Study Sponsor: University of Edinburgh

Study Protocol for EPAD Longitudinal Cohort Study

European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study (LCS)

Protocol EPAD-UoE-001

Medicinal Product: None

Status:	Approved		
Protocol version:	3.0	**Version date:**	28 February 2017
Prepared by:	Craig Ritchie, Miia Kivipelto, Alina Solomon on behalf of the EPAD Consortium		

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

PROTOCOL SIGNATURE PAGE

Medicinal Product None

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PROTOCOL SIGNATURE PAGE

Protocol details	
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Study name/acronym:	**EPAD LCS**
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Protocol approved by:

We, the undersigned, have reviewed and approved this protocol including the appendices.

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Status: Approved 2

Protocol version: 3.0, Version date: 28 February 2017

Medicinal Product None

Protocol EPAD-UoE-001

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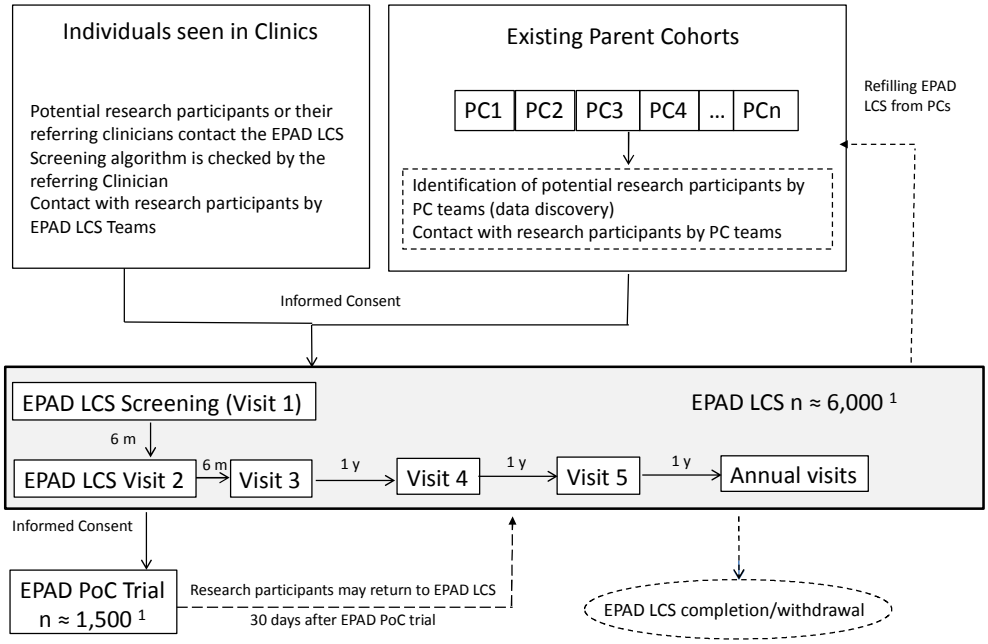
PROTOCOL SYNOPSIS

STUDY TITLE	European Prevention of Alzheimer's Dementia Longitudinal Cohort Study
STUDY NAME	**EPAD LCS**
PROTOCOL NUMBER	EPAD-UoE-001
CHIEF INVESTIGATOR	Professor Craig Ritchie
COORDINATING INVESTIGATORS	Craig Ritchie, Miia Kivipelto, Alina Solomon on behalf of the EPAD Consortium
STUDY RATIONALE	The EPAD project has been established to overcome the major hurdles hampering drug development for secondary prevention of dementia due to Alzheimer's disease (AD), by conducting the EPAD LCS in alignment with the adaptive design EPAD PoC trial. Interventions must start early in the course of AD, but accurate disease models covering the entire course of AD before dementia onset are lacking. Estimating with reasonable confidence an individual's overall probability of developing AD dementia over a defined time period must take into account multiple dimensions simultaneously (e.g. cognition, biomarkers, traditional risk factors - genetic and environmental). Because individuals with similar overall probability may have very different contributions from various components in each dimension, flexible algorithms are needed instead of simple cut-offs to identify a probability-spectrum population adequate for both disease modelling and for providing a sufficient number of potential trial participants (especially in adaptive trials with multiple active experimental drugs being assessed concurrently).
STUDY DESIGN	Prospective, multicentre, pan-European, longitudinal cohort study
STUDY OBJECTIVES	1. To provide a well-phenotyped population (readiness population) for the EPAD PoC trial to minimize trial screening failures 2. To provide a well-phenotyped probability-spectrum population for developing and continuously improving disease models for AD in individuals without dementia. The probability continuum spectrum will be derived from three different dimensions: cognition, biomarkers, and traditional risk factors (genetic and environmental) 3. To use disease models for assessing where and why research participants fall in the overall probability continuum spectrum, and thereafter select research participants for the EPAD PoC trial 4. To provide high quality run in, pre-randomisation data for the EPAD PoC trial against which the impact of various interventions can be measured.

STUDY DIAGRAM	 *1 Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.*
STUDY DESCRIPTION	• EPAD will develop an environment for and then test multiple different interventions for the secondary prevention of AD dementia. EPAD LCS is a key component of this environment, having a well-phenotyped probability-spectrum population in which the overall probability of developing AD dementia is represented across the entire continuum. • EPAD LCS research participants may be recruited from existing Parent Cohorts (PCs) across Europe. Each PC team will be helped to identify potential research participants in their own PC (data discovery), and then contact them. The EPAD LCS team will only contact research participants who express interest in potential EPAD LCS participation. Where potential research participants or their referring clinician contacts the EPAD LCS team directly, they can be included if they match the flexible algorithm. The EPAD LCS screening visit will be conducted after informed consent is obtained. The EPAD LCS population will include approx. 6,000 research participants[1], and population size will be maintained over time by continuously refilling EPAD LCS from the PCs. Some of the EPAD LCS research participants who fulfil trial inclusion criteria will be invited into the EPAD PoC trial (approx. 1,500 research participants[1], subject to separate informed consent). Initial duration of EPAD LCS for 4 years to end of December 2019, and after that extension of consent will be asked from research participants who are still eligible for EPAD LCS. EPAD LCS research participants will not be asked to leave their PCs, and those who participate in the EPAD PoC trial may return to EPAD LCS at least 30 days after trial completion, if they wish to and if they are still eligible for EPAD LCS. • The EPAD LCS and EPAD PoC trial will be run in an exclusive network of highly selected, expert Trial Delivery Centres that will be selected on the basis of strictly applied criteria to ensure the highest possible data quality, successful

[1] Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.

	recruitment and adherence to the EPAD principles.
RECRUITMENT STRATEGY AND PROCEDURES	Research participants will mainly be recruited from existing PC across Europe. There is no set number for PCs, and additional PCs may be considered as needed. PCs considered for EPAD are: active cohorts including research participants without dementia aged at least 50 years; the PC PI is willing to provide research participants for EPAD LCS and EPAD PoC trial; and there is existing consent from research participants for re-contact by PC team or possibility to obtain consent to re-contact by PC team. Potential EPAD LCS research participants will be identified based on data in their own PC (data discovery). Initial contact with research participants will be established by PC teams. Only research participants approached by the PC team who express interest in potential participation in EPAD LCS will be contacted by the EPAD LCS team. In case a potential research participant or their referring clinician contacts the EPAD LCS team directly about participating in the EPAD LCS, the referring clinician will check the flexible algorithm to confirm the suitability of the individual. The EPAD LCS screening visit will be conducted only after obtaining informed consent. This process will be repeated every time the EPAD LCS needs to be refilled from PCs.
RESEARCH PARTICIPANTS	Due to the variety of PCs, some research participants will be e.g. memory clinic patients without dementia, while others will be e.g. PC participants without dementia from the general population. The variety of PC settings will ensure that the EPAD LCS probability-spectrum population can cover the entire continuum of probability for AD dementia development.
ELIGIBILITY CRITERIA	• Age at least 50 years • Characterisation of cognitive, biomarker and risk factors (genetic, environmental) status of research participants based on data collected at the EPAD screening/baseline visit, so that decisions on inclusion can be made with reference to the dual needs of having sufficient heterogeneity across the entire probability-spectrum population for disease-modelling work, and suitable research participants for the EPAD-PoC trial. • Able to read and write and with minimum 7 years of formal education • Willing in principle to participate in the EPAD PoC trial subject to further informed consent • Have a study partner or can identify someone willing in principle to be a study partner
SELECTION PROCESS	• It is important to emphasize that EPAD LCS research participants may fall on a continuum of overall probability for developing AD dementia that is driven by three main dimensions: cognition, biomarkers, and traditional risk factors (genetic and environmental). Components of these dimensions may be continuous in nature, and treating them as such rather than dichotomizing or categorizing by simple cut-offs may result in substantial gains in efficiency and avoidance of information loss when deciding where and why a participant falls in the overall probability continuum spectrum, especially as participants with similar overall probability may have differing contributions from the various components/dimensions. Interrogating the underlying components/dimensions in addition to the overall probability will also allow participant stratification decisions to consider the drivers and needs related to compounds to be investigated in the EPAD PoC trial. • The EPAD LCS will be subject to three main ways to maintain the probability spectrum: [1] oversampling or under-sampling from different types of PCs; [2] a flexible algorithm for identification of potential participants by PC teams (used every three months by the EPAD LCS Data Oversight Committee, hence providing a list of potential EPAD LCS Research Participants, with variations by types of data available in different PCs); and [3] a flexible algorithm for selecting research participants after the EPAD LCS screening (considering parameters listed below)

