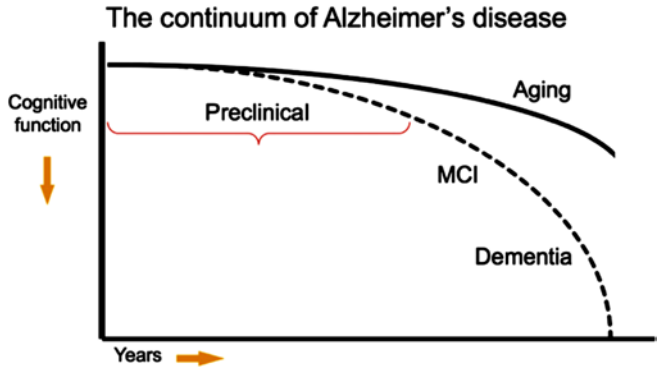

Figure 2. Model of the clinical trajectory of Alzheimer's disease
(Source: Sperling RA et al, Alzheimer's and Dementia 2011;7:280-292)

However, before one or several of these markers can be recommended for daily case management, it is crucial to study their potential value using standardised methods of analysis, and to better understand their temporal involvement in the physiopathological process underlying cognitive impairment and clinical dementia. Such research would allow identifying the best biomarkers or combination of biomarkers for use in clinical practice. Although different

conceptual schemes have recently been proposed and widely advocated, more evidence needs to be accumulated before these schemes can be translated into clinical practice.[7,9-11]

Potential risk factors for Alzheimer's disease have also been extensively studied over the last years. However, apart from advanced age,[12] the presence of apolipoprotein E allele ε4 and other genetic variants more recently identified,[13,14] there are remaining controversies regarding factors that might influence the progression to dementia, and further, regarding the survival after the diagnosis of clinical dementia.[15]

This lack of evidence was strongly acknowledged in the conclusions of a recent State-of-the-Science Conference aiming at assessing the available scientific evidence on prevention of cognitive decline and Alzheimer's disease that was organized by the National Institute on Aging and the Office of Medical Applications of Research of the National Institutes of Health.
From a critical review of the literature, it was concluded that despite promising findings from observational studies on potential preventive strategies (such as anti-hypertensive treatment,[16,17] anti-inflammatory non-steroidal treatment,[18,19] estrogen replacement therapy,[20,21] statin treatment[22,23]), most subsequent randomized trials have failed to show any reduced risk of dementia of Alzheimer's type in treated compared to placebo groups.[24,25] These discrepancies can be at least partly explained by the lack of standardized measurements across studies, and differences in both the type of scales used for measurements and the windows of exposures (the latter applying more to population-based studies).
One of the conclusions of the NIH experts was that "long-term studies on high risk populations (particularly treatment-seeking individuals with symptoms of mild cognitive impairment) should be conducted to delineate risk factors for and natural progression to Alzheimer's disease and to identify the long-term outcomes and factors associated with improvement, decline, and stabilization of cognitive function." This is one of the main purposes of the current project.

2.3. GENERAL AIM

In a large cohort of non-demented participants presenting either a light deviation from expected neuro-psychological performances at a given age and education attainment or isolated cognitive complaints when aged above 60 years, we will investigate factors that may influence the course of cognitive decline as well as the transition to a clinical dementia stage over a follow-up period of at least 5 years.

Among the variety of factors that will be investigated, a more specific focus will be made on the following: biomarkers (derived from plasma, serum, CSF, structural neuroimaging and molecular neuroimaging), vascular risk factors, lifestyle characteristics, psycho-behavioral characteristics, social and human sciences characteristics, and cognitive profiles.

2.4. ALZHEIMER'S DISEASE BIOMARKERS

2.4.1. BLOOD BIOMARKERS

According to the most updated amyloid cascade hypothesis,[26,27] the neural degeneration that occurs in AD-affected brains is the consequence of Aβ peptide hyperproduction and accumulation. This gradual chronic imbalance between Aβ production and clearance would initiate a cascade of neurodegenerative events due to the toxic effect of amyloid that includes gliosis, inflammatory changes, tangles and transmitter loss (Figure 3).

Fragment of Aβ can be measured from blood and CSF but CSF is still seen as an invasive and not cost-effective procedure.

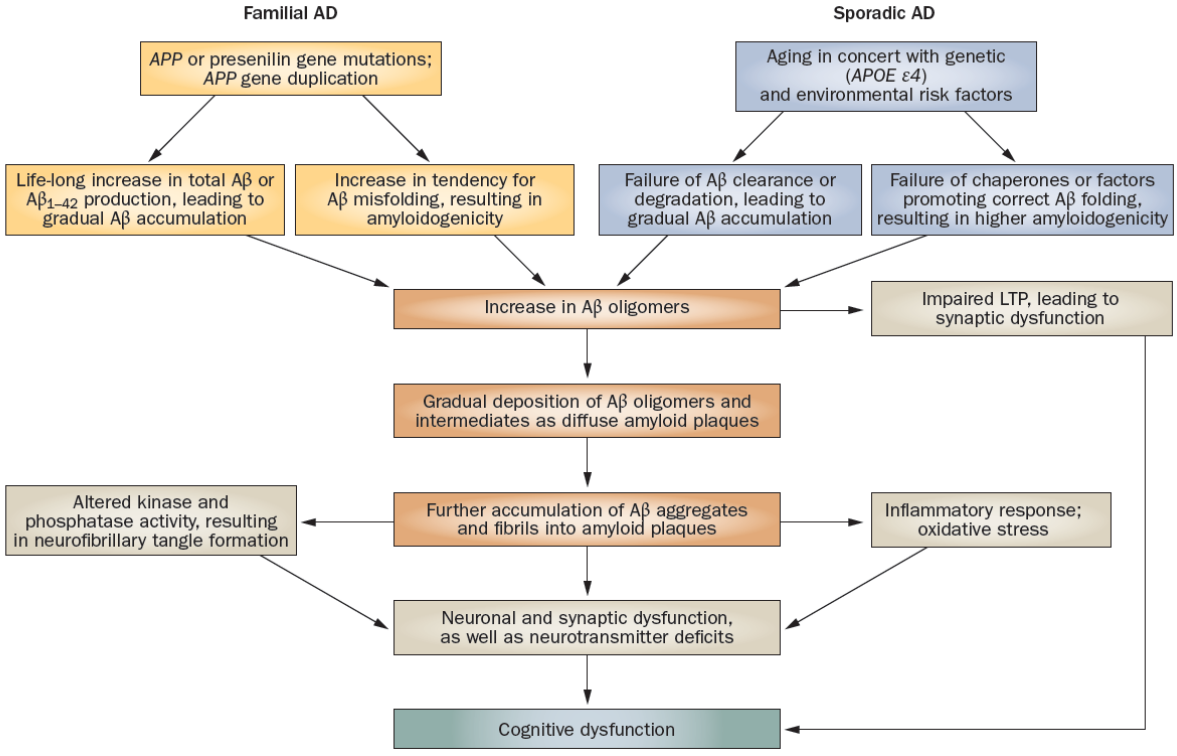

Figure 3 Amyloid cascade hypothesis

(Source: Blennow K et al, Nat. Rev. Neurol 2010[27])

Data on concentrations of Aβ species (β–amyloid 40, 42 and ratios 42/40) in plasma or serum have yielded conflicting results in relation to late life dementia or cognitive impairment risks.[27-29] Some studies have reported no difference between Alzheimer disease patients and controls for

$A\beta_{1-42}$ and $A\beta_{1-40}$ plasma concentrations.[30] Other prospective studies have concluded for an association between $A\beta_{1-42}$ or $A\beta_{1-42}$:$A\beta_{1-40}$ ratio in relation to Alzheimer disease development but the direction of the association was in opposite directions across studies.[31,32]

Other potential blood biomarkers have been proposed mostly related to immune activation but the investigations are still in a discovery phase and further work is needed.[27] It would be of great interest to determine a set of proteins that would be an optimal combination of biomarkers for either prognosis or earlier diagnosis purposes.[33] Another perspective relies on current development towards determination of tau concentrations from plasma.[34]

2.4.2. CEREBROSPINAL FLUIDS BIOMARKERS

Several studies have shown that AD patients present increased levels of total tau (t-tau) and phosphorylated tau (p-tau) and decreased levels of the 42 amino acid form of amyloid-β ($A\beta_{1-42}$) measured from Cerebrospinal fluid (CSF).[35] Neuropathological studies have shown that elevated CSF tau levels are associated with the presence of AD pathology at the brain autopsy and that CSF tau could help discriminating AD from other dementia aetiologies.[36] Some studies have suggested that the ratio CSF t-tau: $A\beta_{1-42}$ could help differentiate in patients having mild cognitive impairment those at low vs. high risk for future development of AD.[27] However the findings are mainly based on cross-sectional studies and longitudinal observations are needed to better assess the utility of these markers and further work is also necessary to define optimal cut-offs for each biomarker or combinations of CSF biomarkers in order to increase their prognosis value (sensitivity and specificity). In order to reach that goal, it will also be necessary to harmonise CSF biomarkers measurements across sites.[37]

2.4.3. STRUCTURAL NEUROIMAGING BIOMARKERS

The recent development of neuroimaging techniques has allowed showing the presence of both structural changes such as global atrophy or hippocampal atrophy in the brain of normal elderly individuals but also markers of vascular pathology such as white matter lesions, silent brain infarcts or microbleeds.[37]

These new and easily accessible features offer new perspectives for both the understanding of the underlying mechanisms leading to dementia (as brought up in a previous paragraph) and the early identification of patients at high risk of developing the disease (i.e. before the first clinical symptoms).[8, 9]

2.4.3.1. BRAIN ATROPHY

On MRI, global brain atrophy is usually measured using visual scales or based on tissue volumes measures and estimated as the ratio between grey matter (GM) + white matter (WM) volumes

divided by total intracranial volume (GM+WM+Cerebrospinal Fluid (CSF)) or head size. Apart from age, only a few factors have been identified as related to severity of brain atrophy but results are inconsistent.[38,39]

Whole brain atrophy has been shown to be a predictor of future dementia in both normal population and Mild Cognitive Impairment samples.[40,41] In patients having reached the clinical stage of dementia, it is also reported that the more severe the whole brain atrophy, the faster patients will decline.[42]

Overall whole brain atrophy seems to be an accurate marker of future cognitive decline in both normal, Mild Cognitive Impairment and Alzheimer's disease patients.

2.4.3.2. HIPPOCAMPAL ATROPHY

Hippocampus plays a key role in memory. Post mortem studies have consistently shown that Alzheimer's disease patients are characterized by shrinkage of that region of the brain. Hippocampal atrophy has been shown to be related to age and smaller hippocampal have also been shown in depressed patients compared to elderly controls as well as in hypertensive individuals.[43,44]

Prospective studies in elderly controls have shown that smaller hippocampal volume at study entry predicts dementia onset over 5-year follow-up suggesting that the shrinkage occurs before the clinical manifestation of dementia.[45] In a subsample of the Rotterdam study, it has been shown that faster decline in hippocampal volume estimated from serial MRI was associated with a higher risk of clinical dementia over 10-year follow-up.[46]

In a study that compared groups of MCI, elderly normal and Alzheimer's disease patients for whole brain atrophy and hippocampal volumes, it was concluded that hippocampal measures best-discriminated MCI patients from controls whereas whole brain atrophy best discriminated MCI from Alzheimer's disease patients.[47]

All these findings support the concept that increased hippocampal volume loss is an indicator of Alzheimer's disease pathology and could be considered as a marker for the efficacy of therapeutic interventions in AD.

2.4.3.3. CORTICAL THICKNESS & SULCI FOLDING

As stated above, there is evidence that anatomic abnormalities in medial temporal lobe regions, especially in the hippocampus, are visible at MRI prior to clinical stage of dementia. With the improvement of MR images analyses, other markers have been shown to be related to dementia stage including cortical thickness and cortical sulci characteristics.[34,48]

2.4.3.4. CEREBROVASCULAR LESIONS BURDEN

White matter lesions (WML) and Silent brain infarctions (SBI) are frequently seen at cerebral MRI of elderly individuals.[49] White matter lesions are hyperintense on proton-density and T2-weighted images and FLAIR (Fluid Attenuated Inversion Recovery), without prominent hypointensity on T1-weighted scans.

Silent Infarcts are defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger with corresponding prominent hypointensities on T1-weighted images, in order to distinguish them from cerebral white matter lesions.

The etiology of WML and SBI is not fully understood but the most frequent hypothesis raised is that they are zones of ischemia due to chronic hypoperfusion (small vessel disease).

Severity and frequency of WML and SBI increase with age and hypertension.[50-52] Moreover, there are consistent reports showing that WML and SBI are predictors of dementia onset.[53,54]

Only a few studies have investigated the link between cerebrovascular lesions on MRI and markers of brain atrophy and results tend to show a specific link, independently of potential confounders.[55]

However until recently, very few studies have assessed the predictive value of small vessel disease and brain atrophy markers on the progression to dementia in MCI patients or normal elderly, in a same model. A report on 152 MCI patients followed on average during two years demonstrates that markers of small vessels disease and markers of atrophy are independent predictors of dementia.[56]

Similarly, in a large population-based study, it was observed that smaller hippocampal volume and larger white matter lesions volume are independent predictors of cognitive decline over 4-year follow-up.[54]

2.4.3.5. MICROBLEEDS

More recent development in MRI methods have allowed the study of new features such as microbleeds, a biomarker of angiopathy.[57,58] Microbleeds have been found to be associated with disease severity in Alzheimer's disease patients[58], and one population-based study has reported cross-sectional association between the number of microbleeds and cognitive performance levels.[59]

2.4.3.6. DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) does reflect water diffusion properties in the brain and its spatial distribution. DTI is derived from Diffusion-weighting MR imaging (DWI)[60,61] which measures the rate of diffusion of water molecules in the brain. There is evidence that the diffusion of water molecules in white brain matter is biased in the direction of the myelinated fibers bundles and is

thus anisotropic. The impairment of fibers bundles then, as it supposedly occurs in Alzheimer's disease, leads to more unconstrained, isotropic diffusion as a consequence of progressive neurodegeneration. Therefore, DTI measures can be assumed to reveal fiber bundle integrity that could be useful to diagnose MCI or AD or predict the likelihood of progression to AD in MCI patients.[62]

2.4.3.7. RESTING STATE FUNCTIONAL MRI

Blood oxygenation level-dependent contrast functional magnetic resonance imaging (fMRI) studies have found that spontaneous low-frequency (<0.08 Hz) fluctuations (LFF) measured during the resting-state showed high temporal coherence between spatially distinct but functionally related regions. These results suggested that LFF may also be appropriate for examining the functional connectivity between different brain regions. With respect to AD, some studies have found that the pathophysiology of Alzheimer's disease may be associated with abnormality in resting-state LFF. However little is known on whether impaired LFF (alone or in combination with other MRI parameters or other biomarkers) can predict future cognitive decline in patients with light cognitive deficits.[37,63,64]

2.4.3.8. SYNTHESIS ON STRUCTURAL NEUROIMAGING BIOMARKERS

Overall the recent and future developments of techniques in the coming years will allow measuring simultaneously several MRI parameters in vivo that could help determining groups of patients at high risk of transition to clinical dementia that could benefit of new therapeutics.[65] It is important to know how these different approaches compare with their ability to differentiate healthy controls from Alzheimer's disease patients.

2.4.4. MOLECULAR NEUROIMAGING - FDG

Radiolabeled glucose analog 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is used to measure cerebral metabolism, a marker of synaptic activity.[66] The topographic distribution of abnormalities of glucose metabolism observed in AD includes parieto-temporal cortex, posterior cingular and precuneus. Hypometabolism does persist after correction for partial volume of cortical atrophy.[67] This has been observed in subjects carrying the epsilon 4 allele of Apolipoprotein E.[68] Decrease in metabolism has been correlated with cognitive decline in older populations as well as in MCI and AD samples.[69]

From a neuropathological study, it was reported that adding ^{18}F-FDG -PET to a clinical diagnosis significantly improves the likelihood of detecting Alzheimer disease pathology.[70] To summarize, the literature suggests that ^{18}F-FDG-PET is a marker of synaptic deficits that is characteristic of neurodegeneration in AD.

The prognostic value of ^{18}F-FDG -PET for AD diagnosis at preclinical phases has been studied in a few longitudinal studies in MCI patients. Most studies included less than 50 participants with amnesic-MCI that were followed up from 1 to 3 years. Between those who experienced AD later or never, regions that differed included parieto-temporal associative cortex, cingular posterior cortex and less frequently hippocampus and dorsolateral prefontal cortex.[71-7667-72] The positive predictive value of ^{18}F-FDG PET ranged from 75 to 100% in these studies.

2.4.5. MOLECULAR NEUROIMAGING - AMYLOID

The pathological features of AD include plaques and tangles which are constituted by amyloid beta peptide (A Beta) and tau protein which presence and severity could only be assessed from brain neuropathological assessment until recently. Recent advances in molecular imaging research have enabled visualization of brain amyloidosis. The rapid development of different compounds suitable for visualizing amyloid would permit pathology-specific diagnosis of AD at an asymptomatic stage in a non-invasive manner, and could also potentially allow early intervention at a stage where symptoms of dementia are not clinically detectable.

2.4.6. TRANSCRIPTIONAL ANALYSIS

Gene expression in the Alzheimer's disease brain has been shown to be altered in several studies. The development of microarrays systems for gene expression profiling permits screening of large numbers of genes for involvement in biologic processes. Gene expression profiles can be used to reflect and predict pathologic processes. Thus, gene expression profiling has been utilized for the characterization of several neurologic and immune disorders. The method has the potential to lead to a better understanding of the molecular mechanisms underlying disease, identify risk for secondary complications, and aid in the development of novel therapeutics.[77]

2.5. ALZHEIMER'S DISEASE RISK FACTORS

2.5.1. VASCULAR RISK FACTORS

These last years, there has been increasing evidence that vascular risk factors are involved in Dementia of Alzheimer's type onset as some of these risk factors could influence the course of dementia progression.

If the pathway linking vascular factors to dementia of vascular type (post-stroke dementia) is well understood, the underlying mechanisms that might relate vascular factors to Dementia of Alzheimer's type are yet to be determined. Whether vascular factors are independent risk factors for Alzheimer's disease or whether they act in synergy with neurodegenerative process is not fully understood.

Among vascular factors that might predict future dementia onset, there is robust evidence for midlife hypertension[78-80] and diabetes mellitus type 2,[81,82] and growing evidence for dyslipidemia[83-85] and obesity.[86-88] However there are important areas that require future investigation: As an example, the contributions of vascular risk factors individually or in combination remain controversial. Some Alzheimer's disease risk factors (diabetes and smoking[89]) are strong in isolation, while others (heart disease and hypertension) act in combination.[90] Obesity and hypertension are independent predictors of late-life cognitive impairment in the Framingham study,[91] whereas diabetes mellitus type 2 is associated with global impairment in the presence of hypertension,[92] although the same cohort reports diabetes being a risk factor for Alzheimer's disease only in the absence of other factors.[93] A prospective study investigating obesity, mid-life blood pressure, smoking and mid-life cholesterol levels describes additive contributions to risk for AD.[84] The "metabolic syndrome", combination of these factors, is associated with dementia in both cross-sectional[94,95] and prospective studies,[96] although hyperinsulinemia, rather than metabolic syndrome, may predict dementia.[97]

In addition, as described above, dementia and faster cognitive decline, while predicted by higher mid-life vascular risk have also been found to be associated contemporaneously with low blood pressure[98], low cholesterol[99] and low BMI[100]. These paradoxical findings could reflect both the complex association of those factors with age and the fact that clinical dementia onset is preceded by decline in weight, blood pressure and cholesterol over several years (reverse causality).[79,101-103]

Both large vessel disease (carotid intima-media thickness or arterial stiffness[104,105]), and small vessel disease (i.e. silent brain infarcts/white matter lesions at cerebral MRI[106,107]) are associated with cognitive impairment and dementia.[54,108,109] It has been hypothesized that they could be mediators for associations between vascular factors and cognitive impairment.

On one hand, MRI structural changes suggestive of atrophy, particularly reduced hippocampal volumes, are associated with more severe cognitive deficits and predict dementia.[46,110] On the other hand, higher vascular risk has been associated with brain volumetric changes.[111,112] Whether this applies to all vascular risk factors has not yet been fully investigated and requires more research.[113] Brain MRI in epidemiology provides a proxy measure of underlying pathology and should be increasingly used to investigate mediating pathways between vascular factors and dementia risk. [114-116]

2.5.2. LIFESTYLE CHARACTERISTICS

For all factors listed in this section, the relationship with the outcome of interest can be considered in two directions. Either they could be risk/protective factors for dementia onset, or evolution in health status could impact directly on these characteristics.

2.5.2.1. DIET

Many of the risk factors for dementia detailed in the previous paragraph (such as hypertension, diabetes and obesity) are also modifiable by diet. It is also possible that diet modifies the risk of dementia. Recent studies have reported that people following a Mediterranean regimen[117,118] may have a lower risk of developing dementia. Other studies found that individuals with high consumption of fish have a lower risk of dementia.[119]

These observations have led to the hypothesis that high dietary intake of anti-oxydants might contribute to a reduced risk of dementia. However, randomized controlled trials with vitamins E and C (both anti-oxydants) supplementation do not confirm the observational studies' findings as most do not show effect of vitamin supplementation on cognitive decline course.[120,121]

Similar inconsistencies between observational studies and randomized trials have been observed for Homocysteine being a risk factor for dementia in population-based studies, and B vitamin supplementation failing to demonstrate an effect in favour of less decline on cognitive outcomes than placebo.[122,123]

From all these observations, it remains unclear whether the associations between some nutrients and reduced dementia risk are causal or whether they are due to uncontrolled confounding.

One cannot rule out that adherence to a Mediterranean diet for example will favour better health outcomes including cardiovascular disease and cognitive ageing.

Because of all these inconsistencies, it remains also important to study the potential impact of cognitive decline over time on diet and its modifications.

Deterioration in functional health and chronic diseases could induce modifications in diet over time leading potentially to food insufficiency or poor dietary intake.[124-126] Change in diet studied longitudinally can reflect underlying health changes and also interfere with cognitive health evolution.[124]

2.5.2.2. PHYSICAL ACTIVITY

Another potential modifiable lifestyle factors, physical exercise, has recently been linked with decreased cognitive decline or dementia incidence[127-129]: individuals who are physically active are at lower risk of dementia than those who are sedentary.[130,131]

Intervention studies even confirmed that exercise training can slow the decrease in cognitive performances in normal as well as in cognitively impaired individuals.[132,133] The mechanisms by

which physical activity can influence cognition needs to be elucidated.[134] From animal models, it is suggested that rats having more intense physical activity have less β–amyloid plaque formation.[135] It also could be that physical activity does act on cognition by lowering vascular risk.[135]

All these results point out the need to precisely measure the level of physical activity in order to better estimate its association with cognitive decline's speed and to assess whether higher physical activity level can delay the onset of clinical dementia or modify the trajectory of cognitive decline once people are demented.

On the other hand, change in health status can be accompanied by a decrease in physical activity. Intervention trials do suggest promoting physical activity could lead to an improvement of physical functioning even in demented individuals.[136]

2.5.3. NEUROPSYCHIATRIC SYMPTOMS

Demented patients do present more often depressive symptoms than non demented individuals.[137-139] However, results from prospective studies are controversial and it is still not known whether 1) depression is a causal factor of dementia; 2) depression is an early sign of dementia (prodrome); 3) depression is a consequence of dementia as an early reaction to perceived loss of cognitive abilities; 4) depression and dementia share common mechanisms or risk factors.[140] One major issue in the published material is the lack of standardisation in the tools used to assess depression, some studies focusing on depressive symptoms, others on major depressive episodes which are different entities and might have potentially different causes and consequences.[141,142]

Less is known on the role of anxiety as a risk factor for dementia. Two prospective studies have reported a higher risk of cognitive decline for patients with high anxiety.[143,144] Anxiety has also been involved in the progression from mild cognitive impairment to Alzheimer's disease[143] and finally prospective evidence also suggests that the related concept of psychological distress, a mixture of anxiety and depression, is associated with Alzheimer's disease.[145]

Given demonstrated high level of co-morbidity between anxiety and depression,[146] it seems important to assess them simultaneously to better understand the true underlying association between anxiety, depression and dementia.

During the course of Alzheimer's disease and related disorders, at a later stage, a variety of neuropsychiatric symptoms can occur until becoming persistent with fluctuating intensity and responses to current treatment. These symptoms are linked to a higher rate of institutionalisation and a more rapid cognitive decline.

Data are scarce on the prevalence of neuropsychiatric symptoms at an earlier stage and prior to clinical dementia.[147-149] Studying neuropsychiatric symptoms longitudinally will contribute to better understand their link with clinical dementia onset in patients with mild cognitive deficits.

Psycho-behavioral symptoms are important features of Alzheimer's disease especially at the advanced stages of clinical dementia. They cause important distress to both patients and their entourage. Some neuropsychiatric symptoms, such as depression as reported above, have been extensively studied in population-based studies as well as in clinical samples in relation to dementia risk but the other neuropsychiatric symptoms have been rarely studied prior to dementia stage.

Nevertheless, studies of samples of patients with mild cognitive impairment do suggest a high prevalence of non-cognitive mood and behavioral symptoms in patients with mild cognitive impairment. These symptoms are usually assessed with the Neuropsychiatric Inventory (NPI) and it has been reported that up to 75% of patients with mild cognitive impairment could suffer from one of these symptoms. Depression, nighttime behaviors, irritability, agitation, apathy, and anxiety are the NPI symptoms most frequently reported.[148]

These symptoms need to be assessed longitudinally in patients at risk of dementia as they may have both clinical and prognostic significance and also because of their potential consequences on disease progression.

2.5.4. SOCIAL AND HUMAN SCIENCES COMPONENT

2.5.4.1. SOCIAL NETWORK

Over the past decades, studies have shown that social relations i.e. social networks, social integration and social engagement positively impact significantly on the mental and physical health individuals.[150,151] Findings from population-based studies suggest that risk of dementia or cognitive decline is higher in those individuals who are isolated or have poor social networks and support.[152,153] A study in 89 individuals with known dementia event showed that social networks modify the relation of some measures of Alzheimer's disease pathology at neuropathological examination to level of cognitive function: for a same level of AD pathology (plaques and tangles), individuals with stronger social support had significantly higher cognitive performances.[154] Little is known on the influence of social networks on the cognitive evolution of patients recruited from clinical settings. As some, if not all, of the different components of social networks might be associated with stable cognitive functions, it is necessary to precisely characterise social networks by their structure (number of ties, proximity of ties), function

(frequency of contact, reciprocity), nature and specificity of a given tie (friends, partner, children) to assess how it can affect cognitive evolution.[155,156]

It is also of interest to study which factor could modify the relations between social network, social engagement and change in cognitive performances as some reports suggest that age, gender and education could be modifying factors.[153,157]

Only very few studies exist with repeated assessment of social networks and little is known on the consequences on the shaping of social networks on cognitive performances.[158]

2.5.4.2. CAREGIVER

Social environment is likely to have an influence on the speed of cognitive decline in the elderly. With worsening of health, patients' condition can require at some stage a caregiver.

Caregivers are usually classified as primary when they provide care of all types and as non-primary when they provide substantial care and services.[159] There are only a few studies that have investigated the care trajectory of AD patients in the period beginning with the first manifestations of cognitive deficits and ending with the diagnosis of Alzheimer-type dementia.[159] It is important to describe the social interactions that characterize the initial phase of the illness trajectory of people with Alzheimer's disease[160] since a greater understanding of early phase dynamics would improve detection and intervention services not only for those with dementia.[161]

Health of caregivers is another matter of interest as caregiving is associated with higher rates of most psychiatric disorders (anxiety, depression), mostly related to stress.[162] These syndromes can be transient experiences of tension but they may also require psychiatric treatment and affect quality of life.[162] Randomized trials have shown that interventions aiming at decreasing the level of burden and stress of caregiving had an effect on both lower incidence of depression in caregiver and delaying institutionalisation in care recipients.[161]

The impact of Alzheimer's disease on the quality of life of the spouses that are patients' primary caregiver was highlighted by various studies.[163-165] They suggest that even at the MCI stage, cognitive impairment could have an impact in terms of burden to spouses and children,[166] on adjustment within couples,[167] as well as on life experience of spouses.[168] Data on stress, anxiety and depression among caregivers of MCI patients are heterogeneous and derived from cross-sectional studies which limits the findings' interpretation.[169] The emotional difficulties in everyday life experienced by MCI patients and their caregivers as well as interventions to overcome them have been rarely explored.[170,171]

2.5.4.3. HEALTH ECONOMIC QUESTIONS

Alzheimer's disease is one of the most expensive diseases to treat in France. The cost is due to the cost of formal personal health services provided (hospital, nursing homes…) and the cost of informal care provided by families and hired caregivers.[172] Little is known on factors that cost of ADRD at different stage of the disease and factors that might be associated with that cost.[173] These are important features to better grasp for the future clinical and policy interventions aiming at reducing dementia's impact on individuals, families and society.

2.6. NEUROPSYCHOLOGICAL ASSESSMENT

The concept of "Mild Cognitive impairment" consists with the idea that there is an intermediate stage between normal cognitive ageing and dementia. Since the concept has been developed, the definitions have evolved. If the first definitions focused more on memory deficits (amnestic Mild Cognitive Impairment), now different subtypes of mild cognitive impairment are defined. However, the utility and reliability of the concept is still largely debated. Indeed, there is a huge variability in conversion rates to clinical dementia of MCI patients (ranging from 2 to 15 percent per year) that could illustrate either that MCI does not discriminate those who will reach clinical dementia stage or that there are still issues in the definition and/or conceptualization of MCI cases.

Therefore new criteria for MCI are about to be proposed that suggest assessing longitudinally several cognitive domains (memory, language, visuo-spatial skills, attentional control) in order to be able to detect a full range of clinical presentation of Alzheimer's disease and related disorders.

2.7. NON ALZHEIMER NEURODEGENERATIVE DISEASE

2.7.1. LEWY-BODY DISEASE

Lewy body disease (LBD) is the second most frequent neurodegenerative disease after Alzheimer's disease (AD).[174] To distinguish these two pathologies seemed to be of minor importance until recently since AD and LBD have the same symptomatic treatment (cholinesterase inhibitors). However, new specific treatments of AD are in development with precise targets on brain lesions eradication.[175] Moreover, frequent symptoms of LBD such as hallucinations and delusions do not have to be treated by usual neuroleptics and antipsychotics, since such treatment aggravate physically and cognitively patients.[176]

Mild cognitive impairment in Lewy body disease (MCI-LBD) is a very recent concept whereas MCI has been described in Alzheimer's disease for more than 15 years. Indeed, in 2009, the Mayo Clinic team from Rochester described a serie of cases diagnosed with MCI, found to have

autopsy-proven LBD.[177] The cognitive domains most frequently affected were attention/executive functioning and visuospatial functioning. Similar reporting was done by Yoshikawa et al. in 2013.[178] Moreover, physical symptoms including discreet parkinsonism, neurovegetative symptoms (constipation, rhinorrhea, increased saliva…) have been described at MCI stage in LBD.[179]

In clinicial practice, LBD diagnosis is difficult, even for specialists, particularly at disease onset, as the current used diagnosis criteria (McKeith[180]), have a high specificity (more than 95%) but a low sensitivity (32%).[181,182] Therefore the majority of the LBD patients - especially those with MCI or mild dementia – are not diagnosed.

2.8. SUMMARY OF RATIONALE

The increasing incidence of Alzheimer's disease and related disorders with the change in the world's age demographic is a source of major public health concern. Early and accurate identification of individuals at high risk of Alzheimer's disease has become a priority.[183,184] 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 and pre-clinical stages have been neglected. A study of the full range of stages of evolution until the clinical dementia or death is therefore of utmost importance to improve our knowledge on Alzheimer's disease and trigger the development of new treatments, especially if between stages transition can be related to neuroimaging markers, blood or CSF biomarkers, vascular damages markers, lifestyle characteristics, neurobehavioral characteristics either alone or in combination. However, if all the above markers have been individually associated with worsening of cognitive status, no prior study has simultaneously explored the association of a large panel of risk factors and markers with the progression through cognitive impairment until Alzheimer's disease in a large sample of study participants. In parallel to improving the knowledge on Alzheimer's disease, it is also important to better estimate the social and economic burden of Alzheimer's disease and their consequences on the individual and its environment.

2.9. GUIDING PRINCIPLES

This protocol has been developed according to the initial memorandum of understanding prepared by the "Comité Plan Cohortes" of the Fondation Plan Alzheimer, and taking on board comments provided by the Scientific Advisory Board (July 2010) and the whole working groups constituted for the preparation of the pilot phase: clinicians, neuro-imaging specialists,

biologists, social sciences researchers (from June 2010 onwards). The cohort is built to fulfil the guiding principles as follows:

- It should be scientifically original and identify hypothesis-driven research, allowing a corpus of new or confirmatory knowledge of a high-level of evidence to be acquired. In addition, the infrastructure (standardised collection of socio-demographic, clinical, imaging, biological data) may allow to respond, in a timely manner, to additional questions that may emerge over time;
- An interdisciplinary approach is set up as the condition of individuals affected by neurodegenerative dementias involves clinical and biological aspects but also environmental, social and economic components;
- While pursuing its own original scientific objectives, the cohort should have the potential for a comparison with other equivalent cohorts around the world;
- This cohort will be including individuals at high risk of developing a neurodegenerative dementia. As such, the cohort is aiming at providing results with an expected impact for those individuals of the same profile, as well as their caregivers and their case management.

2.10. BENEFIT / RISK RATIO

Participants will have regular follow-up of their health status according to the usual care. They will participate in an original research program which is built in order to provide unique findings that will contribute to improve the knowledge on aetiology of ADRD.

Risks imputable to research are reduced. Individuals will have MRI of duration 20 minutes longer than the usual care and blood draw intake. A subsample of those volunteers will have either ^{18}F-FDG PET-Scan or Lumbar puncture for CSF collection or both, the potential risks are low as these exams are often used in clinical practice. A description of risks related to these investigations is provided in the appendices VI and VII.

2.11. EXPECTED IMPACT

One expected impact is to increase knowledge on the progression from early signs of cognitive impairment to Alzheimer disease and estimate associations between these signs and level of biomarkers or types of abnormal imaging.

Another major expected impact is to standardise and harmonise protocols in terms of clinical, laboratory and neuropsychological examinations, CSF sampling, MRI markers and other biomarkers measurement, diagnosis of dementia, support to caregivers and informants.

3. OBJECTIVES OF THE STUDY

3.1. PRINCIPAL OBJECTIVE

To study the 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.

3.2. SECONDARY OBJECTIVES

- 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 Alzheimer's disease 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
    - Risk of developing prodromal AD (pre-symptomatic dementia)
- To study factors associated with change in biomarkers
- To study the frequency of Lewy Body Disease (LBD) symptoms at an early stage and to compare MCI-AD and MCI-LBD participants in term of clinical symptoms, cognition, cerebral imaging characteristics and outcomes

- In the subsample of participants who will reach the clinical stage of dementia, specific objectives will consist in:
    - assessing the evolution of the social, behavioural and quality of life characteristics of the participants and their caregivers over time and their relation with clinical progression of the disease;
    - describing the efficiency of resources that are used over time

4. STUDY DESIGN AND SETTING

4.1. STUDY DESIGN

A multicentre national prospective cohort study will assess, in a sample of at least 2300 participants presenting clinical signs compatible with early stage of Alzheimer's disease and recruited from French memory clinics, factors that predict the transition to clinical dementia stage during follow-up.

