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

ID RCB number: 2010-A01394-35

This biomedical research project is funded by the *Fondation Plan Alzheimer*

Sponsor :

Centre Hospitalier Universitaire de Bordeaux
Direction Générale du CHU de Bordeaux
Direction de la Recherche Clinique et de l'Innovation
12 rue Dubernat - 33404 Talence Cedex
Phone : 05 56 79 47 98 – Fax : 05 56 79 49 26
Website : www.chu-bordeaux.fr

Coordinating investigator :

Pr Geneviève CHENE
CIC-EC7
Bat ISPED, Université de Bordeaux
146 rue Léo Saignat, case n°11
33076 BORDEAUX Cedex
France
Phone : 05 57 57 13 92/12 57 – Fax : 05 57 57 11 72
e-mail: genevieve.chene@isped.u-bordeaux2.fr

Scientific director, co-coordinator

Carole DUFOUIL
CIC-EC7
Bat ISPED, Université de Bordeaux
146 rue Léo Saignat, case n°11
33076 BORDEAUX Cedex
France
Phone : 05 57 57 14 23 – Fax : 05 57 57 11 72
e-mail : carole.dufouil@isped.u-bordeaux2.fr

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)