	• EPAD LCS research participants may be deselected after the screening visit if they do not contribute to the overall probability spectrum. Deselection will be managed by the EPAD LCS Data Oversight Committee, and investigators will be blinded to which dimensions/components do not contribute to the overall probability spectrum in individual research participants. This is necessary because investigators will be blinded to results of CSF, imaging and genetic assessments undertaken in EPAD LCS to avoid biases in clinical assessments that may affect disease modelling work in EPAD LCS
SELECTION PARAMETERS WITHIN EPAD LCS	The following parameters assessed at the EPAD LCS screening visit will be considered for the flexible selection algorithm: **Cognitive parameters** The following parameters from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in the EPAD Neuropsychological Examination (ENE) will be considered, all of which combine to create the RBANS Total Scale Index Score: • Verbal Episodic Memory: List Learning & Story Memory • Visual Episodic Memory: Figure Recall • Visuospatial/Constructional: Figure Copy & Line Orientation • Language: Picture Naming • Attention/Executive Functioning: Semantic Fluency, Digit Span, Coding **Biomarkers** • CSF biomarkers: beta-amyloid, t-tau, p-tau • Neuroimaging parameters (MRI): hippocampal and whole brain volume; vascular burden (WML, infarcts, lacunes, microbleeds, superficial siderosis) **Risk factors** • APOE genotype • Family history of AD/dementia in first degree relatives • Sociodemographic factors: age, sex, education, marital status • BMI • Medical history: cardiovascular and cerebrovascular conditions, chronic respiratory conditions, chronic systemic inflammatory conditions, depression, cancer, general anaesthesia after the age of 50 years, head injury • Lifestyle factors: smoking, drug abuse, alcohol consumption, diet, physical activity, life events, self-rated health and fitness (assessed with standard questionnaires)
EXCLUSION CRITERIA	• Research participants who fulfil diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLB, NINCDS-AIREN Criteria for Vascular Dementia) • CDR>=1 • Known carriers of a Presenilin (PSEN) PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD or any other neurodegenerative disease • Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse or major psychiatric disorders including current major depressive disorder, schizophrenia, schizoaffective or bipolar disorder. • Any cancer or history of cancer in the preceding 5 years (excluding cutaneous basal or squamous cell cancer resolved by excision) • Any current medical conditions that are clinically significant and might make the subject's participation in an investigational trial unsafe, e.g., uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including re-vascularisation procedures; severe renal or hepatic failure; unstable or poorly controlled DM, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or

	localized prostate cancer in male subjects); any clinically relevant abnormalities in blood parameters included in local TDC routine assessments; severe loss of vision, hearing or communicative ability; or any conditions preventing co-operation or completion of the required assessments in the trial, as judged by the investigator • Any contraindications for MRI/PET scan • Any contraindications for Lumbar Puncture • Any evidence of intracranial pathology which, in the opinion of the Investigator, may affect cognition, including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Participants with a MRI scan demonstrating markers of small vessel disease (e.g. white matter changes or lacunar infarcts) judged to be clinically insignificant, or microbleeds are allowed. • Participation in a clinical trial in the last 30 days[2] • Diminished decision-making capacity/not capable of consenting
DATA SOURCES AND COLLECTION	The only data source for this study will be data collected as part of EPAD LCS. Electronic data capture will be used, e.g. for cognitive and neuroimaging data. A central laboratory will be used for all genetic and biomarker measurements, and central reading of all neuroimaging will be undertaken. Investigators will be blinded to results from genetic, biomarker and neuroimaging assessments to avoid bias in clinical assessments that may affect disease modelling work. Overall probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy of current disease models. However, findings with established clinical relevance will be disclosed to participants and, with their consent, to their treating physician for initiation of appropriate treatment.
PRIMARY OUTCOMES	**Cognitive outcomes – RBANS Total Scale Index Score**[3] - Verbal Episodic Memory: List Learning & Story Memory (RBANS) - Visual Episodic Memory: Figure recall (RBANS) - Visuospatial/Constructional: Figure Copy & Line Orientation (RBANS) - Language: Picture Naming (RBANS) - Attention/Executive Functioning: Semantic Fluency, Digit Span, Coding (RBANS)
SECONDARY OUTCOMES	**Cognitive Outcomes** - Working Memory: Dot Counting (NIH EXAMINER) - Choice Reaction Time and Set Shifting: Flanker (NIH EXAMINER) - Paired Associate Learning: Favourites (University of California, San Francisco) **CSF biomarker outcomes** - Aβ, t-tau, p-tau **Neuroimaging outcomes (MRI)** - Hippocampal & whole brain volume
EXPLORATORY OUTCOMES	**Cognitive outcomes** - Allocentric Space: Four Mountains Task (Cambridge University) - Navigation in Egocentric Space: Virtual Reality Supermarket Trolley (University College London) **Other clinical outcomes** - Everyday functioning: Amsterdam Instrumental Activities of Daily Living Questionnaire **Neuroimaging outcomes** - Multi-region structural and functional MRI analysis

[2] Continued participation in the Parent Cohort is expected.

[3] For statistical purposes, the RBANS Total Scale Index Score will serve as the Primary Endpoint.

	- functional regional and network measures
OTHER MEASURES	Sociodemographic and lifestyle factors, family history of AD/dementia in first degree relatives, medical history, comorbidity, medication use, BMI, waist-hip ratio, blood pressure, CDR, MMSE, GDS, STAI, Pittsburgh Sleep Quality Index, Vascular burden (WML, infarcts, lacunes, microbleeds, superficial siderosis), Dementia diagnosed by the participant's physician Physical examination APOE genotype, Polygenic Scores Collection of CSF and blood, urine & saliva samples for future biomarker assessments (emerging AD biomarkers)
FOLLOW-UP	Research participants will be followed-up every 6 months during the first year (to ensure a minimum of two cognitive assessments before potential recruitment into the EPAD PoC trial), and then annually. Cognitive and clinical assessments will be conducted every 6 months during the first year, and then annually. CSF, blood urine and saliva samples will be collected annually. Structural MRI assessments will be done annually, and functional MRI assessments will be done annually in a sub-sets of participants.
STUDY PERIOD	EPAD LCS will initially run until the end of December 2019. Extension of consent will be sought after 4 years. To allow adequate modelling and run in data, research participants will have to have at least 6 months of participation in the EPAD LCS prior to potential recruitment into the EPAD PoC trial. Research participants may leave EPAD LCS due to withdrawn consent, entry into the EPAD PoC trial, entry into another clinical trial or whenever EPAD LCS research participant exclusion criteria are met.
STATISTICAL ANALYSIS	Starting point of modelling is mixed effects models. Model complexity will subsequently increase and ultimately focus on latent trajectory/class models and non-parametric Bayesian models using Gaussian processes. More complex joint modelling methods will integrate various data types (e.g. biomarkers, cognitive) and thus use all available information more efficiently. Cross-validation will be used to check modelling assumptions. For the purpose of the EPAD PoC trial, modelling will identify and rank strata of subpopulations of different probability. Each sub-population will have a profile of biomarkers and other measurements, and this stratification will be used to identify potential treatments, the size of potential treatment effects, and to guide the flow of research participants from EPAD LCS into subsequent arms of the EPAD PoC trial. These strata in the first instance may accord with current definitions of pre-clinical and prodromal AD[4,5,6].

[4] Dubois B et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.

[5] Sperling RA et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92.

[6] Albert MS et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-9

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research and Development
AD	Alzheimer's disease
ADL	Activities of daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
ARC	Algorithm Running Committee
ASL	Arterial spin-labelling
BC	Balancing Committee
BISQ	Brain Injury Screening Questionnaire
BMI	Body Max Index
CBF	Cerebral Blood Flow
CCSC	EPAD Clinical Candidate Selection Committee
CDR	Clinical Dementia Rating
CRF	Case Report Form
CRO	Contract Research Organisation
CSF	Cerebrospinal fluid
CTIMP	Clinical Trial of Investigational Medicinal Product
DLB	Dementia with Lewy Bodies
DPUK	Dementia Platform United Kingdom
DTI	Diffusion Tensor Imaging
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMIF	European Medical Information Framework
ENE	EPAD Neuropsychological Examination
EPAD	European Prevention of Alzheimer's Disease
EPAD DOC	EPAD Data Oversight Committee
EPAD LCS	EPAD Longitudinal Cohort Study
FA	Fractional Anisotropy
FLAIR	Fluid-Attenuated Inversion Recovery
FTD	Fronto-Temporal Dementia
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HATICE	Healthy Ageing through Internet Counselling in the Elderly
IADL	Instrumental Activities of Daily Living
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ISF	Investigator Site File
Knight ADRC	The Charles F. and Joanne Knight Alzheimer's Disease Research Center
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIH-EXAMINER	National Institutes of Health-Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NINCDS-AIREN	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences
PI	Principal Investigator
PC	Parent Cohort
PET	Positron Emission Tomography
PoC	Proof of Concept
PSEN	Presenilin
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
SAE	Serious Adverse Event
SAG	Scientific Advisory Group
SNAC	Swedish National study on Aging and Care
STAI	State-Trait Anxiety Inventory
SWI	Susceptibility Weighted Imaging
TDC	Trial Delivery Centre
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UoE	University of Edinburgh
WML	White Matter Lesion

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Background

Alzheimer's disease (AD) is the leading cause of dementia globally affecting ~7M people in Europe[1]. As the population ages, the number of people with dementia will rise and a concomitant rise in the dependency ratio[2] means that the economic burden of AD will increase dramatically from an already high baseline (~ €262 billion in 2015)[3]. Attempts to impact on disease progression pharmacologically in symptomatic populations remain ongoing, but recent results have been disappointing[4]. There is now consensus that the genesis of AD pathology predates dementia onset by over 20 years[5,6], presenting an opportunity for disease course modification before dementia onset and even prior to the appearance of clinical symptoms. With numerous biologically active agents in late phase trials which affect a range of pathological processes in AD (e.g. anti-oligomerisation, secretase inhibitors, kinase inhibitors and anti-amyloid monoclonal antibodies), the key challenge is to accurately identify individuals with high probability of subsequent AD dementia development, who are suitable for trial inclusion and willing to participate in secondary prevention studies. Current proposals for defining an individual's probability for developing AD dementia based on either biomarkers or clinical symptoms have been focused on the stage of AD close to dementia onset. Disease models and their phenotypic expression needed for probability estimation in earlier stages in the disease process are less well defined but the subject of intense study currently. It is important to firstly develop accurate disease models for AD in early disease stages when people do not yet have symptoms, or express only subjective complaints of cognitive decline, or have only mild cognitive symptoms. These people need to be followed-up longitudinally, and they could be recruited into trials designed to reduce early disease burden or decrease the probability of developing AD dementia.