4.2. SETTING

Participants will be recruited from the "Centre de Mémoire de Ressources et Recherches" (CMRR). These clinical sites are clinical research platforms with dedicated resources to conduct clinical research on Alzheimer and other neurodegenerative diseases. Data collection and procedures of participants in the cohort will mainly conform to the current case management, while aiming at optimising standardisation whenever needed.
Eligible memory clinics are those that may include at least 50 individuals during the inclusion period, have access to MRI (1.5 or 3T) and biobank facilities.

A pilot phase has been run in 5 voluntary memory clinics (Bordeaux, Lille, Marseille, Paris Pitié Salpêtrière, Toulouse).

5. ELIGIBILITY CRITERIA

In this study, at least 2300 participants will be enrolled. All participants who satisfy the following inclusion and non-inclusion criteria are eligible. Co-inclusion in other biomedical research will be possible as far as respective principal investigators and legal sponsors agree.

5.1. INCLUSION CRITERIA

- Aged 18 years and above
- Having at least a light cognitive deficit defined as performing worse than one standard deviation to the mean (compared to age and educational norms) in one or

more cognitive domains (assessed from a neuropsychological tests battery exploring memory, language, praxis, vision, executive functions); this deviation being identified for the first time by tests performed less than 6 months preceding date of inclusion (i.e. signature of informed consent)

Or

Having isolated cognitive complaint regardless of its duration while being 60 years and older (i.e. without cognitive deficit as defined above) (maximum stratum size of 300 participants)

(cut-offs for each neuropsychological test are described in appendix IV);

- Clinical Dementia Rating scale either ≤0.5 and not demented
- Visual and auditory acuity adequate for neuropsychological testing
- Having signed an informed consent
- Being affiliated to health insurance

5.2. NON INCLUSION CRITERIA

- Being under guardianship
- Residence in skilled nursing facility
- Pregnant or breastfeeding women
- Alzheimer's disease caused by gene mutations
- Meeting brain MRI exclusion criteria (pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin, or body) or refusing MRI
- Having a history of intracranial surgery
- Having a neurological disease such as: treated epilepsy, treated Parkinson's disease, Huntington disease, brain tumour, subdural haematoma, progressive supranuclear palsy, history of head trauma followed by persistent neurological deficits
- Stroke that has occurred in the last three months
- Schizophrenia history (DSM-IV criteria)
- Illiteracy, is unable to count or to read

6. STUDY PROCEDURES

6.1. BRAIN MRI

6.1.1. DATA ACQUISITION

Brain MRI will be performed according to a standardized procedure (described in Appendix VIII) at least at baseline and repeated at two and four years follow-up examination. MRI examinations are required to be performed in the 3 months following date of screening (i.e. signature of informed consent).

Locally, images will be checked for quality (absence of head motion or artefacts).

Images will then be transferred using either by CD-ROMs or through secured FTP to the "Centre d'Acquisition et de Traitement de l'Image" (CATI) (Head: J.F. Mangin). Images will be checked centrally for:

- Image quality and artefacts
- Consistency of images parameters and head coils
- Brain positioning

Centres will be contacted for failed acquisitions and participants will be rescanned whenever possible and within the next 3 months.

Data will be stored centrally in anonymous original DICOM format (CD and hard disk) and in analyze format (hard disk).

6.1.2. DATA PROCESSING

6.1.2.1. VISUAL RATING

All imaging processing will be performed blind to any participants' clinical data. At images' reception at the CATI, two medical doctors specially trained will read all images and rate the degree of atrophy using the Scheltens' scale and the extent of white matter lesions using the global index of the Fazekas' scale.

6.1.2.2. AUTOMATED VOLUMETRIC ANALYSES

Measurement of global brain volume

Grey Matter (GM), White Matter (WM) and Cerebro-Spinal Fluid (CSF) segmentation will be obtained using optimized Voxel Based Morphometry (VBM) procedure as described in a previous publication.[185] The extracted GM images will be smoothed with a 10-mm FWHM isotropic Gaussian kernel. Smoothing will be applied to render the data ready for statistical analysis by conditioning the residuals to conform to the Gaussian random field model. The resulting smoothed, normalized regions contained the average amount of GM within a region

surrounding a voxel. This technique will be used to assess atrophy throughout the brain without anatomical priors.

Measurement of hippocampus volume

Volume of the hippocampus and amygdala will be obtained using a fully automatic algorithm, which has been developed in the CNRS laboratory UPR-640 for segmentation of the hippocampus and the amygdala.[186] This method is based on the competitive increase of two regions of interest corresponding to these anatomical structures. It does not require any user input, is fast (about 15 minutes), and can be applied to both normal and atrophied structures since it does not involve comparisons with prior shape. This technique has been validated by comparing automated and manual segmentations on 3D T1-weighted MRIs of 16 young healthy controls and eight patients with AD. Mean differences in volume ($V_M - V_A$ / $V_M + V_A$) were 7% for the hippocampus and 11% for the amygdala in controls and 9% and 16% in AD patients. We are currently extending the approach to segment longitudinal data. In this project, this software will be used to obtain cross-sectional as well as longitudinal measures of hippocampal atrophy.

Diffusion

Diffusion data will be analyzed using voxel-based analysis (SPM5 or TBSS) and region of interest approaches.[187] Tractography will be used to assess diffusion changes in specific fiber tracts (BrainVisa software). For specific target fiber tract, diffusion variables will be assessed at each point along the tracts as previously described.[188]

Microbleeds

Microbleeds will be evaluated visually by two independent raters using gradient echo T2-weighted images and automated detection algorithms will also be developped.[189]

White Matter Lesions

White matter lesions volumes will be assessed using an automated method developed by the CATI and validated.[190]

Silent brain infarcts

Silent brain infarct will be evaluated visually by two independent raters using 3D T1-weighted, FLAIR and spin echo T2-weighted images. Number, location and size of the infarcts will be noted.[49]

For MRI data analysis, we will also use whenever possible some tools developed by the consortium Alzheimer's Disease Neuroimaging Initiative (ADNI)[191] which aims at developing and distributing to the scientific community improved methods for MRI quantification.

6.2. BLOOD AND CEREBRO-SPINAL FLUID DRAW

6.2.1. ROUTINE LABORATORY ASSESSMENT

As part of the usual care, some centers might prescribe a blood analysis in which case laboratory results will be recorded in the e-CRF. The measures collected can be all or part of the following :

complete blood count and platelet, PT, ACT, SV, C-reactive protein, phosphate, calcium, creatinine, sodium, potassium, chlore, AST, ALT, alkalin phosphatase, total bilirubin, glucose, cholesterol (total, HDL, LDL), triglyceride, thyroid-stimulating, hormones, folates, B12 Vitamin.

6.2.2. BLOOD SAMPLING FOR BIOBANK

Serum, plasma and full blood samples are drawn at baseline and then every two years for storage (Biobank: appendix V). In case blood cannot be sampled, attempts should be made to perform sampling again whenever possible within the next 3 months.

Any use of the blood biobank will need to be approved by the study co-coordinators and the scientific committee.

6.2.3. CEREBRO SPINAL FLUID (CSF) SAMPLING

When the participant agrees, a lumbar puncture will be performed at baseline and proposed again every two-year according to a standardised protocol as described in appendix VI.

Participants who refuse to have lumbar puncture (LP) at baseline will be asked to reconsider at a next follow-up visit: M6/M12/M18. Similarly, participants who refuse to have LP at M24 will be asked to reconsider at a next follow-up visit: M30/M36/M42 and participants who refuse to have LP at M48 will be asked to reconsider at a next follow-up visit: M54/M60.

All collected samples will be sent to a central biobank for storage. Any use of the blood biobank will need to be approved by the study co-coordinators and the scientific committee.

6.3. ^{18}F-FDG PET-SCAN

When the participant agrees, a ^{18}F-FDG PET-Scan will be performed at baseline and proposed again every two-year according to a standardised protocol as described in detail in appendix VII.

Participants who refuse to have ^{18}F-FDG PET-Scan at baseline will be asked to reconsider at a next follow-up visit: M6/M12/M18. Similarly, participants who refuse to have ^{18}F-FDG PET-Scan at M24 will be asked to reconsider at a next follow-up visit: M30/M36/M42 and participants who refuse to have ^{18}F-FDG PET-Scan at M48 will be asked to reconsider at a next follow-up visit: M54/M60.

Prior to PET-SCAN, women of childbearing potential, i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have an HCG urine dipstick test performed. If it is positive, the ^{18}F-FDG injection and PET scan will not be performed. Baseline ^{18}F-FDG PET-SCAN examinations are required to be performed in the 3 months following date of screening (i.e. signature of informed consent).

6.3.1. ^{18}F-FDG PET-SCAN DATA ACQUISITION

The 15 minutes 3D-acquisition will start 30 minutes after an intravenous injection (via a catheter) of 2 MBq/Kg of 18F-FDG. The minimum injected dose is 125 MBq, the maximum 250 MBq. The injected volume is 2 mL maximum. Subjects have to be in resting state a few minutes before and during acquisition and at least 20 minutes post-injection. An attenuation correction will be performed using a low dose CT scan.

The absorbed dose in main target organ (vesical wall) per unit administered activity is 0.16 mGy/MBq. The effective dose is 0.019 mSV/MBq corresponding, on average, to a dose of 2.7 mSv per PET scan examination for a participant with a body weight of about 70 kg.

The dose received during transmission scan acquisition needs to be added. For a cerebral exploration, the transmission scan has no diagnostic aim and is only undertaken for attenuation correction. It is therefore a low dose examination which lasts less than 10 seconds, with a field of view of 300*300 mm and a dose-length-product (DLP) of 145 mGy.cm (parameters of a General Electric machine for 140 kV et 120 mA) which is equivalent to an effective dose of 0.3 mSv. The effective dose will therefore be, on average, 3 mSv per PET-Scan examination. A repeated examination being proposed after 24 months and again after 48 months of follow-up, the maximum total effective per participant will be of 9 mSv.

Since the dose received per examination is low (3 mSv) and the examination is repeated only every two years, it is not required to have an exclusion period for the participation to other biomedical research studies involving exposure to ionizing radiation.

6.3.2. ^{18}F-FDG PET-SCAN DATA ANALYSIS

This phase will be carried out with the help of specific tools developed by the engineers of CATI. They will be asked to build a linking of all steps of analyses, with a user friendly interface, allowing to run smoothly and easily different the analyses, with the possibility to tests different parameters, or tools. A special attention will be paid to the control of the accuracy/quality of the different steps.

Reduction of centre effect

Experience from the ADNI project will be used to decrease variability in the images due to systematic differences between cameras: a smoothing kernel will be estimated for each scanner model from phantom acquisitions to smooth all images to a common resolution.[192]

Correction for partial-volume effect

We will correct ^{18}F-FDG TEP data for atrophy by applying a two-compartmental partial-volume correction to all subjects.[193] The correction procedure involves convolving a brain mask (a sum of the grey and white matter segmented images from the subject's T1-weighted MRI) with the point-spread function specific to the ^{18}F-FDG TEP tomograph along all axes This will provide a means for estimating the percentage of brain tissue emitting radioactivity at each voxel. The ^{18}F-FDG PET counts for each voxel will be then adjusted based on the percentage of estimated brain matter.[194]

Voxel-wise analysis

After intensity normalization, we will apply voxel-based methods using SPM8 software to compare different groups of patients or analyze correlations between brain metabolism or amyloid burden with clinical, biological or other neuro-imaging parameters.

Volume-of-interest analysis

Volumes of interest (VOIs) from the automatic anatomical labeling atlas[195] will be delineated on the individual MRI for each subject as followed:

The T1 MRI images will be segmented into the cortical and sub-cortical grey matter, white matter and cerebellum directly using histogram analysis, threshold methods and morphological operators. A parcellation of the cortex into 76 structures will then be performed in three steps: i) non-linear registration of the subject's T1 MRI segmented cortex on the MNI template segmented grey matter and application of the inverse transformation to the automatic anatomical labeling atlas, ii) masking of this resampled volume of labels by the segmented cortex structure and filling of the cortex mask using a Voronoi diagram and iii) minimization of the gyri interface distance to the nearest sulci bottoms extracted using the Brainvisa software using a regional deformable model. Hippocampi will be individually automatically segmented onto three-dimensional T1-weighted MR-images.

AAL segmentation will provide uptake values in 76 anatomical regions. This will allow a measure of global amyloid burden, providing an index for each subject, as well as asymmetry indexes. This will also allow regional measurements of metabolic activity using ^{18}F-FDG.

Prediction algorithms using imaging data

The characteristics which allow for discriminating between different patients groups will be extracted either from the voxel-based analysis, or by using anatomical regions of interest. They will be classified with SVM, along with other clinical and neuroimaging data.

7. ASSOCIATED TREATMENTS

All treatments are allowed and must be recorded in the CRF.

A participant may be willing to take part in a pharmacological clinical trial during the ongoing follow-up period of MEMENTO. Principal investigators and sponsor of both the trial and MEMENTO should be informed and agree. The participant would then be allowed attending only the trial visits during the trial period. As it is indeed of utmost importance that attrition remains as low as possible over the follow-up, the participant will be invited to pursue the follow-up visits of MEMENTO once the trial has ended.

8. ENDPOINTS

8.1. PRIMARY ENDPOINT

The primary endpoint is the progression to clinical dementia stage according to standardized classifications (DSM-IV for dementia and NINCDS-ADRDA for Alzheimer's disease). (appendix X, appendix IX)

8.2. SECONDARY ENDPOINTS

Secondary endpoints are:

- Mortality
- Loss of autonomy based on functional activity assessment
- Institutionalisation
- Speed of cognitive decline based on change in cognitive performances
- Cardiovascular event (Stroke and Coronary events)
- Quality of life
- Prodromal AD (Pre-symptomatic dementia)
- Longitudinal evolution of biomarkers measured from blood, CSF, structural neuroimaging and molecular neuroimaging (^{18}F-FDG PET).

Ad hoc designated committees will validate dementia diagnosis (and aetiology), cardiovascular events, and mortality causes.

9. DATA COLLECTION AND FOLLOW-UP

All CMRR staffs involved in the implementation of the study procedures will be trained in two ways:

- On site visits
- Specific Training sessions for neuropsychological and neuropsychiatric assessments (CDR, and NPI-C)

This should contribute to improve standardisation across sites.

9.1. STUDY CALENDAR

- Start of inclusions: April 8th 2011
- Duration of the inclusion period: 39 months
- End of inclusion period: June 30th 2014
- Duration of each participant's participation: 5 years +/- 3 months
- Total duration of the study: 10 years

9.2. TABLE SUMMARISING PARTICIPANTS' FOLLOW-UP

	Screening	Baseline (Month 0)	Month 6		Month 12	Month 18		Month 24	Month 30		Month 36	Month 42		Month 48	Month 54		Month 60
	Center	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center	Center	Phone	Center
Explain Study	✓																
Obtain Consent	✓																
Inclusion and Non Inclusion Criteria[1]		✓															
Socio-demographic characteristics		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
Medical history or event		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
Physical, neurological examinations		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
Medication		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
Clinical Dementia Rating scale	✓		✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
Full neuropsychological battery[2]	✓		✓[a]		✓	✓[3]		✓	✓[3]		✓	✓[3]		✓	✓[3]		✓
AD-8 dementia screening interview				x			x			x			x			x	
Mini-Mental State Examination	✓		✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
Subjective complaint assessment (Visual analogic Scale)		✓	x		✓	x		✓	x		✓	x		✓	x		✓
Neuropsychiatric Inventory		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓		✓
Neuropsychiatric Inventory Questionnaire				x			x			x			x			x	
Lifestyle (Mini Nutritional Assessment, alcohol and smoking habits, International physical activity questionnaire)		✓			✓			✓			✓			✓			✓
Autonomy in daily life activities (Lawton IADL and Katz ADL scales)		✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	x	✓
Motricity (SPPB)		✓			✓			✓			✓			✓			✓
Quality of life (EQ-5D)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lewy Body disease signs assessment		✓			✓			✓			✓			✓			✓
Human sciences and health economic component		✓			✓			✓			✓			✓			✓
Blood sampling laboratory assessment[4]		✓			✓			✓			✓			✓			✓
Biobank[5]		✓						✓						✓			
DNA Sample collection[6]		✓						✓						✓			
RNA collection		✓						✓						✓			
Brain structural MRI		✓						✓						✓			
Positron emission tomography – Scan (FDG)[1]		✓	✓[6]		✓[6]	✓[6]		✓	✓[6]		✓[6]	✓[6]		✓	✓[6]		✓[6]
CSF collection by lumbar puncture		✓	✓[7]		✓[7]	✓[7]		✓	✓[7]		✓[7]	✓[7]		✓	✓[7]		✓[7]

[1] HCG urine dipstick tests are performed for women of childbearing potential
[2] Digit span, visuo-sptatial span, Grober & Buschke test, DMS 48, Verbal Fluency, Praxis, DO 80, Rey figure, TMT A & B, BREF
[3] For participants not demented at previous examination but CDR≥1
[4] In case blood sampling is performed as part of usual care, the laboratory results will be recorded and can include part or all of the following: Complete blood count platelet, TP, TCA, VS, C-reactive protein, phosphate, calcium, creatinine, Sodium, potassium, chlore, AST, ALT, alkalin phosphatase , total bilirubin, Glucose, cholesterol (total, HDL, LDL), triglycerids, Thyroïd-stimulating, Folates, B12 Vitamins (Optional)
[5] At inclusion if a usual care blood sampling is planned after informed consent was signed, an additional maximum of 30 mL of blood will be collected and stored in the biobank. Otherwise, participants will have specific blood intake from which a maximul of 30 mL will be collected for biobank storage.
[6] Performed only if participant does not state to refuse genetic tests in informed consent
[7] Participants who refuse to have 18F PET FDG at baseline will be asked to reconsider at 6, 12, 18 month follow-up, those who refused to have 18F PET FDG at 24-month will be asked to reconsider at 30, 36, 42 month follow-up, and those who refused to have 18F PET FDG at 48-month follow-up will be asked to reconsider at 54, and 60 month follow-up
[8] Participants who refuse to have lumbar puncture at baseline will be asked to reconsider at 6, 12, 18 month follow-up, those who refused to have lumbar puncture at 24-month will be asked to reconsider at 30, 36, 42 month follow-up, and those who refused to have lumbar puncture at 48-month follow-up will be asked to reconsider at 54, and 60 month follow-up

ABBREVIATIONS : AD=Alzheimer's Disease IADL=Instrumental Activities in Daily Living, ADL=Activities in Daily Living, FDG= [18F]-fluorodeoxyglucose, SPPB=Short Physical Performance Battery, MRI=Magnetic Resonance Imaging, DNA= DeoxyriboNucleicAcid, RNA= RiboNucleicAcid, EQ-5D=Euroqol

9.3. SIGNATURE AND INFORMED CONSENT

Written informed consent must be obtained prior to the initiation of any study procedure. The investigating physician informs the participant of the objectives, type of constraints and foreseeable risks of the study. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form. No subject should be obliged to participate in the study. Participants must be given ample opportunity to enquire about details of the study. The information must make clear that refusal to participate or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care.

The participant must be made aware of (and give consent to) the fact that monitors, auditors, and representatives of Independent Ethic Committees and regulatory authorities are granted direct access to the subjects medical records without violating subject confidentiality, and to the extent permitted by applicable regulations. The participant should be informed that by signing the informed consent form, the participant authorises such access.

The participant must be informed that biological samples taken within the framework of the study are anonymised and stored at a central location. These samples are to be used for the scientific objectives. The participant signs and dates the informed consent. The informed consent is dated and countersigned by the investigator or a delegated person who explained the study. The investigator or his delegate also inscribes his complete address and telephone number on the consent form. The informed consent is signed in one original and two copies obtained by triplication. One of the copies of the signed informed consent is given to the participant.

Signed informed consents are retained by the investigator and made available (for review only) to the study monitor, auditor and inspector, upon request. An anonymised copy of the signed consent form is provided to the sponsor or its delegate.

9.4. SCREENING PHASE

Screening phase will be undertaken during the course of a standard consultation in a CMRR which is usually organised in several steps within a maximum of six months.

A screening assessment for eligibility is performed.

Signed and written informed consent (screening date) for the study must be obtained at the latest at the screening visit and prior to the initiation of any study related interviews or specific investigation (such as blood or CSF sampling, or brain imaging examinations).

Screening procedures include:

- Demographic information: date of birth, sex

- Clinical Dementia Rating Scale[196]

It is used to characterize six domains of cognitive and functional performance applicable to Alzheimer's disease and related disorders: Memory, orientation, judgment & problem solving, community affairs, Home & Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the participant and a reliable informant that can be contacted by phone if not present at a given study visit interview. A global CDR staging score is derived from the 6 domains score using an algorithm. If an informant is not present at the visit, it is required to identify one and to contact him/her by phone.

- Subjective complaint: visual analogic scale

It is a self-assessment scale including 10 questions on complaints that the participants have to rate from 0 to 10.

- Full Neuropsychological Battery
    - *Global cognition*: Mini-Mental State Examination [197]

      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) [198]

          The tests 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[199]

          The tests 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)[200]
        - The test consists in a visual recognition memory task.

- *Language and semantic Memory*
  - Verbal Fluency [201]

    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) [202]

    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*[203]

  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*[204]

  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 Part A and B[205,206]

    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 [207,208]

    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.

- Optional Neuropsychological Battery
    - Visuospatial span (forward and backward) [209]

      The test is a subtest of the Wechsler battery that assesses spatial memory.
    - *Visuo Spatial abilities*[204]

      Rey-Osterrieth Complex Figure Test copy at 30 minutes.
- Assessment of inclusion and non-inclusion criteria

- For women of childbearing potential, i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have an HCG urine dipstick test performed.

9.5. BASELINE VISIT (M0)

The baseline visit needs to be undertaken within three months following the informed consent signature (screening date).

At baseline visit, the following information is recorded

- Socio-Demographic information:
    - Educational background
    - Professional background
    - Level of income (direct and indirect)
    - Life conditions (housing, family)
- Lifestyle
    - Alcohol consumption
    - Smoking habits
    - Diet habits according to a brief food frequency questionnaire[210]
    - Physical activity using International Physical activity questionnaire[211]
    - Social network
    - Leisure activities
- Relevant medical history with specific inquiry on :
    - Family history of Alzheimer's disease or related disorders
    - Cardiovascular disease and vascular risk factors
- Current medical conditions

- Current medication :
    - For each treatment the dosage and the dose are recorded
    - Specific questions on Substitution Hormonal therapy for women
    - Non pharmacological care

- Complete physical examination including
    - Height, weight measurements
    - Waist, hip, arm, calf, head measurements
    - Laterality assessment
    - Blood pressure measurement according to the following protocol:
        - Three measures on the right arm after two minutes of rest in sitting position
    - Neurological examination

- Motricity will be assessed using the Short Physical Performance Battery (SPPB),[212] an objective assessment tool for evaluating lower extremity functioning in older persons. Measures include Balance, Gait, and Lower Extremity Strength.

  The Balance subscale consists of side-by-side, semi-tandem, and tandem stands.

  The Gait, or Walking Speed, subscale has the participant walk an 8-meter course at his or her usual speed.

  The Lower Extremity Strength subscale is assessed by the time it takes for the participant to stand up and sit down in a chair as quickly as possible five times (repeated chair stands).

- Autonomy

  The IADL and ADL scales will be used to assess the level of autonomy.[213,214]

- Neuropsychiatric Inventory (NPI-C)[215]

  The NPI-C is a clinician and informant based behavioural rating system developed and validated for the assessment of mental state and behavioural abnormalities in dementia. The NPI-C records the presence or absence, severity (rated from 0 to 3), and frequency (rated 0 to 4) of 12 symptom fields: delusions, hallucinations, agitation, depression/dysphoria, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep disorders, eating disorders.

  An index of severity is created for each behavioural variable.

- Lewy Body disease signs assessment
    - Three tests of the Visual Object and Space Perception Battery (VOSP)[216] 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)[217]
- Hallucinations assessment, adapted from Parkinson's Disease-Associated Psychotic Symptoms Questionnaire[218]
- Fluctuation assessment, adapted from "Clinician assessment of fluctuation"[219]
- Neurovegetatives disorders exploration (orthostatic hypotension, hypersalivation, rhinorrhea, photophobia, constipation)
- Depression assessment using Mini International Neuropsychiatric Interview (MINI)[220]

- 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).[221]
- Blood sampling (participant has to be fasting for at least 8 hours prior to blood draw) for:
  - If the participant has blood sampling as part of usual care, local laboratory assessment include part or all of the following :
    - Haematology: complete blood count platelet,
    - PT, ACT, SV, C-reactive protein
    - Clinical chemistry: phosphate, calcium, creatinine, Sodium, potassium, chlore, AST, ALT, alkalin phosphatase, total bilirubin, Glucose, cholesterol (total, HDL, LDL), triglycerids.
    - Thyroïd-stimulating, Folates, B12 Vitamins
  - Biobank: see appendix V.
- Lumbar puncture:

  A lumbar puncture is proposed to all participants for the purpose of research. It is optional and to be performed in the 3 months following the screening date.

  Nevertheless, if a lumbar puncture is prescribed by the clinician and performed for the sake of case management, the results of dosages performed will be reported in the CRF and CSF will also be sampled for the biobank. Whether participants are informed about the results will also be collected. See appendix VI.

- Informant: in case the participant comes with somebody to the visit, this "informant" will be asked a few questions (self-reported) in order to qualify him/her (informant vs. caregiver). If the informant is a caregiver, he/she will be administered a specific questionnaire in order to qualify and quantify the level of care he/she provides and to estimate the burden of the care on his/her own life. For participants coming alone to the consultation, they will be asked to provide the name of an informant that will be contacted by phone and administered a standardized questionnaire. If the informant present during the visit is the participant's spouse, he/she will be asked to fill self-administered questionnaire on quality of life (LEIPAD questionnaire).[222]

- Human sciences, social sciences and economy questionnaires :
    - Social network characteristics
    - Daily life description
    - Economic consequences of the participants' condition (society and family levels): level of help needed and received

- Brain MRI (appendix VIII): To be performed in the 3 months following screening date

- ^{18}F-FDG PET-Scan (appendix VII): Optional and to be performed in the 3 months following screening date

9.6. FOLLOW-UP VISITS

9.6.1. MONTH 6 (M6), MONTH 18 (M18), MONTH 30 (M30), MONTH 42 (M42), MONTH (M54)

Visits M6, M18, M30, M42, and M54 need to be completed within the 6, 18, 30, 42, 54 ± 3 months following the screening date.

For any of these follow-up examinations, it is advised that it takes place at the study center (memory clinic), but in case the clinical investigator considers otherwise, it is allowed to have a simplified follow-up by phone.

9.6.1.1. INTERVIEW AT STUDY CENTER

Procedures at months 6, 18, 30, 42, 54, include:

- Change in demographics since last visit
- Medical events since last visit
- Subjective complaint: visual analogic scale
- Stress exposure
- Clinical Dementia Rating scale
- Mini-Mental State Examination (MMSE)

- Quality of life
- ADL, IADL
- Current medications
- Physical and neurological examinations
- If CDR≥1, the full neuropsychological battery will be administered
- NPI-C
- 18F-PET-FDG :
    - Participants who refuse to have 18^F PET FDG scan at baseline will be asked to reconsider at 6 month and if they agree will have follow-up 18^F PET FDG scans at M30 and M54
    - Participants who refuse to have 18^F PET FDG scan at M0-M6-M12 will be asked to reconsider at 18 month and if they agree will have follow-up 18^F PET FDG scan at M42
    - Participants who refuse to have 18^F PET FDG scan at M0-M6-M12-M18-M24 will be asked to reconsider at 30 month and if they agree will have follow-up 18^F PET FDG scan at M54
- Lumbar puncture :
    - Participants who refuse to have lumbar puncture at baseline will be asked to reconsider at 6 month and if they agree will have follow-up lumbar puncture at M30 and M54
    - Participants who refuse to have lumbar puncture at M0-M6-M12 will be asked to reconsider at 18 month and if they agree will have follow-up lumbar puncture at M42
    - Participants who refuse to have lumbar puncture at M0-M6-M12-M18-M24 will be asked to reconsider at 30 month and if they agree will have follow-up lumbar puncture at M54

9.6.1.2. INTERVIEW BY PHONE

Procedures at months 6, 18, 30, 42, 54, include:

- Reasons for conducting the interview by phone
- Change in demographics since last visit
- Medical events since last visit
- Quality of life
- ADL, IADL
- Current Medications

If an informant is available by phone, the following questionnaires will be administered:

- Neuropsychiatric Interview-Q
- AD-8 dementia screening interview

9.6.2. MONTH 12 (M12), MONTH 24 (M24), MONTH 36 (M36), MONTH 48 (M48), MONTH 60 (M60)

Visits M12, M24, M36, M48, and M60 need to be completed within 12, 24, 26, 48, and 60 months ± 3 months following the screening date.

Procedures at months 12, 24, 36, 48, 60 include:

- Change in demographics since last visit
- Medical events since last visit
- Subjective complaint: visual analogic scale
- Clinical Dementia Rating scale
- Full neuropsychological battery will be administered
- Neuropsychiatric Interview-C
- Lifestyle (Alcohol consumption, Smoking habits, MNA, Physical activity, Social network, Leisure activities)
- Current medical conditions
- Current medication
- Physical examination including weight measurement, blood pressure measurement and Neurological examination
- Motricity using the Short Physical Performance Battery (SPPB)
- Autonomy / Quality of life
- Lewy Body disease signs assessment
- Blood sampling for Local laboratory assessment & possibly biobank
- Informant/Caregiver questionnaires, including LEIPAD self-assessment questionnaire for spouses[222]
- Human sciences, social sciences and economy questionnaires
- 18F-PET-FDG :
    - Participants who refuse to have 18^F PET FDG scan at M0-M6 will be asked to reconsider at 12 month and if they agree will have follow-up 18^F PET FDG scans at M36 and M60

- Participants who refuse to have 18^F PET FDG scan at M0-M6-M12-M18-M24-M30 will be asked to reconsider at 36 month and if they agree will have follow-up 18^F PET FDG scan at M48
- Participants who refuse to have 18^F PET FDG scan at M0-M6-M12-M18-M24-M30-M36-M42-M48-M54 will be asked to reconsider at 60 month

▪ Lumbar puncture :

- Participants who refuse to have lumbar puncture at M0-M6 will be asked to reconsider at 12 month and if they agree will have follow-up lumbar puncture at M36 and M60
- Participants who refuse to have lumbar puncture at M0-M6-M12-M18-M24-M30 will be asked to reconsider at 36 month and if they agree will have follow-up lumbar puncture at M48
- Participants who refuse to have lumbar puncture at M0-M6-M12-M18-M24-M30-M36-M42-M48-M54 will be asked to reconsider at 60 month

9.6.3. MONTH 24 (M24), MONTH 48 (M48)

- Lumbar puncture:

  Lumbar puncture is optional and needs to be performed within the 3 months following M24 or M48 visits. M24 lumbar puncture will be proposed to participants who had lumbar puncture at baseline (M0) as well as to participants who refuse to have lumbar puncture at M0-M6-M12-M18. M48 lumbar puncture will be proposed to participants who had lumbar puncture at baseline or 24 months (M0 or M24) as well as to participants who refuse to have lumbar puncture at M0-M6-M12-M18-M24-M30-M36-M42.

- Brain MRI (appendix VIII): To be performed at M24 ± 3 months or M48 ± 3 months visits.

- ^{18}F-FDG PET-Scan (appendix VII): Optional and to be performed at M24 ± 3 months or M48 ± 3 months visits. ^{18}F-FDG PET-Scan will be proposed to participants who had lumbar puncture at baseline (M0) as well as to participants who refuse to have ^{18}F-FDG PET-Scan at M0-M6-M12-M18. M48 ^{18}F-FDG PET-Scan will be proposed to participants who had ^{18}F-FDG PET-Scan at baseline or 24 months (M0 or M24) as well as to participants who refuse to have ^{18}F-FDG PET-Scan at M0-M6-M12-M18-M24-M30-M36-M42.

9.7. VALIDATION OF CLINICAL ENDPOINTS

9.7.1. VALIDATION OF DEMENTIA CASES

From Month 6 to Month 60, a participant will be considered as having possibly reached the clinical stage of dementia if he/she has a deterioration of cognitive performances and/or behavioral deficits severe enough to interfere with his/her social life or his/her autonomy in daily life.(DSM-IV-TR and NINCDS-ADRDA criteria)[223,224]

The diagnosis of clinical dementia of Alzheimer type will be based on the DSM-IV and NINCDS-ADRDA criteria [224] (appendix IX) and the severity of dementia will be rated using the Clinical-Dementia Rating scale (≥1).

All incident cases will be validated by a panel of expert neurologists/geriatricians who will review available data from the case file to classify dementia cases according to dementia subtypes (Alzheimer[224], vascular[225], frontotemporal[226], and Lewy body dementia[180]).

From data recorded, an alert will be sent to the coordinating center in case of dementia diagnosis by the clinician.

Once this alert has been received, a standardised "case file" will be generated by the coordinating centre and sent to members of the "dementia validation panel". They will be asked to send their diagnosis within two weeks of file reception. In case of consensus, the final diagnosis will be recorded. Otherwise, a phone meeting will be organised in order to reach consensus.

The committee will have a face-to-face meeting once a year to review some of the cases.

9.7.2. VALIDATION OF CARDIOVASCULAR EVENTS

If, at a visit, a cardiovascular event is reported, an alert will be sent to the coordinating center. Data will be collected on dates of the event, place of hospitalization and hospital records where possible.

From the information gathered, a standardised "case file" will be generated by the coordinating centre and sent to the members of the "cardiovascular event validation panel". They will be asked to send their diagnosis within two weeks of file reception. In case of consensus, the final diagnosis will be recorded. Otherwise, a phone meeting will be organised in order to reach consensus.

The committee will have a face-to-face meeting once a year to review some of the cases.

Outcomes will be coded according to the tenth revision of the International Classification of Diseases.

9.7.3. VALIDATION OF CEREBROVASCULAR EVENTS

If, at a visit, a cerebro-vascular event is reported, an alert will be sent to the coordinating center. Data will be collected on dates of the event, place of hospitalization and hospital records where possible.

From the information gathered, a standardised "case file" will be generated by the coordinating centre and sent to the members of the "cerebro-vascular event validation panel". They will be asked to send their diagnosis within two weeks of file reception. In case of consensus, the final diagnosis will be recorded. Otherwise, a phone meeting will be organised in order to reach consensus.

The committee will have a face-to-face meeting once a year to review some of the cases.

Outcomes will be coded according to the tenth revision of the International Classification of Diseases.

9.7.4. FOLLOW-UP OF DEMENTED PARTICIPANTS

Once participants are classified as clinically demented, they will pursue follow-up in the cohort and have specific assessment at subsequent waves (every 6 months) that will include:

- Change in demographics since last visit
- Medical events since last visit
- Clinical Dementia Rating scale
- MMSE
- Neuropsychiatric Interview-C
- Current medical conditions
- Current medication
- Physical examination including weight measurement, Blood pressure measurement and Neurological examination
- Motricity using the Short Physical Performance Battery (SPPB)
- Autonomy
- Quality of life
- Informant questionnaire including ZARIT scale

Other tests and explorations performed during the usual MEMENTO follow-up visits will be optional and performed at the investigator’s discretion and as deemed clinically relevant.

9.8. DISCONTINUATION AND WITHDRAWAL

Though participants have the right to interrupt their participation temporarily or definitely at any time, it is of utmost importance that attrition in the study remains as low as possible. Therefore, appropriate actions may be taken to favour completeness of follow-up visits over the whole duration of the study.

9.8.1. TEMPORARY DISCONTINUATION

If participants are not willing or able to complete the full schedule of assessments at any visit, those assessments or procedures they are able to complete should be conducted. If participants are no longer willing or able to travel to the clinic for interim visits (Month 6 (M06), Month 18 (M18), Month 30 (M30), Month 42 (M42), Month 54 (M54)), as much information should be collected via telephone as possible.