To date, trials of potentially disease modifying drugs in AD have followed a pattern of intervention with a single agent in lengthy and costly trials for people with dementia or other clinically defined states thought proximal in time to the onset of dementia. Only a few recent studies have applied adaptive design principles that could avoid exposing very large numbers of research participants to doses of experimental drugs that could have been identified as ineffective earlier in the course of the study. As each trial works in isolation of other trials, there have been a vast number of research participants exposed to a placebo arm that could, given the right infrastructure, have been shared between studies. These traditionally designed trials have not led to any new licensed drugs for either the symptomatic treatment of dementia or its secondary prevention for over 10 years. Moreover, the basis for decisions to move into these trials was often on limited Phase 2 data, which did not fully address uncertainty regarding optimal dosing, research participant selection and choice of outcome for the confirmatory study.

The European Prevention of Alzheimer's Dementia (EPAD) is a project to develop an environment for and then test multiple different interventions for the secondary prevention of AD dementia. EPAD has three principal cost-effective solutions to address the problems listed above: [1] Accurate identification and recruitment of a high-probability asymptomatic or minimally symptomatic population of individuals with clear expression of AD pathology willing to participate in PoC studies; [2] Selection of candidate interventions (including combinations) in a pre-competitive space; and [3] creation of a trial environment to deliver

high quality and accurate data to inform faster and conclusive decisions on whether to progress intervention(s) to confirmatory studies. The EPAD project is running across Western Europe with 37 partners from academia and the commercial sector.

1.2. Overall Rationale for EPAD LCS

The EPAD project has been established to overcome the major hurdles hampering drug development for secondary prevention of AD dementia, by conducting the EPAD LCS (fed mainly from existing Parent Cohorts (PC) across Europe) in alignment with the adaptive design EPAD PoC trial. Both EPAD LCS and EPAD PoC trial will be run in an exclusive network of highly selected, expert Trial Delivery Centres (TDC) that will be selected on the basis of strictly applied criteria to ensure the highest possible data quality, successful recruitment and adherence to the EPAD principles.

While interventions must start early in the course of AD, accurate disease models covering the entire course of AD before dementia onset are lacking. Estimating with reasonable confidence an individual's overall probability of developing AD dementia over a defined time period must take into account multiple dimensions simultaneously (e.g. cognition, biomarkers, traditional risk factors - genetic and environmental). This will allow any given individual to be placed somewhere on a probability spectrum from negligible probability to high probability. Because individuals with similar overall probability may have very different contributions from various components in each dimension, flexible algorithms are needed instead of simple cut-offs to identify a probability-spectrum population adequate for both disease modelling and for providing a sufficient number of potential trial participants (especially in adaptive trials with multiple arms testing drugs with different mechanisms of action).

EPAD LCS is designed to address the dual need for development of accurate longitudinal models for AD covering the entire disease course, and development of adequate infrastructure for facilitating identification of research participants and clinical trial recruitment. EPAD LCS will have a probability-spectrum population selected mostly from already existing PCs across Europe to facilitate fast recruitment. Different types of PCs will be considered (e.g. memory clinic-based, population-based). Due to the variety of PCs, some EPAD LCS research participants will be e.g. memory clinic patients without dementia, while others will be e.g. participants without dementia from the general population. The variety of PC settings will ensure that the EPAD LCS probability-spectrum population can cover the entire continuum of probability for AD dementia development. Some potential participants identified by their referring clinician, or the referring clinician themselves, will contact the EPAD LCS teams directly. To enable access to the EPAD LCS for these potential participants, the referring clinician will check if they match the flexible algorithm. Regular EPAD LCS follow-up with clinical, cognitive and biomarker assessments will provide a well-phenotyped probability-spectrum population, generating high-quality data for updating disease models, for easier identification of individuals suitable for trial inclusion, and for use as trial run-in data and reference for evaluating intervention efficacy.

The flow of research participants from the population at large to the trial is divided into the following stages: firstly, EPAD will engage existing PCs from across Europe who may have eligible research participants for the EPAD LCS. The next step is drawing research

participants from the PCs into the EPAD LCS to maintain a suitable population of approximately 6,000 research participants. This main form of recruitment for the EPAD LCS is complemented with research participants who come from a clinical setting, they or their referring clinician will contact EPAD LCS centres directly. Finally, research participants in the EPAD LCS who fulfil trial inclusion criteria (approximately 1,500 research participants), will be invited to enter the EPAD PoC trial for evaluation of treatment for secondary prevention of AD dementia. This trial is a standing, adaptive, PoC trial that could involve multiple arms running concurrently. Successful graduation through PoC into phase 3 confirmatory trials of single or combinatorial interventions will be based on success against an intermediary, target specific biomarker and then success against a cognitive measure.

Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approximately 1,500 in the EPAD PoC, hence the need to replenish each from PCs as participants are lost through attrition. EPAD LCS will initially run until the end of December 2019, and extension of consent will be sought prior to this date.

2. OBJECTIVES

The EPAD LCS, a key component of the overall EPAD Project, has four aims:

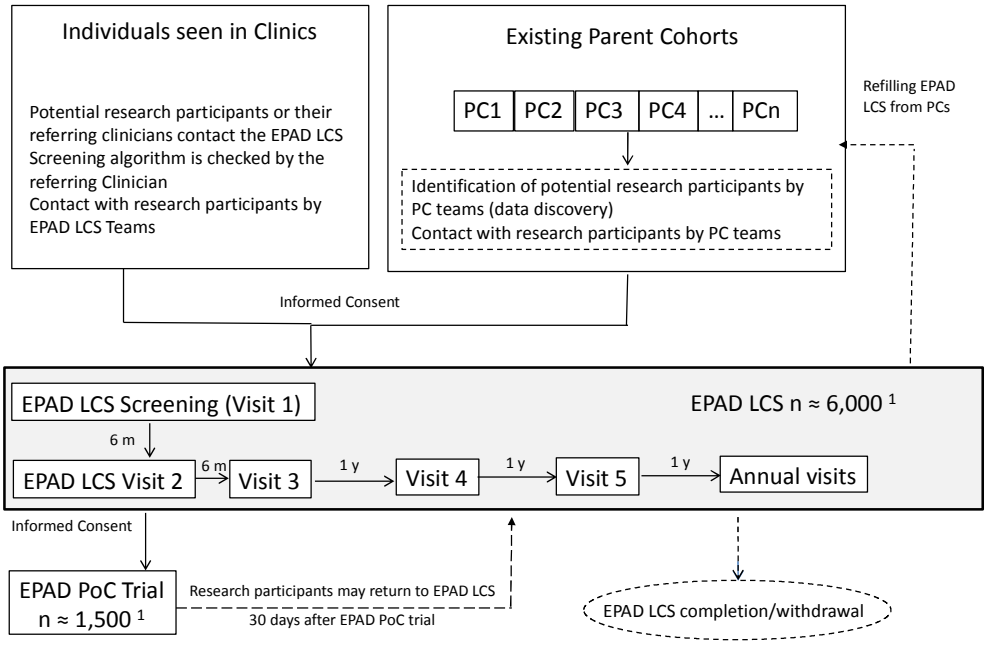
1. To provide a well-phenotyped population (readiness population) for the EPAD PoC trial to minimize trial screening failures
2. To provide a well-phenotyped probability-spectrum population for developing and continuously improving disease models for AD in individuals without dementia. The probability continuum spectrum will be derived from three different dimensions: cognition, biomarkers, and traditional risk factors (genetic and environmental)
3. To use disease models for assessing where and why research participants fall in the overall probability continuum spectrum, and thereafter select research participants for the EPAD PoC trial
4. To provide high quality run in, pre-randomisation data for the EPAD PoC trial against which the impact of various interventions is measured.

3. RESEARCH METHODS

3.1. Study Design and Rationale

EPAD LCS is a prospective, multicentre, Pan-European, cohort study that will have a well-phenotyped probability-spectrum population to address the dual need to develop accurate longitudinal models for AD covering the entire disease course, and to create a pool of highly characterized individuals for the EPAD PoC trial. EPAD LCS participants will be recruited from different types of existing PCs across Europe (e.g. memory clinic-based, population-based) to ensure fast recruitment of a probability-spectrum population covering the entire continuum of probability for AD dementia development.

The study design is summarised in Figure 1.



[1] Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.

Figure 1: Research participants flow to the EPAD LCS and into the EPAD PoC trial

3.2. Study Description and Rationale for Design Elements

3.2.1. Flow of Research Participants from PCs to EPAD LCS

Research participants will mainly be recruited from existing PCs across Europe. This provides the major advantage of shortened recruitment process into EPAD LCS. Selection of PCs for EPAD does not imply sharing of PCs data with EPAD, and EPAD will not have access to individual-level data from PCs.

There will be two classes of PCs considered for EPAD LCS (Table 1). The classes differ in way of research participant recruitment, and type of data, and hence suitability for EPAD.

Table 1: Classes of PCs

Research cohorts	Observational study with research participants from the general population
	Observational study with research participants recruited from other sources
	Prevention trial
	Pre-existing trial readiness cohort
Clinical/routine care cohorts	Memory clinic based
	General practitioner/primary care based

To ensure the engagement of PCs, they will be selected based on close connections with core partners in the EPAD Consortium, maximally leveraging those involved in European Medical Information Framework (EMIF, http://www.emif.eu/) and regional initiatives like the Dementias Platform UK (DPUK, http://www.dementiasplatform.uk/). EMIF is highly relevant in the context of EPAD because it aims to develop a common information framework of participant-level data that will link up and facilitate access to diverse medical

and research data sources, opening up new avenues of research. Importantly, AD is included in EMIF as one of the initial research areas to provide a focus and guidance for the development of the framework. The EMIF Platform will initially be able to, on its own, leverage data on around 40 million European research participants by means of federation of healthcare databases and cohorts from 7 different countries, designed to be representative of the different types of existing data sources (population-based registries, hospital-based databases, cohorts, national registries, biobanks, etc.). The DPUK is developed and led by the UK Medical Research Council, and aims to accelerate progress in early detection, improved treatment and ultimately prevention of dementias. The DPUK is creating the world's largest population study for use in dementia research, bringing together two million participants aged 50 and over, from over 30 existing cohort studies and registers within the UK.