If needed, attempts will be made to get information about the participants' vital status and dementia status by contacting his/her general practitioner and/or an informant. In case it is suspected that the participant has reached the clinical stage of dementia, the AD8 scale will be administered to the informant. It is a brief, sensitive measure that validly and reliably differentiates between non-demented and demented individuals based on informant.[227]

There might be circumstances when participants may take advantage in participating into another biomedical research, especially pharmacological clinical trials. On a case by case basis, it is possible that coordinating investigator and sponsor of the other biomedical research and MEMENTO investigators and sponsor, agree to allow temporary discontinuation of follow-up visits in MEMENTO. The participant would then be allowed attending only the trial visits during the trial period. In order to avoid attrition of the MEMENTO study over follow-up, the participant will be invited to pursue the follow-up visits of MEMENTO once the trial has ended.

9.8.2. PREMATURE DISCONTINUATION

A participant prematurely discontinues the study if:

- he/she withdraws informed consent,
- he/she dies before the end of he study.

When a participant withdraws his/her consent to participate in the study, no new information must be collected and recorded in the database after the date of withdrawal. Similarly, no samples must be collected after that date in the context of the research study.

Withdrawals must be reported to the coordinating center as soon as possible (by fax and by letter). The investigator must document the date, reason and any answers given in response to

the participant, in the participant's medical records. In case the participant discontinues the study prematurely, the end-of-study page of the CRF is completed.

9.8.3. LOSS 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 withdraw), 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.

The coordinating center should be informed as soon as possible (by fax and by letter) that a participant is lost to follow up.

Attempts will be made to get information about the participants' vital status and dementia status by contacting his/her general practitioner and/or an informant. In case it is suspected that the participant has reached the clinical stage of dementia, the AD8 scale will be administered to the informant. It is a brief, sensitive measure that validly and reliably differentiates between non-demented and demented individuals based on informant.[227]

9.9. CONSTRAINTS RELATING TO THE STUDY

Co-inclusion in other biomedical research will be possible as far as investigators and legal sponsors of each of the study involved agree (cf 9.8.1. Temporary discontinuation)

9.10. COLLECTION OF BIOLOGICAL SAMPLES

Blood and CSF samples are collected at the study site. The study site is responsible for cryopreservation, separation and storage of all samples collected at the study site as prescribed by the protocol.

The samples that have to be transported to a central biobank are stored at the study site until shipment. The study site provides yearly reports of the use and fate of the blood samples to the CIC-EC7.

All laboratories involved shall use the human materials sampled in the study only in accordance with the agreed protocol, the international Good Clinical Practice principles as laid down by the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (ICH GCP), the EU Clinical Trial Directive and relevant other legislation or regulatory requirements as may be required in the Territory.

The CIC-EC7 shall supply study sites with guidance on handling and storage of the materials, and other related relevant information.

10. MANAGEMENT OF ADVERSE EVENTS, NEW FACTS AND/OR CASE OF PREGNANCY

10.1. DEFINITIONS

Adverse event (article R.1123-39 of the French Public Health Act)

Any harmful event occurring in a person taking part in a biomedical research study, whether or not that event is linked to the study or to the product being investigated in the study.

Adverse effect of a clinical trial for not health product (article R.1123-39 of the French Public Health Act)

Any adverse event related to the research meaning *any adverse related to procedures, methods, practiced action or products under study or products needed for the study.*

Serious adverse event (article R.1123-39 of the Public Health Act and the ICH E2B guide)

Any adverse event that:

- ✓ results in death,
- ✓ is life-threatening,
- ✓ requires hospitalisation or prolongation of existing hospitalisation,
- ✓ results in persistent or significant incapacity/disability,
- ✓ is a congenital anomaly/birth defect,
- ✓ or any other medically important condition,

and when regarding a medicinal product, whatever the administered dose.

Unexpected adverse effect (article R.1123-39 of the French Public Health Act, paragraph #8)

Any adverse effect of which the nature, the severity, or progression do not concord with the information on the products, the procedures, methods, practiced actions performed during the research.

The expectedness criteria is assessed regarding the informations described in the protocol or the investigator brochure, about the products under study, products needed for the study, the procedures, methods, practiced actions during the research.

If the serious effect is related to an health product used for the study, the expectedness criteria is assessed regarding the current reference for this health product (cf. Summary of Characteristics of the product) when it is used according to its market authorisation.

New information (order dated 24 May 2006)

New safety information which could lead to re-evaluation of the benefit/risk ratio of the study, or which may be sufficient to envisage modifications to documents concerning the study, to the way the study is conducted, or, if necessary, to the way the product is used.

10.2. DESCRIPTION OF EXPECTED ADVERSE EFFECTS IN MEMENTO AND ITS ANCILLARY STUDIES

Expected adverse effects are:

- ✓ Illness detection (such as tumour, aneurysm) with study imaging procedures (MRI, PET-scan),
- ✓ Adverse effect of the tracer ^{18}F-FDG, such as listed in the summary of characteristics of the product,
- ✓ Adverse effect of the tracer florbetapir such as listed in the summary of characteristics of the product (Ancillary study MEMENTO-AMYGING).
- ✓ Adverse effect of the tracer flutemetamol such as listed in the investigator's brochure (Ancillary study MEMENTO-AMYGING).
- ✓ Adverse effect of the mydriatic eye drops such as listed in the summary of characteristics of the product used for the retina exploration (Ancillary study MEMENTO-VASCOD)
- ✓ Vasovagal reaction and headaches after lumbar puncture,
- ✓ Haematoma and vasovagal reaction after blood sampling,
- ✓ Adverse effects of the medical treatments of dementia or Alzheimer's disease such as reported in the summary of characteristics of the products.

If these adverse effects have or lead to a seriousness criteria as described above (Cf. § 10.1 Definition of serious adverse event), they must be notified immediately to the sponsor (Cf. § 10.3).

10.3. ACTION TO BE TAKEN IN CASE OF SERIOUS ADVERSE EVENT, NEW INFORMATION OR PREGNANCY

The investigator evaluates each adverse event with regard to its seriousness.

He-she must notify the sponsor, without delay from the day of becoming aware of any serious adverse event (SAE) or new safety information, occurring:

- from the date the consent form is signed,
- during the follow-up period of the participant as planned in the protocol,

Without time limit when it could be due to the study

TYPE OF EVENT	NOTIFICATION METHOD	TIME LIMIT FOR NOTIFYING THE SPONSOR
Non-serious AE	In the case report form (e-CRF)	Not to be immediately notified to the sponsor
Expected or unexpected SAE	Immediately reported in the electronic case report form (e-CRF) or via SAE file by e-mail or fax	**Sponsor to be notified immediately**
New safety information	Immediately reported in the electronic case report form (e-CRF) or via SAE file by e-mail or fax	**Sponsor to be notified immediately**
Pregnancy	Pregnancy declaration form, by fax	**Sponsor to be notified** on confirmation of the pregnancy

Unité de sécurité et de Vigilance des Essais Cliniques (Safety and Vigilance unit)

CHU de Bordeaux

Direction de la Recherche Clinique

Email: Vigilance.essais-cliniques@chu-bordeaux.fr

Fax: 05.57.82.12.62

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All these events must be monitored until they are **completely resolved**. The investigator will send the sponsor additional information concerning the evolution of the event if not mentioned in the initial report.

IN CASE OF PREGNANCY

Pregnancy occurring during the period or immediately after a study does not constitute an SAE. However, a pregnancy must be notified (Pregnancy declaration form, pregnancy follow-up declaration form) because it requires particular monitoring throughout its duration. Any abnormality observed in the foetus or child will then be notified as an SAE (electronic reporting

via e-CRF). Any elective termination of pregnancy, medical termination of pregnancy or spontaneous abortion must give rise to a notification of pregnancy (and SAE notification).

10.4. DECLARATION OF UNEXPECTED SERIOUS ADVERSE EFFECTS AND NEW SAFETY INFORMATION BY THE SPONSOR

The vigilance unit declares any unexpected serious adverse effect occurring during the study or any information which could compromise the security of participants, as soon as possible and no later than seven days after knowledge by the sponsor:

- to the ANSM [the National Agency for the Safety of medicines and health Products],
- to the relevant ethics committee. If necessary, the committee ensures that participants in the study are informed of this effect and that they confirm their consent.

10.5. ANNUAL SAFETY REPORT

At the anniversary date of the first inclusion, the sponsor drafts a safety report that includes:

- the list of serious adverse events potentially related to the research (effects), both expected and unexpected,
- a critical analysis of the safety of study participants.

This report is sent to the ANSM and the CPP within 60 days of the anniversary date of the first inclusion.

11. STUDY COMMITTEES

11.1. COMMITTEE CHARTER

Membership and specific roles and relationships of committees for the Memento cohort are described in the MEMENTO Committee Charter (Appendix XI).

11.2. SCIENTIFIC STRATEGY COMMITTEE

The study scientific committee is the group that provides overall scientific strategy supervision for the study and facilitates scientific activities on behalf of the sponsor and the “Fondation Plan Alzheimer”.

Its composition is detailed in appendix XII The chair for a cycle of 3 years (2014-2016) is Pierre Ducimetière, then the vice-chair, Hugues Chabriat, will become chair and a new vice-chair will be nominated by the scientific committee. The scientific committee meets thrice per year.

11.3. EXECUTIVE COMMITTEE

The Executive Committee is the group in charge of making decisions for the cohort. It is the formal link between the Memento Scientific Strategy Committee, the Steering Committee and Memento operations. The Executive committee is formed by the co-chairs of the scientific strategy group, the Director General of the Fondation Plan Alzheimer and the two co-principal investigators. The Executive Committee meets once per month (either physically or via tele- or videoconference).

11.4. STEERING COMMITTEE

The steering committee is the operational team that undertakes the day-to-day management of the MEMENTO cohort, and receives all proposals of new scientific projects for feasibility diagnosis. Its composition is detailed in appendix XII. The steering committee is chaired by one of the two co-PIs and meets every two-month mainly through tele- or video-conferences.

11.5. GENERAL ASSEMBLY

The General Assembly includes members of the Scientific and Steering Committees, and representatives from all stakeholders. Currently, the latter includes: the mission Pilotage Plan Alzheimer, pharmaceutical industry, national health agencies and health insurance, France Alzheimer. This large Assembly meets once a year physically with the aim of reviewing main facts and results of the previous year, and discussing the plans for the next period.

11.6. ENDPOINT REVIEW COMMITTEE

An Endpoint Review Committee will be appointed for this study. It will be composed of different validation committees specific to the following clinical endpoints:

- Clinical dementia
- Cardiovascular events
- Cerebro-vascular events
- Death (and cause of death)

Guiding principles of endpoint review committees are detailed in appendix XIII.

12. STATISTICS

12.1. SAMPLE SIZE

Sample size was calculated under the assumption that the cumulative incidence of clinical dementia over 5-year follow-up will be 20%.[228-231]

Therefore an initial sample of 2300 individuals, recruited over the period of inclusion, and then annually increased by an equivalent number to the deaths or lost to follow-up occurring in the

past year will provide a power of at least 83% to show a hazard ratio of clinical dementia of 1.2 for each unit increase in any exposition level (α=0.05, standard deviation of exposure =1, cumulative dropout rate=10%).

Once the target size will have been reached, a plan for maintaining a sample in the range of 2300-2500 will be implemented after discussion with the Scientific and Steering Committees.

12.2. ANALYSIS OF THE PRIMARY ENDPOINT

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

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

Recent work has pointed out the necessity of handling drop-outs and death separately in longitudinal studies in the elderly.[232] Although effort will be made to minimize dropputs rates in this cohort, adequate statistical methods will be applied in order to take into account missing participants in the analyses.[232,233]

12.3. ANALYSIS OF THE SECONDARY ENDPOINT

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

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

12.4. COMPARISONS WITH NATIONAL DATABASE (BNA)

The "Plan Alzheimer" has introduced an exhaustive recording of all participants attending a CMRR or a memory clinic in France.

The following information is required to be recorded for each participant:

- Age
- Gender
- Place of birth
- Education level
- Long disease pension
- Diagnosis (Dementia, MCI, not demented)
- If dementia, aetiology
- Mini-Mental State Examination score

Analyses will be undertaken to compare this national database with our cohort for the above characteristics. This will provide useful information on potential bias selection in our cohort.

13. MONITORING THE STUDY

13.1. ON SITE MONITORING

A monitoring plan, describing quality control of collected data in comparison to on-site source data, is developed as a separate document.

13.2. MRI AND PET MONITORING

Processing of MRI and PET data will be performed by the "Centre d'acquisition et de traitement Automatisé des Images" (CATI, Head: Jean-François Mangin, Saclay). Quality control at the different steps of MRI and PET data acquisition will be made.

14. ACCESS TO DATA AND SOURCE DOCUMENTS

14.1. ACCESS TO DATA

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

The investigators will make available to the people with a right of access to these documents under the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control, and auditing the biomedical research.

14.2. SOURCE DATA

Source data must be available to document the existence of the study patients and should substantiate integrity of study data collected. Source data must include the original documents relating to the study, the medical treatment and medical history of the patient.

The following information should be included in the source medical records:

- Demographic and socio-economic data (date of birth, sex, education, working status) at inclusion (updates at follow-up visits will be included with human science data and health economics assessment)
- Study name and protocol number in which the patient participates
- Date of signing informed consent form
- Details related to the inclusion criteria
- Medical history and physical examination details
- Current medications
- Results of relevant examinations

- Laboratory print-outs
- Visit dates
- Any other relevant information relating to the patient care

For the following information, the source documentation will either be the "notebook for follow-up of patients with a cognitive complaint or a MCI[a]" and "neuropsychological tests battery notebook" for neuropsychological tests battery developed by the Alzheimer Methodology Group[b] jointly with CMRRs physicians or, in case sites are willing to use their own patient file templates, the usual medical or neuropsychological patient file:

- Clinical Dementia Rating scale
- Full neuropsychological battery
- Subjective complaint assessment (Visual analogic Scale)
- Neuropsychiatric Inventory
- Stress scale
- Lifestyle (Mini Nutritional Assessment, alcohol and smoking habits, International physical activity questionnaire)
- Autonomy in daily life activities (Lawton IADL and Katz ADL scales)
- Motricity (SPPB)
- Quality of life (EQ5-ED)
- Human sciences and health economic component

Data collected for each study participants are recorded in an electronic case report form (e-CRF). The clinical investigators are responsible for ensuring that all sections in the e-CRF are completed correctly and that entries can be verified against source data.

14.3. CONFIDENTIALITY OF DATA

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to investigational drugs, research studies and people taking part in them, particularly as regards their identity and the results obtained. These people, like the investigators themselves, are subject to professional secrecy.

[a] " Cahier de suivi - Patient ayant des troubles cognitifs ou une plainte cognitive "
[b] http://www.fondation-alzheimer.org/node/397

During the biomedical research study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialist personnel involved) will be made anonymous. Under no circumstances may the uncoded names or addresses of the people concerned appear in it. For coding subjects, the two first letter of the name and the two first letter of the first name of the subject will be recorded, accompanied by a code number unique to this study showing the order of inclusion of the subject

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to the individual data concerning him-her/self, which is strictly necessary for quality control of the study.

15. QUALITY CONTROL AND ASSURANCE

15.1. INSTRUCTIONS FOR COLLECTING DATA

All the information required by the protocol must be entered in the electronic case report form (e-CRF) provided by the sponsor and an explanation must be provided for each piece of information which is missing. The data must be collected as and when they are obtained, and transcribed into these forms in a clear and legible manner.

Treatments and clinical events are coded in the eCRF in order to perform data control and analysis. The following dictionaries are used for coding of medical terms and treatments:

- MedDRA Version 13.0 (medical terms)
- WhoDrug, B format, version June 2011 (treatments)

15.2. STUDY MONITORING

The study will be monitored by a clinical research technician. He will be responsible to the coordinating investigator for:

- The logistics of and monitoring the study,
- Producing reports concerning its state of progress,
- Verifying that the case report forms are updated (request for additional information, corrections, etc.),
- Sending samples,
- Transmitting SAEs to the sponsor.

He will work in accordance with the standard operating procedures, in cooperation with the clinical research associate appointed by the sponsor.

15.3. QUALITY CONTROL

A clinical research associate appointed by the sponsor will regularly visit each study centre during the process of setting up the study, one or more times during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed:

- Informed consent,
- Compliance with the study protocol and the procedures set out in it,
- The quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, appointment diaries, the originals of laboratory results etc.),
- Management of medicinal products if appropriate.

Each visit will be recorded in a written monitoring report.

15.4. DATA MANAGEMENT

The CIC-EC7 is responsible for the data management of the study. The e-CRF data are entered in a data management system, which is fully validated and compliant to 21 CFR, part 11. Data entry is done either on site (electronic CRF).

Data validation checks are performed at regular intervals and may result in data queries. The resolved queries are to be confirmed and updates subsequently in the database by the investigator.

When all data have been received, all data problems are solved and all data checks and quality control have been performed, a data review meeting has been held, the study database is considered clean and can be locked.

Details regarding data management will be described in a specific Data management plan.

15.5. AUDIT AND INSPECTION

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

16. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator or investigators undertake to conduct this study in compliance with French law n° 2004-806 of 9th August 2004 and following Good Clinical Practice (I.C.H. version 4 of 1st May 1996 and the decision of 24th November 2006) and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004) (appendix XIV).

The study is being conducted in accordance with this protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards obtaining consent and the notification and follow-up of serious adverse events.

This study was approved by the ethics committee of CPP SOOM 3 (appendix I) on 26/10/2011 and was authorised by the AFSSAPS on 06/12/2010 (appendix II).

CHU de Bordeaux, the sponsor of this study, has taken out an insurance policy covering third party liability with HDI Gerling (appendix III) complying with the provisions of article L1121-10 of the French Public Health Act.
The data recorded in this study will be subject to computer processing by CIC-EC7 in compliance with law n°78-17 of 6th January 1978 concerning data processing, files and civil liberties modified by law 2004-801 of 6th August 2004.
This research falls within the framework of the "Reference methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the modified law of 6th January 1978 relating to information, files and civil liberties. This change has been approved by the decision of 5th January 2006. CHU de Bordeaux signed a commitment to comply with this "Reference methodology" in 2011.
The collection of physiological samples to be undertaken for this study was declared to AFSSAPS at the same time as the request was made to authorise the study. After the study, conservation of the collection of physiological samples will be declared to the Minister for Research and to the director of the Regional Hospitalisation Agency (and submitted to the ethics committee for approval if there is any change in the aim of the study).

AMENDMENTS TO THE PROTOCOL

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the investigational medicinal products, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is the subject of a written amendment to be submitted to the sponsor; prior to implementing it, the latter must obtain approval from the ethics committee and authorisation from ANSM.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of patients or the benefits, risks or constraints of the study is the subject of a new Participant Information and Informed Consent form which must be completed and collected according to the same procedure as used for the previous one.

17. 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 who signed a consent form
    - All other documents and letters relating to the study
  - **For a period of 30 years following the end of the study**
    - The original copies of informed consent forms signed by participants

  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
  - **For a period of 30 years following the end of the study**

- A copy of the informed consent forms signed by the participants
- Documents relating to serious adverse events

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

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.

18. RULES RELATING TO PUBLICATIONS

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

18.1. SCIENTIFIC COMMUNICATIONS

Analysis of the data provided by the study centres is performed by the CIC-EC7 under the responsibility of the coordinating investigators. This analysis results in a written report which is submitted to the sponsor whom representative forwards it to the ethics committee and the relevant authority.

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

Publication of the main results should mention the name of the legal sponsor, the name of "Fondation Plan Alzheimer", 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 (Vancouver Agreement, February 2006).

18.2. COMMUNICATION OF THE RESULTS TO PARTICIPANTS

In accordance with the law n° 2002-303 of 4th March 2002, participants are informed, at their request, of the overall results of the study.

18.3. DATA SHARING

The collection and management of data will be carried out by CIC-EC7.

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 Scientific Strategy Committee.

CIC-EC7 will systematically be involved in data collection, management and analysis.

B. ANCILLARY STUDY: MEMENTO-AMYGING

MEMENTO-AmyGing :
"Longitudinal study of brain Amyloid imaGing in MEMENTO"

This biomedical ancillary study has received funding from
Fondation Plan Alzheimer, AVID corporation and GE-Healthcare corporation

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1. SUMMARY OF THE ANCILLARY STUDY

COORDINATING INVESTIGATOR	**Pr Geneviève CHENE**
SCIENTIFIC DIRECTION COMMITTEE	Dr Marie-Odile Habert (Nuclear Medicine), Pr Florence Pasquier (Neurology), Carole Dufouil (Methodology)
TITLE	MEMENTO-AmyGing: Longitudinal study of brain Amyloid imaging in MEMENTO,
RATIONALE / BACKGROUND	Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting approximately 7.3 million people in Europe. AD is a clinicopathologic entity for which the definitive diagnosis requires both the presence of the clinical signs of dementia and pathological evidence of amyloid plaque in the brain (obtained at autopsy). Currently, diagnosis of AD at early stage of the disease is hampered by the lack of noninvasive and validated biomarkers of the underlying pathology. On one hand, it is suggested that between 10% and 20% of patients currently diagnosed with AD, based on clinical evidence solely, lack AD pathology at autopsy, and on the other hand community physicians may not diagnose AD in 33% of patients with mild signs and symptoms. Thus, there is a need for validated diagnostic biomarker that could help clinicians separate patients who do not have AD from those who have pathological signs and should be referred for further evaluation and care management. Furthermore, little is known on the prognosis value for dementia conversion of current biomarkers of AD pathology at a preclinical or presymptomatic stage. Recently, ^{18}F-labeled positron emission tomography (PET) imaging agents have been developed that bind with high affinity to the amyloid-β (Aβ) peptide fibrils that constitute amyloid plaques, and thus, have potential value as an imaging biomarkers for amyloid deposits in subjects with cognitive impairment or isolated cognitive complaints.
OBJECTIVES	The principal objective of this ancillary study is to investigate the prospective association between PET amyloid load, measured twice two years apart, through either Florbetapir (^{18}F) or Flutemetamol (^{18}F) radioligands, and dementia incidence over up to 5 years of follow-up in a sample of individuals presenting with a spectrum of cognitive profiles ranging from isolated cognitive complaints to cognitive deficits without dementia. The secondary objectives are the following:

	– To assess the amyloid load at baseline – To estimate the prevalence of positive amyloid at baseline – To estimate the incidence of positive amyloid over 2-year follow-up – To assess the association between change in amyloid load and clinical evolution of participants (both functional and cognitive) – To estimate the prevalence of new research criteria for preclinical Alzheimer's disease – To investigate long-term outcome of preclinical Alzheimer's disease according to NIA-AA criteria – To assess the determinants of change in amyloid load over two years – To study the interrelationships between biomarkers – To assess the added value of amyloid binding agent (Florbetapir (^{18}F) and Flutemetamol (^{18}F)) in combination with other biomarkers (neuropsychological, genetics, plasma, serum, CSF, structural neuroimaging, ^{18}F-FDG-PET) to predict clinical dementia onset – To assess the diagnostic accuracy of amyloid agent Florbetapir (^{18}F) and Flutemetamol (^{18}F) to differentiate AD from other types of dementia (differential diagnosis) – To study the link between amyloid binding agent and survivalstudy design
STUDY DESIGN	Longitudinal cohort Study
INCLUSION CRITERIA	- To be included in MEMENTO; - To have signed a specific MEMENTO-AmyGing informed consent form, prior to any amyloid PET procedures - To tolerate the (^{18}F) PET scan procedures, in the opinion of the clinical site investigator; - Clinical Dementia Rating scale ≤0.5 and not demented.
EXCLUSION CRITERIA	- To have a current clinically significant psychiatric condition that neurologists/geriatricians feel would preclude the ability to have a research PET scan; - To be pregnant or breastfeading women. - To have Hypersensitivity to the tracer or to the excipient listed in the summary of the product carateristics (florbetapir Amyvid®) or the Investigator's Brochure (flutemetamol) / in the summary of the product carateristics (flutemetamol Vizamyl®). - To have a relevant history of severe drug allergy or hypersensitivity (relevant severe drug allergies should be determined by the clinical site investigator or co-clinical site investigator). If a subject has a history of severe drug

	allergies, it may be dangerous for them to participate in a study with a novel compound; - To have ever participated in an experimental study with an amyloid targeting agent (e.g. anti-amyloid immunotherapy, γ-secretase or γ-secretase inhibitor) unless it can be documented that the subject received only placebo during the course of the trial; - To receive any investigational medications, or have participated in a trial with investigational medications within the last 30 days; - To have participated less than 1 year ago in a biomedical research with injection of one of the amyloid radioligand or to be enrolled in an ongoing biomedical research including amyloid PET scan; - To have had a radiopharmaceutical imaging or treatment procedure within 7 days prior to the study imaging session;
STUDY TREATMENTS/STRATEGIES/ PROCEDURES	**Florbetapir (^{18}F)** The 15 minutes 3D-acquisition will start 50 minutes after an intravenous injection (via a catheter) of 370 MBq of Florbetapir (^{18}F). The injected volume is 1 mL minimum and 10 ml maximum. **Flutemetamol (^{18}F)** The 20 minutes 3D-acquisition will start 90 minutes after an intravenous injection (via a catheter) of 185 MBq of Flutemetamol (^{18}F). The injected volume is 10 mL maximum. HCG urine dipstick tests will be performed at inclusion and on PET imaging day for women of childbearing potential.
OUTCOMES	- Progression to clinical dementia stage according to standardized classifications (DSM-IV and NINCDS-ADRDA) as described in the MEMENTO protocol. - Other outcomes of interest • Amyloid load at baseline • Prevalence of positive amyloid • Incidence of positive amyloid • Longitudinal evolution of amyloid load measured through either Florbetapir (^{18}F) or Flutemetamol (^{18}F) • Speed of cognitive decline based on change in cognitive performances • Longitudinal evolution of biomarkers measured from blood, CSF, structural neuroimaging (MRI) and glucose metabolism molecular neuroimaging (^{18}F-FDG PET). • Mortality • Loss of autonomy based on functional activity assessment • Institutionalization

	• Cardiovascular event (Stroke and Coronary events) • Quality of life • Prodromal AD (Pre-symptomatic dementia) • Etiology of dementia, when converted
STUDY SIZE	A sample of 800 participants (400 participants for each radioligand)
NUMBER OF CENTRES PLANNED	Up to 30 centers
STUDY DURATION	Inclusion period in MEMENTO-AmyGing will be 30 months Duration of participation of each participant will be two years Total study duration = 54 months Follow-up for some outcomes assessed through MEMENTO will be up to 5 years
STATISTICAL ANALYSIS OF THE DATA	We assume a cumulative rate of clinical dementia ranging from 15 to 25% over up to 5 years of follow-up, and a prevalence of positive amyloid load from 20% to 50% and an overall drop-out rate of 10% over 5 years.. Under the assumption of a cumulative incidence of 20% over follow-up and a prevalence of 30% of positive amyloid at baseline PET-Scan, the sample size (n=800) will convey at least 80% power to show a relative risk of 1.6 of developing AD over follow-up in participants positive at baseline amyloid PET-Scan at the type I error level of α=0.05.
POTENTIAL IMPACT	One expected impact is to increase knowledge on the progression from early signs of cognitive impairment to AD and estimate associations between these signs and level of biomarkers assessed through imaging or blood or CSF samples.

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting approximately 7.3 million people in Europe. It is a progressive disease, where dementia symptoms gradually worsen over a number of years. As a result of increased life expectancy worldwide, it is expected that the number of demented people will increase from 25 million in 2000, to 63 million in 2030 and to 114 million in 2050.[234] In addition to being devastating at an individual/familial level, dementia is very costly for the society and it is therefore both a public health and economic major concern. [235]

The definite diagnosis of Alzheimer's disease requires both the presence of the clinical signs of dementia and pathological evidence of amyloid plaques at the brain post-mortem examination performed according to widely used protocols such as Consortium for the Establishment of a Registry for Alzheimer's Disease (CERAD) or National Institute of Aging (NIA) Reagan guidelines.[236,237]

However, in the large population based neuropathological study, CFAS[238], the study of 456 donated brain showed that the association between β-amyloid neuritic plaques in the neocortex and clinical dementia (DSM-IIIR) was stronger at 75 years old (Odds-Ratio (OR)=8.6, 95% Confidence Interval (CI)=3.8-19.6) than at 95 years old (OR=2.5, 95% CI=0.92-4.1). It was also observed that at older age, mixed pathological features (including vascular pathological factors) were more frequent and they might lower the burden of Alzheimer's pathological required to produce dementia. This unique observation has several potential implications: therapeutic interventions targeting solely Alzheimer's pathology are likely to be more efficient at early stage and therefore early detection could allow disease-modifying medications to delay the pathophysiological processes underlying AD.

In line with these observations, recent biomedical research on the disease has aimed to search for biomarkers[239] that allow both early detection of AD and to accurately delineate its progression. Newly proposed, but not yet validated, clinical criteria for the diagnosis of dementia due to AD require both clinical signs of the disease, including memory loss and functional impairment as well as biomarker evidence of the disease.[5,240,241] In the proposed new series of definition of dementia stages, clinical criteria for mild cognitive impairment (MCI) due to AD similarly require biomarker evidence.[6]

The amyloid cascade hypothesis is the most prominent assumption for the aetiology of AD.[26] It suggests that sufficient accumulation of an amyloid precursor protein derivative, beta amyloid (Aβ), is the primary influence that drives significant biochemical, histological and clinical changes in the pathogenesis of AD. In line with these hypotheses, amyloid imaging was

developed in an attempt to provide an in vivo measurement of one of the key pathologic hallmarks of AD, fibrillar amyloid β (Aβ) plaques and shows great potential to meet these aims.

However, if the amyloid cascade hypothesis is the most prominent, amyloid plaques are not a perfectly accurate diagnosis marker. Indeed, on one hand between 10% and 20% of patients currently diagnosed with AD based on clinical evidence solely, lack AD pathology at autopsy,[242] and, on the other hand, that amyloid deposition can occur in normal aging as well.

A number of compounds that were first developed for the imaging of amyloid[243,244] failed to provide a direct visualisation of amyloid and tau proteins in humans due to the poor passage across the blood–brain barrier, inadequate brain permeability and/or low affinity to Aβ aggregates..[245,246]

More recently, several Positron Emission Tomography (PET) ligands have been developed that demonstrate some affinity for amyloid plaques,[247,248]among which 'Pittsburgh Compound-B' (PIB). The first PIB study in humans was performed in mild AD patients, where uptake patterns were consistent with amyloid plaque deposition described in post mortem studies of AD brains,[249] providing the first direct in vivo visualisation of brain amyloid. In vitro, PIB has been shown to bind specifically to extracellular and intravascular fibrillar Aβ deposits in post mortem AD brains[250,251]. At PET tracer concentrations, PIB does not significantly bind to other protein aggregates such as NeuroFibrillary Tangles (NFTs) or Lewy bodies, hence a suitable tracer for diagnostically discriminating between AD and non-AD dementias.[252,253] PIB was originally labeled with ^{11}C, limiting its use to PET centres with cyclotrons nearby.

Therefore, over the last years, efforts have focused on developing a ^{18}F equivalent to ^{11}C-PIB, which may offer greater clinical utility and easier availability. Three potential agents have been developed: Flutemetamol (GE-067), a 3´-fluoro-derivative of PiB, Florbetaben (BAY-94-9172, AV-1) and Florbetapir (AV-45), which are stilbene and styrylpyridine derivatives, which exhibit high-affinity binding for fibrillary amyloid similar to PIB (Table 1). They have been developed for commercial distribution, which is possible because of the 110 min physical half-life of ^{18}F.

	Pittsburgh compound B	Flutemetamol	Florbetapir	Florbetaben
Synonyms	PiB	GE-067, 3'-fluoro-PIB	AV-45	BAY-94-9172, AV-1
Chemical group	Benzothiazole	Benzothiazole	Styrylpyridine	Stilbene
Isotope label	Carbon-11	Fluorine-18	Fluorine-18	Fluorine-18
Amyloid affinity (Ki, nM)	0·9	0·7	2·2	2·4
Plasma metabolites	Polar	Polar	Polar and non-polar	Polar and non-polar
Typical injected dose (MBq)	250–450	185	300	300
Typical imaging time (min)	40–90	80–100	50–70	90–130
Effective radiation dose (mSv; μSv/MBq)	1·3–2·4 (5·3)	6·3 (33·8)	5·8 (19·3)	4·4 (14·7)

Table 1. PET Tracers characteristics (source = Lancet Neurol 2011; 10: 667–70)

Two main types of research studies have been conducted so far: some assessing the utility of amyloid imaging for differential diagnosis[254-256] and others focusing on the association between amyloid imaging and cognitive performances. In a review of the literature[257], the inconsistency of results was underlined. Most studies on cognition in MCI or "Normal" patients used PIB to assess amyloid load and some failed to show any association[258] whereas others found that amyloid positive patients had lower cognitive performances than amyloid negative patients[259,260]even if the associations were sometimes weak.

It should be noted that most studies were based on small samples (<58 participants MCI or demented, <170 "normal") and that all were cross-sectional. Three studies have investigated the link between baseline amyloid load and subsequent cognitive changes and all have shown significant associations for some cognitive tests, the cognitive domains involved varying across studies.[257]

The utility of Amyloid imaging in the prediction of Alzheimer-type dementia in subjects with MCI has also been investigated and has provided more consistent and positive results in studies with a number of patients varying from 12 to 159 and a mean follow-up of a maximum of 2.4 years.

However, many questions remain pending and the amyloid imaging added value for predicting conversion to clinical dementia needs to be assessed from large samples of non-demented participants and taking into account other biomarkers (MRI, CSF, genetic, blood).

The aim of the MEMENTO-AmyGing study is to perform repeated amyloid imaging, 2 years apart, using 2 ^{18}F PET ligands, Flutemetamol (GE-067) and Florbetapir (AV-45), in 800 MEMENTO participants (400 for each PET ligands) and to study the association between amyloid load and amyloid load change and the risk of conversion to clinical dementia over time.

BENEFIT / RISK RATIO

The benefit for the patient is unknown. The risk is reduced because the products needed for the study procedures are radioactive agents used at minimal doses with short half-life and no pharmacological activity and synthesized according to relevant quality standard. PET-SCAN with 18-fluorine is used in routine. Each participant accepting PET imaging will receive maximum 2.7 mSv for FDG PET and 6.3 mSv for Flutemetamol or 7 mSv for Florbetapir PET imaging. The dose received during transmission scan acquisition needs to be added. For a cerebral exploration, the transmission scan has no diagnostic aim and is only undertaken for attenuation correction. It is therefore a low dose examination which lasts less than 10 seconds, and the parameters are set such as the maximum dose-length-product (DLP) is 145 mGy.cm and the maximum effective dose is 0.3 mSv. For example, for a Siemens camera, the recommended parameters are: 100 kV, 60 mA.s, pitch 1, giving a DLP of 115 mGy.cm. The total dose received for FDG-PET and amyloid PET will therefore range from 9.6 to 10.3 mSv.

This point, as well as the respect of the injected doses, is carefully monitored by the CATI. Since the cumulated dose received for FDG and amyloid PET examination is roughly of 10 mSv and examinations are only repeated every two years, an exclusion period for the participation to other biomedical research studies without benefit involving exposure to ionizing radiations is not required.

3. OBJECTIVES OF THE ANCILLARY STUDY

3.1. PRINCIPAL OBJECTIVE

The principal objective of this ancillary study is to investigate the prospective association between PET amyloid load, measured twice two years apart, through either Florbetapir (^{18}F) or Flutemetamol (^{18}F) radioligands, and dementia incidence over up to 5 years of follow-up in a sample of individuals presenting with a spectrum of cognitive profiles ranging from isolated cognitive complaints to cognitive deficits without dementia.