Other cohorts not part of EMIF and DPUK will also be included as needed, and cohort owners outside EPAD will be also contacted. Given the interest and potential usefulness of general practitioner/primary care cohorts for the EPAD Register, novel strategies will be developed to enable recruitment of research participants through these sources. In addition, cohorts or registers of high utility to EPAD may be encouraged to expand their recruitment, especially where this is low cost e.g. primary care based registers.

PC eligibility criteria:

- Active cohorts including research participants without dementia aged at least 50 years
- Willingness of PC PI to provide research participants for EPAD LCS and EPAD PoC trial
- Existing consent from research participants for re-contact by PC team or possibility to obtain consent to re-contact by PC team

Potential EPAD LCS research participants will be identified for each PC team based on data in their own PC, using a flexible search algorithm adapted to the types of data available in each PC. To ease the search process, a data discovery software tool will be provided to PCs by EPAD. Queries will be run that provide counts of research participants according to the search algorithm. Only the PC team will have access to research participant IDs in their own PC, and these IDs and individual-level data will not be available to EPAD.

Research participants identified through this search process in a PC will be contacted by the respective PC team. EPAD will not directly contact research participants at this stage. Before contacting research participants, the PC teams will check that consent to re-contact is in place. During the contact, the PC research team will inquire if each contacted research participant:

- Has no fundamental objections to participating in a clinical trial
- Is interested in being contacted by the EPAD LCS staff at the local TDC for receiving further information about EPAD LCS
- Has not been diagnosed with dementia

PC teams will keep a record of the outcome of contacts with research participants from their own PCs regarding EPAD LCS, i.e. agreed/declined/no response yet. This tracking is important in order to avoid re-contacting research participants who have declined interest in EPAD LCS.

After being contacted by the PC team, potentially eligible research participants for EPAD LCS who express interest in EPAD LCS will be contacted by the EPAD LCS staff at the local TDC, who will provide detailed oral and written information about EPAD LCS and the overall EPAD project, and answer any questions that research participants may have about the study. In case a potential research participant or their referring clinician contacts the EPAD LCS team directly about participating in the EPAD LCS, the referring clinician will check the flexible algorithm to confirm the suitability of the individual. At the point of consent, the study journey for these participants is the same as for participants selected via PCs. Clear oral and written information will be provided concerning potential participation in the EPAD PoC trial, i.e. that participation in EPAD LCS does not automatically imply eligibility for the EPAD PoC trial, and that trial participation is subject to separate informed consent. Assessments and data collection for EPAD LCS will take place only after the Informed Consent Form (ICF) has been signed.

3.2.2. Selection Process

It should be noted that as one objective of the EPAD LCS is for disease modelling, the introduction of selection bias by over-specifying criteria for EPAD LCS inclusion needs to be minimised. Replacing traditional simple cut-offs with flexible algorithms in the selection process is also essential in the context of a probability spectrum based on multiple dimensions (cognition, biomarkers, and traditional risk factors). Moreover, as we will follow a non-disclosure policy of theoretical probability, some research participants provided by PCs will be, of negligible probability of decline at baseline. Of course, over time their own biomarker status and cognitive profile may change making them eligible for the EPAD PoC trial. Such research participants are of great value to EPAD as longitudinal data is collected on them over years before potential entry into the EPAD PoC trial. Ultimately, selection algorithm flexibility will facilitate maintenance of the probability spectrum, including the refilling of EPAD LCS as specific groups of research participants are drawn from EPAD LCS into the EPAD PoC trial.

The selection algorithm will be continuously adapted as the project progresses and more data from the EPAD LCS and EPAD PoC trial are gathered. This process of data monitoring, algorithm adaptations and maintenance of balance in EPAD LCS between disease modelling and creating a pool of well-phenotyped potential participants for the EPAD PoC trial will reside with a small group called the Balancing Committee (BC).

EPAD LCS will use three main tools to maintain the probability spectrum:

1. A flexible algorithm for identification of potential research participants by PC teams. The algorithm will be applied every three months by the EPAD BC, with variations by types of data available in different PCs.
2. Oversampling or under-sampling from different types of PCs
3. A flexible algorithm for deselecting research participants after the EPAD LCS screening/baseline visit (considering parameters listed in section 3.3.2).

EPAD LCS research participants may be deselected after the screening visit if they do not contribute to the overall probability spectrum. Deselection will be managed by the EPAD LCS BC, and investigators will be blinded to which dimensions/components do not

contribute to the overall probability spectrum in individual research participants. This is necessary because investigators will be blinded to results of CSF, imaging and genetic assessments to avoid biases in clinical assessments that may affect disease modelling work in EPAD LCS. Before signing the ICF, research participants will receive clear oral and written information about the non-disclosure policy of theoretical probability, and about the fact that they may be deselected after screening/baseline assessments.

3.3. EPAD LCS Study Population

Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS. Population size will be maintained over time by continuously refilling EPAD LCS from the PCs. Initial duration of EPAD LCS will be 4 years to December 2019, and after that extension of consent will be asked from research participants who are still eligible for EPAD LCS. EPAD LCS research participants will not be asked to leave their PCs, and those who participate in the EPAD PoC trial (approx. 1,500 research participants with at least 6 months' follow-up in EPAD LCS) may return to EPAD LCS at least 30 days after trial completion, if they wish to and if they are still eligible for EPAD LCS.

Due to the variety of PCs, some EPAD LCS research participants will be e.g. memory clinic patients without dementia, while others will be e.g. PC participants without dementia from the general population. PCs variety will ensure that the EPAD LCS probability-spectrum population can cover the entire continuum of probability for AD dementia development.

3.3.1. Eligibility Criteria

1. Age at least 50 years
2. Characterisation of cognitive, biomarker and risk factors (genetic, environmental) status of research participants based on data collected at the EPAD screening/baseline visit, so that decisions on selection/deselection can be made with reference to the dual needs of having sufficient heterogeneity across the entire probability-spectrum population for disease-modelling work, and suitable research participants for the EPAD PoC trial (Balancing Committee decision)
3. Able to read and write and with minimum 7 years of formal education
4. Willing in principle to participate in the EPAD PoC trial subject to further informed consent
5. Have a study partner or can identify someone willing in principle to be a study partner

A study partner for an EPAD LCS research participant can be a relative or friend indicated by the participant, who is at least 18 years old, who may or may not live together with the participant, and who is available either for face to face or telephone contact with the EPAD LCS staff at the local TDC. As EPAD LCS research participants do not have dementia, have no or only slight impairment (i.e. Clinical Dementia Rating, CDR 0 or 0.5), and are fully capable of providing informed consent (see Exclusion criteria below), the primary role of the study partner in EPAD LCS will be as informant. Prior to EPAD LCS assessments, study partners will receive oral and written information about EPAD LCS and the overall EPAD project, and will sign an ICF.

3.3.2. Exclusion Criteria

1. Research participants who fulfil diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLB, NINCDS-AIREN Criteria for Vascular Dementia)
2. CDR>=1
3. Known carriers of a Presenilin (PSEN) PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD or any other neurodegenerative disease
4. Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse; or major psychiatric disorders including current major depressive disorder, schizophrenia, schizoaffective or bipolar disorder.
5. Any cancer or history of cancer in the preceding 5 years (excluding cutaneous basal or squamous cell cancer resolved by excision)
6. Any current medical conditions that are clinically significant and might make the subject's participation in an investigational trial unsafe, e.g., uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including re-vascularisation procedures; severe renal or hepatic failure; unstable or poorly controlled DM, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects); any clinically relevant abnormalities in blood parameters included in local TDC routine assessments; severe loss of vision, hearing or communicative ability; or any conditions preventing co-operation or completion of the required assessments in the trial, as judged by the investigator
7. Any contraindications for MRI/PET scan
8. Any contraindications for Lumbar Puncture
9. Any evidence of intracranial pathology which, in the opinion of the Investigator, may affect cognition including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Research participants with a MRI scan demonstrating markers of small vessel disease (e.g. white matter changes or lacunar infarcts) judged to be clinically insignificant, or microbleeds are allowed.
10. Participation in a Clinical Trial of an Investigational Product (CTIMP) in the last 30 days (continued participation in the parent cohort is expected). Participation in a non-CTIMP is not an exclusion criterion
11. Diminished decision-making capacity/not capable of consenting at Visit 1 or Visit 2.

If at a subsequent annual EPAD LCS visit health professionals suspect diminished consent capacity according to local TDC routine procedures, a formal assessment of the research participant's capacity to consent will be conducted (e.g. University of California, San Diego Brief Assessment of Capacity to Consent, UBACC[7]. The participant will be offered the opportunity to continue in the EPAD LCS under suitable local regulations regarding capacitous participants who have consented to enter a longitudinal study who subsequently

loose capacity. Capacity will be assessed at each study visit using the correct legal framework.

3.3.3. Role of the Balancing Committee (BC) & Algorithm Running Committee (ARC)

As EPAD LCS aims to have a probability-spectrum population suitable for both disease modelling and creating a pool of well-phenotyped potential participants for the EPAD PoC trial, research participants who are considered as not contributing to the overall probability spectrum will be deselected from EPAD LCS after the screening/baseline visit.

To estimate an individual's overall probability of developing AD dementia, three different dimensions including multiple parameters will be taken into account in EPAD LCS.

a. Cognitive parameters

The following parameters from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in the EPAD Neuropsychological Examination (ENE, described in section 3.4.1) will be considered:

- Verbal Episodic Memory: List Learning & Story Memory
- Visual Episodic Memory: Figure Recall
- Visuospatial/Constructional: Figure Copy & Line Orientation
- Language: Picture Naming
- Attention/Executive Functioning: Semantic Fluency, Digit Span, Coding

b. Biomarkers

- CSF biomarkers (details in section 3.4.3): beta-amyloid, t-tau, p-tau
- Neuroimaging parameters (MRI, details in section 3.4.4): hippocampal and whole brain volume; vascular burden (WML, infarcts, lacunes, microbleeds, superficial siderosis)

c. Risk factors

- APOE genotype
- Family history of AD/dementia in first degree relatives
- Sociodemographic factors: age, sex, education, marital status
- BMI
- Medical history: cardiovascular and cerebrovascular conditions, chronic respiratory conditions, chronic systemic inflammatory conditions, depression, cancer, general anaesthesia after the age of 50 years, head injury
- Lifestyle factors: smoking, drug abuse, alcohol consumption, diet, physical activity, life events, self-rated health and fitness (assessments described in detail in section 3.4.6)

Because individuals with similar overall probability may have very different contributions from various components in each dimension, a flexible selection algorithm will be used instead of simple cut-offs.

The Balancing Committee will agree the use of this data to select / deselect individual participants and the Algorithm Running Committee will provide the output for the Parent Cohorts.

3.4. EPAD LCS Data Sources and Collection

The only data source for this study will be the data collected as part of the EPAD LCS study. Electronic data capture will be used as appropriate, e.g. for cognitive and imaging data. Central laboratories will be used for all CSF and genetic assessments, and central reading of all neuroimaging will be undertaken. Investigators will be blinded to results from CSF, genetic, and neuroimaging assessments to avoid bias in clinical assessments that may affect disease modelling work. Overall probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy of current disease models. However, findings with established clinical relevance will be disclosed to participants and, with their consent, to their treating physician for initiation of appropriate treatment.

The assessments chosen for EPAD LCS are based on recommendations developed by five Scientific Advisory Groups (SAGs) within EPAD (Clinical and Cognitive Outcomes, Epidemiology, Fluid Biomarkers, Genetics, and Imaging). The SAGs each have approximately six expert members, as well as external advisors. SAGs recommendations were based on reviewing the current literature, following widely accepted practices, and minimizing participant burden.

3.4.1. Cognitive Outcomes

Both research and clinical trials in AD have been highly heterogeneous in their choice of clinical and cognitive outcomes and even more diverse in the type of measures used to capture and quantify them. This heterogeneity has reflected not only the constant evolution of scientific knowledge about brain functioning and its functional correlates but also commercial interests, personal preferences, subject tolerance and concerns over acceptability to regulatory authorities. Within this context the EPAD project presents two further challenges: [1] the outcomes refer to a greater distance from clinical AD diagnosis than has been attempted in previous trials, and [2] the outcome measures should be scientifically objective and unlikely to be seen as favouring a specific EPAD PoC trial sponsor.

Given these issues, the EPAD Clinical and Cognitive outcomes SAG was tasked with formulating recommendations for the EPAD Neuropsychological Examination (ENE) based on an objective extensive review of current knowledge on the early, asymptomatic stage of AD. The following criteria were used to compare the relative merits of different tests:

- Available translations
- Good psychometric properties (priority was given to measures with high sensitivity rather than specificity, as the battery is for signal detection and not diagnosis)
- Alternative forms or ability to easily create fully alternative versions, to permit retesting more than once per year (particularly important as some research participants in EPAD LCS may be recruited into the EPAD PoC trial later on)
- Validated preferably by reference to longitudinal data in relation to either preclinical through prodromal AD[8,9,10] populations, APOE genotype or amyloid positivity

- Normative data available
- Limited (or well-defined) practice effects
- Preference for non-proprietary material (for previously existing tests)
- Suitable for non-specialist administration

The final ENE battery was thus chosen to adequately cover all relevant cognitive domains, with greatest possible sensitivity to early-stage changes, cross-cultural transferability, and availability of parallel forms, while also providing both accuracy and processing time measures. A total battery administration time of approximately 2 hours including breaks was designed to minimize the burden for participants. Because EPAD LCS needs to provide a trial readiness cohort for the EPAD PoC trial, the EPAD cognitive test battery was also developed to be "modulable", i.e. to allow individual components to be selected out corresponding to specific drug targets if necessary during the EPAD PoC trial. In addition, each component task will have four alternative forms for retesting.

The ENE battery will be administered using an electronic tablet device, every six months during the first year, and then annually to all participants in EPAD LCS. Results from these testing waves will provide normative data for the cohort for either the whole population or sub-groups. The ENE battery is summarized in Table 2 and described in detail below according to the order of test administration.

Table 2: Cognitive outcomes[7]

Cognitive domains	Tests
Primary outcomes	
Verbal Episodic Memory	List Learning & Story Memory (RBANS)
Visual Episodic Memory	Figure Recall (RBANS)
Visuospatial/Constructional	Figure Copy & Line Orientation (RBANS)
Language	Picture Naming (RBANS)
Attention/Executive Functioning	Semantic Fluency, Digit Span, Coding (RBANS)
Secondary outcomes	
Working memory	Dot counting
Choice reaction time and set-shifting	Flanker
Paired associate learning	Favourites (Delay, Learning & Recognition)
Exploratory outcomes	
Allocentric space	Four Mountains Task
Egocentric space	Supermarket Trolley Virtual Reality

As noted above in Table 2, for statistical purposes the RBANS Total Scale Index Score will serve as the Primary Endpoint. In addition, all Clinical Outcome Assessments (COAs) measuring cognition were categorized by validation level as denoted in Table 2 above. For LCS purposes, Primary outcomes include anchor or criterion measure(s) that have been accepted by regulatory authorities in previous registration trials. The RBANS will serve as the criterion measure for this study. Secondary outcomes are those either in need of

[7] For statistical purposes, the RBANS Total Scale Index Score will serve as the Primary Endpoint.

additional psychometric validation, validation of alternative forms and/or lack normative data. As reflected in Table 2, the Dot counting, Flanker and Name/Face pair measures fall into this category. Exploratory outcomes are those untested in large population-based studies and/or in need of psychometric validation. The Four Mountains and Supermarket Trolley tests are exploratory outcomes in this LCS.

An additional goal of the LCS is to help validate the secondary and exploratory cognitive outcome measures against a known and accepted criterion measure. Specifically, through validation within the LCS the Secondary outcome measures may be potentially considered to be used as a Primary Endpoint in future proof of concept or registration trials. The exploratory outcome measures would require two independent studies with convergent findings for full psychometric validation. Thus, the LCS will help provide initial evidence for the exploratory outcomes to be potentially elevated to secondary endpoint status in future studies or trials (e.g., EPAD PoC study).

In order to meet GCP requirements computerized measures must comply with Title 21 CFR Part 11/European Union Annex 11. Although the EPAD LCS is done in compliance with GCP, including the Primary Endpoint, it should be noted that the computerized secondary and exploratory measures are undergoing additional validation in this LCS and, thus, do not yet fully meet GCP.

Verbal Episodic Memory

a. List Learning/Recall (RBANS)[11,12]

List Learning measures rote verbal memory for unrelated information. In the immediate recall subtest, the participant hears a list of 10 semantically unrelated words and must repeat the words back to the examiner. The word list is presented to the participant a total of four times, evaluating ability to learn verbal information after repeated exposure. For List Recall, after a delay with intervening tasks, the participant will recall the 10 words learned in the List Learning subtest. Immediately following the participant is read 20 words (i.e., 10 targets, 10 foils) and asked to respond ‘yes’ or ‘no’ to indicate whether each word was on the word list.

b. Story Memory (RBANS)[11,12]

The task measures memory for conceptually related verbal information. The participant hears a story that is two sentences in length and must repeat the story back to the examiner. The participant hears the story two times; therefore, the subtest also measures verbal learning. Following a delay with intervening tasks, the story is recalled to assess long-term verbal memory encoding and retrieval.

Visual Episodic Memory and Visuospatial/Constructional Analysis

a. Figure Copy (RBANS)[11]

The Figure Copy task requires the copying of a complex geometric design from a model, implicating visuospatial reasoning, attention to visual details, motor programming, and, to a lesser degree, organization and fine-motor ability. After a delay, the figure is redrawn from memory without prior warning to measure long-term free recall for conceptually-related visuospatial information and incidental memory (i.e., memory for information that was encoded without specific effort to do so).

b. Line Orientation (RBANS)[11]

The Line Orientation task assesses the ability to correctly identify the angle and spatial orientation of lines in two-dimensions. The participant is presented a drawing with 13 equal lines fanning out in different directions from a central point, all lines are numbered (1-13). Below this drawing is another containing only two lines from the above array, and they are asked to identify what two number lines the drawing matches.

Language

Picture Naming (RBANS) [11,12]

The Picture Naming task measures confrontation naming skills. This is a direct assessment of expressive language skills often impaired in global and specific types of aphasia, specifically dysnomia. The participant is shown 10 drawings of common objects and asked to name each one. The drawings are simple line drawings to avoid any perceptual confusion that more complex drawings may create.

Attention/Executive Functioning

a. Semantic Fluency (RBANS)[11,12]

The Semantic Fluency task measures the participant's ability to retrieve and express words using a semantic prompt. This is a direct assessment of expressive language skills often impaired in global and expressive aphasia. The participant is asked to say as many words as possible associated with a specific category (e.g., fruits and vegetables) of objects within a fixed time limit.

b. Digit Span (RBANS)[11,13]

The Digit Span subtest is a measure of auditory registration and brief focused attention. The participant listens to a series of digits read out by the examiner at one per second (e.g., 2–9) and is asked to repeat the digits in the same order.

c. Coding (RBANS)[37]

The Coding subtest is a measure of brief, focused, visual attention, visual scanning and processing speed. Participants are presented a page containing a key at the top containing symbols, and an associated number below each (1-9). The rest of the page contains rows of boxes with symbols (in a random sequence), and a blank box below each. Using the key, the participant is asked to fill in the number corresponding to each symbol, as quickly as possible and complete as many in order in 90 seconds.

Working Memory

Dot Counting (NIH EXAMINER)[15-18]

This verbal working memory task is presented on a computer screen as a mixed array of green circles, blue circles and blue squares, and the participant is instructed to count all of the blue circles on the screen and remember the final total. The examiner then switches the display to a different mixed array of green circles, blue circles and blue squares. The participant is instructed to count the blue circles in the new display. The number of different displays presented to the participant in each trial increases from two to seven over six trials. After counting the blue circles on all of the displays presented within a trial, the participant

recalls the total number of blue circles in each of the different displays in the order in which they were presented.

Choice reaction time and set-shifting

Flanker (NIH EXAMINER)[15-18]

The Eriksen Flanker Task is a set of response inhibition tests used to assess the ability to suppress responses that are inappropriate in a particular context. The target is flanked by non-target stimuli which correspond either to the same directional response as the target (*congruent* flankers), to the opposite response (*incongruent* flankers), or to neither (*neutral* flankers). In the tests, a directional response (usually left or right) is assigned to a central target stimulus. Various forms of the task are used to measure information processing and selective attention.