3.2. SECONDARY OBJECTIVES

The secondary objectives are the following:

- To assess the amyloid load at baseline
- To estimate the prevalence of positive amyloid at baseline
- To estimate the incidence of positive amyloid over 2-year follow-up

- To assess the association between change in amyloid load and clinical evolution of participants (both functional and cognitive)
- To estimate the prevalence of new research criteria for preclinical Alzheimer's disease
- To investigate long-term outcome of preclinical Alzheimer's disease according to NIA-AA criteria[7]
- To assess the determinants of change in amyloid load over two years
- To study the interrelationships between biomarkers
- To assess the added value of amyloid binding agent (Florbetapir (^{18}F) and Flutemetamol (^{18}F)) in combination with other biomarkers (neuropsychological, genetics, plasma, serum, CSF, structural neuroimaging, ^{18}F-FDG-PET) to predict clinical dementia onset
- To assess the diagnostic accuracy of amyloid agent Florbetapir (^{18}F) and Flutemetamol (^{18}F) to differentiate AD from other types of dementia (differential diagnosis)
- To study the link between amyloid binding agent and survival study design

3.3. GENERAL STUDY DESIGN

It is a multicentre prospective study within the MEMENTO cohort. Clinical sites will be eligible if they can be supplied in Flutemetamol (^{18}F) and in Florbetapir (^{18}F) within 6 hours following its production. The list of centers that can be supplied with each of the radioligand is provided in Appendix XVI.

Participants can be included concomitantly to one of these MEMENTO follow-up visits: baseline (M0), 6 months (M6), 12 months (M12), 18 months (M18), 24 months (M24), 30 months (M30) and 36 months (M36).

4. ELIGIBILITY CRITERIA

4.1. INCLUSION CRITERIA

Participants to MEMENTO-AmyGing should have already met inclusion and no exclusion criteria for the main protocol "Determinants and Evolution of Alzheimer's disease and Related Disorders" and should be included in MEMENTO.

In addition, participants to MEMENTO-AmyGing should meet the following specific inclusion criteria:

1. To tolerate the (^{18}F) PET scan procedures, in the opinion of the clinical site investigator;
2. Clinical Dementia Rating scale ≤0.5 and not demented;

3. To have signed a specific MEMENTO-AmyGing informed consent form, prior to any amyloid PET procedures.

4.2. NON INCLUSION CRITERIA

Individuals will be excluded from MEMENTO-Amyging enrollment if they:

1. To have a current clinically significant psychiatric condition that neurologists/geriatricians feel would preclude the ability to have a research PET scan;
2. To be pregnant or breast-feeding women
3. To have hypersensitivity to the tracer or to the excipient listed in the summary of the product carateristics (florbetapir Amyvid®) or the Investigator's Brochure (flutemetamol) / in the summary of the product carateristics (flutemetamol Vizamyl®).
4. To have a relevant history of severe drug allergy or hypersensitivity (relevant severe drug allergies should be determined by the clinical site investigator or co-clinical site investigator). If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study with a novel compound;
5. To have ever participated in an experimental study with an amyloid targeting agent (e.g. anti-amyloid immunotherapy, γ-secretase or γ-secretase inhibitor) unless it can be documented that the subject received only placebo during the course of the trial;
6. To receive any investigational medications, or have participated in a trial with investigational medications within the last 30 days;
7. To have participated less than 1 year ago in a biomedical research with injection of one of the amyloid radioligand or to be enrolled in an ongoing biomedical research including amyloid PET scan;
8. To have had a radiopharmaceutical imaging or treatment procedure within 7 days prior to the study imaging session.

5. DATA COLLECTION AND FOLLOW-UP

5.1. INVESTIGATIONAL MEDICINAL PRODUCT AND TRACER

5.1.1. INVESTIGATIONAL PRODUCTS

They are described in Florbetapir (^{18}F) SCP and Flutemetamol (^{18}F) Investigator's brochure or SCP.

5.1.2. PREPARATION AND ADMINISTRATION OF TRACER

They are described in clinical supply guidance documents of both products.

5.2. RADIOLIGANDS' AVAILABILITY BY CENTER

MEMENTO-AmyGing comprises two radioligands. In order to prevent any bias in the radioligand proposed to participants, the study will be organised according to this two-step procedure (Figure 4) :

- For the first 200 participants included in MEMENTO-AmyGing in centers from groups A, D and E (Appendix XVI), the PET-SCAN will be performed using Flutemetamol (^{18}F) and the following 200 participants included in MEMENTO-AmyGing, the PET-SCAN will be performed using Florbetapir (^{18}F),
- Conversely, for the first 200 participants included in MEMENTO-AmyGing in centers from groups B, C and F (Appendix XVI), the PET-SCAN will be performed using Florbetapir (^{18}F) and for the following 200 participants included in these centers, the PET-SCANwill be performed using Flutemetamol (^{18}F).

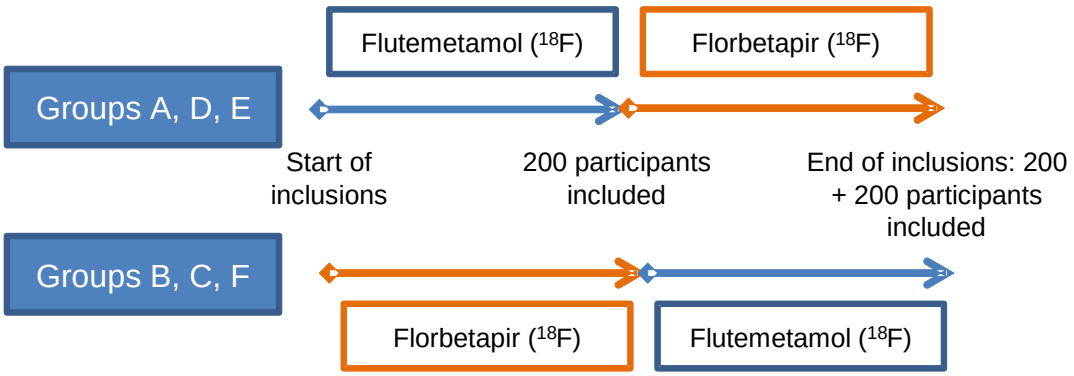


Figure 4. PET Tracers supplying among both group centers

5.3. SCREENING VISIT

All participants will be screened for MEMENTO-AmyGing at M0 or M6 or M12 or M18 or M24 or M30 or M36 visits of the main protocol, the MEMENTO study. Amyloid (^{18}F) PET Imaging should be performed in the 3 months following MEMENTO-AmyGing informed consent signature. Women of childbearing potential, i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have an HCG urine dipstick test performed.

5.4. AMYLOID (^{18}F) PET IMAGING PROCEDURES

The effective dose is 7 mSv for a participant for who the dose of florbetapir administred is 370 MBq and 6.3 mSv for a patient receiving a dose of flutemetamol of 185 MBq.

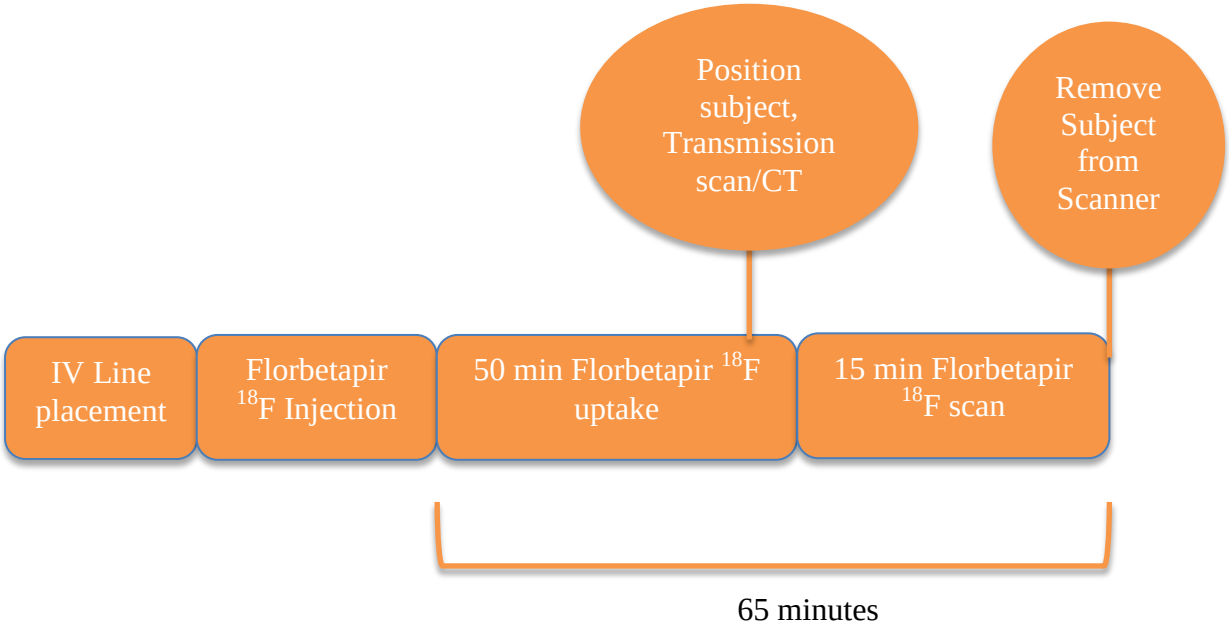
Close contact with infants and pregnant women should be restricted during the initial 24 hours following the injection.

5.4.1. FLORBETAPIR (^{18}F)

Florbetapir (^{18}F) PET Imaging Day

- Women of childbearing potential i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have an HCG urine dipstick test performed before imaging. If it is positive, the Florbetapir (^{18}F) injection and PET scan will not be performed.
- Participants will first have a catheter placed for intravenous (i.v.) administration of Florbetapir (^{18}F). Participants will receive a single i.v. bolus of approximately 370 MBq of Florbetapir (^{18}F) followed by brain PET imaging for 15 minutes, beginning approximately 30 and 50 minutes post-injection.
- If the image is not interpretable due to technical artifact (scanner failure, patient motion) the patient may be asked to reenter the scanner and have a second 15 minutes scan performed.
- Any adverse events will be recorded during the imaging visit.

  Flow of procedures during AmyGing-Florbetapir (^{18}F) visit

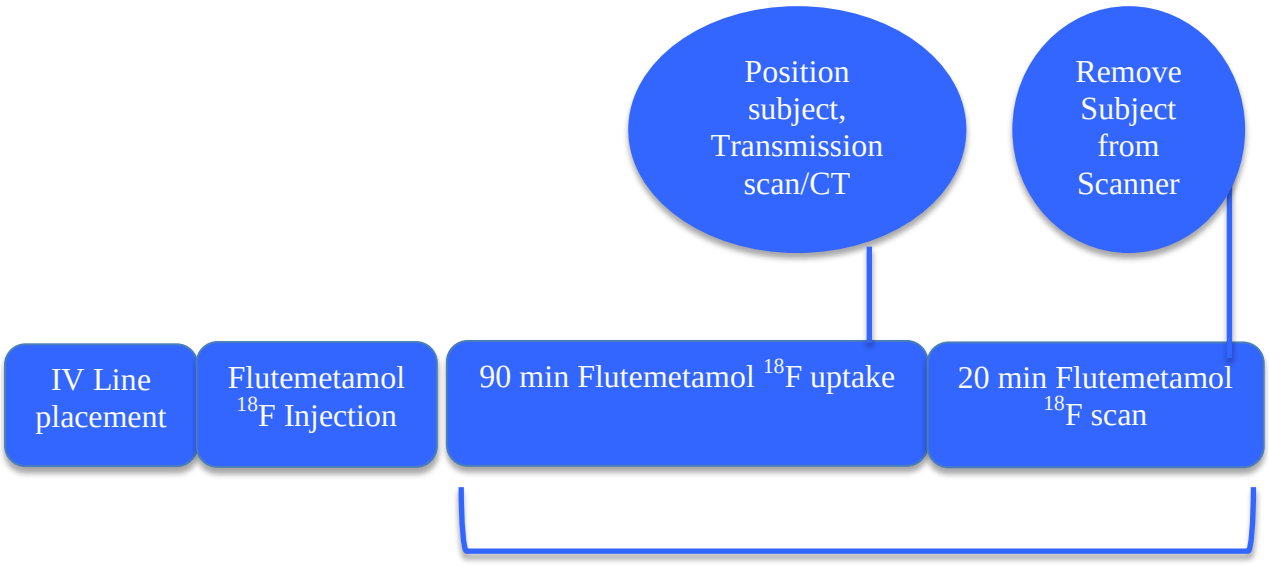


5.4.2.FLUTEMETAMOL (^{18}F)

- Women of childbearing potential i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have an HCG urine dipstick test performed before imaging. If it is positive, the Flutemetamol (18F) injection and PET scan will not be performed.
- Participants will first have a catheter placed for intravenous (i.v.) administration of Flutemetamol (^{18}F). Flutemetamol (^{18}F) should be administered "as-is" with no volume adjustment (e.g. no adjustment dose to a specific volume).
- Flutemetamol (^{18}F) cannot be diluted with a simple saline diluent; it must be diluted with the full array of formulation excipients.
- Recommended administered activity is 185 MBq.
- Typical imaging parameters include the full brain (cerebrum and cerebellum) in a single Field Of View with an image acquisition of 20 minutes at 90 minutes post-injection. The acquisition mode may be a single static or multi-frame dynamic.
- If the image is not interpretable due to technical artifact (scanner failure, patient motion) the patient may be asked to reenter the scanner and have a second 20 minutes scan performed.

- Any adverse events will be recorded during the imaging visit.

<u>Flow of events during AmyGing-Flutemetamol (^{18}F) visit</u>



Total duration = 110 minutes

5.5 EXPOSURES TO IONIZING RADIATION DURING THE COURSE OF MEMENTO-AMYGING

The table below summarizes potential total exposures to radiation during the course of the study

	PET-FDG	PET amyloid		TOTAL
		Florbetapir	Flutemetamol	
1rst examination	3	7	6	
2nd examination	3	7	6	
3rd examination	3			
Total	9	14	12	23(Florbetapir)/21(Flutemetamol)

6. PRIOR AND CONCOMITANT TREATMENTS

All medications (prescription or over the counter (OTC)) that have been started prior to screening may be continued during the course of the study. All medications that are continued or are started during the study are documented trough the MEMENTO e-Case Report Form.

A mild anxiolytic may be given prior to performing the imaging session for the purpose of reducing anxiety. This should be discussed with the clinical site investigator (CMRR) prior to administration.

Based on maximum total exposure to ionizing radiation of Memento-Amyging participants, they should be forbidden to participante to any other research including ionizing radiation without direct beneficial during the four-year from 1rst FDG-PET examination to 3rd FDG-PET examination.

7. OUTCOMES AND IMAGES ANALYSIS

7.1. PRIMARY OUTCOME OF INTEREST

Primary outcome is the progression to clinical dementia stage according to standardized classifications (DSM-IV and NINCDS-ADRDA) as described in the MEMENTO protocol.

7.2. SECONDARY OUTCOMES

- Amyloid load at baseline
- Prevalence of positive amyloid

- Incidence of positive amyloid
- Longitudinal evolution of amyloid load measured through either Florbetapir (^{18}F) or Flutemetamol (^{18}F)
- Speed of cognitive decline based on change in cognitive performances
- Longitudinal evolution of biomarkers measured from blood, CSF, structural neuroimaging (MRI) and glucose metabolism molecular neuroimaging (^{18}F-FDG PET**).**
- Mortality
- Loss of autonomy based on functional activity assessment
- Institutionalization
- Cardiovascular event (Stroke and Coronary events)
- Quality of life
- Prodromal AD (Pre-symptomatic dementia)
- Etiology of dementia (when converted)

7.3. IMAGES' COLLECTION AND ASSESSMENT

A PET Imaging Manual (PIM) will be implemented at each nuclear imaging center and followed for image acquisition and on-site quality control. Acquired images will be centralized and analyzed by the CATI, similarly to TEP-FDG images in the main MEMENTO protocol.

7.4. IMAGES QUANTITATIVE EVALUATION

Standard uptake value ratios (SUVR) for target areas such as the medial frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate cortex and the precuneus will be calculated with respect to the entire cerebellum.

Analysis pipelines designed for large series of images, and dedicated to PET amyloid imaging, will be developed by the CATI. The CATI will allow both regions of interest analyses, as described above, and voxel-based analyses. SUVR ratios obtained with CATI software will be compared to ratios obtained with the each of the radiopharmacist (AVID and GE-Healthcare) softwares.

7.4.1. IMAGE ANALYSIS' RESULTS

Both study site clinicians and MEMENTO-AmyGing participants will be blinded to the PET amyloid imaging results. Indeed, US Food and Drug Administration recommendations[a] acknowledge that PET-amyloid imaging can not be used for predicting the development of AD-associated dementia and is not for monitoring patient responses to AD therapy. At preclinical

[a] http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm299678.htm

stage of AD, the evidence so far is such that PET-amyloid radioligands use is limited to research protocol.Further studies are needed to prove their clinical utility.

If during the course of the study, new facts occur that do show the interest of releasing results to clinicians or participants, the data monitoring committee will review the available facts and advise the study scientific strategy committee on the release of the examinations results to the participants or the clinicians. Such changes would lead to protocol revisions accordingly.

8. STUDY CONDUCT

8.1. STUDY CALENDAR

Start of inclusions: June 2014

Duration of the inclusion period: 30 months

End of inclusion period: December 31th 2016

Duration of each participant's participation: 24 months

Total duration of the study: 54 months

At the end of MEMENTO-AmyGing follow-up, participants will be followed up to 3 additional years within the MEMENTO protocol for most non PET-amyloid outcomes.

PARTICIPANTS FOLLOW-UP SUMMARY TABLE

		Screening	Baseline (Month 0)	Month 12	Month 24	Month 36
AMYGING[9]	Explain Study	❶❷❸ ❹❺❻❼	❶❷❸ ❹❺❻❼			
	Obtain Consent		❶❷❸ ❹❺❻❼			
	Inclusion and Non Inclusion Criteria[1]		❶❷❸ ❹❺❻❼			
	Baseline PET Amyloid scanning[1]		❶❷❸ ❹❺❻❼			
	Follow-up PET amyloid scanning[1]				❶❷❸ ❹❺❻❼	

1: HCG urine dipstick tests are performed for women of childbearing potential
2: For MEMENTO-Amyging, there are 7 scenarios (❶❷❸❹❺❻❼) of schedule of assessments depending on when informed consent is signed (M0 ❶, M6 ❷, M12 ❸, M18 ❹, M24 ❺, M30 ❻ or M36 ❼ of Memento)

8.2. SIGNATURE OF INFORMED CONSENT

During M0 or M6 or M12 or M18 or M24 or M30 or M36 MEMENTO visits, the MEMENTO-AmyGing study will be explained to the participant. A separate written Informed Consent must be obtained for the MEMENTO-AmyGing study, prior to the initiation of any MEMENTO-Amyging related interview or investigation.

The information should be clear that refusal to participate or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care and follow up in the MEMENTO cohort.

The informed consent is signed in one original and two copies obtained by triplication. One of the copies of the signed informed consent is given to the participant. Signed informed consents are retained by the investigator and made available (for review only) to the study monitor, auditor and inspector, upon request. An anonymised copy of the signed consent form is provided to the sponsor or its delegate.

8.3. SCREENING VISIT

All participants will be screened for MEMENTO-AmyGing at M0 or M6 or M12 or M18 or M24 or M30 or M36 visit of the main MEMENTO protocol. The screening assessment for eligibility will be performed by the investigator. Women of childbearing potential, i.e. women of childbearing age who are not menopausal, or surgically sterile or, not refraining from sexual activity or not using reliable methods of contraception (oestroprogestative or intrauterine device), will have a urine pregnancy dipstick test performed.

8.4. FOLLOW-UP VISIT

The follow-up PET amyloid scan will be performed using the same radioligand as at baseline scan and need to be completed within the 24 ± 3 months following the screening date for Memento-amyging.

8.5. IMAGING DAY

- Women of childbearing potential will have a urine pregnancy dipstick test prior to injection (A serum pregnancy test may be obtained, if required);
- A physician, Principal Investigator (PI), or designated staff clinician will see the participant prior to dosing;
- Subjects will be observed continuously for signs of adverse events or serious adverse events;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;

- The PET scanner image acquisition will be performed according to protocol;
- A physician, Principal Investigator (PI), or designated staff clinician will see the participant prior to discharge.

8.6. STUDY WITHDRAWAL

Participants may voluntarily withdraw from the study for any reason at any time, without any impact on their follow-up in the MEMENTO cohort. When a participant withdraws his/her consent to participate in the study, no new information must be collected and recorded in the database after the date of withdrawal.

Withdrawals of consent to participate in the study must be reported to the CIC-EC7 as soon as possible (by fax and by letter). The investigator must document the date, reason and any answers given in response to the participant, in the participant's medical records. If a participant explicitly states his/her wish not to contribute data to the study, the CIC-EC7 should be informed in writing of the participant's decision.

Participants withdrawing from the study without stating this wish have previously consented to follow-up in the study, and data up to this time can be included in the study if it is anonymised.

9. MANAGEMENT OF ADVERSE EVENTS, NEW FACTS AND/OR CASE OF PREGNANCY OCURING IN MEMENTO-AMYGING

The reporting of adverse event and serious adverse event must follow the procedure of the main protocole MEMENTO (Main protocol chapter A.10.3.).

9.1. DEFINITIONS

See chapter A.10.3. of the main protocol MEMENTO

9.2. DESCRIPTION OF EXPECTED ADVERSE EFFECTS IN MEMENTO-AMYGING

See chapter A.10.3. of the main protocol MEMENTO

9.3. ACTION TO BE TAKEN IN CASE OF SERIOUS ADVERSE EVENT, NEW INFORMATION OR PREGNANCY

See chapter A.10.3. of the main protocol MEMENTO

9.4. DECLARATION OF UNEXPECTED SERIOUS ADVERSE EFFECTS AND NEW SAFETY INFORMATION BY THE SPONSOR

See chapter A.10.3. of the main protocol MEMENTO

9.5. ANNUAL SAFETY REPORT

See chapter A.10.3. of the main protocol MEMENTO

10. STUDY COMMITTEES

10.1. INDEPENDENT DATA AND SAFETY MONITORING BOARD

An independent data and safety monitoring board will be constituted. It will be composed of at least one representant with the following specialities: vigilance, clinician (neurologist/geriatrician, statistician, nuclear medicine, ethicist), statistician and will meet every year.

Its role is to review data of the MEMENTO-AmyGing study, annualy, in order to evaluate safety, study conduct, and scientific validity and integrity of the trial. The IDSMB provide the sponsor with expertise and recommendations regarding study modification, continuation or termination.

10.2. ENDPOINT REVIEW COMMITTEE

There will be no specific endpoint review committee set up for MEMENTO-AmyGing. All cause-dementia and its etiological diagnosis will be validated through MEMENTO procedures.

11. STATISTICAL ASPECTS

11.1. SIZE OF THE STUDY

A cut-off from global SUVR measures will be determined to define pathological amyloid load. We hypothesized 800 participants to be recruited. We assumed a cumulative rate of clinical dementia ranging from 15 to 25% over 5 years, a prevalence of the pathological amyloid load ranging from 20% to 50% and an overall drop-out rate of 10% over 5 years, independent of the amyloid load level measured. For each case, 1000 datasets of 800 subjects were randomly simulated, based on the previous hypotheses.

With a 0.05 two-sided significant level and a statistical power ≥ 80%, the minimum hazard ratios statistically significant (based on a proportional hazard Cox univariate regression with a constant instant risk) of a pathological amyloid load are presented in the following table.

	Pathological amyloid load prevalence			
Minimum significant hazard ratio (power=80%)	20%	30%	40%	50%
Dementia cumulative rate				
15%	1.9	1.8	1.8	1.8
20%	1.7	1.6	1.6	1.6
25%	1.6	1.6	1.5	1.5

11.2. STATISTICAL METHODS

All statistical analyses will be performed separately for each radioligand. If the results are homogeneous, pooled analyses will be undertaken, adjusting for radioligand

The performance of ^{18}F-PET radioligand PET amyloid imaging to predict incident AD will be assessed through a proportional hazard ratio Cox model, with AD diagnosis as the dependent variable and amyloid-β load as the main independent variable. The amyloid-β load association will be considered quantitatively (through the Standardized uptake values Ratios).

Other models will be computed, including other biomarkers, in order to assess the added predictive value of each biomarker for the risk of dementia of Alzheimer's disease.

Hosmer and Lemeshow test and an "area under receiver operating characteristic"(AUC) will be performed to assess the calibration and the discrimination of these models.

A comparison of the AUC for non-dependent models will be performed.

All statistical analyses, tests and modeling strategies will be documented in a Statistical Analysis Plan, validated before the end of inclusions in this study.

12. RIGHT OF ACCESS TO PERSONAL DATA AND SOURCE DOCUMENTS

The rules described in MEMENTO protocol will apply.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. STUDY MONITORING

Study monitoring will be performed according to MEMENTO monitoring plan.

13.2. QUALITY CONTROL

The rules described in the MEMENTO protocol will apply. The CATI will be in charge of quality control of PET scan images. Monitoring visits will be performed by Clinical Research Assistant from the coordination center (CIC-EC7) in the nuclear medicine and pharmacy departments involved in the study.

13.3. DATA MANAGEMENT

The CIC-EC7 is responsible for data management. Data will be entered in an eCRF dedicated to Memento-Amyging. Adverse events will be recorded in the MEMENTO eCRF.

14. PUBLICATION POLICY

The MEMENTO “access to data and ancillary studies” charter will apply.

C. ANCILLARY STUDY: MEMENTO-VASCOD

Memento - Vascod

"VAScular Component Of Dementia in MEMENTO"

This biomedical ancillary study has received funding from PHRC 2012

1. SUMMARY OF THE ANCILLARY STUDY

TITLE	MEMENTO-VAScular Components of Dementia (VASCOD)
RATIONALE / BACKGROUND	Alzheimer's disease is a neurodegenerative disorder thought to be caused by the accumulation of the peptide amyloid–β and the hyperphosphorylated tau protein in the brain. There are increasing arguments in favor of an important role of vascular damages in the development and progression of Alzheimer's disease. The time course of these vascular alterations and how they relate to dementia and Alzheimer's disease pathology remain unclear, as no protocol that allows the development of the diverse vascular pathology to be scored, and hence to be tracked with ageing, has so far been developed and widely validated. The aims of this project are to investigate, in a large clinical sample of patients presenting either isolated cognitive complaints or light to mild cognitive deficits, how vascular risk factors and vascular alterations (assessed at macro and micro levels) relate to cerebrovascular disease and cognitive decline.
OBJECTIVES	The primary objective of this ancillary study is to investigate the prospective association between vascular risk factors, inflammation markers and vascular damages on cognitive decline and neurodegeneration progression over up to 3 years of follow-up in a sample of individuals presenting with a spectrum of cognitive profiles ranging from isolated cognitive complaints to cognitive deficits without dementia. The secondary objectives are the following - To investigate the role of vascular risk factors (diabetes, hypertension, hypercholesterolemia) and vascular damages on progression to clinical dementia over up to 3-year follow-up. - To study whether the interaction between changes in markers of macrovascular and microvascular structures on cognitive deficits progression. - To study the association between in BP, hypertension, antihypertensive treatments and vascular damages, progression of cerebrovascular disease seen at MRI and cognitive decline and dementia risk - To assess the temporality of vascular damages burden on neurodegeneration - To assess the association between retinal vasculature defect and brain neurovascular damages - To study the link between vascular damages and AD pathology (CSF and TEP amyloid imaging) biomarkers in the subsample of participants having all measures available - To investigate how inflammatory markers mediate the association between vascular damages and neurodegeneration - To assess whether vascular factors and neurodegenative factors act independently or synergistically on the course of cognitive decline - To assess simultaneously the impact of vascular damages on end organs (brain, eye, and kidney)

	- To study the correlation between cerebral blood flow, measured by Arterial spin-Labeled (ASL) MRI and cognitive decline - To study whether genetic polymorphisms revealed from GWAS of Alzheimer's disease of vascular factors could modulate the association between vascular damages and cognitive decline
STUDY DESIGN	Longitudinal cohort Study
INCLUSION CRITERIA	- To be included in MEMENTO - To have signed a specific MEMENTO-Vascod informed consent form, prior to any Vascod ancillary study related procedures - To be aged 50 years old and above - To have a Clinical Dementia Rating scale ≤0.5 and to be not demented
EXCLUSION CRITERIA	- To be under guardianship - To live in skilled nursing facility - To be Pregnant or breast feeding women - In case participant agrees to have a brain MRI : Meet brain MRI exclusion criteria (Same criteria as in Memento main protocol)
PROCEDURES	MANDATORY - Large arteries stiffness will be studied using pulse wave velocity and central blood pressure assessment - Cognitive testing - Behavioral and mood scales - The following Inflammatory markers will be measured from Memento centralized biobank specimen : IL-6, IL-10, IL-12, IL-18, RANTES (CCL5), IP-10 (CXCL10) - Genetic polymorphisms of Alzheimer's disease and vascular factors will be measured from DNA material extracted from centralized biobank - Urinary albumin excretion assessment OPTIONAL - Cerebral vessels will be assessed through an MRI examination inluding intracranial 3D-TOF MR angiography (to assess brain arteries level of stenosis) and Arterial Spin-Labeling (to assess cerebral blood flow in coupling with neuronal activity) - Ocular assessment will consist in visual acuity and axial length measurements; microcirculation state will be assessed by retinography and retinal thickness measurement
OUTCOMES	<u>Main outcome of interest:</u> The main outcome of interest is the change in cognitive performances over up-to 3-year of follow-up <u>Secondary outcomes of interest:</u> - Progression to clinical dementia of Alzheimer's type according to standardized criteria (DSM-IV and NINCDS-ADRDA classifications)

	- Change in CSF and blood amyloid biomarkers of AD - Change in brain atrophy and hippocampal volumes - Progression of small vessels disease markers (white matter lesions, lacunar infarcts, microbleeds)
STUDY SIZE	A sample of at least 350 participants
NUMBER OF CENTRES PLANNED	10
STUDY DURATION	Duration of the inclusion period : 37 months Duration of participation of each participant : 36 months Total study duration : 73 months
STATISTICAL ANALYSIS OF THE DATA	A sample size of 320 evaluable participants (under the assumption that drop-out rate will not be larger than 10% over 3-year will have 90% power to detect a difference in mean of at least 0.6 times the common SD for a risk factor prevalence of 10%, with a 0.05 two-sided significance level. We will use random intercept growth curve models to examine the relationship between each exposure and level and rate of change in each cognitive outcome. To account for practice effects, we will include an indicator for first test encounter in all models. We will also estimate annual rate of change for each cognitive test in linear age models. These models will be adjusted for potential confounders. To assess the effect of each vascular damage progression on rate of change, we will repeat mixed models allowing covariates to be time dependent. Because of the potential bias induced by selective survival and loss to follow-up in studies of determinants of cognitive aging, we will use inverse probability.
POTENTIAL IMPACT	A complete multidimensional assessment of vascular function in a large sample should allow elucidating the impact of vascular damages (at the macro- and micro-circulation levels) on the progression of cognitive decline and towards clinical dementia. This project will bring new insights into the sequence of events that lead to brain structural changes and how they relate to cognitive decline and ultimately to dementia. This is of major importance for the understanding of the etiology of sporadic Alzheimer's disease. If our results are in favor of such an impact, they might contribute to delineate, at an early phase, profile of participants at high risk of dementia with a strong vascular component for whom the proposed treatments and prognosis would need to be assessed carefully.

2. RATIONALE AND GENERAL DESCRIPTION

2.1. BACKGROUND

Alzheimer's disease is a neurodegenerative disorder thought to be caused by the accumulation of the peptide amyloid-β and the hyperphosphorylated tau-protein in the brain. The disease progresses until dementia, a severe stage that patients reach when they lose their autonomy. This stage is characterized by a highly heterogeneous phenotype.

Until recently, it was estimated that around two-thirds of sporadic dementia cases were due to Alzheimer's disease while only ten per cent of cases occurred as a consequence of a stroke and were labeled as "Vascular dementia". However, body of evidence is emerging from population-based neuropathological studies showing mixed pathophysiology i.e. presence of amyloid plaques and neurofibrillary tangles that are typical of AD and also infarcts and white matter abnormalities that are markers of cerebrovascular disease.[238,261-266] It is therefore very likely that more dementia cases than initially envisaged are mixed dementias. Underlying mechanisms and risk factors of these cases remain still poorly understood.[267]

Since many years, it has well been established that age and the allele ε4 of the apolipoprotein E genotype are the main risk factors for dementia.[12,268] More recently, large-scale genome-wide association studies have provided compelling evidence that variants in four novel susceptibility genes (CLU, PICALM, CR1, BIN1) are risk factors for the disease. [13,14]However, none of these risk factors is modifiable while major hope for dementia prevention relies on the identification of modifiable risk factors but they could modulate the effect of some risk factors of dementia.

2.2. VASCULAR RISK FACTORS AND DEMENTIA RISK

Since almost 20 years, evidence for an association between vascular risk factors and dementia is accumulating,[90,267,269] hypertension and diabetes being primary examples.

2.2.1. HYPERTENSION

Hypertension has been shown to be the most important modifiable risk factor for prevention of cerebrovascular disease[52,270,271] but whether hypertension affects cognitive function and dementia onset is still a matter of debate. A recent systematic review[272] concluded that midlife high blood pressure levels were related to dementia risk later in life, whereas hypertension in late life was either not or inversely related to dementia risk. Similarly, double-blind randomised controlled trials aiming at lowering blood pressure, mainly in patients with history of vascular disease or diabetes, have not demonstrated clear effects on cognitive outcomes.[273] The relationship between blood pressure and cognitive function is complex and, in addition,

inconsistencies regarding the relationship between BP and cognition may also result from differences in definition, methods and assessment techniques of both BP and cognition.

2.2.2. DIABETES

Observational studies show consistent relationships between diabetes mellitus and both cognitive dysfunction and abnormal changes on brain MRI (larger brain atrophy and higher load of small vessel diseases markers).[274-276] However, a recent randomised trial, ACCORD MIND, comparing the impact of an intensive vs. standard control of glycated haemoglobin on brain structure and function in 2,977 type 2 diabetics' patients, aged of 62.5 on average and followed-up over 40 months, did not show the superiority of the intensive therapy for improving cognitive outcome.[277] Another study in 16,667 patients with type 2 diabetes, of mean age 64.9 years, showed that severe hypoglycemic episodes were associated with a greater risk of dementia over 3.8 years of follow-up on average.[278]

The results described above underline the complexity of the relationship between vascular risk factors and neurocognition. More large observational studies, using standardized measurements of vascular risk factors and cognitive performances, collecting markers of both subclinical cerebrovascular disease and vascular damages are needed in order to better understand the interrelationship between vascular risk factors, cognitive performances and brain-imaging sequelae, especially in a population of older age.

2.3. NEUROVASCULAR CHANGES AND NEURODEGENERATION

From the basic research point of view, two main hypotheses are suggested to explain neurovascular dysfunctions in AD that were summarized in a recent publication.[279]

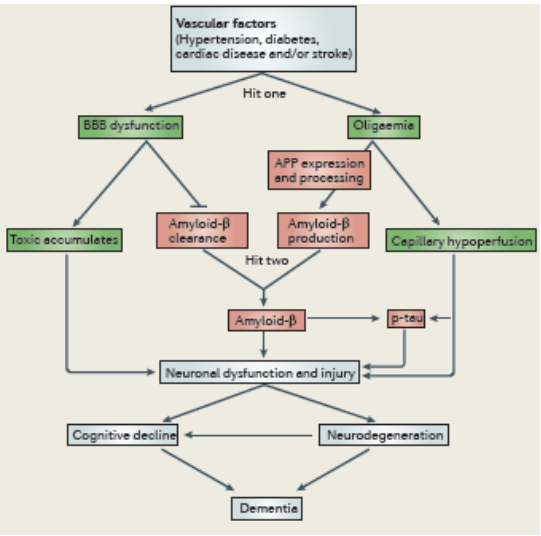


Figure 5. The two-hit vascular hypothesis for Alzheimer's disease

(Source: Zlokovic BV et al Nature reviews neuroscience, 2011)

Neuronal dysfunction and injury could occur through two pathways: in the first pathway, vascular risk factors could lead to a dysfunction of blood-brain barrier then causing toxic accumulation or impaired amyloid-β clearance. In the second pathway, vascular risk factors would cause oligaemia that could in turn cause capillary hypoperfusion or enhance the production and retention of amyloid−β and tau-protein in the brain.

Patients with Alzheimer's disease or associated disorders frequently show focal changes in brain microcirculation.[279] The time course of these vascular alterations and how they relate to dementia and Alzheimer's disease pathology remain unclear, as no protocol allowing scoring of the diverse vascular pathology development and tracking of this development with ageing, has so far been developed.

A hypothetical model for the time course of vascular alterations in relation to neurocognitive disorders is therefore proposed in Figure 6. Most of these vascular alterations biomarkers have been investigated separately in relation to cognitive dysfunction and the results can be synthetized as follows.

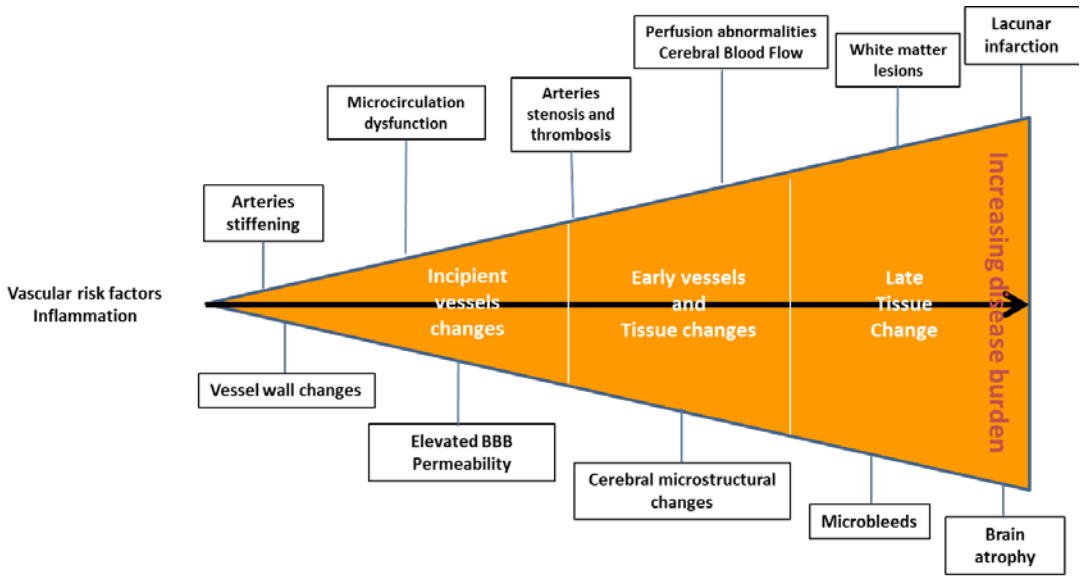


Figure 6. Hypothetical model for the time course of vascular alterations

2.3.1. INFLAMMATION

Inflammation occurs in the vasculature as a response to injury, lipid peroxidation, and perhaps infection. A recent meta-analysis of 40 studies measuring peripheral blood cytokine concentrations in AD and healthy control subjects provided evidence that AD came with an inflammatory response, associated with higher levels of IL-6, TNF-α, IL-1β, TGF-β, IL-12 and IL-18. IL-6 and IL-18 concentrations have also been shown to be strongly associated with the development and aggravation of cardiovascular diseases.[280] Chemokines are mediators of leukocytes trafficking, which participate in the recruitment of leukocytes to sites of inflammation and injury. Evidence is emerging that chemokines and their receptors are involved in AD.[281] In asymptomatic individuals, high systemic levels of RANTES (CCL5) and IP-10 (CXCL10) are independent predictors of ischemic stroke.[282]

Oxidative stress is a well-known etiology of cardiovascular disease and AD. Some novel oxidation-specific biomarkers, including lipoprotein-associated and secretory phospholipases A2 (Lp-PLA2 and sPLA2) and oxidized phospholipids on apolipoprotein B-100 particles (oxPL/apoB100), have been associated with a higher risk of coronary artery disease events and their association with dementia or cognitive decline should be assessed.[283,284]

2.3.2. RETINAL MICROVASCULATURE

Owing to the homology between the retinal and cerebral microvasculature, changes in the retinal vasculature may reflect similar changes in the cerebral vasculature. The use of retinal digital image analysis has become increasingly common over the past decade, and offers increasingly sophisticated techniques to analyse different aspects of retinal microvasculature, such as the width of retinal micro-vessels. Semi-automated, computer-based retinal imaging programs have proven to be highly accurate and reproducible in assessing *in vivo* architectural changes in the retinal vascular network.[285] Data from recent population-based studies linked changes in retinal vascular caliber with demographic factors (e.g., age, race/ethnicity), various systemic medical conditions (e.g., blood pressure, diabetes),[286-288] environmental and lifestyle factors (e.g., smoking),[289] and genetic risk factors.[290] There are also reports associating changes in retinal vascular caliber with clinical cardiovascular outcomes such as stroke and coronary heart disease.[291,292]

Analysis of retinal microvessels characteristics may offer an opportunity in dementia pathologies. A recent study by Berisha et al found that AD participants had narrower venules,

and decreased blood flow in these venules (both measured by a laser Doppler instrument).[293] Of note, this study was too limited (9 probable AD and 8 controls) to generalize the results.

To date, few studies have explored retinal microvascular changes in cognitive impairment, i.e 3 studies in diabetic patients[294-296] and 5 in population-based elderly samples.[297-299]

In patients with type 1 diabetes, the presence of retinal microaneurysms was associated with poorer performance on some tests of IQ performance (Block Design, Digit Symbol Test), and information-processing speed[296] while proliferative diabetic retinopathy (PDR) was associated with poorer performance on measures of psychomotor efficiency.[294] In patients with type 2 diabetes, the presence of diabetic retinopathy assessed prior to a coronary artery bypass grafting surgery was associated with a higher risk of short- and long-term cognitive impairment.[295] In the cross-sectional analysis of the ARIC Study,[297] a large population-based study of 15 792 participants, the authors found that the presence of retinal microvascular abnormalities (presence of any retinopathy, microaneurysms, retinal haemorrhages and exudates) was independently associated with a small decrease in cognitive function. This study lends further evidence that vascular permeability may be an important element in cerebral vascular changes leading to cognitive decline, as the retinal abnormalities most consistently associated with cognitive impairment were microaneurysms and retinal haemorrhages rather than arteriolar narrowing. However cognitive performances were not contemporaneously evaluated with the retinal photography in this study (interval of 3 years) and visual acuity was not measured which may have had an effect on the outcomes, if those who could not optimally perform the cognitive tests had visual impairment. In the longitudinal sub sample of the same study, Lesage et al[300] found a decline of the Word Fluency score in persons with retinal abnormalities (any retinopathy, microaneuvrysm and focal arteriolar narrowing) but no associations were found for other cognitive domains and with arteriolar or venular diameter.

Using a computer-assisted grading method of retinal abnormality assessment, Patton et al[298] found a cross-sectional association of suboptimal retinal vascular network geometry and cognition but no association with arteriolar and venular diameters. Among 1988 participants from the Blue Montain Eye Study, retinal venular dilation were associated with global cognitive impairment as well as retinopathy signs in persons with arterial hypertension.[301]

The only study with a clinical diagnosis of dementia found an association between retinopathy and focal arteriolar narrowing with dementia, but only in individuals with hypertension; this study cross-sectional study however did not give information on the temporal process.[299]

Overall, the results on population-based studies are conflicting and mainly from cross-sectional analysis. No study has extensively measured cognitive functioning, including dementia

diagnosis, together with retinal microvasculature including vessels caliber in a repeated manner. Several studies used retinal data acquired in the 90's while the quality of the retinal photographs has increased in the last years with more sophisticated techniques of analysis. Another important point to take into account is the participant's visual acuity as it could be an important confounding factor. Finally, systemic diseases (hypertension, diabetes, cardiovascular diseases, and depression) as well as smoking or alcohol consumption should also be included in the analysis as they may interact in the relation between micro-vascular abnormalities and dementia or cognitive decline.

2.3.3. THICKNESS OF THE RETINAL NERVE FIBER LAYER

The eye is an extension of the brain, and retinal examination may therefore be considered as a window for the evaluation of some cerebral structures. Indeed, the optic nerve is made up of nerve fibers which are initiated in the retina and end in the brain, at the level of the lateral geniculate nucleus. These fibers, not myelinized in the retina, are myelinized only after having passed through the lamina cribosa, therefore after leaving the eye, strictly speaking. Thickness of the retinal nerve fiber layer (RNFL) therefore corresponds to an axonal thickness, and is a good candidate biomarker of cerebral axonal degeneration. In the 80's and 90's, several post-mortem histological studies have indeed evidenced an important degeneration of the nerve fibers of the optic nerve and the retina, in AD patients,[302-305] although other studies did not evidence such alterations.[306,307]

RNFL thickness became measurable in vivo in humans only with the development of a new technology at the beginning of the 90's: the optical coherence tomography (OCT).[308]This technique performs an optical echography of the different layers of the retina or the cornea. Since the end of the 90's, it has therefore become possible to measure RNFL thickness in OCT, with a good reproducibility.[309,310]This examination is performed without radiations, in a few seconds per eye. It is therefore non-invasive and relatively cheap (in particular by comparison with MRI examinations).

Since a few years, the measurement of RNFL thickness has shown its interest as a biomarker of cerebral axonal degeneration in multiple sclerosis.[285]By contrast, very few data are available in AD. To our knowledge, only five case-control studies, each one including less than 30 patients, have suggested an important decrease of RNFL thickness in AD patients, by comparison with controls.[286-289,293] In one of these studies, the decrease in RNFL thickness also correlated with disease severity.[288] Another study has suggested that RNFL thinning occurs very early in the disease process, since RNFL decreased also in subjects with mild cognitive impairment (MCI). Overall, available histological, clinical and OCT data therefore suggest a progressive decrease of

RNFL during AD. These data remain however partial, having been performed in very small series of patients. It is therefore important to confirm these results in series of larger sample sizes.

2.3.4. MICROALBUMINURIA

A few population-based studies have shown a link between micro albuminuria and either decline in cognitive functions or increased risk for dementia. These findings add to a growing body of work that supports an association between changes in kidney function and changes in brain function, in older individuals. One potential explanation is that the brain and the kidney are highly vascular structures that respond to diseases such as hypertension and diabetes mellitus in similar ways at the microscopic level. In nephrosclerosis, gradual alterations in the kidney endothelial cells, glomeruli, and interstitial spaces lead to glomerular leakage of serum proteins into the urine. If a similar process was occurring at the endothelial level in brain microvessels, serum proteins would pass into the brain extracellular space. Neuropathologic studies show that white matter hyperintensities represent enlarged perivascular spaces and perivascular demyelination. These changes are what one might expect if the brain extracellular spaces were exposed to proinflammatory proteins that, in health, should remain inside the vascular space. While there is no direct proof that this process occurs, it has been previously shown that white matter hyperintensities are indeed associated with microalbuminuria. The association of albuminuria and cognition could therefore have much broader implications for understanding the role of cerebrovascular disease in late-life cognitive impairment.

2.3.5. ARTERIAL STIFFNESS

Larger artery stiffness, as assessed by the aortic pulse wave velocity (PWV) or augmentation index (AIx), independently predicts cardiovascular risk in a variety of populations.[311,312] Stiffening of the large arteries may also contribute to atherosclerosis, in part by changes in mechanical stress within the arterial wall and a reduction in shear stress.[313] Arterial stiffness is the main determinant of pulse pressure which, in turn, has been shown to be a strong determinant of remodeling of compliance of both large arteries and cerebral arterioles. Age is an important risk factor for arterial stiffening and traditional cardiovascular risk factors are associated with more severe arterial stiffening.[314]

An association between arterial stiffness and cognitive performances has been reported mainly from cross-sectional data of small size studies. Similarly there are only a few reports on the association between arterial stiffness and white matter lesions severity independent of other cardiovascular risk factors.[315-321] One potential mechanism is that increased stiffness is

associated with abnormal microvascular structure and function. Abnormal microvascular reactivity may therefore increase susceptibility to intermittent microvascular ischemia and tissue damage.[314]

2.3.6. CEREBRAL BLOOD FLOW

The amount of blood flowing into the brain may play an important role in neurodegeneration.[279,322,323] Cerebral Blood Flow (CBF) is regulated by local neuronal activity and metabolism. Intracerebral arteries control the local increase in CBF that occurs during brain activation. This is why progressive CBF reductions have potentially progressive serious consequences on neurons.

Only a few epidemiological studies have investigated the association between decreased CBF and cognitive performances or dementia. In a sample of 1730 community dwelling participants non demented at enrolment, CBF velocity was measured using transcranial Doppler (TCD) and MRI of the hippocampus was available in a subsample . Reduced CBF velocity was related to higher rate of dementia and lower hippocampal volumes after adjusting for potential confounders.[324,325]

CBF can also be measured from Arterial spin-Labeled (ASL) MRI, an innovative noninvasive method for assessing perfusion. It uses endogenous arterial blood water as a tracer to quantify CBF. Its noninvasive nature and high reproducibility over time render it attractive for large scale scanning and longitudinal assessments of CBF. Most of published work on MRI-ASL so far has consisted in demonstrating its ability to help differentiate AD patients from matched controls or other types of dementia (Fronto-Temporal) by showing distinct patterns of hypoperfusion or hyperperfusion.[326,327]

2.3.7. CEREBRAL ARTERIES STENOSIS

A non-invasive MR technique, not requiring contrast injection, allows an evaluation of cerebral arteries degree of stenosis: large Field Of View MR-angiography. Stenosis of cerebral arteries is a risk factor for stroke and is associated with subclinical vascular brain damages.

2.3.8. SUBCLINICAL VASCULAR BRAIN DAMAGES

Cerebrovascular risk factors cause cognitive impairment through mechanisms that remain poorly elucidated. Exposure to certain risk factors is already known to be associated with subclinical vascular brain damage, including White Matter Hyperintensities (WMHs), subclinical infarcts, and cerebral microbleeding that affect cognitive function.[328]

WMHs are areas of increased signal often observed on fluid attenuated inversion recovery (FLAIR) or T2-weighted MRI scans of the brain in elderly individuals, occurring in most of

healthy individuals aged 60 and older.[51] Age is the strongest predictor of WMHs, but cerebrovascular factors including hypertension, atherosclerosis, history of transient ischemic attack have also been related to a larger load of WMHs.[329] The etiology of WMHs is controversial, with suggested mechanisms ranging from ischemia and regional hypoperfusion to blood–brain barrier leakage, inflammation, and neurodegeneration. Ischemic microangiopathy is most commonly causally involved because WMHs correlate with vascular disease and microangiopathy in vivo and in pathological studies and are more common in individuals with vascular risk factors.[330]

Infarcts are visible as focal lesions with roughly the same intensity as cerebrospinal fluid on both CT and MRI. They can be separated from WMHs based on hypodensity on T1-weighted MRI. Infarcts are classified as silent if patients—by definition— are free of stroke-like symptoms. A recent review showed that 8 to 28% of elderly after the age of 65 without stroke could have radiological or pathological evidence of cerebral infarction.[49] These subclinical infarcts share the same risk factors as WMHs and are associated with subtle deficits in physical and cognitive function. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia.

Brain Microbleeds (BMBs) are seen as small, homogeneous, round foci of low signal intensity on magnetic resonance imaging gradient echo (GRE) T2* sequences. The pathological abnormalities underlying BMBs is not fully elucidated.[331] MBMs' overall prevalence in "healthy" old adults was estimated to 5% in a systematic review [57] and a recent cross-sectional analysis of data from a large population-based cohort has suggested that MBMs were associated with worsening of cognitive functions independently of vascular and other cerebrovascular factors.[332] The link between MBMs and neurodegeneration was confirmed by a study showing an association between Aβ deposition and MBMs prevalence.[333]

2.4. SYNTHESIS

The review above shows the multidimensionality of vascular damages that could contribute to neurodegeneration as summarized in Figure 6. To date these markers have never been studied neither simultaneously nor longitudinally in order to assess their impact on neurodegeneration.

2.5. BENEFIT/RISK RATIO

The potential risks of procedures performed during the MEMENTO-VASCOD study are reduced because they are all used in routine.

3. OBJECTIVES OF THE STUDY

3.1. PRINCIPAL OBJECTIVE

The primary objective of this ancillary study is to investigate the prospective association between vascular risk factors, inflammation markers and vascular damages on cognitive decline and neurodegeneration progression over up to 3 years of follow-up in a sample of individuals presenting with a spectrum of cognitive profiles ranging from isolated cognitive complaints to cognitive deficits without dementia.

3.2. SECONDARY OBJECTIVES

The secondary objectives are the following

- To investigate the role of vascular risk factors (diabetes, hypertension, hypercholesterolemia) and vascular damages on progression to clinical dementia over up to 3-year follow-up.
- To study whether the interaction between changes in markers of macrovascular and microvascular structures on cognitive deficits progression.
- To study the association between in BP levels, antihypertensive treatments and vascular damages, progression of cerebrovascular disease seen at MRI and cognitive decline and dementia risk
- To assess the temporality of vascular damages burden on neurodegeneration
- To assess the association between retinal vasculature defect and brain neurovascular damages
- To study the link between vascular damages and AD pathology (CSF and TEP amyloid imaging) biomarkers in the subsample of participants having all measures available
- To investigate how inflammatory markers mediate the association between vascular damages and neurodegeneration
- To assess whether vascular factors and neurodegenative factors act independently or synergistically on the course of cognitive decline
- To assess simultaneously the impact of vascular damages on end organs (brain, eye, and kidney)
- To study the correlation between cerebral blood flow, measured by Arterial spin-Labeled (ASL) MRI and cognitive decline
- To study whether genetic polymorphisms revealed from GWAS of Alzheimer's disease of vascular factors could modulate the association between vascular damages and cognitive decline

4. STUDY DESIGN

It is a multicentre prospective study within the MEMENTO cohort. Ten clinical sites will participate in this ancillary study.

Participants can be included (informed consent signed) concomitantly to any Memento follow-up visit.

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

Participants to MEMENTO-Vascod should be included in MEMENTO.

In addition, participants to MEMENTO-Vascod should meet the following specific inclusion criteria:

1. To have signed a specific MEMENTO-Vascod informed consent form, prior to any Vascod ancillary study related procedures
2. To be aged 50 years old and above
3. To have a Clinical Dementia Rating scale ≤0.5 and to be not demented;

5.2. NON INCLUSION CRITERIA

Individuals will be excluded from MEMENTO-Vascod enrollment if they:

1. Are under guardianship
2. Live in skilled nursing facility
3. Are Pregnant or breast feeding women
4. In case participant agrees to have a brain MRI : Meet brain MRI exclusion criteria (Same criteria as in Memento main protocol)

6. STUDY PROCEDURES

In order to test the possible time course of vascular alterations in relation to neurocognitive disorders, the Memento-Vascod project will require investigations (in Orange on Figure 7) in addition to those already collected in Memento (in green on Figure 7). They are detailed below according to a hypothetical calendar time.

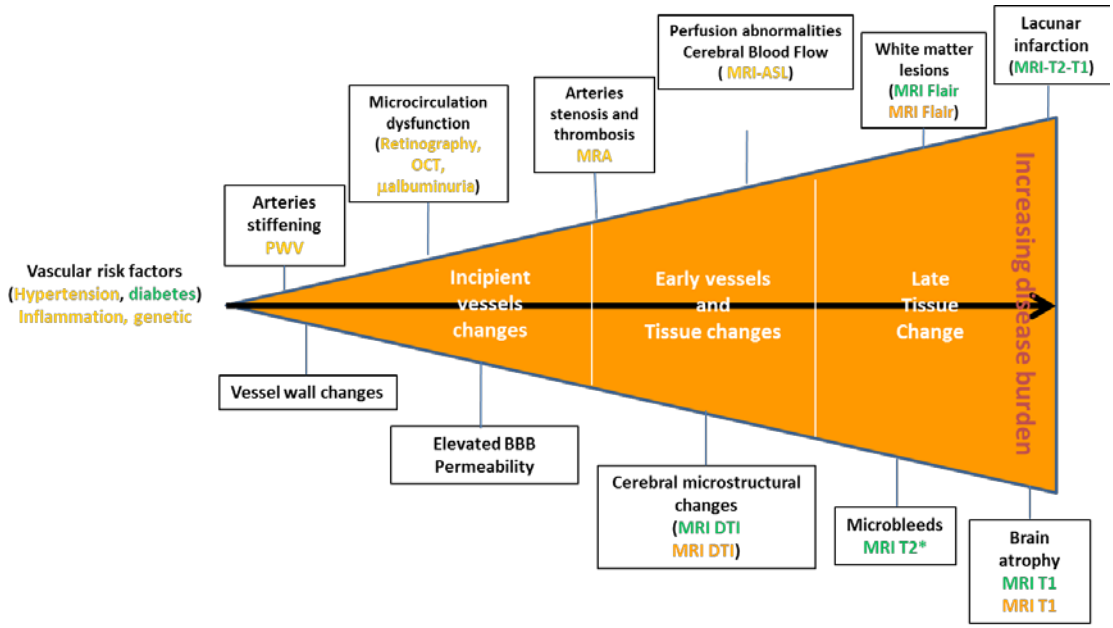


Figure 7. Assessing the time course of vascular alterations in MEMENTO-Vascod

6.1. INFLAMMATION MARKERS

The following inflammation markers will be measured on samples kept in the centralized biobank on samples planned in the Memento protocol: IL-6, IL-10, IL-12, IL-18, RANTES (CCL5) , IP-10 (CXCL10), There will be no additional blood sample performed for participants enrolled in Memento-Vascod.

6.2. GENETIC MARKERS

Recently, genome-wide association studies (GWAS) have enabled the discovery of numerous common genetic variants associated with an increased risk of developing Alzheimer's disease, vascular Risk Factors, stroke, and covert cerebrovascular disease. They will be measured from DNA extracted from centralized biobank for the full MEMENTO sample for power optimization.

6.3. PULSE WAVE VELOCITY AND CENTRAL BLOOD PRESSURE

Central aortic blood pressure parameters will be evaluated. To ensure the standardisation of these measurements an identical device will be used in all centers. The assessment takes 10 minutes.

Pulse Wave system allows recording a high fidelity peripheral artery blood pressure waveform. From peripheral measurements, the PW software derives the central aortic blood pressure waveform and a range of central arterial indices of ventricular-vascular interaction. Measurements of central aortic blood pressure parameters using the PW device have been performed in number of international and multicenter studies.

Arterial stiffness will be assessed by the pulse wave velocity measurement. The PW System measures the velocity of the blood pressure waveform between any two superficial artery sites.

The measured parameters will be:

- Carotid-femoral Pulse Wave Velocity
- Derived central systolic pressure
- Derived central Pulse Pressure
- Derived central Augmentation Index
- Derived central Augmentation Pressure
- Carotid Systolic Pressure
- Carotid Pulse Pressure
- Carotid Augmentation Index
- Carotid Augmentation Pressure

Other criteria might be evaluated according to the state of knowledge at the time of the analysis.

6.4. URINARY ALBUMIN EXCRETION ASSESSMENT

Urinary albumin excretion (UAE) will be performed through a single first-morning urine sample that the participant will be asked to collect in a collection container. Abnormal UAE will be defined as an albumin/creatinine ratio ≥3.4 mg/mmol (equivalent to ≥30 mg/g).

6.5. OCULAR ASSESSMENTS

The following ophthalmological examinations will be performed:

- Visual acuity using the Early Treatment Diabetic Retinopathy Study (*ETDRS*) scale,

and after pupil dilation:

- Axial length measurement,
- Examination with SD-OCT,

- Colour photographs of the retina, centered on the macula and on the optic nerve (digital non mydriatic retinal camera).

The duration of the examination will be about 30 min to 1 hour for each subject. The examinations performed and the material used (eye drops, ophthalmological devices) in the framework of this study are of routine use in ophthalmology and do not present particular risks. Pupil dilation, necessary for performing the eye examinations, leads to a transitory visual disturbance, during 2 to 3 hours. Because of the visual disturbance due to pupil dilation, a transport in taxi (back and forth from the subject's home to the examination centre) will be advised to all participants.

RNFL thickness and when possible choroidal thickness will be measured with a second generation OCT device (SD-OCT). While usual echographies use ultrasounds, the first generation OCT (Time Domain- TD) lights the retina with a laser emitted by a superluminescent diode. Since 2007, a modification of the functioning of OCT has emerged, with the implementation of a spectroscope, giving birth to the Spectral Domain OCT (SD-OCT), or Fourier Domain OCT.[290] Numerous advantages appear with this new SD-OCT: the quality of the images is excellent, thanks to a scanning velocity of 18,000 to 40,000 scans/sec, when TD-OCT performed 400 scans/sec; the longitudinal resolution reaches 5 to 7 microns; there are no mirror movements to manage, thus the "photograph" is very rapid and therefore eliminates the artefacts due to eye movements. The SD-OCT signal strength is excellent and allows for a remarkable image quality. An "optical biopsy" of the retina is obtained in vivo, and in real time, with resolutions close to histopathology.

In retinal pathology, OCT has become absolutely essential for macular diseases: it allows a reliable diagnosis for macular holes and vitreo-macular tractions. It allows the quantification of retinal and sub-retinal thicknesses, so important in case of neovascular AMD and diabetic macular edema. But the new SD-OCT also allows measurements which were impossible or unreliable, in particular RNFL thickness, measured around the optic disc, according to a standardized procedure, integrated in the software of the device. Several studies have shown that this new generation OCT has allowed a major gain in the reproducibility of this parameter.[291,292,334,335]

From centralized interpretation of retinal photographs, the following paramaters will be measured:

- Presence of retinal microvascular abnormalities (microaneurysms, micro-hemorrhages, cotton wool spots, arteriovenous nicking), observed on colour retinal photographs

- Arteriolar and venular diameters, using a computer-assisted grading method with high reproducibility (Figure 8). To gauge generalized narrowing, vessel diameters are combined into central retinal arteriolar equivalents (CRAE) and central retinal venular equivalents (CRVE) with formulas[335], and the ratio of equivalents (Arterio-veinous ratio [AVR]) is calculated. These measurements will be centralized and performed by a person certified for the use of the IVAN software.

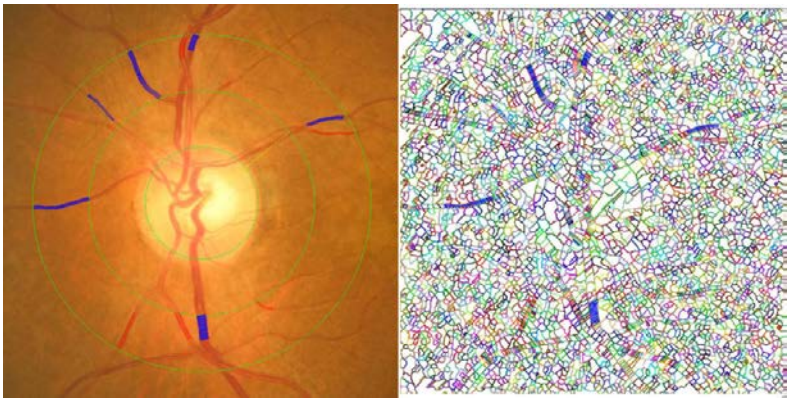


Figure 8. Retinal vessel measurement by IVAN software (image and splats display showing relatively larger arterioles (CRAE 183.62 mm) and venules (CRVE 251.12 mm) and an AVR (0.73), arterioles in red and venules in blue).

- RNFL thickness, measured (in microns) from a standardized examination with SD-OCT, on a peri-papillary scan. The measurement is provided by the software integrated with the SD-OCT, and has shown excellent validity and reproducibility in several publications.[291,292,334] In particular, the reproducibility of the measurement of RNFL thickness is definitely higher with this new generation OCT, by comparison with the preceding generation (TD, Stratus®).

6.6. CEREBRAL BRAIN MRI

The cerebral MRI performed at the MEMENTO-Vascod baseline visit and will include the following sequences

N°					
1		Parameters checking	0 : 10	~39 : 00	~56 : 00 - ~66 : 00
2		3D-T1	9 : 00		
3		MRA-TOF	~8 : 00		
4		pCASL	~8 : 00		
5		3DmultiGRE (T2*)	~9 : 00		
6		T2FLAIR	~5 : 00		
7	Opt	Ultra high in-plane TSE T2/PD for the hippocampus	7 : 00		
8	Opt	DTI1-4 (Diffusion tensor DWI EPI) + B0MAP (carte de champ B0)	4 : 30 x 2-4 1 : 45		

Compared to Memento MRI protocol there are three additional sequences:

- Magnetic Resonance Angiography will be a flow compensated 3-dimensional time-of-flight sequence of the intracranial part of internal carotid arteries, the circle of Willis and of its branches. Scan parameters will be obtained in order to visualize the following intracranial arteries: anterior, middle and posterior cerebral arteries, basilar artery and vertebral arteries (V4), internal carotid arteries.
- Arterial Spin Labeling (ASL) scan will be performed using a protocol as close as possible to that recommended by the COST Action on Arterial Spin Labeling in dementia (http://www.aslindementia.org/). A 2D pCASL sequence will thus be adapted in all centres in close collaboration with a French expert team.
- Ultra high in-plane resolution TSE T2/PD sequence for the hippocampus aims at acquiring high resolution coronal slices perpendicular to the main axis of the hippocampus. In-plane resolution will be about 0.3x0.3mm². The whole hippocampus will be covered with about 2mm thick slices, and the sequence may include a 100% gap between slices to allow reducing acquisition time.

6.7. NEUROPSYCHOLOGICAL TESTING, BEHAVIORAL AND MOOD SCALES

Consequences of vascular damages can differ from what is expected with normal ageing or neurodegenerative disease. A group of experts has proposed standardized criteria to assess thses consequences that have been adapted in France.[336,337] In order to fit with these criteria, the MEMENTO usual assessments will be completed as follows:

- The Digit symbol substitution test of Wechsler[216] : It consists of (e.g. nine) digit-symbol pairs (e.g. 1/-,2/⊥ ... 7/Λ,8/X,9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g. 90 sec) is measured.
- The stroop test[338] : it consists in reading colors' names with colors interference.
- The MOCA battery : a short screening battery to detect deficits in executive functions and psychomotor speed [337]
- Goldberg scale for anxiety and depression symptoms[339]

7. ASSOCIATED TREATMENTS

All medications that are continued or are started during the study are documented through the MEMENTO e-Case Report Form.

8. OUTCOMES

8.1. PRIMARY OUTCOME

The primary endpoint is the change in cognitive performances over 3-year follow-up

8.2. SECONDARY OUTCOMES

- Progression to clinical dementia stage according to standardized classifications (DSM-IV and NINCDS-ADRDA)
- Change in CSF and blood amyloid biomarkers of AD
- Change in brain atrophy and hippocampal volumes
- Progression of small vessels disease markers (white matter lesions, lacunar infarcts, microbleeds)

9. STUDY CONDUCT

9.1. STUDY CALENDAR

- Start of inclusions: November 2014
- Duration of the inclusion period: 37 months
- Duration of each participant's participation: 36 months
- Total duration of the study: 73 months

9.2. SCHEDULE OF ASSESSMENTS IN MEMENTO-VASCOD

		Screening	Baseline (Month 0)	Month 12	Month 24	Month 36
VASCOD	Explain Study	✓	✓			
	Obtain Consent		✓			
	Pulse wave velocity		✓		✓	
	Neuropsychological, behavioral and mood scales		✓	✓	✓	✓
	Microalbuminuria		✓		✓	
	Ocular assessment*		✓		✓	
	Cerebral MRI*		✓			

* Optional examinations

9.3. SIGNATURE OF INFORMED CONSENT

During any MEMENTO visits, the MEMENTO-Vascod study will be explained to the participant. A separate written Informed Consent must be obtained for the MEMENTO Vascod study, prior to the initiation of any MEMENTO-Vascod related interview or investigation.

The information should be clear that refusal to participate or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care and follow up in the MEMENTO cohort.

The informed consent is signed in one original and two copies obtained by triplication. One of the copies of the signed informed consent is given to the participant. Signed informed consents are retained by the investigator and made available (for review only) to the study monitor, auditor and inspector, upon request. An anonymised copy of the signed consent form is provided to the sponsor or its delegate.

9.4. SCREENING VISIT

All participants will be screened for MEMENTO-VASCOD either at any visits of the main MEMENTO protocol. The screening assessment for eligibility will be performed by the investigator.

9.5. BASELINE VISIT

Once inclusion is confirmed, the following investigations will be performed in the six months following informed consent signature:

MANDATORY

- Pulse wave velocity assessment
- Neuropsychological testing and behavorial and mood scales
- Measurement of microalbuminuria
- Selected genotypes will be measured and inflammory markers dosages will be performed from specimen stored at the centralised biobank collected at either M0 or M24 of the MEMENTO study.

OPTIONAL

- Cerebral MRI
- Ophtalmological exams: visual acuity, optical biometry, colour photographs of the retina and SD-OCT,

9.6. YEAR 2 FOLLOW-UP VISIT

MANDATORY

- Pulse wave velocity assessment
- Neuropsychological testing and behavorial and mood scales
- Measurement of microalbunemuria
- Inflammory markers dosages will be performed from specimen stored at the centralised biobank collected at either M24 or M48 of the MEMENTO study

OPTIONAL

- Ophtalmological exams: visual acuity, optical biometry, colour photographs of the retina and SD-OCT,

9.7. YEARS 1 AND 3 FOLLOW-UP VISITS

- Neuropsychological testing and behavorial and mood scales

9.8. WITHDRAWAL

Participants may voluntarily withdraw from the ancillary study for any reason at any time, without any impact on their follow-up in the MEMENTO cohort. When a participant withdraws his/her consent to participate in the study, no new information must be collected and recorded in the database after the date of withdrawal. Similarly, no samples must be collected after that date in the context of the research study.

Withdrawals of consent to participate in the study must be reported to the coordinating center as soon as possible in the electronic CRF. The investigator must document the date, reason and any

answers given in response to the participant, in the participant's medical records. If a participant explicitly states his/her wish not to contribute data to the study, the coordinating center should be informed in writing of the participant's decision. Participants withdrawing from the study without stating this wish have previously consented to follow-up in the study, and data up to this time can be included in the study if it is anonymised.

9.9. PARTICIPANTS' COMPENSATION

For any inconvenience and extra expenses participant might have encountered during the study, a compensation will be paid to each participant (120 euros for the baseline visit and 80 euros for the year 2 follow-up visit if evaluations are performed). The total amount of compensation is up to 200 euros.

10. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

Reporting of adverse event and serious adverse event must follow the same procedure described in the MEMENTO main protocol (chapter A.10.3. of the main protocol MEMENTO)

10.1. DEFINITIONS

See chapter A.10.3. of the main protocol MEMENTO.

10.2. DESCRIPTION OF EXPECTED SERIOUS ADVERSE EFFECTS IN MEMENTO-VASCOD

See chapter A.10.3. of the main protocol MEMENTO.

10.3. ACTION TO BE TAKEN IN THE CASE OF AN ADVERSE EVENT OR NEW FACT

See chapter A.10.3. of the main protocol MEMENTO.