Paired-Associate Learning

Favourites (Immediate Recall, Delayed Recall, and Recognition) (University of California, San Francisco)[19,20]

On the Favourites Memory task, participants are asked to remember people and their favourite food and animal. On both learning trials, participants are shown each of four different faces twice, each paired once with a favourite vegetable / fruit name and once with a favourite animal name. Each pair is shown for 5 seconds in a pseudorandom order. After each learning trial, the faces reappear one at a time, and the participant is asked to recall the food and the animal associated with that face. After 10 minutes, delayed recall and recognition trials are administered.

Allocentric Space

Four Mountains Task (Cambridge University)[21]

The test assesses linkage between the episodic and spatial functions of the hippocampus, which permits representation of spatial information in an allocentric form and hence encoding of the context in which events occur. Computer-generated landscapes comprised of four hills (of varying shape and size) surrounded by a distant semi-circular mountain range are presented with a sample image for 10 seconds following which the participant is immediately presented with four alternative images, one of which (the target image) shows the same topography as the sample image, seen from a novel viewpoint, from which they must identify the target image by pressing a key. Non-spatial features (lighting, vegetation, weather conditions) of both target and foil landscapes are varied between presentation and testing, such that transient local features of the image cannot be relied on to solve the task.

Navigation in Egocentric Space

Virtual Reality Supermarket Trolley (University College London)[22]

This test, which is sensitive to deterioration in the precuneus, retrosplenial cortex and entorhinal connections measures egocentric spatial orientation (as opposed to allocentric space) through presentation of 14 video vignettes in an ecological virtual supermarket from a first person perspective. A route through the supermarket in which the participant is behind

the trolley involves a series of 90° turns, and at the end the participant is required to point in the direction of the entry.

3.4.2. Other Clinical Outcome Assessments (COAs)

The Amsterdam Instrumental Activities of Daily Living Questionnaire was chosen following a review of currently available measures and examination of their previous performance in both epidemiological studies and clinical trials. Selection criteria were the following:

- Known neurophysiological links to cognition
- Sensitive to at least Mild Cognitive Impairment
- Good repeat-test reliability
- Validated in European countries
- Dimensional or otherwise able to demonstrate change over time

Changes in everyday activities in pre-clinical AD are detectable only using scales specifically designed for this purpose – the more widely used ADL and IADL questionnaires are unlikely to be sensitive to very early changes.

Everyday Functioning

The Amsterdam Instrumental Activities of Daily Living Questionnaire[27,28]

This is an informant-report checklist recorded by the clinician, aimed at detecting early activities of daily living changes associated with pre-clinical stage dementia. The test has high internal consistency and retest reliability with construct validity established by comparing estimated trait levels with clinical and demographic measures.

This assessment will be done annually.

3.4.3. CSF Biomarker Outcomes

CSF samples will be collected annually in all EPAD LCS research participants and analysed at a central lab (University of Gothenburg, Sweden). A common protocol for sample collection, storage and shipment will be used at all EPAD TDCs. Measurements will include AD-related markers (Aβ, t-tau and p-tau), and this data will be used for disease modelling and for staging of disease pathology. A detailed CSF sampling manual will be provided.

If an individual participant has had a lumbar puncture and CSF sample collected and stored according to the CSF sampling manual procedure within 12 months of the Visit 1 first assessment of the EPAD LCS then this sample can be provided for analysis for the Visit 1 baseline data.

If an individual participant refuses a lumbar puncture at Visit 3 or a subsequent annual visit this will be defined as missing data. If the participant refuses a lumbar puncture at two sequential visits, then they will be withdrawn from the EPAD LCS as a non-compliant participant.

3.4.4. Neuroimaging Outcomes

Secondary Outcomes

- Hippocampal and whole brain volume

Exploratory outcomes

- Multi-region structural MRI analysis
- Functional regional and network measures

Other Measures

- Vascular burden (WM lesions, infarcts, lacunes, microbleeds and superficial siderosis)

Neuroimaging assessments were chosen based on evidence from available studies with an emphasis on secondary prevention of AD (defined from an imaging perspective as amyloid pathology in the brain without necessary signs of accompanying neurodegeneration). Pertinent literature on earlier disease stages covered subjective memory complaints, subjective cognitive impairment and healthy controls. Longitudinal data were mainly considered, but also cross-sectional data, especially when stratified for amyloid status and APOE4. Another aspect important for EPAD LCS was the usefulness of the imaging data for the subsequent EPAD PoC trial. The choice of imaging assessments additionally factored in participant burden, implementation and costs, while avoiding redundancies between imaging measures and non-imaging procedures.

Magnetic Resonance Imaging (MRI) can provide both structural and functional information about the brain, which confer complementary information regarding disease susceptibility, pathology and impairment. The MRI acquisition is divided into core image acquisition, which all subjects enrolled in the LCS undergo, and advanced image acquisition, which includes functional MRI, which only a sub-set of sites with suitable equipment and experience will acquire.

Core MRI Imaging

MRI was chosen because compared to CT it provides lower radiation exposure and the possibility to determine vascular pathology while allowing for quantification of grey matter structures such as the hippocampus and other AD signature regions. MRI is also much better suited to a longitudinal setting, with early-stage subtle changes over time detected in AD-sensitive regions, which can predict future cognitive decline and onset of dementia.

Annual MRI provides a fair balance between research participants' burden and determination of (non-linear) trajectories of atrophy. The core MRI examination for all TDCs (all EPAD LCS participants) are performed to assess study eligibility, for baseline assessment that can be used for subsequent safety monitoring in POC studies, and for quantitative analysis of brain structure and vascular lesions. Multi-region structural MRI analysis, including whole brain and hippocampal volume analysis, will be performed to better understand how brain volumes change over time in the study population. ADNI-like protocols and quality control will be used to ascertain precision in measuring change (direct longitudinal measurement

techniques rather than segmentation only). The core MRI examination can be completed in around 30 minutes.

Advanced MRI Imaging

A subset of TDCs that have MRI centres with the necessary technology and experience will additionally acquire more advanced MRI during the same visits as the core MRI listed above. The acquisition of the advanced sequences will depend on the capabilities of the sites and may include on or more of the following types of acquisition:

- 3D-SWI or 3D-T2*
- Diffusion tensor Imaging (DTI)
- Arterial Spin Labelling (ASL)
- Resting state functional MRI (rs-fMRI)

The advanced sequences may extend the scan time so the total MRI examination could be approx. 45 – 60 minutes.

If an individual participant has had an MRI to the specifications in the Core EPAD Scanning protocol within 12 months of the Visit 1 first assessment of the EPAD LCS then this scan can be provided for analysis for the Visit 1 baseline data.

3.4.5. Genetic Assessments

The primary genetic assessment will include APOE genotype. The samples will also be sequenced at low coverage (e.g. 2-5 times) in the University of Edinburgh. Current literature indicates that rare variants of strong genetic effect (APP, PSEN1&2) are too rare in the population to justify testing in the EPAD LCS. In addition, most of these rare mutations are observed in those with early onset AD and are unlikely therefore to be included in the EPAD LCS.

3.4.6. Other Measures

- *Date of birth – subject to local regulations*
- *Age*
- *Sex*
- *Ethnicity* (*Subject to local regulations)* as *categorized* into one of following groups:
  - Caucasian/white (includes people of Mediterranean, European, Hispanic, Middle Eastern origin)
  - Asian (includes people of Chinese, Indian, Pakistani, Bangladeshi, Japanese origin)
  - Black (includes people of African descent e.g. African American)
  - Combination of previous groups
  - Other
- *Education* as registered in number of years of formal education, as defined per country excluding short courses and internships in working/ learning program

- *Handedness*
- *Marital status*: married or cohabiting / widowed / divorced / single
- *Family history of AD* in number of family members of first degree with history compatible with AD
- *Body height* without shoes as recorded to the nearest cm
- *Body weight* as measured to the nearest 0.1 kg without wearing shoes or heavy clothing. Body weight and height are used to calculate BMI
- *Hip-waist circumference* as assessed to the nearest 0.1 cm
- *Medical history* (yes/no):
  - Stroke
  - Diabetes (type 1 or 2)
  - Hypertension
  - Hypercholesterolemia
  - Myocardial infarction
  - Chronic ischemic heart disease
  - Chronic obstructive pulmonary disease
  - Asthma
  - Depression
  - Rheumatoid arthritis
  - Any cancer
  - General anaesthesia after the age of 50 years
  - Head injury assessed with the Brain Injury Screening Questionnaire (BISQ[29])
  - Mild Cognitive Impairment
  - Other conditions (listed as free text)
- *Current medication*: name of drugs; treatment duration (<1year / 1-5years / >5years)
- *Lifestyle factors*:
  - Smoking: never / past / current
  - Alcohol consumption: units/week
  - Drug abuse/misuse: never / past / current; name of drug where applicable
  - Diet: Healthy Ageing through Internet Counselling in the Elderly (HATICE, www.hatice.eu) questionnaire
  - Physical activity, defined as leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating. Frequency will be assessed as: daily; 2-3 times a week; once a week; 2-3 times a month; a few times a year; or not at all[30]
  - Life events: brief questionnaire based on the Swedish National study on Aging and Care (SNAC, http://www.snac-k.se/) questionnaire

  - Self-rated health and self-rated fitness: Likert-type questions with response options very good / good / satisfactory / relatively poor / very poor [30]

- *Dementia diagnosed by the participant's physician:* yes/no; type of dementia; date of diagnosis

- *Mini-Mental Status Exam (MMSE)*. The MMSE is a 30-item mental status questionnaire that assesses a participant's mental status (orientation, memory, attention, language, visual-spatial abilities, and calculation). A total MMSE score is calculated by summing of all correct items out of a possible 30 points. The utility of MMSE, along with global indicators such as CDR, is principally as a clinical descriptor.[31] MMSE was included in the standard clinical assessment as a standard measure that is regularly used in studies and recognized by regulatory authorities.