10.4. DECLARATION AND RECORDING OF UNEXPECTED SERIOUS ADVERSE EVENTS AND NEW FACTS

See chapter A.10.3. of the main protocol MEMENTO.

11. STUDY COMMITTEES

11.1. ENDPOINT REVIEW COMMITTEE

There will be no specific endpoint review committee set up for MEMENTO-Vascod. All cause-dementia and its etiological diagnosis will be validated through MEMENTO procedures.

12. STATISTICS

12.1. SAMPLE SIZE

We hypothesize 350 participants to be recruited. With a drop-out rate of 10% over 3 years, the 3-years cognitive decline will be evaluated in 320 subjects. We assume (i) a 0.05 two-sided significant level, (ii) a cognitive decline estimated by a variable normally distributed and (iii) a common standard deviation between subgroups.

With a statistical power of 90%, we could detect a significant difference between 2 groups (risk factor present vs absent) of at least 0.6 times the common SD for a risk factor prevalence of 10%, 0.49 times for a prevalence of 20% and 0.36 times for a prevalence of 50%.

We expect that the statistical power of our comparisons will increase using sophisticated modelisation (see “analysis of primary endpoint” chapter): decreased variability after covariate adjustment and random effects, repeated measures for a same patient, all patients with at least one measure contribute to the analysis.

12.2. ANALYSIS OF THE PRIMARY ENDPOINT

We will use random intercept growth curve models to examine the relationship between each exposure and level and rate of change in each cognitive outcome. To account for practice effects, we will include an indicator for first test encounter in all models.

We will also estimate annual rate of change for each cognitive test in linear (or non linear if appropriate) age models. These models will be adjusted for potential confounders.

To assess the effect of each vascular damage progression on rate of change, we will repeat mixed models allowing covariates to be time dependent.

Because of the potential bias induced by selective survival and loss to follow-up in studies of determinants of cognitive aging, we will use inverse probability weights to account for selective loss to follow-up or mortality.

Any other relevant analysis methods could be used regarding their appropriateness to the data, and will be described in specific Statistical Analysis Plans.

12.3. ANALYSIS OF THE SECONDARY ENDPOINTS

Time to clinical dementia, will be analyzed using time to event methods – Kaplan Meier plots and Cox regression with delayed entry models.

All multivariable analysis will be systematically adjusted by age, gender and a center effect will be accounted for. To model Change random effects model will be computed. All analyses will be described in specific Statistical Analysis Plans.

13. RIGHT OF ACCESS TO PERSONAL DATA AND SOURCE DOCUMENTS

The rules described in MEMENTO protocol will apply.

14. QUALITY CONTROL AND ASSURANCE

14.1. STUDY MONITORING

Study monitoring will be performed according to MEMENTO monitoring plan.

14.2. QUALITY CONTROL

The rules described in the MEMENTO protocol will apply. The CATI will be in charge of quality control of cerebral MRI images. For each of the additional investigations related to MEMENTO-Vascod (pulse wave velocity, retinal assessment), training session to each protocol will be organised in order to minimize heterogeneity between centers. Quality control measures will be developed for retinal colour photography. For retinal assessment there will be a central reading.

14.3. DATA MANAGEMENT

The CIC-EC7 is responsible for data management. Data will be entered in an eCRF dedicated to MEMENTO-Vascod. Adverse events will be recorded in the MEMENTO eCRF

15. PUBLICATION RULES

The MEMENTO “access to data and ancillary studies” charter will apply.

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APPENDICES' LIST

APPENDIX I: ETHIC COMMITTEE AUTHORISATION

COMITÉ DE PROTECTION DES PERSONNES
SUD-OUEST ET OUTRE MER III

Président : Professeur Emmanuel CUNY

DOSSIER ENREGISTRÉ CPP N° : 2010/110
Numéro d'enregistrement : 2010-A01394-35

RECU LE
25 MARS 2013
RECHERCHE CLINIQUE

DESTINATAIRE : CHU de Bordeaux
Patrick CASSAI
DRCI
12 rue Dubernat
33404 Talence cedex

Vos réf. : protocole CHUBX 2010/47 étude MEMENTO.

Bordeaux, le 11 mars 2013.

Avis favorable avec remarques en date du 15 décembre 25010.
Avis favorable en date du 23 février 2011.
Avis favorable à la modification substantielle n° 1 en date du 28 septembre 2011.
Avis favorable avec remarques à la modification substantielle n° 2 en date du 26 octobre 2011.
Avis favorable à la modification substantielle n° 2 en date du 21 décembre 2011.
Avis favorable à la modification substantielle n° 3 en date du 21 décembre 2011.
Avis favorable à la modification substantielle n° 4 en date du 25 janvier 2012.
Avis favorable à la modification substantielle n° 5 en date du 29 février 2012.
Avis favorable à la modification substantielle n° 6 en date du 28 mars 2012.
Avis favorable à la modification substantielle n° 7 en date du 25 avril 2012.
Avis favorable à la modification substantielle n° 8 en date du 29 août 2012.
Avis favorable à la modification substantielle n° 9 en date du 19 décembre 2012.

PROMOTEUR : CHU de Bordeaux
12 rue Dubernat
33404 Talence cedex

COORDONNATEUR : Professeur Geneviève CHENE
CIC-EC7 ISPED
Université Victor Segalen
146 rue Léo Saignat
33076 Bordeaux cedex

En date du **27 FEVRIER 2013**, conformément aux dispositions du Code de la Santé Publique, le Comité de Protection des Personnes Sud-Ouest et Outre-mer III a examiné la demande de modification substantielle au protocole de recherche biomédicale intitulé :

"UNE COHORTE DE PERSONNES CONSULTANT DANS LES CENTRES MEMOIRES DE RESSOURCES ET DE RECHERCHE AFIN D'AMELIORER LES CONNAISSANCES SUR LA MALADIE D'ALZHEIMER ET LES MALADIES APPARENTEES."

L'amendement fait suite aux remarques émises par l'ANSM et concerne :
- la modification du protocole ;
- la mise à jour de la note d'information et de consentement ;
- la mise à jour de la note d'information accompagnant ;

Le Comité à l'unanimité des membres votant émet un

AVIS FAVORABLE A LA MODIFICATION SUBSTANTIELLE N° 10.

Le Président du Comité

Professeur Emmanuel CUNY.

Service de Pharmacologie clinique – Groupe Hospitalier Pellegrin – Bât. 1A
Place Amélie Raba Léon – 33076 BORDEAUX CEDEX
TÉL/FAX : 33-(0)5.57.81.76.07 – E-mail : cpp.soom3@u-bordeaux2.fr
Site Internet : www.cpp-soom3.u-bordeaux2.fr

1/2

COMITÉ DE PROTECTION DES PERSONNES SUD-OUEST ET OUTRE MER III

DOSSIER ENREGISTRÉ CPP N° : 2010/110
Numéro d'enregistrement : 2010-A01394-35

DOCUMENTS EXAMINES PAR LE COMITE

- Courrier de demande d'avis du promoteur en date du 6 février 2013 ;
- Description de l'amendement n° 10 du 6 février 2013 ;
- Protocole de recherche version 4.0 daté du 6 février 2013 ;
- Note d'information destinée aux participants version 3.0 du 6 février 2013 ;
- Note d'information destinée à l'accompagnant version 2.0 du 6 février 2013 ;
- Copie de l'attestation d'assurance prenant en compte le nouveau titre de l'étude.

MEMBRES PRESENTS

Catégorie médecins ou personnes qualifiées dans la recherche biomédicale :
- Professeur Emmanuel CUNY (titulaire)
- Docteur Igor GALPERINE – pédiatre (titulaire)
- Professeur Didier LACOMBE - pédiatre (titulaire)
- Professeur Simone MATHOULIN-PELISSIER - compétente en matière biostatistique ou d'épidémiologie (titulaire)
- Docteur Mélina FATSEAS (suppléante)
- Docteur Driss BERDAÏ (suppléant)
- Docteur Antoine BENARD - compétent en matière biostatistique ou d'épidémiologie (suppléant)

Catégorie médecins généralistes
- Docteur Stéphane FRAIZE (titulaire)

Catégorie pharmaciens hospitaliers :
- Mademoiselle Marie-Claude SAUX (titulaire)
- Madame Joëlle JOUNEAU (suppléante)

Catégorie infirmiers
- Madame Marie VIGUIER (titulaire)

Catégorie personnes qualifiées dans le domaine de l'éthique :
- Monsieur André CALAS (titulaire)

Catégorie psychologues :
- Professeur Pascal-Henri KELLER (titulaire)
- Madame Eva TOUSSAINT (suppléante)

Catégorie travailleurs sociaux :
- Madame Jacqueline BROTHIER (titulaire)
- Madame Christiane GABORIAU (suppléante)

Catégorie juridique :
- Professeur Jean-Pierre DUPRAT (titulaire)
- Monsieur Didier CUGY (titulaire)

Catégorie Représentants des associations agréées de malades et d'usagers du système de santé :
- Monsieur François DUPUY (titulaire)
- Monsieur Michel PERDRISET (titulaire)
- Madame Jacqueline PRUVOST (suppléante)

Service de Pharmacologie clinique – Groupe Hospitalier Pellegrin – Bât. 1A
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Site Internet : www.cpp-soom3.u-bordeaux2.fr

APPENDIX II: ANSM AUTHORISATION

Fax émis par : 0155873372 ANSM DP3 ATU 04-03-13 11:18 Pg: 1/1

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION DE MODIFICATION (S) SUBSTANTIELLE (S) D'ESSAI(S) CLINIQUE(S) NE PORTANT PAS SUR UN PRODUIT DE SANTE (ESSAI(S)-HPS)

Nombre de pages : 1
(Incluant la page de garde)

Envoi par Télécopie **Date :** 1/03/13

Identifiants de la (des) modification(s) et du (des) essai(s) concerné(s)			
Promoteur	**Centre Hospitalier Universitaire de Bordeaux**		
Réf. Essai(s)		**Réf. Modification(s)**	
N° ID RCB	**Réf. ANSM**	**Réf. ANSM**	**Réf. Promoteur** (item D.1 du formulaire de demande d'AMS)
2010-A01394-35	B101404-30	S101404-3002	MODIFICATION N° 10 DU 06/02/2013

Expéditeur	**Destinataire** (**demandeur** : nom / société / tél.)
ANSM / Direction Produit NEURHO / Equipe SYNAPS	Julie BOUSSUGE-ROZE Centre Hospitalier Universitaire de Bordeaux 05.57.82.07.17
Dossier suivi par : Julie Duvernois Tél : 33 (0) 1 55 87 33 41/ Fax : 33 (0) 1 55 87 33 32	Fax **05.56.79.49.26**

Vu le code de la santé publique et notamment les articles L. 1123-9, R. 1123-37 et vu la ou les autorisations d'essais cliniques délivrées par l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) pour le ou les essais cliniques ci-dessus référencés ;

Vu le dossier de demande d'autorisation de modification(s) substantielle(s) adressé à l'ANSM ;

L'autorisation mentionnée à l'article L. 1123-9 du code de la santé publique est accordée pour la (les) modification(s) substantielle(s) identifiée(s) ci-dessus, pour les aspects relevant de la compétence de l'ANSM.

La chef produits neurologie, psychiatrie, anesthésie
Direction des médicaments en neurologie, psychiatrie, antalgie, rhumatologie, pneumologie, ORL, ophtalmologie, stupéfiants

Catherine DEGUINES

Je vous demande de transmettre toute demande d'informations complémentaires concernant ce dossier par courriel adressé à la boite : **hps-essaiscliniques@ansm.sante.fr**. Je vous précise qu'il vous est possible d'utiliser à cet effet le système de messagerie électronique sécurisée Eudralink. Lors de l'envoi de ces dossiers, je vous demande de veiller à reporter dans l'objet du message les mentions suivantes :

- pour les MS transmises à l'ANSM pour information : **MSI/ Réf ANSM du dossier Direction Produit NEURHO / Equipe SYNAPS;**
- pour les MS soumises pour autorisation ou pour les dossiers mixtes (comportant des modifications soumises pour autorisation et d'autres pour information) : **MSA/ Réf ANSM du dossier Direction Produit NEURHO / Equipe SYNAPS.**

Si vous ne recevez pas toutes les pages de cette télécopie, veuillez contacter le secrétariat de la Direction Produit NEURHO / Equipe SYNAPS au : 33 (0) 1 55 87 33 41.

143/147, bd Anatole France - F-93285 Saint-Denis cedex - tél. +33 (0)1 55 87 30 00 - www.ansm.sante.fr **Page 1 sur 1**

APPENDIX III : INSURANCE CERTIFICATE

Biomedicinsure
COURTIER EN ASSURANCES
Parc d'Innovation Bretagne sud
C.P. 142 - 56038 VANNES CEDEX
Tel. +33(0)2 97 69 19 19
Fax +33(0)2 97 69 11 11
biomail@biomedic-insure.com

HDI GERLING

ATTESTATION D'ASSURANCE
RESPONSABILITE CIVILE
PROMOTEUR DE RECHERCHE BIOMEDICALE

ADHESION n° 906742010035

Nous, soussignés HDI-GERLING - TOUR OPUS 12, 77, Esplanade de la Défense 92914 PARIS LA DEFENSE agissant en qualité d'assureur, attestons par la présente que :

CHU DE BORDEAUX
12 RUE DUBERNAT
33404 TALENCE CEDEX

(1680) 90674

a souscrit un contrat de Responsabilité Civile sous le n°

Conforme aux dispositions légales et réglementaires Françaises sur les recherches biomédicales et notamment aux dispositions de la loi 88.1138 du 20/12/1988, modifiée par les textes subséquents: loi 90.86 du 23/01/1990, décret 91-440 du 14/05/1991, loi 94.630 du 25/07/1994, décret 97-888 du 01/10/1997, décret 2002-722 du 03/05/2002, loi 2004.806 du 09/08/2004, décret 2006-477 du 26/04/2006.

Description précise de la recherche assurée :

Determinants and evolution of alzheimer`s disease and related disorders. - MEMENTO
Protocole n° CHUBX 2010/47
Investigateur : PR Geneviève CHENE

La garantie est conforme à l'obligation d'assurance instituée par les textes de la loi précitée, article L 1121-10 du Code de la Santé Publique, à la charge du promoteur, tant pour sa responsabilité que pour celle des intervenants.

La garantie prévue au contrat restera acquise à l'Assuré en cas de modification affectant la prise d'effet du protocole.

La présente attestation est valable pour la durée de la recherche concernée et sa présentation vaut présomption de garantie à la charge de l'assureur.

Fait , le 29 novembre 2010

Le Courtier
BIOMEDIC INSURE INDUSTRIES
Jean-Pierre DANIEL

Biomedicinsure
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L'Assureur
HDI-GERLING

HDI-Gerling Industrie Versicherung AG
Capital 125.000.000 EUR
TOUR OPUS 12 - LA DEFENSE 9
77, Esplanade du Général de Gaulle
F 92914 PARIS LA DEFENSE CEDEX
Tél. : +33 1 44 03 56 00 - Fax : +33 1 44 03 56 56

517/2010

APPENDIX IV: CUT-OFFS FOR EACH NEUROPSYCHOLOGICAL TEST

CONSIGNES GENERALES

- Pour tous les seuils indiqués, il s'agit de la valeur au-dessous de laquelle (≤) les sujets sont éligibles dans MEMENTO sauf pour le TMT (A et B) pour lequel il s'agit de la valeur au-dessus de laquelle (≥) les sujets sont éligibles.
- Pour les normes présentées selon le niveau d'études, se référer au tableau suivant :

❶	aucun diplôme
❷	CEP (certificat d'études primaires) ou diplôme étranger de même niveau
❸	brevet des collèges, BEPC, brevet élémentaire ou diplôme étranger de même niveau
❹	CAP, BEP ou diplôme étranger de même niveau
❺	baccalauréat technologique ou professionnel ou diplôme étranger de même niveau
❻	baccalauréat général, brevet supérieur, capacité en droit, ou diplôme étranger de même niveau
❼	diplôme de niveau Bac+2 ou diplôme étranger de même niveau
❽	diplôme de niveau supérieur à Bac+2 ou diplôme étranger de même niveau

I. DMS 48: Epreuve de reconnaissance visuelle

Source: Barbeau et al – L'évaluation des troubles de la mémoire, SOLAL éditeur, Marseille – 2004:85-101

Pour chaque classe d'âge, le calcul du seuil correspond à la valeur strictement inférieure à la moyenne – 1 écart-type.

Les seuils présentés correspondent au nombre de bonnes réponses.

1. Reconnaissance immédiate

Age	Seuil - Set 1
29 ans et moins	47
30-39 ans	47
40-49 ans	46
50-59 ans	46
60-69 ans	46
70-79 ans	43
80-89 ans	41
90 ans et plus	42

2. Reconnaissance à 1 heure

Age	Seuil - Set 2
29 ans et moins	47
30-39	47
40-49	46
50-59	46
60-69	46
70-79	44
80-89	42
90 ans et plus	44

II. RL/RI 16: rappel libre et indicé

Source: Coyette et al (à paraître), consensus d'après Dubois et al

Les seuils présentés ne concernent que l'épreuve de rappel libre et indicé immédiat.

1. Total des rappels libres

Il s'agit de la somme des rappels libres (RL1+RL2+RL3).

Age	Seuil
29 ans et moins	35
30-49	29
50-64	24
65-74	22
75 ans et plus	21

2. Total des scores totaux

Il s'agit de la somme des scores totaux (RL+RI), aux rappels 1, 2 et 3 (RL1+RI1 + RL2+RI2 + RL3+RI3).

Seuil unique: 46

III. Praxies Gestuelles

Source: Mahieux et al, Revue Neurologique 2009:560-567

Un seuil est défini pour chaque série de gestes, en fonction de l'âge et du niveau d'études (voir consignes générales).

Le seuil correspond au 5ème percentile (< ou égal).

1. Gestes symboliques

Age	Niveau d'études		
	❶ ❷	❸ ❹	❺ ❻ ❼ ❽
< 65 ans	4	3	4
65-74 ans	4	4	4
75 ans et plus	4	4	4

2. Mimes d'action

Age	Niveau d'études		
	❶ ❷	❸ ❹	❺ ❻ ❼ ❽
< 65 ans	8	7	9
65-74 ans	8	9	7
75 ans et plus	7	8	8

3. Gestes abstraits

Age	Niveau d'études		
	❶ ❷	❸ ❹	❺ ❻ ❼ ❽
< 65 ans	7	6	7
65-74 ans	6	5	5
75 ans et plus	5	6	7

IV. Trail Making Test

Source: Tombaugh et al – Archives of clinical Neuropsychology – 2004:203-214

Il s'agit du temps en secondes pour réaliser le test. On utilise le seuil du 16ème percentile (> ou égal) (valeur entière de la moyenne de la somme des 10ème et 20ème percentiles). Pour les participants âgés de 55 ans et plus, le seuil varie selon le niveau d'études (voir consignes générales).

1. TMT - PART A

Age	Seuil
18-24 ans	29
25-34 ans	36
35-44 ans	41
45-54 ans	44

Age	Seuil Niveau d'études	
	❶ ❷ ❸ ❹ ❺ ❻	❼ ❽
55-59 ans	45	45
60-64 ans	44	40
65-69 ans	51	42
70-74 ans	54	58
75-79 ans	66	62
80-84 ans	84	82
85 ans et plus	83	101

2. TMT - PART B

Age	Seuil
18-24 ans	63
25-34 ans	65
35-44 ans	78
45-54 ans	79

Age	Seuil Niveau d'études	
	❶ ❷ ❸ ❹ ❺ ❻	❼ ❽
55-59 ans	101	91
60-64 ans	94	82
65-69 ans	123	76
70-74 ans	159	110
75-79 ans	178	159
80-84 ans	231	189
85 ans et plus	265	251

V. Empan numérique: ordre direct et ordre inverse

Source: Wechsler et al – MEM-III –ECPA 1997

A partir du score total (direct + inverse), la note standard est calculée (voir tableaux fournis ci-dessous).

Le seuil d'inclusion dans MEMENTO est de 6 (inférieur ou égal) (moyenne = 10, écart-type=3).

Note standard	Age								
	20-24	25-29	30-34	35-44	45-54	55-64	65-69	70-74	≥75
19	30	30	-	30	30	28-30	27-30	24-30	22-30
18	29	29	30	29	29	27	26	23	20-21
17	28	28	29	28	28	26	24-25	21-22	19
16	26-27	27	28	27	26-27	24-25	22-23	20	18
15	23-25	25-26	27	25-26	24-25	22-23	20-21	18-19	17
14	21-22	23-24	26	24	23	20-21	19	17	16
13	20	22	24-25	22-23	21-22	19	18	16	-
12	19	20-21	22-23	20-21	19-20	17-18	16-17	15	15
11	18	19	20-21	18-19	17-18	16	15	14	14
10	17	17-18	18-19	17	15-16	14-15	14	13	13
9	16	16	17	15-16	14	13	13	12	12
8	15	15	16	14	13	12	12	11	11
7	14	14	15	13	12	11	11	10	10
6	13	13	14	-	11	10	10	9	9
5	-	-	13	12	10	9	9	8	8
4	12	12	-	11	9	8	8	7	7
3	11	11	12	10	8	7	7	6	6
2	10	10	11	9	7	6	6	5	5
1	0-9	0-9	0-10	0-8	0-6	0-5	0-5	0-4	0-4

VI. Figure complexe de Rey

Source: Meyers, J. E., & Meyers, K. R. (1995). Rey Complex Figure Test and Recognition Trial: Professional manual. Psychological Assessment Resource.

Il s'agit du score de notation.

Age	Copie ($16^{ème}$ centile)	Rappel Immédiat 3 minutes ($16^{ème}$ centile)
29 ans et moins	34	19,5
30 - 34 ans	34	19
35 - 39 ans	33,5	18
40 - 44 ans	33,5	16,5
45 - 49 ans	33	15,5
50 – 54 ans	32,5	14,5
55 – 59 ans	32	13
60 – 64 ans	31,5	12
65 – 69 ans	30,5	10
70 – 74 ans	29,5	9
75 – 79 ans	28,5	7,5
80 ans et plus	27	4,5

VII. Batterie rapide d'efficience frontale

Source: Dubois et al – Neurology – 2000:1621-1626

Il s'agit d'un seuil unique: 16

VIII. DO 80

Source: Manuel DO80 –ECPA

Un seuil est défini en fonction de l'âge et du niveau d'études (voir consignes générales).

Age	Durée de la scolarité	
	❶ ❷ ❸	❹ ❺ ❻ ❼ ❽
≤59 ans	75	78
60 ans et plus	72	75

APPENDIX V: BIOBANKS PROCEDURES

1. PRÉLÈVEMENTS SANGUINS

La prise de sang pour constitution de la biobanque est réalisée UNIQUEMENT si le participant signe le consentement éclairé de participation à l'étude MEMENTO.
Le prélèvement sanguin est réalisé même si le participant n'est pas à jeun.

Prélèvement sanguin: 28ml - 5 tubes

- ♣ 3 tubes Vacutainer: Tube Sec 10 ml, Tube EDTA 6 ml, Tube Heparinate de Lithium 6 ml
- ♣ 2 tubes TEMPUS de 3ml (9ml de capacité totale, 6 ml de stabilisateur)

Des kits de prélèvements et d'aliquots pour la biobanque sont fournis pour chaque participant. Chaque kit est UNIQUE et correspond à un participant. **Attention** les tubes sont déjà identifiés pour chaque participant dans le centre.

Tous les éléments du kit (sauf les cartouchières absorbantes, les bouchons de couleur et les pipettes de transfert) sont identifiés par des étiquettes résistantes à la cryogénie portant: le nom de l'étude, l'identifiant du participant (N°centre + N°participant) créé lors de l'inclusion du participant dans l'étude et la désignation du tube ou sachet.

2. TECHNIQUE

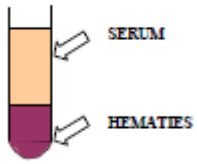
Arrivée au laboratoire
- Noter l'heure d'arrivée du prélèvement sur la feuille de suivi des prélèvements
- Vérifier si tous les items de la feuille de suivi ont été complétés, sinon contacter le service clinique.

Constitution des aliquots de sang total:
- Homogénéiser le tube Héparinate de Lithium, 5/6 fois en le retournant sans agiter,
- Oter délicatement le bouchon du tube (Ne pas jeter ce bouchon). A l'aide d'une pipette de transfert en polyéthylène transférer: 1 ml de Sang total dans 2 cryotubes. Fermer ces cryotubes et refermer le tube Héparinate de Lithium

Centrifugation et aliquotage
- Mettre des gants en latex non poudrés
- **Centrifuger en même temps les 3 tubes Sec, EDTA et Héparinate de Lithium d'un même participant à 2500g pendant 10 minutes à +20°C, sans frein.**

2.1 Sur le tube SEC de 10ml :

2 phases distinctes sont obtenues après centrifugation:

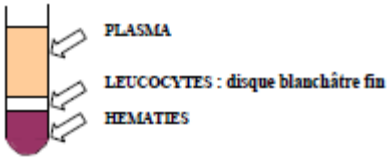


Oter le bouchon du tube sec et à l'aide d'une pipette de transfert, prélever le sérum (phase supérieure) et le répartir dans les microtubes.
- ♦ 0,25ml de Sérum dans les microtubes.

Arrêter de prélever à 0,3 cm des hématies.

2.2 Sur le tube EDTA de 6ml :

3 phases distinctes sont obtenues après centrifugation

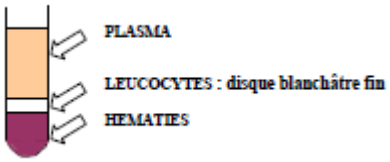


Oter le bouchon du tube EDTA et à l'aide d'une pipette de transfert:

- Prélever le plasma (phase supérieure) et transférer 0,25ml dans chaque microtube.
- Vérifier que tous les aliquots sont bien remplis, s'il reste du plasma jeter l'excédent dans la poubelle biologique en s'arrêtant à 0,3 cm au-dessus de la couche de leucocytes.
- Prélever l'anneau de globules blancs (environ 1,25ml) et le transférer dans le microtube

2.3 Sur le tube Héparinate de Lithium de 8ml :

3 phases distinctes sont obtenues après centrifugation



Oter le bouchon du tube Héparinate de lithium et à l'aide d'une pipette de transfert :

- Prélever le plasma (phase supérieure) et le transférer 0,25ml dans chaque microtube.
- Vérifier que tous les aliquots sont bien remplis, s'il reste du plasma jeter l'excédent dans la poubelle biologique en s'arrêtant à 0,3 cm au-dessus de la couche de leucocytes.
- Prélever l'anneau de globules blancs (environ 1,25ml) et le transférer dans le cryotube

- Mettre touts les cryotubes directement à -80°C

2.4 Prélèvement sur tube TEMPUS®

- Remplir les tubes jusqu'au trait noir
- Les tubes TEMPUS® remplis doivent être immédiatement vortexés ou secoués vigoureusement durant 10 à 15 secondes.

- Mettre les deux tubes directement à -80°C

APPENDIX VI : LUMBAR PUNCTURE

Protocole à suivre pour les prélèvements de Liquide Céphalorachidien (LCR)

Important:

- Avant d'effectuer les prélèvements, s'assurer que le laboratoire ou le service (selon les centres) est disponible pour les recevoir et les techniquer en vue de leur conservation.
- Utiliser les kits prévus pour le prélèvement fournis par le centre coordinateur.

1. <u>Conditions de prélèvement :</u>

Les prélèvements sont effectués le matin entre 9H et 13H.

- Pour toute ponction lombaire, prélever sur un **tube en polypropylène de 10mL** fourni dans le kit, **4 ml** minimum de liquide.
- **Prélever directement** le LCR dans le tube de 10 mL à partir de l'aiguille de ponction, ceci est **ESSENTIEL** pour les dosages (pas de transvasement).
- ***Prévoir une mesure de la protéinorachie*** (sur un autre tube éventuellement) et si possible une ***cytologie***.
- Le placer sans attendre dans un sachet avec de la **glace** pour le maintenir à +4°C

Joindre la fiche de demande et de suivi préanalytique (Fiche PL), en précisant :

- La date, l'heure et l'aspect du prélèvement – les conditions d'acheminement
- Le nom du médecin prescripteurLe destinataire: Traitement local dans le service ou au laboratoire associé à l'étude
-

Le tube doit être traité en moins de 4 heures (Fiche PL).

2. <u>Traitement des échantillons de LCR dans le service ou au laboratoire local de stockage</u>

- Noter l'heure d'arrivée du prélèvement sur la feuille de suivi.
- Dès son arrivée au laboratoire, le tube destiné au dosage des biomarqueurs est centrifugé 10 minutes à **1000g** à **+ 4°C** sans frein. Le LCR est ensuite réparti dans des tubes en polypropylène Eppendorf® LoBind 1,5 mL (fournis dans le Kit prélèvement LCR) sous forme d'aliquots de 0,4ml. Ces tubes sont identifiées grâce aux étiquettes fournies et stockés **à -80°C**.

Tout incident survenu lors de la centrifugation ou de la mise en aliquot devra être noté sur la feuille de suivi.

- Vérifier que tous les items de la feuille de suivi ont été complétés, sinon contacter le service clinique.

Le transport des aliquots vers le laboratoire centralisé sera effectué sous forme congelée par transporteur spécialisé, régulièrement selon le nombre de ponction lombaire effectué sur le site.

APPENDIX VII: 18F-FDG PET-SCAN TECHNICAL MANUAL

1. Introduction

Ce document décrit les différentes étapes de certification par le CATI d'un site de médecine nucléaire équipé d'une caméra à positons en vue de sa participation à l'étude MEMENTO. Le but est la standardisation et l'optimisation des paramètres d'acquisition et de reconstruction des images cérébrales en TEP, et l'obtention de données nécessaires à la minimisation de l'effet «centre ».

Étant donné que l'inclusion des participants se fera sur plusieurs années, cette visite devra être répétée.

2. Procédure de qualification des sites TEP

Afin de s'assurer que les sites choisis répondent aux critères définis par le CATI pour participer à l'étude MEMENTO en tant que centre d'imagerie, ils devront respecter les différentes étapes décrites ci-dessous :

2.1. Remplir un questionnaire de pré-qualification de site d'imagerie TEP

Ce formulaire, rempli par le site, contient les coordonnées des personnes concernées, les caractéristiques techniques des caméras et des systèmes informatiques associés et d'autres informations indispensables au bon déroulement de l'étude.

Il est également demandé au site d'envoyer au CATI un examen TEP-^{18}FDG réalisé en routine (sur CD anonymisé) pour une pré-évaluation des paramètres d'acquisition et reconstruction.

2.2. Visite du centre – Acquisition de fantômes

Pendant la visite du centre (décrite ci-après), des données seront acquises à l'aide de 2 fantômes: (i) un fantôme de *Jaszczak* à sphères chaudes et froides ; (ii) un fantôme anthropomorphique *3D d'Hoffman*. Les données reconstruites seront ensuite transmises au CATI *via* un réseau (*Keosys*®) ou *via* CD/DVD pour vérification et analyse. Le site recevra alors un rapport concernant la visite du centre ainsi que la procédure de contrôle qualité effectuée sur les acquisitions du fantôme. Cette note avisera le personnel du site s'il est qualifié ou non pour commencer l'acquisition TEP-^{18}FDG chez les premiers participants de la cohorte MEMENTO.

2.3. Acquisition du premier participant

Une fois l'examen du premier participant terminé, les données devront être transférées rapidement *via* réseau ou par envoi de CD/DVD au CATI.

Le site NE devra PAS réaliser d'examen sur un second participant tant que le CATI n'aura pas vérifié les données du premier participant et n'aura pas procédé au contrôle qualité scientifique et technique.

Une fois que les données du premier participant auront été validées, le site recevra un bref rapport leur indiquant qu'ils peuvent commencer l'acquisition de nouveaux participants.

Ces étapes sont nécessaires pour assurer au CATI et au promoteur de l'étude MEMENTO que les centres suivent les indications du protocole et des documents source ainsi que les procédures d'acquisition et de reconstruction des images, de manière à ce que les données obtenues soient estimées acceptables par le processus d'assurance qualité du CATI.

3. Visites des centres partenaires

3.1. Préparation de la visite sur site

Ces visites seront effectuées par une équipe composée du chef de projet du WP2[a] CATI et d'un technicien de la société *Esprimed*® spécialisé en physique médicale. Elles auront lieu avant l'examen TEP-^{18}FDG du premier participant de la cohorte MEMENTO afin de familiariser le personnel de l'équipe technique à l'acquisition d'images spécifiques au protocole de la cohorte, le traitement et l'archivage des données ainsi que les procédures de transfert des données.

[a] Work Package 2 – Acquisitions TEP/TEMP

Ces visites seront précédées de l'envoi de la planification détaillée de la visite et des informations qui seront nécessaires à la réalisation des acquisitions. Les fantômes de *Jaszczak* et *3D d'Hoffman* seront également envoyés au centre quelques jours avant la visite de certification.

Cette dernière sera programmée environ un mois avant l'inclusion prévue du premier participant dans l'étude. Un calendrier sera établi en fonction des besoins du site et des disponibilités de la caméra.

3.2. Visite du centre

3.2.1. Objectifs de la visite

- Rappeler les objectifs de MEMENTO, le rôle du CATI, et celui du site ;
- Présenter les procédures d'imagerie TEP et les documents sources ;
- Mettre au point des protocoles d'acquisition caméra-spécifique et traceur-spécifique ;
- Effectuer l'acquisition des fantômes de *Jaszczak* et *3D d'Hoffman* ;
- Vérifier les procédures de transfert de données en format DICOM (réseau Keosys® ou CD/DVD) vers le CATI ;
- Informer sur la procédure de retour d'informations depuis le CATI (*feedback*) pour chaque examen reçu ;
- Répondre aux questions et anticiper les problèmes éventuels ;
- Confirmer les coordonnées des contacts ;
- Fournir un classeur ou un cahier de suivi réunissant: (i) les coordonnées des contacts ; (ii) le manuel des procédures techniques ; (iii) les formulaires d'information d'examens TEP et de transfert de données; (iv) les informations concernant le serveur *Keosys*® (code utilisateur, mot de passe, procédure de transfert des données); (v) une section « correspondance » contenant tous les échanges (courrier, courriels, fax, téléphone) entre le CATI et le site ;

3.2.2. Planification de la visite

La visite devrait durer une demi-journée en fonction de la disponibilité des personnes concernées, et comprendra 2 sessions. Le déroulement type d'une visite de site est décrit ci-dessous :

Participants suggérés :

L'investigateur principal du site, un médecin nucléaire (si différent de l'investigateur principal), le radiopharmacien, un(e) technicien(ne) de médecine nucléaire, la personne qualifié en physique médicale, le cadre de santé, ARC, etc.

La session 1 (*1/2 heure*)

Étapes principales :

(i) Introduction, présentation de l'étude MEMENTO et du rôle du CATI ;
(ii) Présentation des procédures d'acquisition et des documents à envoyer au CATI.

La session 2 (3 heures)

Étapes principales :

(iii) Visite rapide des installations et de(s) la(es) caméra(s) utilisée(s) dans le cadre du protocole et vérification des procédures de contrôle qualité ;
(iv) Vérification de la synchronisation des horloges du système d'acquisition TEP et des activimètres ;
(v) Mise en place, si nécessaire, d'un protocole de calcul de l'activité corrigée de l'activité résiduelle et de la décroissance ;
(vi) Mise en place du protocole d'acquisition et reconstruction d'images des fantômes ;
(vii) Remplissage des fantômes de *Jaszczak* et *3D d'Hoffman*. Les membres de l'équipe du CATI/Esprimed® auront à leur charge de fournir et de préparer les fantômes en compagnie d'une personne agréée du centre. Il sera demandé au centre de prévoir 250 MBq de ^{18}F afin d'assurer ces préparations ;
(viii) Acquisition des 2 fantômes avec le protocole mis en place (durée d'acquisition fixée à 3 x 5 min) ;
(ix) Vérification visuelle des images reconstruites avec si nécessaire essai d'autres paramètres de reconstruction ;
(x) Vérification des procédures de transfert des données, envoi des images acquises ;
(xi) Transmission des informations utiles pour la suite du protocole et répondre aux questions éventuelles.

Suite à la visite technique, un rapport sera envoyé au site. Ce rapport technique sera conservé dans le classeur de l'étude et servira de référence pour le site.

Le CATI doit être averti de toute modification dans le service concernant la caméra (*upgrade*, changement de modèle) ou les logiciels associés le plus tôt possible, et avant de réaliser une nouvelle acquisition chez un participant. Une nouvelle visite devra être programmée dans certains cas.

4. Acquisition des images TEP pour les participants de la cohorte MEMENTO

4.1. TEP au 18FDG

4.1.1. Commande de la dose de 18FDG

Une demande d'examen TEP-^{18}FDG spécifique à l'étude sera faxée par le service clinique investigateur (annexe 1). La commande de la dose s'effectuera selon la procédure habituelle du site.

4.2. Réalisation de l'examen

(i) Il sera demandé aux participants passant leur imagerie le matin de ne pas manger ni boire de boissons sucrées à partir de minuit précédent la date d'examen et ce jusqu'à la fin de l'examen. Il sera demandé aux participants passant leur imagerie plus tard dans la journée de ne pas manger ni boire de boissons sucrées 6h avant l'examen. Remarque: la concentration de sucre dans le sang sera vérifiée avant l'injection par glycémie capillaire. L'injection pourra être effectuée si, et seulement si, cette dernière est égale ou inférieure à 160 mg/dl, sinon l'examen devra être différé ;
(ii) Les participants seront pesés: le poids et la taille devront être notés ;
(iii) La dose administrée au participant par voie intraveineuse est de 2 MBq/Kg de ^{18}F-FDG (minimum 125 MBq ; maximum 250 MBq). Le participant doit être laissé au repos neurosensoriel (assis ou allongé) dans une pièce calme et peu éclairée pendant au moins 20 minutes post-injection. Il sera demandé au participant de fermer les yeux pendant 10 minutes et de ne pas parler pendant tout le temps de repos ;
(iv) L'activité préparée, l'heure de mesure, et l'heure d'injection ainsi que le volume injecté devront être notés. Après injection, l'activité de la seringue remplie d'un volume de sérum physiologique égal au volume injecté, et l'heure de cette mesure devront également être notés ;

(v) L'activité « réelle » injectée (corrigée de l'activité résiduelle ET de la décroissance) devra être calculée: c'est cette valeur qui devra être entrée au moment de l'acquisition ;

(vi) L'acquisition des images d'émission doit démarrer 30 minutes après injection (minimum 25 min, maximum 35 min). Après 20 minutes de repos, il est possible d'envoyer le participant aux toilettes et de l'installer dans la caméra ;

(vii) Les participants seront positionnés au centre du champ de vue. Le repérage de la ligne orbito-méatale au laser permet d'être plus reproductible (annexe 2). Le participant doit être informé de la nécessité de garder la tête immobile. Des moyens de contention peuvent être utilisés si disponibles ;

(viii) L'acquisition (3 x 5 min) et la reconstruction des images seront effectuées selon le protocole défini après la visite de certification.

4.3. Archivage, anonymisation et transfert des données

(i) L'archivage des images reconstruites TDM et TEP, **et si possible des sinogrammes**, se fera selon les procédures habituelles du service ;

(ii) L'anonymisation des données s'effectuera selon la procédure suivante: **XXX-YYYY-NNPP-MSS-T** où **XXX** représente le n° du centre ; **YYYY** le n° d'inclusion du participant ; **NNPP** les deux premières initiales du nom et prénom du participant ; **MSS** le code de suivi (M0 pour l'examen initial, M48 pour l'examen à 2 ans) ; **T** le traceur (F pour ^{18}F-FDG) ;

(iii) Le transfert des données TDM et TEP en format DICOM au CATI (via *Keosys*® ou CD/DVD) s'effectuera selon le protocole sécurisé mis en place lors de la visite de certification ;

(iv) L'envoi au CATI des documents associés à l'examen, c'est-à-dire la fiche d'information-examen et la fiche de transfert des données, se fera de préférence par e-mail (en format pdf) ou par fax ;

E-mail: mguyot@imed.jussieu.fr
Fax: 01 53 82 84 46

4.4. Contrôle de qualité

Le CATI accusera réception des données et des documents associés dans les 3 jours suivants leur envoi.

Les images envoyées au CATI feront l'objet d'un contrôle de qualité. Parmi ces contrôles, figureront:

- la vérification de l'anonymisation des images ;
- la vérification du nombre d'images reçues et de l'intégrité des volumes reconstruits ;
- la vérification de la compliance aux paramètres d'acquisition et de reconstruction requis dans le cadre du protocole MEMENTO ;
- la recherche d'éventuels artéfacts.

Si des questions surviennent lors des vérifications du contrôle qualité, le CATI contactera les personnes du site concernées pour y répondre.

Après réception d'informations complémentaires, le centre recevra par e-mail une information sur la réussite ou l'échec de l'acquisition vis à vis des normes de qualité du CATI.

4.5. Acquisitions TEP non conformes

Dans l'hypothèse où une acquisition TEP – ^{18}FDG ne serait pas utilisable suite à un problème d'ordre technique alors un nouvel examen TEP pourra être planifié, si le participant est d'accord. En revanche, si le problème est du fait du participant lui-même (agitation, claustrophobie) l'examen TEP – ^{18}FDG ne sera pas refait.

5. Effets secondaires possibles imputables au FDG

Des effets indésirables suite à l'administration de 18F-FDG n'ont jamais été rapportés. Comme la quantité de substance administrée est très basse, le risque le plus important d'effets secondaires est lié à la radiation. L'exposition à des radiations ionisantes peut entrainer un cancer ou le développement d'anomalies héréditaires. Les examens réalisés dans les services de

médecine nucléaire impliquent des niveaux de radiation (dose efficace) de moins de 20 mSv. Aussi ces effets secondaires ont une probabilité très faible d'être observés.

6. Documentation technique de l'étude

La documentation technique se trouve dans le classeur de l'étude. Il est recommandé aux investigateurs de s'en tenir au classeur de l'étude comme unique source d'informations concernant les aspects d'imagerie TEP de l'étude, tels que la fiche d'enregistrement de l'acquisition, le report des évènements lors du contrôle qualité, les mises à jour des logiciels, etc... De plus, le classeur sert de document de référence pour le site, résumant toutes les procédures techniques spécifiques à l'étude. Le classeur technique doit contenir:

- Les références des personnes à contacter ;
- Le manuel des procédures techniques ;
- La fiche d'informations pour l'examen TEP et les instructions pour la compléter ;
- La fiche de transfert des données d'imagerie TEP/TDM ;
- Les informations concernant le serveur *Keosys*®, le code utilisateur et le mot de passe ;
- Une section « Communications avec le CATI » permettant de conserver les enregistrements de tous les échanges entre le CATI et le centre partenaires.

Le classeur sera fourni à chaque site le jour de la visite technique de mise en place en même temps que les instructions concernant la maintenance des documents techniques.

7. Communication avec le CATI et résolution de problèmes

Toute requête concernant les données sera adressée au service de Médecine Nucléaire du site comme cela aura été défini lors de la visite de contrôle technique. Toute question concernant la conduite technique de l'étude, qu'il s'agisse de problèmes de commande ou réception du radio pharmaceutique, de l'acquisition des fantômes et des participants, du traitement des images, de la création et du transfert des fichiers, etc., doit être adressée au CATI. Ce dernier doit être averti de toute modification dans le service concernant la caméra (upgrade, changement de modèle) ou les logiciels associés le plus tôt possible, et avant de réaliser une nouvelle acquisition chez un participant.

WP2 CATI
INSERM U678 – LIF
91 Boulevard de l'Hôpital
75634 Paris Cedex 13 Pour toutes les questions techniques au participant de la réalisation des examens TEP, l'anonymisation et le transfert de fichiers, le remplissage des fiches techniques ou toute autre question, veuillez contacter :

Hugo Bertin
Attaché de Recherche Clinique
Téléphone Fixe: 01 53 82 84 17
Fax: 01 53 82 84 46
E-mail: hbertin@imed.jussieu.fr

APPENDIX VIII: CEREBRAL MRI ACQUISITIONS INSTRUCTIONS

A. INSTRUCTIONS POUR LA REALISATION DES IRM

1. MATERIEL

- Les examens d'un **même centre** doivent toujours être réalisés sur la **même machine IRM**, avec la **même antenne**.

- S'il y a un **changement logiciel et/ou matériel** au cours de l'étude, il faut absolument en **informer le CATI.** Si le changement est logiciel, il faudra s'assurer avec les ingénieurs d'applications que les paramètres des séquences peuvent être reproduits exactement. Si le changement est matériel (antenne, chaîne de radio fréquence…), il faudra en aviser le CATI le plus tôt possible; la compatibilité devra alors être assurée par la réalisation d'un nouveau test et/ou le passage d'un fantôme dans le centre.

- L'antenne utilisée sera une **antenne multi-canaux (8 ou 12 uniquement)**, si le centre dispose d'une telle antenne. Cependant, la procédure de validation préliminaire peut éventuellement écarter cette antenne si les hétérogénéités de champs sont trop importantes et leurs manifestations trop visibles sur les images.

2. INSTALLATION DU PARTICIPANT

Le participant doit être installé :

- le plus confortablement possible

- en assurant un **bon centrage** dans l'antenne

- en **corrigeant parfaitement les éventuelles inclinaisons latérales** (permettant d'obtenir des coupes « sagittales pures » parallèles au plan inter hémisphérique)

- dans le plan neuro-orbitaire (PNO) (cf Figure 1) si la position est confortable pour le participant.

Sa **tête doit être immobilisée** et placée **au centre de l'aimant.**

Le bon positionnement est très important puisque certaines acquisitions sont faites en sagittal stricte ou en axial stricte. Il est donc essentiel d'y apporter un soin particulier. Cependant, il sera bien sûr à adapter si le participant ne peut pas se placer dans la position idéale en étant assez confortable pour ne pas bouger.
Une **pastille** de vitamine E sera collée sur le **côté droit du participant**. La boîte sera fournie par le CATI.

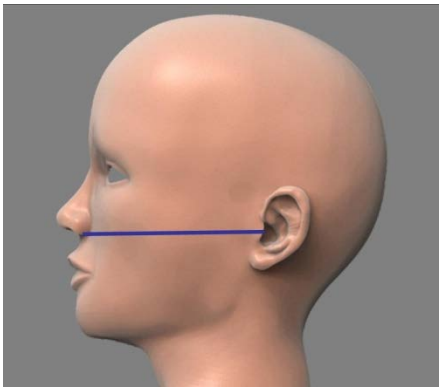


figure 1: Placement du participant en PNO si possible dans la machine

3. SEQUENCES

- Les séquences incluses dans le protocole sont résumées dans le tableau ci-après. Elles sont détaillées dans les pages suivantes. Les IRM doivent être **acquises dans l'ordre donné** et **sauvegardées dans le même ordre, avec uniquement les reconstructions demandées**.

- Si le participant ne parvient pas à rester immobile dans l'IRM pendant tout l'examen ou s'il veut interrompre celui-ci, l'acquisition ne comportera alors que les premières séquences toujours en respectant l'ordre. Pour la cohorte MEMENTO, le protocole minimal doit inclure le 3DT1, le FLAIR et la T2*. Ces trois séquences seront refaites si un mouvement trop important est noté.

N°		Séquence	orientation	Durée (min)		
1		Repérage 3 plans		0 : 10	20 : 30	41 : 00 – 50 : 00
2		3D-T1	Sag stricte	9 : 00		
3		2D-T2 FLAIR	Ax bicalleux	4 : 00		
4		2D-T2* (GRE)	Ax bicalleux	5 : 30		
5		2D-T2 FSE 1 écho	Ax bicalleux	1 : 45		
6	Opt	IRMf (BOLD EPI) au repos	Ax oblique	10 : 00		
7	Opt	Tenseur de diffusion (DTI – DWI EPI) + carte de champ B0	Ax stricte	4 : 30 x 2-4 1 : 45		

4. SEQUENCES VALIDEES PAR CENTRE

Les paramètres des acquisitions doivent être ceux qui ont été validés par le CATI.
Un examen IRM test complet sera envoyé au CATI pour évaluation de la qualité à partir des paramètres du protocole CATI v1. L'examen sera analysé par le CATI et un retour sera fait au plus vite avec un compte rendu sur la validation et/ou les paramètres à modifier. Les acquisitions ne doivent pas commencer avant le retour de la validation.

5. ORIENTATION DES COUPES

Les acquisitions doivent **couvrir l'ensemble de l'encéphale** et tout le crâne. Il faudra être particulièrement vigilant au **positionnement du participant dans l'antenne** afin d'éviter une perte de signal dans les coupes inférieures (cf figure 2)

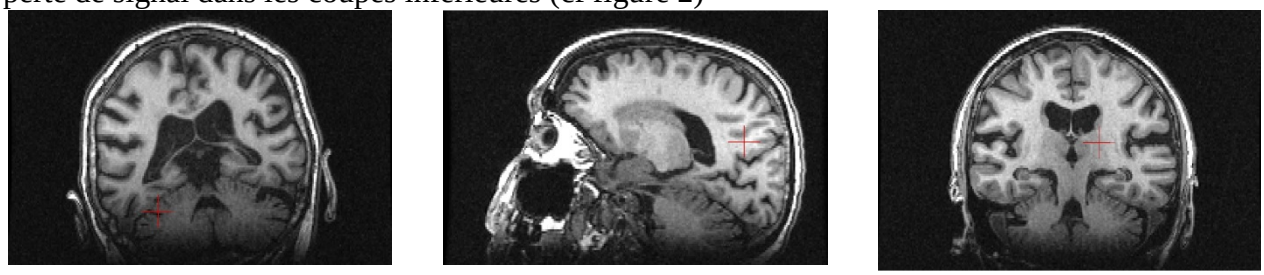


figure 2: Problèmes d'obscurcissement des coupes inférieures

5.1. Acquisitions 2D (FLAIR, T2*, T2): plan bicalleux

Pour les acquisitions 2D FLAIR, 2D T2* et 2D T2, les coupes seront axiales, orientées dans le plan bi-calleux: une des coupes de l'acquisition doit être tangente au splenium et au genou du corps calleux de C1 jusqu'au vertex, coupes positionnées du bas vers le haut (caudal vers crânial) (cf figure 3).

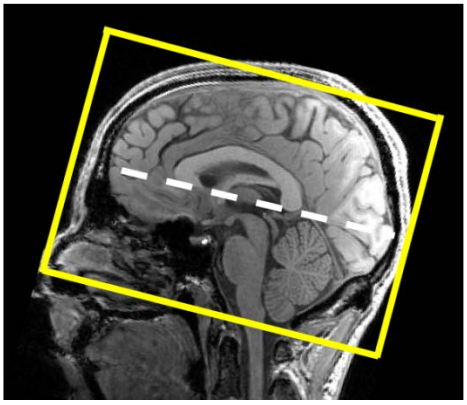


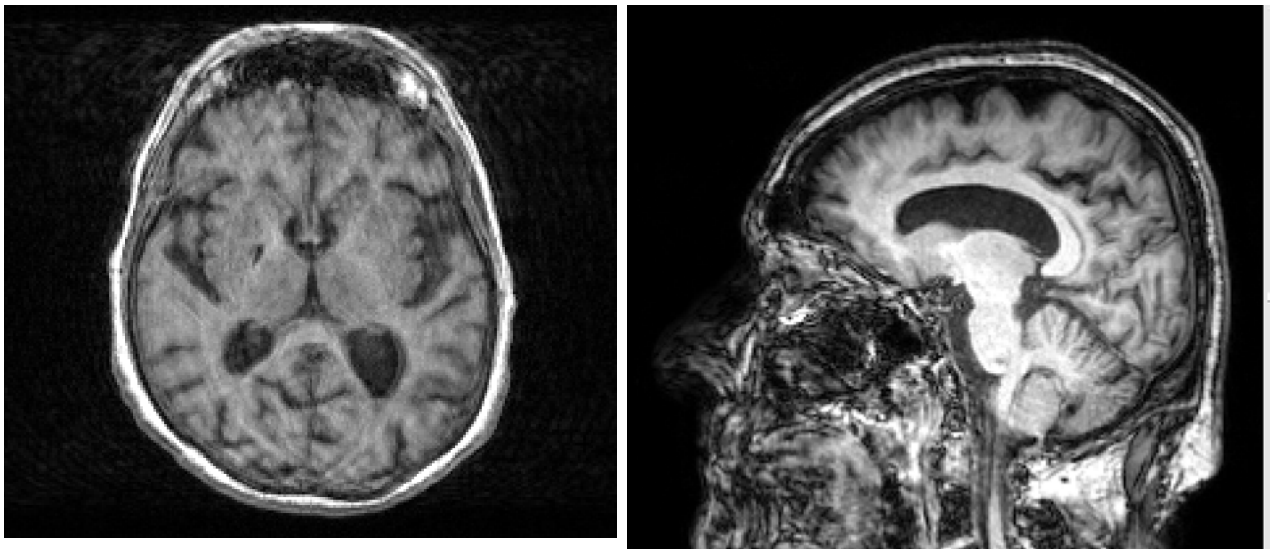
figure 3: Placement des coupes pour les acquisitions FLAIR, T2, T2* en bicalleux

5.2. Acquisitions IRMf

Le bloc de coupes doit être obliqué de façon à assurer une bonne couverture du cerveau et du cervelet.

6. CONTROLE DU MOUVEMENT LORS DE L'ACQUISITION

La **qualité** de l'acquisition 3DT1 doit être **vérifiée**, avant de faire les acquisitions suivantes. Si elle n'est pas satisfaisante (mouvement du participant, cf Figure 4), elle doit être refaite **immédiatement**.



SIEMENS 1.5T *Philips 3T*

figure 4: Artefacts de mouvement

7. CONTROLE QUALITE CENTRALISE

Afin de s'assurer que les paramètres des séquences sont ceux qui ont été validés et que la qualité des acquisitions est suffisante, une **relecture centralisée** sera menée par le CATI.

8. ACQUISITION LONGITUDINALE

Dans un centre donné, il est fondamental que les **PARTICIPANTS SOIENT TOUJOURS SCANNES AVEC LES MEMES SEQUENCES AU DETAIL PRES** (TR, TE etc ….) **ET AVEC UN POSITIONNEMENT IDENTIQUE**. Il est indispensable d'utiliser exactement la **même IRM**, la **même antenne**, le même positionnement, les mêmes séquences et les mêmes orientations de coupes lorsque l'IRM est refaite à un participant pour le suivi longitudinal. En cas de problème, le CATI pourra contacter le centre d'acquisition pour **demander une nouvelle IRM** pour le participant.

9. ANONYMISATION DE L'EXAMEN

Les coordonnées rentrées dans la machine doivent être le **numéro d'identification du participant dans l'étude: N° centre + N° participant + code lettres**. Le nom complet du participant ne doit en aucun cas apparaître dans les entêtes DICOM.

10. SAUVEGARDE ET TRANSFERT

Les données **DICOM** contenant toutes les séquences et les reconstructions sont transmises par CD ou sur le serveur FTP centralisé.
Elles doivent être **conservées localement** et rester accessibles, afin de pouvoir vérifier le positionnement lors d'IRM ultérieures.

B. PROTOCOLE CATI V1

1. Repérage 3 Plans
2. **Séquence 3D T1** positionnement en PNO. **<u>Coupes non obliquées sagittales</u>**.

	1.5T	3T
Séquence	Inversion récupération [IR-FSPGR, MP-RAGE]	
Matrice	256x256	
FoV	256x256mm²	
coupe	1.3mm	1mm
Voxel	1mm isotrope, sans interpolation	
Nex	1	
Phase	Antéro-postérieure	
Facteur d'accélération	NON	
Coupes	160	176

*L'option de **calibration B1** pour les antennes en réception seulement et l'option de **corrections de distorsions** dues aux non linéarités des gradients seront **désactivées sauf s'il est possible de sauvegarder la T1 avec et sans correction** (auquel cas les deux/quatre images doivent être sauvées).*

3. **Séquence 2D FLAIR** dans le plan bicalleux (coupes positionnées sur la séquence n°1)

séquence	T2 FLAIR
matrice	240x240 ou 256x256
FoV	240x240mm² ou 256x256mm²
coupe	5 mm entrelacées jointives
Voxel	1x1mm², sans interpolation
Nex	1
Phase	Droite-gauche
Facteur d'accélération	2
Coupes	35

4. **Séquence 2D T2*** (même position de coupes que le FLAIR).

séquence	GRE pondérée en T2
matrice	240x240 ou 256x256
FoV	240x240mm² ou 256x256mm²
coupe	5 mm entrelacées jointives
Voxel	1x1mm², sans interpolation
Nex	1
Phase	Droite-gauche
Facteur d'accélération	NON
Coupes	35

5. **Séquence 2D T2** (même position de coupes que le FLAIR)

séquence	TSE ou FSE pondérée en T2 (simple écho)
matrice	240x240 ou 256x256
FoV	240x240mm² ou 256x256mm²
coupe	5 mm entrelacées jointives
Voxel	1x1mm², sans interpolation
Nex	1
Phase	Droite-gauche
Facteur d'accélaration	2
Coupes	35

6. **Séquence BOLD**: Coupes axiales de C1 au vertex (de bas en haut) – obliquer de façon à couvrir tout le cerveau et le cervelet

	1.5T	3T
séquence	GRE EPI	
matrice	64x64	
FoV	192x192mm²	
coupe	5 mm jointives entrelacées	3 mm jointives entrelacées
Voxel	3x3mm²	
Nex	1	
Fréquence	Postéro-antérieure	
Facteur d'accélération	2	
Coupes	24	43
Répétitions	250	

<u>Consignes à donner au participant:</u> Le participant devra avoir les yeux fermés sans dormir. Penser à lui rappeler qu'il essaie de ne penser à rien et qu'il ne bouge absolument pas. Penser à ôter toute éventuelle stimulation sonore et/ou visuelle.

Tenseur de diffusion: coupes axiales strictes de C1 jusqu'au vertex, perpendiculaires au grand axe de l'aimant (**ne pas obliquer les coupes**), positionnées du **bas vers le haut** (caudal vers crânial).

Séquence	DWI EPI
Matrice	128x128
FoV	256x256mm²
Coupe	2 mm jointives entrelacées
Voxel	2x2mm²
Nex	1
Phase	Postéro-antérieure
Facteur d'accélération	2
Coupes	70
Valeur de b	1500s.mm^{-2}
Plan de Fourier partiel	6/8 (0.75)
Nombre de directions	15 x 2-4

La séquence est **répétée 2 ou 4 fois**, avec **2 ou 4 jeux de 15 directions différents**. Une image en b=0 sera acquise pour chaque jeu de directions. **Les jeux de directions seront fournis par le CATI.**

Ceci a pour but de générer une acquisition finale avec entre 30 et 60 directions, tout en s'adaptant à la capacité du participant à rester longtemps dans la machine. Chaque jeu de directions permet une couverture uniforme de l'espace Q, et les 4 jeux sont complémentaires.

Cette séquence est accompagnée de **l'acquisition d'une carte de champ** pour corriger les distorsions géométriques des images EPI.

Séquence	b0_mapping
Matrice	64x64
FoV	256x256mm²
Coupe	4 mm jointives entrelacées
Voxel	4x4mm²
Nex	1
Phase	Droite-gauche
Coupes	35

APPENDIX IX :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-MentalState, 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.

APPENDIX X: 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 XI: MEMENTO COMMITTEES' CHARTER

Memento Committees Charter
4th November 2014, version 4.0

MEMENTO COHORT : Cohort of outpatients from French Research Memory Centers in order to improve knowledge on alzheiMer's disEase aNd relaTed disOrders

PURPOSE OF THIS DOCUMENT:

To describe membership and any specific roles and relationships of committees for the Memento cohort

Key points for information and definitions

Memento Study Group

The different components of the Memento Study Group (or Memento network) are the following:

Memento Principal investigators

Geneviève Chêne – Memento Principal Investigator (CIC-EC7)
Carole Dufouil – Memento co-Principal Investigator (CIC-EC7)

Memento Executive Committee

Philippe Amouyel – General Director (Fondation Plan Alzheimer)
Pierre Ducimetière –Chair Memento Scientific Strategy Committee
Hugues Chabriat – co-Chair Memento Scientific Strategy Committee
Geneviève Chêne – Memento Principal Investigator
Carole Dufouil – Memento co-Principal Investigator

Memento Main Funder

Fondation Plan Alzheimer

Memento Sponsor

Bordeaux University Hospital (CHU Bordeaux)

Memento Scientific Strategy Committee

Independent scientific experts : Pierre Ducimetière (Chair), Hugues Chabriat (Co-chair), Annick Alpérovitch, Lisa Berkman, , David Clayton, Françoise Forette, Mony de Leon, Ronald Petersen, Philip Scheltens, Marie Vidailhet
Member on hold : Yves Levy
Non-independent members: Philippe Amouyel, Geneviève Chêne, Carole Dufouil
Permanent observer: one representative from Sponsor, Memento project manager, Jean-François Mangin (director of Center for Imaging analysis, CATI), one representative of French Federation of Memory Clinics

Memento Steering Committee

Geneviève Chêne - Chair, alternatively with CD
Carole Dufouil – Chair, alternatively with GC
Helen Savarieau – Memento Project manager, coordinating Center (CIC-EC7)

Investigating centers: one representative from each clinical site of the participating CMRRs Amiens, Hôpital Nord et Hôpital Sud (Pr Olivier Godefroy); Angers, CHU d'Angers (Pr Olivier Beauchet); Besançon, Hôpital Jean Minjoz, Hôpital Saint Jacques (Pr Pierre Vandel); Bobigny, Hôpital Avicenne (Dr Catherine Belin); Bordeaux, Hôpital Pellegrin (Pr François Tison), Hôpital Xavier Arnozan (Dr Sandrine Harston) ; Brest, Hôpital de la Cavale Blanche (Pr A. Gentric) ; Clermont -Ferrand, Hôpital Gabriel Montpied (Pr I. Jalenques) ; Colmar, Hôpitaux civils de Colmar (Dr François Sellal) ; Dijon, Hôpital général, Centre de gériatrie de Champmaillot (Dr Olivier Rouaud) ; Grenoble, Hôpital de la Tronche (Dr Olivier Moreaud) ; Lille, Hôpital Roger Salengro (Pr Florence Pasquier) ; Lyon, Hôpital des Charpennes (Pr Pierre Krolak-Salmon) ; Marseille, Hôpital La Timone (Pr Mathieu Ceccaldi) ; Montpellier, CHU Gui de Chaulliac (Dr Audrey Gabelle) ; Nantes, hôpital Nord Laënnec (Dr Martine Vercelletto) ; Nancy, CHU de Nancy (Pr A. Benetos) ; Nice, Hôpital de Cimiez (Pr Renaud David) ; Paris, Hôpital de la Salpêtrière (Pr Bruno Dubois) ; Hôpital Broca (Pr Olivier Hanon) ; Groupe Hospitalier Lariboisière (Pr Jacques Hugon) ; Poitiers, CHU La Milétrie (Pr Marc Paccalin) ; Rouen, Hôpital Charles Nicolle (Pr Didier Hannequin) ; Saint-Étienne, Hôpital Nord (Dr Marie-Odile Barrellon), Hôpital la Charité (Dr Chantal Girtanner) ; Strasbourg, Hôpital de Hautepierre, Hôpital de jour Saint François (Dr Frédéric Blanc) ; Toulouse, Hôpital Casselardit (Pr Bruno Vellas) ; Tours, Hôpital Bretonneau (Pr Caroline Hommet).

National Database on Alzheimer: one representative (currently, Philippe Robert)
Center for imaging analysis (CATI): three representatives (Jean-François Mangin (director), Marie Chupin (MRI acquisitions), Marie-Odile Habert (PET-Scan imaging acquisition)
Centralised Biobank : one representative (currently, Nathalie Fievet)
Sponsor (CHU Bordeaux): one representative (currently, Laetitia Lacaze-Buzy)
Any scientist in charge with an ongoing project may be asked to join upon the two co-PIs invitation.

Memento coordinating Center

CIC-EC7, Bordeaux: Helen Savarieau, Project Manager ; Vincent Bouteloup, Biostatistician; Christophe Bouvier, Data Manager , Julie Erraud, Lisa Le Scouarnec, Julie Lidier, Nathalie Thiery, Clinical Research Associates.

Memento secretariat

memento_scsecretary@isped.u-bordeaux2.fr

MEMENTO EXECUTIVE COMMITTEE

Roles and responsibilities

- Broad statement: the Memento Executive Committee is the group in charge of making decisions for the cohort. It is the formal link between the Memento Scientific Strategy Committee, the Steering Committee and Memento operations.
- Specific roles and responsibilities
  - responsible for ensuring that activities of the cohort are not in conflict with the cohort principles and policies
  - maintain confidentiality of all cohort information that is not already in the public domain
  - examine recruitment rates and provide advice to deal with any recruitment problems
  - monitor follow-up rates and review strategies of the coordinating center to deal with major problems
  - censure sites that are deviating from the protocol
  - ensure that proposals are not in conflict with the cohort development or results
  - update the scientific strategy committee regularly on all proposals submitted
  - make final decision on any proposal, presentation or manuscript submission
  - prepare meetings of the Scientific Strategy Committee and the General Assembly

Composition

- The Executive committee is formed by the two co-chairs of the scientific strategy group, the Director General of the Fondation Plan Alzheimer and the two co-principal investigators.

Organization of meetings

- The Executive Committee meets once per month (either physically or via tele- or videoconference).

Relationships

- The Executive Committee is the formal link between the Memento Scientific strategy, the Steering Committee the sponsor, and Memento operations. The relationships between these groups are summarised in Figure 1.

MEMENTO SCIENTIFIC STRATEGY COMMITTEE

Roles and responsibilities

- Broad statement: the Scientific Strategy Committee is the group that provides overall scientific strategy supervision for the cohort on behalf of both the main funder (Fondation Plan Alzheimer) and the sponsor (Bordeaux University Hospital, CHU de Bordeaux).
- Specific roles and responsibilities are to:
  - provide expert oversight of the scientific strategy of the cohort
  - maintain confidentiality of all cohort information that is not already in the public domain
  - comment any amendments to the protocol, where appropriate
  - comment any proposals by the co-Principal Investigators, Executive or Steering Committee concerning any major change to the design of the cohort
  - assess the impact and relevance of any accumulating external evidence
  - oversee that the cohort conduct is compliant with ethical principles of clinical research and respects participants' best interests
  - review regular reports of the cohort from Steering Committee
  - oversee the timely reporting of cohort results, including to investigators and participants
  - comment on the Memento "access to data and publications policy charter"
  - comment on any proposals (as defined in Memento "access to data and publications policy charter")

Composition

- Membership consists of a small number of members with experience in Alzheimer disease or cohort studies and should include a minimum of 6 independent members. The non-independent members will include the co-Principal Investigators, the General Director of the Fondation Plan Alzheimer or his-her representative and the Chair of the Scientific Advisory Board of the Fondation Plan Alzheimer. The exact membership will reflect the needs of the cohort. If during the study conduct, it is felt that the committee would benefit from additional expertise, then the chairs can co-opt a person onto the Committee for a specific discussion.
- Chair and co-Chair: Pierre Ducimetière and Hugues Chabriat. The chair and co-chair have no conflict of interest with the cohort.
- Membership
  - Independent scientists: Annick Alpérovitch, Lisa Berkman, David Clayton, Mony de Leon, Françoise Forette, Ronald Petersen, Philip Scheltens, Marie Vidailhet.
  - On hold: Yves Levy
  - Fondation Plan Alzheimer: Philippe Amouyel, General Director.
  - The two co-principal investigators of the cohort: Geneviève Chêne, Carole Dufouil
  - Four permanent observers: Joël Ménard as Chair of the SAB of the Fondation Plan Alzheimer, Memento project manager, one representative from the sponsor and one representative from the French Federation of Memory Clinics.
- Terms of office
  - Members are appointed by the Fondation Plan Alzheimer board of governors, based on proposals from the Memento Executive Committee. The duration of the mandate of the chair and co-chair is of 3 years, starting in 2011. At the end of this term, the co-chair becomes "chair" and a new co-chair is nominated. The chair and co-chair have no conflict of interest in relation to the study conduct.
  - The membership is renewed every three years, starting in 2011. At the end of this term, members are asked whether they wish to stand for a new term.

Conflicts of interest

- Any competing interests should be disclosed. Scientific Strategy Committee members must complete and return the form in Appendix 12 or **Erreur ! Source du renvoi introuvable.**. Any attendee who is not member of the Scientific Strategy Committee (“observer”) must sign a confidentiality agreement before the start of the meeting (**Erreur ! Source du renvoi introuvable.**).

Organization of meetings

- The Scientific Strategy Committee meets twice per year. The Memento Executive Committee prepares the agenda of the meetings.

Relationships

- With principal investigators and other Memento committees, main funder and Sponsor. The relationships between these committees are summarized in Figure 1.
- Payment to members. Members will be reimbursed for reasonable travel costs and accommodations. No other payments or rewards are envisaged.

MEMENTO STEERING COMMITTEE

Roles and responsibilities

- Broad statement: the Steering Committee is the group that oversees the overall conduct of the cohort on behalf of both the main funder (Fondation Plan Alzheimer) and the sponsor (Bordeaux University Hospital, CHU de Bordeaux).
- Specific roles and responsibilities
  - maintain confidentiality of all cohort information that is not already in the public domain
  - ensure that scientific objectives can be achieved within the expected study timeline and if needed suggests alternative scenarios
  - assess the impact and relevance of any accumulating external evidence
  - comment on any amendments to the protocol, where appropriate
  - comment on any major change to the design of the cohort
  - approve all working groups and review their progress
  - comment on any proposal, abstracts, presentations and manuscripts
  - review regular reports of the cohort from Coordinating Center, in particular all indicators related to the conduct of the cohort (enrolment curve, follow-up rates) and to the conduct of the sub-analysis and ancillary studies
  - oversee the timely reporting of cohort results, including to investigators and participants
  - comment on the Memento “access to data and publications policy charter”

Composition

- Membership consists of all collaborators of the cohort from: the coordinating center, the investigating sites, the "Banque Nationale Alzheimer", the center for imaging analysis (CATI), the biobank centers that host the biological collections, "the Fondation Plan Alzheimer" and the sponsor. Any scientist in charge with an ongoing project may be asked to join upon the two co-PIs invitation.
- Chair and co-Chair: The steering committee is alternatively chaired by one of the co-PIs.
- Membership
  - Co-PIs: Geneviève Chêne, Carole Dufouil
  - Coordinating Center: Helen Savarieau, project manager
  - investigating centers: one representative from each participating CMRR
  - National Database on Alzheimer: one representative (currently, Philippe Robert)
  - center for imaging analysis (CATI): three representatives (Jean-François Mangin (director), Marie Chupin (MRI acquisitions), Marie-Odile Habert (PET-Scan imaging acquisition)
  - Biobank centers that will host the biological collections "Fondation Plan Alzheimer": one for each of the biobank
  - Sponsor (CHU Bordeaux): one representative (currently, Laetitia Lacaze-Buzy)
  - Any scientist in charge with an ongoing project may be asked to join upon the two co-PIs invitation
  - Permanent observers: all staff of the Coordinating Center

Organization of meetings

- The Steering Committee meets every three months (mostly via tele- or videoconference).