- *Clinical Dementia Rating Scale (CDR)*. The CDR[32] is comprised of two separate semi-structured interviews one with the individual and another with a reliable collateral source (informant, i.e., partner, family member or relative, friend, or any other closely related individual) conducted by blinded independent, CDR certified Raters. During the interview, the clinician assesses the participant's current status in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) and rated accordingly using a 5-point scale (0 = no impairment, 0.5 = questionable impairment, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia, http://knightadrc.wustl.edu/cdr/aboutcdr.htm). Outcome measures of the CDR are a Global CDR score (derived from an algorithm developed by the Knight ADRC), the CDR sum of boxes (CDR-sb, the sum of all six domains), and a CDR rating for each domain.

- *Physical examination*, including e.g. neurological examination, blood pressure and pulse measurements.

- *Depression*, The Geriatric Depression Scale (GDS)[23,24] is a 30-item self-report assessment recorded by the clinician, used to identify depressive symptomatology in the elderly. The GDS questions are answered "yes" or "no". One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-9 as "normal", 10-19 as "mildly depressed", and 20-30 as "severely depressed". A diagnosis of clinical depression should not be based on GDS results alone. The test has well-established reliability and validity with 92% sensitivity and 89% specificity when evaluated against diagnostic criteria. Although a shorter version (15 items) has been validated, the longer version is more likely to have a normal distribution—hence better adapted for use as a dimensional scale—without reliance on theoretical clinical cut-off points. The larger range of items also permits a finer analysis by symptom cluster and not just overall score.

- *Anxiety*, The State-Trait Anxiety Inventory (STAI)[25] is a psychological inventory based on a 4-point Likert Scale consisting of 40 self-report questions. The STAI measures separately both state anxiety (fear, nervousness, discomfort and autonomic nervous system arousal induced by specific situations) and trait anxiety (chronic feelings of stress, worry, discomfort experienced on a day-to-day basis). Each type of anxiety has its own scale of 20 different questions on a score range from 20 to 80, with higher scores correlating with greater anxiety.

- *Sleep*, The Pittsburgh Sleep Quality Index[26] is a self-rated questionnaire that assesses sleep quality and disturbances over a one-month time interval. Nineteen items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and sleep-related daytime

dysfunction. The sum of scores for the seven components gives a global score. The index has adequate internal consistency and high retest reliability, with a diagnostic discriminability of 89.6% sensitivity and 86.5% specificity for good and poor sleepers.

Changes in depression, anxiety and sleep measures have been associated with both early biomarker change and cognitive dysfunction.

3.4.7. Biological Samples

- Blood samples will be collected at each annual visit (fasting overnight prior to sampling)
- Urine samples will be collected at each annual visit
- Saliva samples will be collected at each annual visit (refraining from caffeinated product prior to sampling)

Detailed instructions for the documentation, collection and management of the biological samples will be provided in a separate EPAD Sample Instruction Manual. Blood, Urine, Saliva and CSF samples will be collected annually in all EPAD LCS participants for potential future analyses of emerging AD biomarkers. All biological samples will be stored at University of Edinburgh, UK with reference to appropriate regulatory procedures.

3.4.8. Visit Windows

The requirements of the protocol may necessitate the participant attending the clinic on more than one occasions to complete the requirements of each Visit. For Visit 1 all assessments should be completed within 28 days of the first assessment of the visit. For all following visits, all assessments should be completed within ± 21 days of the planned visit date based on the start of the study, i.e. tethered to the first assessment of Visit 1. This guide provides a 42-day window for each visit, assessments that take place outside of these windows will be collected and included the analysis.

3.5. Study Completion or Withdrawal

The initial duration of EPAD LCS will be from April 2016 to December 2019, and extension of consent will be asked for prior to December 2019 assuming the EPAD LCS has funding to be maintained. Research participants will exit the EPAD LCS if:

- They withdraw consent at any time during the study
- They enter the EPAD PoC trial (after signing a separate Informed Consent Form). To allow adequate modelling and run-in data, research participants have to be followed for at least 6 months in the EPAD LCS before potential recruitment into the EPAD PoC trial
- They enter another clinical trial (continued participation in the parent cohort is expected)
- Due to investigator's decision, e.g. research participant considered as not contributing to the overall probability spectrum, safety reason or research participant not compliant with protocol procedures
- Sponsor's decision to stop the study

For research participants selected for the EPAD PoC trial, the first EPAD PoC trial visit will become the last EPAD LCS visit. Research participants who complete the EPAD PoC trial,

and still fulfil criteria for inclusion in EPAD LCS may return to EPAD LCS if they wish to at least 30 days after trial completion.

Any research participant who exits the EPAD LCS must be reported. Information about exiting EPAD LCS, date and reason (if given by the research participant) will be recorded. Also for these research participants, the investigator must complete the Case Report Form (CRF) including the clinical summary.

Alternative medical care for research participants exiting EPAD LCS is to be arranged by the TDC investigator if necessary. For those research participants who discontinued due to the occurrence of adverse events potentially related to study procedures, follow-up must be reported until the adverse event has abated, or until a stable situation has been reached, with findings being recorded in the eCRF.

4. STATISTICAL ANALYSIS METHODS

4.1. Determination of Sample Size

A constant sample size of approx. 6,000 research participants for the EPAD-LCS is considered sufficient for a readiness cohort that should provide approx. 1,500 research participants for the EPAD PoC trial. The EPAD-LCS sample size will be maintained constant through continuous recruitment from the PCs. Involvement of multiple PCs connected to EPAD Consortium members or outside EPAD will ensure that the PCs continue to provide the necessary number of research participants over time.

The estimated number of research participants to be entered in EPAD LCS from 2016 until end of 2019 is 4,500.

Strategies for motivation and engagement, as well as improving the research experience for participants will be developed in EPAD LCS, including proven techniques like newsletters, websites and telephone contact from the TDCs. There is a selection bias from PCs as it is likely that it will be those research participants who are most motivated who will agree to join the EPAD LCS with a clear intent of entering the EPAD PoC trial.

4.2. Research Participants Stratification

In EPAD LCS, it is important to recognize that participants may fall on a continuum of overall risk that is driven by various underlying dimensions or components. The three main components are comprised of (i) biomarker processes related to AD; (ii) processes related to cognition; and (iii) traditional risk factors (both genetic and environmental). These processes and risk factors may be continuous in nature and treating them as such rather than choosing to dichotomize or categorize may result in substantial gains in efficiency and avoidance of loss of information when deciding where and why a participant falls in the overall risk continuum spectrum, especially as participants with similar overall risk may have differing contributions from the various components/domains. Additionally, interrogating the underlying domains in addition to the overall predicted risk will allow participant stratification decisions to take account of the drivers and the needs related to the compounds to be investigated in the EPAD PoC trial.

As EPAD LCS participants are followed-up and longitudinal data accumulates, disease modelling analyses will be conducted taking into account longitudinal change in clinical profiles and biomarkers. The longitudinal modelling of cognitive outcomes and biomarkers will be used to characterise these processes dynamically and relate their trajectories to the probability of AD dementia development or other meaningful intermediate disease states. The modelling will identify and rank strata of sub-populations of different probability. Each sub-population will have a profile of biomarkers and other measurements, and this stratification will be used to identify potential treatments, the size of a potential treatment effect, and to guide the flow of research participants from the EPAD LCS into subsequent arms of the EPAD PoC trial.

4.3. Disease Modelling

The starting point of the modelling will be mixed-effects models. The complexity of the models investigated will subsequently increase and may ultimately focus on latent trajectory/class models and non-parametric Bayesian models using Gaussian processes. Analyses will involve turning models of longitudinal change in phenotype and in biomarkers to a probability prediction model and intermediate phenotype definition. Models of longitudinal change in phenotype and biomarkers will initially be developed separately. The models will then be combined in a sequential way to maximise probability prediction. The longitudinal and joint modelling of cognitive outcomes and biomarkers will be used in order to characterise these processes dynamically and relate their trajectories to future probability of onset of AD dementia.

Analyses of cognitive outcomes will be carried out at both the individual cognitive domain and composite score levels. The latter will be defined using the primary endpoint from the EPAD PoC trial. That is, the modelling at the composite score level in the EPAD LCS will be based on the RBANS Total Scale Index.

Robustness of models developed will be evaluated using cross-validation.

For modelling purposes, most of the work will be implemented using R, Stata and WinBUGS. More efficient multi-core computer code will also be used to speed up modelling efforts.

4.4. Interim Analyses

As data accrues in the EPAD LCS, interim analyses are planned every 6 months so as to: [1] inform selection algorithms for EPAD LCS; [2] provide updated information for improving selection into the EPAD PoC trial; and [3] provide updated disease models. On a monthly basis, the EPAD DOC sub-group will review the balance within the LCS *viz a viz* the probability risk spectrum. This will allow decisions to be made on sampling using the 3 mechanisms listed above. Moreover, the EPAD DOC sub-group will be aware of the virtual pipeline of drugs being developed by the CCSC and the needs of new trial appendices in terms of the required population needed for that appendix in terms of severity.

4.5. Handling of Missing Data

In order to most appropriately handle missing data, it will be important to make a concerted effort to collect the reasons why research participants missed visits or did not provide

information. Joint models (e.g. selection or pattern mixture models) or multiple imputation will be considered to deal with various different missing data mechanisms, such as missing due to death, missing due to participant withdrawal, intermittent "missingness" due to poor outcome etc. Sensitivity of results to the assumed type of missingness will be assessed.

5. SAFETY DATA AND COMPLAINT COLLECTION AND REPORTING

As EPAD LCS is not a Clinical Trial of Investigational Medicinal Product (CTIMP), only adverse events (AE) potentially related to EPAD LCS study procedures (e.g. lumbar puncture for CSF sampling) will be reported in the eCRF, and only serious adverse events (SAE) potentially related to EPAD LCS study procedures will be reported directly to the Sponsor. It should be noted that all procedures in the EPAD LCS protocol are approved medical procedures, and investigators in all participating TDCs are required to comply with local reporting routines for (S)AEs associated with such procedures. The nature of the AE and SAE reporting will change in the EPAD PoC trial, where research participants drawn from EPAD LCS into the EPAD PoC trial will be monitored according to the requirements of a CTIMP study.