MEMENTO GENERAL ASSEMBLY

Roles and responsibilities

- Broad statement: the General Assembly is the group that reviews overall progress of the cohort on behalf of their respective institutions.
- Specific roles and responsibilities
  - maintain confidentiality of all cohort information that is not already in the public domain
  - provide expertise to the cohort
  - comment on the overall progress of the conduct and results of the cohort

Composition

- Membership consists of a broad number of members including all committees and collaborators and all potential stakeholders.
- Chair and co-Chair: Pierre Ducimetière and Hugues Chabriat. The chair and co-chair of the Scientific Strategic Committee.
- Membership
  - Chair, Vice Chair of the Scientific Strategy Committee: Pierre Ducimetière, Hugues Chabriat
  - Co-PI: Geneviève Chêne, Carole Dufouil
  - Fondation Plan Alzheimer: Philippe Amouyel (General Director), Marie-Eve Joel (SAB),
  - Network of CMRRs: one to two representative-s by participating CMRR
  - Groupe Méthodologies Alzheimer: Sandrine Andrieu, Martine Bungener
  - National Database on Alzheimer: Philippe Robert
  - Pharmaceutical Industry: one representative of each pharmaceutical industry founder of the Fondation Plan Alzheimer and of Wyeth-Pfizer
  - National Health Agencies/ Health Insurance: one representative of InVS, HAS, and Cnamts
  - Sponsor, CHU Bordeaux: Philippe Vigouroux
  - France Alzheimer: Michèle Micas
  - Independent members of the Scientific Strategic Committee: Annick Alpérovitch, Lisa Berkman, David Clayton, Mony de Leon, Françoise Forette, Ronald Petersen, Philip Scheltens, Mary Vidailhet
  - On hold: Yves Levy
  - Permanent observers: Joël Ménard (Chair of the SAB of the Fondation Plan Alzheimer), Helen Savarieau (Memento project manager), Sylvie Ledoux (Scientific delegate for the Fondation Plan Alzheimer).
    The composition of the General Assembly is renewed every three years and its new composition is endorsed by the board of governors of the "Fondation Plan Alzheimer" based on proposals from the Director of the "Fondation Plan Alzheimer" and the 2 co-PI.

Organization of meetings

- The General Assembly meets once per year (physically). The Memento Executive Group prepares the agenda of the meetings.

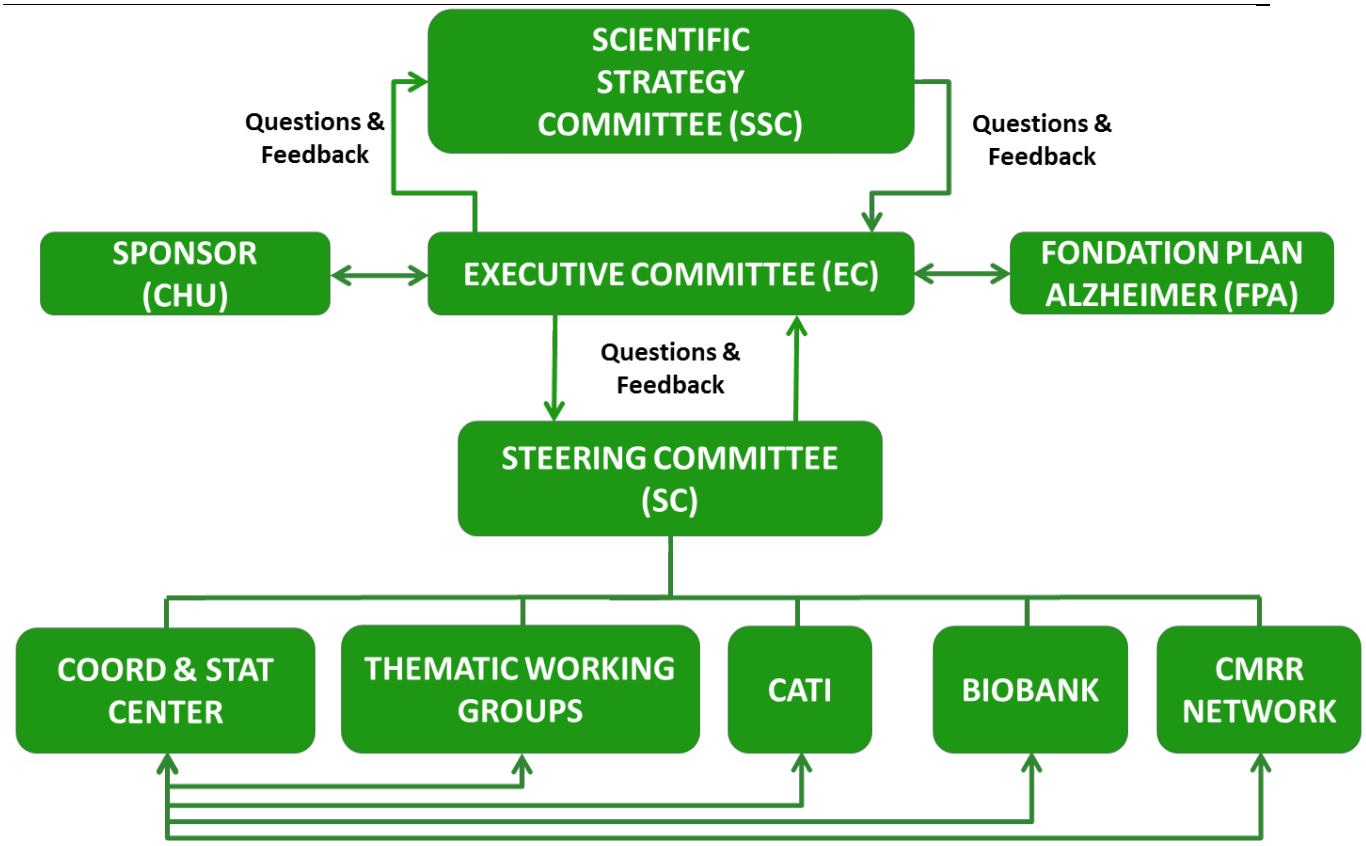


FIGURE 1. Relationships between Memento committees

Appendix 12. Agreement and competing interests form for Independent members of the Memento Scientific Strategy Committee

Agreement to join the Memento scientific strategy committee (SSC) as an-independent member and disclosure of potential competing interests

Please complete the following document and return original to the Memento secretariat.

(please initial box to agree)

	I have read and understood the Memento data access and publication policy charter version 4.0, dated November 4th 2014
	I have read and understood the Memento committees Charter version 4.0, dated November 4th 2014
	I agree to join the Memento Scientific Strategy Committee (SSC) as an independent member
	I agree to treat all sensitive Memento data and discussions confidentially

The avoidance of any perception that independent members of a SSC may be biased in some fashion is important for the credibility of the decisions made by the SSC and for the integrity of the cohort.

Potential competing interests should be disclosed via the Memento secretariat. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent SSC member should remove the conflict or stop participating in the SSC. **Table 1** lists potential competing interests.

	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for independent members of Scientific Strategy Committee members.

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing product or technique to the study
- Career tied up in a product or technique assessed by study
- Hands-on participation in the study
- Involvement in the running of the study
- Emotional involvement in the study
- Intellectual conflict e.g. strong prior belief in the study's hypotheses
- Involvement in regulatory issues relevant to the study procedures
- Investment (financial or intellectual) or career tied up in competing projects
- Involvement in the writing up of the main study results in the form of authorship

Appendix 13: Agreement and competing interests form for non-independent members of the Memento Scientific Strategy Committee

Agreement to join the Memento scientific strategy committee (SSC) as a non-independent member and disclosure of potential competing interests

Please complete the following document and return original to the Memento secretariat.

(please initial box to agree)

	I have read and understood the Memento access to data and publications policy charter version 4.0, dated November 4th 2014
	I have read and understood the Memento committees Charter version 4.0, dated November 4th 2014
	I agree to join the Memento Scientific Strategy Committee (SSC) as a non independent member
	I agree to treat all sensitive Memento data and discussions confidentially

The avoidance of any perception that members of a SSC may be biased in some undisclosed fashion is important for the credibility of the decisions made by the SSC and for the integrity of the cohort.

Possible competing interests should be disclosed via the Memento secretariat. In many cases simple disclosure up front should be sufficient. **Table 1** lists potential competing interests.

	No, I have no competing interests to declare other than involvement in the Memento cohort
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Ongoing advisory role to a company providing product or technique to the study
- Intellectual conflict e.g. strong prior belief in the study's hypotheses
- Involvement in regulatory issues relevant to the study procedures
- Investment (financial or intellectual) in competing projects

Appendix 14: Agreement and confidentiality agreement for observers

Agreement to attend the Memento scientific strategy committee (SSC) and treat all information confidentially

Please complete the following document and return original to the Memento secretariat

(please initial box to agree)

	I have received a copy of the memento access to data and publication policy charter, version 4.0, dated November 4th 2014
	I have received a copy of the Memento committees Charter, version 4.0, dated November 4th 2014
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

APPENDIX XII: COMPOSITION OF SCIENTIFIC AND STEERING COMMITEES

EXECUTIVE COMMITTEE

- Philippe Amouyel – General Director (Fondation Plan Alzheimer)
- Hugues Chabriat – co-Chair Memento Scientific Strategy Committee
- Pierre Ducimetière – Chair Memento Scientific Strategy Committee
- Geneviève Chêne – Memento Principal Investigator
- Carole Dufouil – Memento co-Principal Investigator

SCIENTIFIC STRATEGY COMMITTEE

- Independent scientific experts: Hugues Chabriat (Co-Chair), Pierre Ducimetière (Chair), Annick Alpérovitch, David Clayton, Mony de Leon, Ronald Petersen, Philip Scheltens, Marie Vidailhet
- Non-independent members : Philippe Amouyel, Geneviève Chêne, Carole Dufouil
- Permanent observer: one representative from Sponsor, Memento project manager, Jean-François Mangin (director of Center for Imaging analysis, CATI), one representative of the sponsor

MEMENTO STEERING COMMITTEE

- Geneviève Chêne - Chair, alternatively with CD
- Carole Dufouil – Chair, alternatively with GC
- Helen Savarieau – Memento Project manager, coordinating Center (CIC-EC7)
- Investigating centers: at least one representative from each clinical site of the participating CMRRs.
- Center for imaging analysis (CATI): three representatives (Jean-François Mangin (director), Marie Chupin (MRI acquisitions), Marie-Odile Habert (PET-Scan imaging acquisition)
- Centralised Biobank : one representative (currently, Nathalie Fievet)
- Sponsor (CHU Bordeaux): one representative (currently, Laetitia Lacaze-Buzy)
- *Any scientist in charge with an ongoing project may be asked to join upon the two co-PIs invitation.*

GENERAL ASSEMBLY

Membership

- Chair, Vice Chair of the Scientific Strategy Committee: Françoise Forette, Pierre Ducimetière
- Co-PI: Geneviève Chêne, Carole Dufouil
- Fondation Plan Alzheimer: Philippe Amouyel (General Director)
- Network of CMRRs: one to two representative-s by participating CMRR
- Groupe Méthodologies Alzheimer: Sandrine Andrieu, Martine Bungener
- National Database on Alzheimer: Philippe Robert
- Pharmaceutical Industry: one representative of each pharmaceutical industry founder of the Fondation Plan Alzheimer and of Wyeth-Pfizer
- National Health Agencies/ Health Insurance: one representative of InVS, HAS, and Cnamts
- Sponsor, CHU Bordeaux: Philippe Vigouroux
- France Alzheimer: Michèle Micas
- Independent members of the Scientific Strategic Committee: Annick Alperovitch, Hugues Chabriat, David Clayton, Mony de Leon, Ronald Petersen, Philip Scheltens, Marie Vidailhet
- Permanent observers: Joël Ménard (Chair of the SAB of the Fondation Plan Alzheimer), Helen Savarieau (Memento project manager), Sylvie Ledoux (Scientific delegate for the Fondation Plan Alzheimer). The composition of the General Assembly is renewed every three years and its new composition is endorsed by the board of governors of the "Fondation Plan Alzheimer" based on proposals from the Director of the "Fondation Plan Alzheimer" and the 2 co-PI.

APPENDIX XVIII: GUIDING PRINCIPLES OF ENDPOINT REVIEW COMMITTEES

1. OBJET

Cette procédure décrit les tâches de l'équipe projet Memento du CIC-EC7 pour l'organisation et la documentation de la validation des événements par les Comités de Validation des Evénements (CVE) cérébrovasculaires, cardiovasculaires, des démences et des causes de décès.

2. DOMAINE D'APPLICATION

Cette procédure est applicable à l'étude Memento et à ses études ancillaires gérées par le CIC-EC7.

3. DÉFINITIONS

Comité de validation des événements (anglais : « *endpoint review committee* ») : groupe d'experts dont le rôle est d'étudier et qualifier tout ou partie des évènements cliniques ou biologiques survenant dans une ou plusieurs recherches biomédicales utiles pour l'analyse des critères de jugement de l'étude.

ABREVIATIONS

ARC	Attaché de Recherche Clinique
CIC-EC7	Centre d'Investigation Clinique – Epidémiologie Clinique 7
CMRR	Centre Mémoire de Ressources et de Recherche
CP	Chef de Projet
eCRF	Electronic Case Report Form
CS	Conseil Scientifique
CVE	Comité de Validation des Evénements
DM	Data Manager
EI	Evénement Indésirable
HLGT	High-Level Group Term
HLT	High-Level Term
MedDRA	Medical Dictionary for Regulatory Activities (thesaurus de codage des EI)

4. PROCÉDURE OPÉRATOIRE

4.1. FONCTIONNEMENT DES COMITES DE VALIDATION DES EVENEMENTS MEMENTO

La mise en place d'un CVE à quatre composantes est prévue dans le protocole de l'étude Memento pour la validation des événements suivants :

- événements cardiovasculaires
- événements cérébrovasculaires
- démences
- causes de décès

Chaque composante fonctionne comme un CVE autonome avec son propre rythme de réunions et son président. La liste des membres du CVE est approuvée par le conseil scientifique (CS). Un accord de participation (Enregistrement N° 49) comportant une clause de confidentialité et une clause de conflit d'intérêt est signé par chaque membre du CVE dès sa nomination. Un exemplaire signé est conservé par l'équipe projet dans le dossier de l'étude.

Les principes de validation et les documents de référence sont détaillés dans un document spécifique à chaque CVE. Ces principes sont définis avec les membres des différents CVE lors de la première réunion de chaque comité. Ils sont approuvés par le CS.

La validation de chaque événement est effectuée indépendamment par deux experts, au fur et à mesure que l'on dispose d'une documentation suffisante. Les CVE se réunissent à intervalle régulier pour statuer sur les discordances, et au moins une fois par an.

4.2. PRÉPARATION DE LA DOCUMENTATION

Le DM ou le statisticien de l'étude MEMENTO édite sur une base mensuelle :

1) Une liste des participants de l'étude présentant un événement éligible pour la revue par le CVE :

- Diagnostic de démence posé par l'investigateur

- Evénements cérébrovasculaires codé dans MedDRA avec le High-Level Group Term (HLGT) 10007963 « Troubles vasculaires du système nerveux central »
- Evénements cardiovasculaires codés dans MedDRA avec le HLGT 10011082 « Troubles artériels coronaires », HLT 10042600 « Arythmies supraventriculaires » ou HLGT 10019280 « Défaillances cardiaques »
- Décès notifié par l'investigateur

2) Les résumés cliniques des participants ayant un évènement éligible, établis à partir d'extractions des informations pertinentes de la base de données, en fonction des spécifications de chaque CVE (Cf. procédures des CVE en anglais)

3) Le nom de deux experts sélectionnés aléatoirement dans la liste de chaque CVE (Un expert d'un CMRR ne recevra néanmoins pas le dossier d'un participant suivi dans le CMRR où il exerce)

Après validation de la liste de participants ayant un événement éligible pour la revue par le CP, l'ARC Memento en charge de la coordination des CVE vérifie avec les autres ARC du centre de coordination la disponibilité des pièces nécessaires pour la constitution d'un dossier de validation :

- Démences
  - Compte-rendu clinique d'IRM
  - Courrier de résumé de la visite à laquelle le diagnostic de démence a été posé
- Cérébrovasculaires et cardiovasculaires
  - Compte-rendu d'hospitalisation (CRH)
  - Courrier de consultation spécialisée en cas de prise en charge ambulatoire
  - Compte-rendu de SAMU si décès
  - Compte-rendu d'imagerie
- Causes de décès
  - Compte-rendu d'hospitalisation (CRH)
  - Compte-rendu de SAMU si décès
  - Certificat de décès

Les ARC des sites cliniques sont sollicités pour fournir des documents complémentaires ou compléter des données manquantes. Les dossiers sont vérifiés à distance ; la validation d'un événement ne justifie pas un monitoring sur site préalable.

Après vérification du contenu des documents par le CP et leur anonymisation, l'ARC coordinateur des CVE met à la disposition des experts les documents relatifs au cas à valider dans un dossier Cirrus. Les experts ont 15 jours pour statuer sur le cas à valider au moyen d'une fiche de validation standardisée qu'ils déposent en retour sur Cirrus.

Les données des fiches de validation sont saisies dans l'eCRF par l'ARC du centre coordinateur en charge du site dont dépend le cas validé. Le CP ou l'ARC du centre coordinateur transmettent mensuellement par écrit à l'investigateur du site concerné les demandes d'informations complémentaires du CVE, et lui envoient la liste des événements/items pour lesquels l'avis du CVE est discordant du sien.

4.3. ORGANISATION D'UNE REUNION EN FACE A FACE OU PAR TELE/VISIOCONFERENCE :

Une réunion plénière est organisée au moins une fois par an (en face-à-face) ou selon les règles prévues pour chaque CVE. Pour les réunions présentielles, une feuille de présence (Enregistrement N°28) préparée par l'ARC coordinateur des CVE est signée par les personnes présentes et est conservé dans le dossier de l'étude. Lorsque la réunion se fait sous forme de conférence téléphonique ou visioconférence, une attestation de participation (Enregistrement N°48) est envoyée aux participants qui doivent la compléter et la faxer ou la scanner et l'envoyer par courriel à l'ARC coordinateur des CVE après la réunion.

Les conclusions de la validation de chaque cas et de chaque item et les demandes de renseignements complémentaires sont notées pendant la réunion par le CP ou l'ARC en charge de la coordination des CVE sur une feuille de validation supplémentaire. Le données sont saisies dans l'eCRF comme précisé au § 4.2. Un compte-rendu des décisions prises par le CVE est conservé dans le dossier de l'étude.

APPENDIX XIV: HELSINKI DECLARATION

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX XVI: ACCESS TO MEMENTO DATA AND PUBLICATIONS CHARTER

Access to Memento data and Publications Charter
4th November 2014, version 4.0

MEMENTO COHORT: Cohort of outpatients from French Research Memory Centers in order to improve knowledge on alzheiMer's disEase aNd relaTed disOrders

PURPOSE OF THIS DOCUMENT:

To describe Memento general principles and path to follow for data access, ancillary project and publication submission.

KEY POINTS FOR INFORMATION AND DEFINITIONS

Memento Study Group
The different components of the Memento Study Group (or Memento network) are the following:

Memento Principal investigators
Geneviève Chêne – Memento Principal Investigator (CIC-EC7)
Carole Dufouil – Memento co-Principal Investigator (CIC-EC7)

Memento Executive Committee
Philippe Amouyel – General Director (Fondation Plan Alzheimer)
Pierre Ducimetière – Chair Memento Scientific Strategy Committee
Hugues Chabriat – co-Chair Memento Scientific Strategy Committee
Geneviève Chêne – Memento Principal Investigator
Carole Dufouil – Memento co-Principal Investigator

Memento Main Funder
Fondation Plan Alzheimer

Memento Sponsor
Bordeaux University Hospital (CHU Bordeaux)

Memento Scientific Strategy Committee

Independent scientific members: Pierre Ducimetière (Chair), Hugues Chabriat (Co-Chair), Annick Alpérovitch, Lisa Berkman, David Clayton, Mony de Leon, Françoise Forette, Ronald Petersen, Philip Scheltens, Marie Vidailhet
On hold: Yves Levy
Non independent members: Philippe Amouyel, Geneviève Chêne, Carole Dufouil
Permanent observers: Joël Ménard, one representative from Sponsor, Memento project manager, Jean-François Mangin (director of Center for Imaging analysis, CATI), one representative of French Federation of Memory Clinics

Memento Steering Committee

Geneviève Chêne (GC) - Chair, alternatively with CD

Carole Dufouil (CD) – Chair, alternatively with GC

Coordinating Center: Project manager (Helen Savarieau, CIC-EC7). Other staff members are permanent observers.

Investigating centers: one representative from clinical site of participating CMRRs Amiens, Hôpital Nord et Hôpital Sud (Pr Olivier Godefroy); Angers, CHU d'Angers (Pr Olivier Beauchet); Besançon, Hôpital Jean Minjoz, Hôpital Saint Jacques (Pr Pierre Vandel); Bobigny, Hôpital Avicenne (Dr Catherine Belin); Bordeaux, Hôpital Pellegrin (Pr François Tison), Hôpital Xavier Arnozan (Dr Sandrine Harston) ; Brest, Hôpital de la Cavale Blanche (Pr Armelle Gentric) ; Clermont -Ferrand, Hôpital Gabriel Montpied (Pr Isabelle Jalenques) ; Colmar, Hôpitaux civils de Colmar (Dr François Sellal) ; Dijon, Hôpital général, Centre de gériatrie de Champmaillot (Dr Olivier Rouaud) ; Grenoble, Hôpital de la Tronche (Dr Olivier Moreaud) ; Lille, Hôpital Roger Salengro (Pr Florence Pasquier) ; Lyon, Hôpital des Charpennes (Pr Pierre Krolak-Salmon) ; Marseille, Hôpital La Timone (Pr Mathieu Ceccaldi) ; Montpellier, CHU Gui de Chaulliac (Dr Audrey Gabelle) ; Nantes, hôpital Nord Laënnec (Dr Martine Vercelletto) ; Nancy, CHU de Nancy (Pr Athanase Benetos) ; Nice, Hôpital de Cimiez (Pr Renaud David) ; Paris, Hôpital de la Salpêtrière (Pr Bruno Dubois) ; Hôpital Broca (Pr Olivier Hanon) ; Groupe Hospitalier Lariboisière (Pr Jacques Hugon) ; Poitiers, CHU La Milétrie (Pr Marc Paccalin) ; Rouen, Hôpital Charles Nicolle (Pr Didier Hannequin) ; Saint-Étienne, Hôpital Nord (Dr Marie-Odile Barrellon), Hôpital la Charité (Dr Catherine Girtanner) ; Strasbourg, Hôpital de Hautepierre, Hôpital de jour Saint François (Dr Frédéric Blanc) ; Toulouse, Hôpital Casselardit (Pr Bruno Vellas) ; Toulouse, Hôpital Purpan (Dr Jérémie Pariente) ; Tours, Hôpital Bretonneau (Pr Caroline Hommet).

National Database on Alzheimer: one representative (currently, Philippe Robert)

Center for imaging analysis (CATI): three representatives (Jean-François Mangin (director), Marie Chupin (MRI acquisitions), Marie-Odile Habert (PET-Scan imaging acquisition)

Centralised Biobank: one representative (currently, Nathalie Fievet)

Sponsor (CHU Bordeaux): one representative (currently, Laetitia Lacaze-Buzy)

Any scientist in charge with an ongoing ancillary project may be asked to join upon the two co-PIs invitation.

Memento coordinating Center

CIC-EC7, Bordeaux: Helen Savarieau, Project Manager; Vincent Bouteloup, Biostatistician; Christophe Bouvier, Data Manager; Julie Erraud, Julie Le Scouarnec, Julie Lidier, Nathalie Thiery, Clinical Research Assistants.

Memento secretariat

memento_scsecretary@isped.u-bordeaux2.fr

For the purpose of this document,

- **Sub-studies, ancillary studies, abstracts and manuscripts will be referred to as "proposals". Contrary to sub-studies, ancillary studies necessitate an extension of data collection and specific ethics approval should thus be obtained.**
- **Corresponding authors/applicants of a proposal will be referred to as the "authors".**
- **All data collected according to the most recent version of the protocol at the submission date is referred to as "Memento data". The list of variables is included in the "Memento variables catalog" and covers raw monitored data as contained in the central database managed at the CIC-EC7.**
- **As a general principle, core dataset corresponding to each follow-up wave will be made available within the 6 months after completion and cleaning.**
- **Moreover access to raw images (MRI and PET) centralised at the CATI or to any centralized biological material should require specific authorisations.**

Memento co-principal investigators are responsible to advertise this policy by any means (presentation at meetings, website) and to provide all documents upon request (principles of governance; access to data and publications policy; submission forms; Memento questionnaire contents, Memento variables catalog).

1. Background on Memento : principles of data sharing

Memento is a cohort funded by the Fondation Plan Alzheimer and sponsored by the Bordeaux University Hospital (CHU Bordeaux).

This cohort aims at studying the **evolution of a variety of potentially early signs** (cognitive complaints, deficit in some domain of cognition, psycho-behavioural disturbances, changes in imaging or biological markers) of Alzheimer's disease and related dementia and to estimate the **prognostic value of different markers** (neuro-psychological, vascular, psychopathological, socio-educational, genetic, biological, neuro-imaging) on the progression to clinical dementia or severe cognitive deterioration stages, and then to death.

The cohort is also a **translational research platform** open to sub-studies and ancillary studies proposed by any *bona fide* researcher. Memento scientific gain should aim at being maximised, while maintaining and promoting data confidentiality and security, cohort scientific integrity and high quality of publications. In addition, legitimate interests of Memento collaborators, and all Memento participants, in particular capacity-building among Memento collaborators' teams, should be promoted.

The approval process will be followed for all data collected or acquired within the Memento cohort, through the e-CRF, MRI (images and biomarkers), PET imaging (images and biomarkers), and biological specimen.

No Memento proposal should be undertaken without prior discussion within the Memento study group and authorisation of the Memento Executive Committee.

Authors are encouraged to include Memento collaborators in their Proposal's Study Team for the sake of capacity building.

2. General approval process of any proposal

- **Once the Memento Principal investigators have given input to the authors developing a full proposal, the Memento Secretariat is responsible for co-ordinating the approval process and for all circulations, and should be copied on all correspondence (**memento_scsecretary@isped.u-bordeaux2.fr**).**
- **Authors are responsible for ensuring they start the approval process and contact the Memento Principal Investigators with enough time to meet any submission deadlines (for grant applications, communications to scientific congress…)**
- **Authors are responsible for all submissions and for keeping the Memento Secretariat informed at any time.**
- **The Memento Executive Committee is responsible for making sure that all relevant parties in Memento have been informed about and have no objection to the proposal. The Executive Committee is responsible for making the final decision and informing the authors.**

STEP 1 : INITIATION

Ideas for all proposals should first be discussed (as early as possible and before drafting the document) with Memento Principal Investigators in order to identify any Memento data to be included in the proposal, and any need for data analysis. When imaging data are required, a representative of the CATI should systematically be involved in the discussions from the beginning. A brief outline of the proposal that authors would like to develop should be emailed to the Memento Principal Investigators and copied to the Memento Secretariat (memento_scsecretary@isped.u-bordeaux2.fr). At this stage, assessment criteria of the Memento Principal Investigators include: feasibility, absence of competition with ongoing research within Memento, potential for capacity-building within the Memento network.

STEP 2 : SUBMISSION

After discussion with the Principal Investigators, the authors should fill a proposal form (Appendix 17 for sub-study or ancillary study, Appendix 2 for abstract or manuscript information) to be sent to the Memento Secretariat (memento_scsecretary@isped.u-bordeaux2.fr) and examined by the Executive Committee. The Memento Executive Committee is responsible for ensuring that the proposal is scientifically original and not in conflict with the cohort development or results.

STEP 3 : CIRCULATION

In order to facilitate abstract submissions, this step is bypassed for any abstract proposal, approval being directly endorsed by the Executive Committee (see paragraph 4.)

After queries have been satisfactorily dealt with by the authors and the proposal has been approved by the Executive Committee, the Memento Secretariat will circulate the full proposal for review, comment and formal approval among the Memento Steering Committee members and the Memento Scientific Strategy Committee members. They are responsible for ensuring that the content/ science of any proposal is suitably high to be undertaken/published. Within the Memento Steering Committee, the co-PIs, the Fondation Plan Alzheimer and the Sponsor are specifically responsible for ensuring that any use of the Memento data is not in conflict with and does not compromise the integrity of the cohort. It can then be recommended: acceptance, rejection or that further work is needed. The proposal will be considered accepted if no comment is received within the given number of working days for approvals.

All substantive revisions/comments to the proposal from the Memento Executive Committee, and Steering Committee, must be addressed before approval/submission. Minor comments should be addressed, or responded to. Responses to comments and minor re-writing need not to be circulated. However, any major changes or re-analysis in response to reviewers should be re-circulated by the Memento Secretariat, to the Memento Executive Committee, and Steering Committee.

STEP 4 : FINAL APPROVAL

Once all the relevant parties have been consulted and have no more comment on the proposal, the Executive Committee makes a final decision regarding proposal acceptance that is circulated to the authors by the Memento secretariat.

The author of the proposal must report when requested to the Memento secretariat on proposal or publication progress at any time.

3. Specific recommendations for any sub-study or ancillary study proposal

3.1. The **Executive Committee** considers the proposal at the meeting following its submission .

3.2. The Memento Steering Committee considers the proposal at their next following meeting and makes recommendations. The **Scientific Strategy Committee** considers the proposal and makes recommendations within the same timeframe as the Steering Committee.

3.3. In any case, the need for contract agreement will be discussed at the Executive Committee level and the contract finalised before the sub-analysis or ancillary study can start.

3.4. PI of a sub-study or ancillary study could be asked to present progress of the study at any meeting of the Scientific Strategy Committee.

4. Specific recommendations for abstracts proposal

4.1. A brief outline/idea for all proposed abstracts should first be discussed with Memento Principal Investigators and copied to the Memento Secretariat (memento_scsecretary@isped.u-bordeaux2.fr) at **LEAST 15 working days ahead of the submission deadline**. .

Prior to developing the full draft abstract, an agreement on the concept and proposed authorship must be reached.

4.2. .The **Memento Executive Committee** has a **maximum of 5 working days** to consider the proposal and make recommendations.

4.3. After queries have been dealt with by the authors, and the proposal has been reviewed and approved by the Memento Executive Committee, the author can submit the abstract. The corresponding author sends the submitted abstract to the Memento Secretariat for records tracking, as soon as possible.

4.4. The Memento secretariat will send the abstract to the **Memento Steering Committee** and the **Memento Scientific Strategy Committee** for information.

5. Specific recommendations for manuscripts proposal

A list of all those collaborating in Memento ("Memento Study Group") should be added as an appendix to all Memento publications. An up to date list and additional information regarding mentions on funding and sponsoring should be obtained from the Memento Secretariat (memento_scsecretary@isped.u-bordeaux2.fr).

5.1. The **Memento Executive and Steering Committees** have a **maximum of 15 working days** to consider the proposal.

5.2. After queries have been satisfactorily dealt with by the authors and the final version of the manuscript has been reviewed and approved by the Memento Executive Committee, the author can submit the manuscript. The author sends the submitted manuscript to the Memento Secretariat for records tracking, as soon as possible.

5.3. The Memento Secretariat will regularly send an updated list of manuscripts to the **Scientific Strategy Committee** for information.

5.4. Revised manuscripts following any reviewer and editorial comments should be circulated by the Memento Secretariat to the Memento Executive and Steering Committees at least **10 working days** prior to re-submission to the journal or any other one.

Appendix 17. Memento Sub-study/ Ancillary study Outline

Please complete the following form to allow the Executive and Steering Committees to evaluate your proposal – we encourage you to carefully read the guidance on the "Access to Memento data and Publications Policy Charter" (sections 2 and 3) and the following reminder to increase the acceptability of your proposal.

Please observe that proposals, in order to be endorsed, must comply with Memento principles:

1. Once the Memento Principal investigators have had input and have agreed to the authors developing a full proposal, the Memento Secretariat is responsible for co-ordinating the approval process and for all circulations, and should be copied on all correspondence.
2. Authors are responsible for ensuring they start the approval process and contact the Memento Principal Investigators with plenty of time to meet any submission deadline.
3. Authors are responsible for all submissions and for keeping the Memento Secretariat informed at any time.
4. Authors are encouraged to include Memento collaborators in their Proposal's study team for the sake of capacity-building
5. The Memento Executive Committee is responsible for making sure that all relevant parties in Memento have been informed about and have no objection to the proposals. The Executive Committee is responsible for making the final decision and for releasing it to the authors.

Please send this proposal to:

- Memento secretariat (memento_scsecretary@isped.u-bordeaux2.fr) and
- Cc Memento co-PI (Genevieve Chene (genevieve.chene@isped.u-bordeaux2.fr) and Carole Dufouil (carole.dufouil@isped.u-bordeaux2.fr)

Memento Sub-study/ Ancillary study Outline

Proposal title	
Submitted by	
Affiliation	
Collaborators of Memento involved in the proposal	
Study team & roles	
Background and scientific hypotheses	
Justification for use of Memento	
Objectives	
Feasibility assessment	
Deliverables and timelines	
Significance (added value compared to current scientific consensus and ongoing projects)	
Possible limitations	
Standard Memento data items required	
Additional data items (if biobank access, specify material needed)	
Sample size/power calculations	
Estimated costs and sources of specific funding	

Appendix 18. Abstract/Manuscript Information Form

Please complete the following form to allow the Executive and Steering Committees to evaluate your abstract or manuscript – we encourage you to carefully read the guidance on the "Access to Memento data and Publications Policy Charter" (sections 2 ,4 and 5) and the following reminder to increase the acceptability of your proposal..

Please observe that publications, in order to be endorsed, must comply with Memento principles:

1. Once the Memento Principal investigators have had input, the Memento Secretariat is responsible for co-ordinating the approval process and for all circulations, and should be copied on all correspondence.
2. Authors are responsible for ensuring they start the approval process and contact the Memento Principal Investigators with plenty of time to meet any submission deadline.
3. Authors are responsible for all submissions and for keeping the Memento Secretariat informed at any time.
4. Authors are encouraged to include Memento collaborators in their writing group for the sake of capacity-building
5. The Memento Executive Committee is responsible for making sure that all relevant parties in Memento have been informed about and have no objection to the publication. The Executive Committee is responsible for making the final decision and for releasing it to the authors.

Please send this form to:

1. Memento secretariat (memento_scsecretary@isped.u-bordeaux2.fr) and
2. Cc Memento co-PI (Genevieve Chene (Genevieve.chene@isped.u-bordeaux2.fr) and Carole Dufouil (carole.dufouil@isped.u-bordeaux2.fr))

Memento Abstract and manuscript Information form

Abstract/manuscript proposed title	
Corresponding author	
Affiliation	
Collaborators of Memento involved,	
Language for publication/presentation	
Publication type	
Target Journal/Congress	
Planned date of Journal/Congress submission (for abstracts or journal submission) or presentation (for posters or oral presentations)	
Scope of intended audience	
Regulatory implications, if any	

APPENDIX XIX: MEMENTO-AMYGING PARTICIPATING CENTERS BY GROUP

Group A
LILLE
AMIENS
ROUEN
PARIS-LARIBOISIERE
Group B
PARIS-BROCA
PARIS-SALPETRIERE
BOBIGNY
NANTES
POITIERS
ANGERS
TOURS
BESANCON
BREST
Group C
SAINT-ETIENNE
CLERMONT-FERRAND
GRENOBLE
LYON
Group D
STRASBOURG
DIJON
COLMAR
NANCY
Group E
TOULOUSE
BORDEAUX
Group F
MONTPELLIER
MARSEILLE
NICE