5.1. Definitions and Classifications

In EPAD LCS, an AE is defined as any untoward medical occurrence in a research participant that according to the investigator's clinical judgement may have at least a possible relation to an EPAD LCS study procedure.

A SAE is any AE that: results in death of the EPAD LCS participant; is life-threatening; requires hospitalisation; or results in persistent or significant disability or incapacity. Life-threatening in the definition of an SAE refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Planned hospitalisations for reasons unrelated to EPAD LCS procedures do not meet SAE criteria.

In the case of findings concerning research participants that are not related to EPAD LCS procedures but are discovered during the course of EPAD LCS and have established clinical relevance (i.e. require additional monitoring or treatment), the investigator should take appropriate medical action (in emergency situations), or refer the research participant to the primary care physician. Such findings will not be considered (S)AEs and will not be recorded as such in the eCRF.

5.2. Identification, Assessment, Recording and Reporting of (S)AEs

(S)AEs will be recorded from the time a research participant undergoes the first EPAD LCS procedure until 30 days after the participant has completed the EPAD LCS (last procedure). Participants will be asked about the occurrence of (S)AEs at every EPAD LCS visit, and they will have the possibility to contact the local TDC if they experience (S)AEs following study procedures.

When an (S)AE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The investigator will then record all relevant information in the eCRF and on the SAE form (if the AE meets the criteria of serious). Information to be collected includes type of event, onset date,

investigator assessment of severity, date of resolution as well as treatment required, investigations needed and outcome. The severity assessment will be made by the investigator according to the following categories: mild (event easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities); moderate (event sufficiently discomforting to interfere with normal everyday activities); or severe (event that prevents normal everyday activities). The Chief investigator may not downgrade an event that has been assessed by an investigator as SAE, but can upgrade an AE to an SAE if appropriate.

Once the investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the Sponsor via the ACCORD Research Governance & QA Office immediately or within 24 hours. If the investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received. The SAE form will be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the investigator in the Investigator Site File (ISF).

SAEs will be followed-up by the investigator until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and / or referral to the general physician or a medical specialist.

ACCORD will inform Investigators at participating sites of any arising safety information.

5.3. Complaints related to EPAD LCS

Research participants who have concerns related to EPAD LCS will have the possibility to discuss them with the TDC staff either by phone or during study visits. Research participants who wish to make a complaint will be instructed to do this through the local complaints procedure as described in the Research Participant Information Sheet.

6. ETHICAL AND REGULATORY CONSIDERATIONS

The investigator must ensure that this study is conducted in full conformance with the principles of the "World Medical Association Declaration of Helsinki" (52nd WMA General Assembly, Edinburgh, Scotland, October 2000, including the Notes of Clarification as added in 2002, Washington, and 2004, Tokyo, and 2008, Seoul, and 2013, Fortaleza), International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and local legislation of the country in which the research is conducted, whichever affords the greater protection to the individual.

6.1. Independent Ethics Committee or Institutional Review Board

This protocol, the Research Participant Information Sheet, Study Partner Information Sheet, Study related information videos on EPAD and Amyloid, ICF for research participants, ICF

for study partners, and any material as requested, are submitted to the applicable Ethics Committee by the investigator according to local legislation. Approval from the Ethics Committee must be obtained before starting the study, and should be documented in a letter to the Sponsor and investigator specifying the date on which the ethics committee met and granted the approval, the composition of the ethics committee, and version and date of all submitted documents.

6.2. Informed Consent

As the EPAD project is extended over time and multi-staged, staged consent will be used as decision making model. Staged consent feeds relevant/indispensable/ 'material' information – bit by bit, extended over time - to research participants and study partners, and asks informed consent at every moment in which important decisions need to be made by research participants and study partners. Although informed consent is given for a specific stage of the EPAD journey, information about the 'totality of EPAD' will always and explicitly be made available to research participants and study partners. This includes information about the consequences and implications of participation, about the choices to be made in the next stages of the project, and about the future of EPAD.

a. *Process of contacting research participants from PCs*

EPAD will ensure that eligible research participants from PCs are appropriately approached. One condition for selecting PCs for EPAD LCS is existing consent from research participants for re-contact by PC teams, or possibility to obtain consent to re-contact by PC teams according to local rules and regulations. It is the responsibility of PIs of PCs to ensure that appropriate consent for re-contact by PC teams is in place, and PIs of PCs are required to confirm this to EPAD before they approach any research participants for EPAD LCS.

Initial direct contact with research participants potentially eligible for EPAD LCS will be established by PC teams designated by the PIs of the respective PCs. EPAD will not directly contact research participants at this stage. PC teams will inquire if research participants are interested in potential EPAD participation, and will provide information about EPAD (e.g. general letter about EPAD, EPAD LCS information sheet). Only after a positive response from the PC research participant, EPAD can contact that person. This positive response is not a consent to participate in EPAD, only a consent to being contacted by EPAD.

b. *Process of recruitment into EPAD LCS*

The initial contact of EPAD (i.e. EPAD LCS staff at the local TDC) with a potential research participant will include detailed oral and written information about EPAD LCS and the EPAD project (including the fact that EPAD is a public-private partnership and that potential commercial applications may result from research). Specific videos to assist learning on the concepts underpinning EPAD will also be used by the EPAD TDC teams to help potential research participants learn about the project. Research participants will have the opportunity to ask questions. Clear information will be provided on the relation between EPAD LCS and EPAD PoC trial, i.e. that participants are potentially entering on a trajectory that may involve trial participation later on, that informed consent for EPAD LCS does not imply consent for the EPAD PoC trial, that eligibility for EPAD LCS does not imply eligibility for the EPAD PoC trial, and that trial

participation is subject to a separate informed consent form. Potential EPAD LCS participants will also be informed that they may be deselected from EPAD LCS after the screening/baseline visit. It will additionally be made clear that participants can continue to be involved in the PCs, and it is possible to withdraw from EPAD LCS without being forced to withdraw from PCs.

Potential EPAD LCS participants will also be asked (either by PC teams or local TDC) if they can identify someone willing in principle to be their study partner, i.e. a relative or friend aged at least 18 years, who may or may not live together with the participant, and who is available either for face to face or telephone contact with the EPAD LCS staff at the local TDC. EPAD LCS will recruit participants with no or only minor impairments, and is therefore unlikely to include people who do not have the capacity to consent to or participate in EPAD LCS without support from a study partner. The study partner will thus primarily have the role of informant, and will not provide consent on behalf of the participant. Personal information about the research participant will not be disclosed to the study partner without the participant's consent. Study partners will also receive detailed information about EPAD LCS and the EPAD project, as well as on their role in EPAD LCS.

There is no obligation for the potential participant or study partner to make a decision during the initial contact with the local TDC, and no minimum or maximum time limits are defined for making this decision.

Prior to enrolment in EPAD LCS (i.e. the screening/baseline visit), written informed consent must be obtained from each research participant and study partner after adequate explanation of the aims, methods, source of funding, the anticipated benefits and potential risks of the study and the discomfort it may entail. Two copies of each Informed Consent Form are signed: one is given to the signer and one is retained in the Investigator Site File on site.

Consent procedures will make it clear that consent can be refused at any stage, and research participants and study partners can withdraw from the EPAD LCS at any time. During scheduled EPAD LCS visits the research participants and study partners will be informed about new developments within the EPAD project, and will be asked if they wish to continue participation. Special attention will be given at each visit to the decision-making capacity of the participant.

Consent for EPAD LCS can only be withdrawn by the research participant. A study partner or PI of the PC cannot withdraw consent on behalf of the participant. In addition, as per ICH-GCP guidelines, a research participant can be withdrawn from EPAD LCS by the EPAD investigators if they have any concerns about the research participant's ongoing involvement in the project. Investigators can additionally withdraw participants from EPAD LCS after the screening/baseline visit if they are considered to not contribute to the overall probability spectrum (detailed in section 3.3.2).

EPAD LCS research participants and study partners may withdraw consent at any time. The EPAD-LCS will make use of a tiered model for the withdrawal of consent, with the following choices:

a. not to be re-contacted by EPAD any further (this implies not to have new data collected), while allowing for the further use of already collected data;

b. not to be re-contacted by EPAD any further (this implies not to have new data collected), and to stop the further or future use of already collected data; or

c. not to be re-contacted by EPAD any further (this implies not to have new data collected), and to remove all personal data from EPAD.

If there are relevant changes within EPAD that could influence their decision to participate in EPAD in-between annual visits, participants and study partners are updated by EPAD. This can be done by regular newsletters or targeted contacts.

6.3. Potential Disclosure of Risk Information

Given that one of the objectives of EPAD LCS is disease modelling, EPAD LCS will have a probability-spectrum population covering the entire continuum of probability for AD dementia development. As accurate disease models covering the entire course of AD before dementia development are currently lacking, EPAD LCS will apply a policy of non-disclosure of overall probability. To avoid bias in clinical assessments that may affect disease-modelling work, investigators will be blinded to results from CSF, neuroimaging and genetic assessments. Some eligible research participants may be deselected after the screening/baseline visit if they do not contribute to the overall probability spectrum, i.e. deselected participants can fall anywhere on the probability spectrum from negligible to high probability as deselection is based entirely on the balance of the probability spectrum at any given time. Investigators will be blinded to which components or dimensions do not contribute to the overall probability spectrum in individual research participants.

Investigators cannot be blinded to results of cognitive tests and related clinical assessments. Such results may be disclosed to research participants because these assessments are routinely used in clinical practice, and a dementia diagnosis or CDR $\geq$ 1 represent exclusion criteria. EPAD LCS participants will be individuals with no or only minor impairments, but some of them may develop dementia during the course of the study. In the event that a research participant has CDR $\geq$ 1, or the investigator observes significant cognitive and functional decline suggestive of dementia development, the research participant will be referred to their primary care physician for appropriate monitoring and treatment.

The EPAD LCS information and consent process will carefully explain the uncertainties associated with biomarker testing, including the lack of clinical validation and the absence of a definite pathway between probability and disease state. EPAD LCS research participants will also be informed that, for some of them, a later invitation to participate in the EPAD PoC trial may mean learning about some of the components/dimensions in their probability status at the time of trial participation. Written and visual education materials will be provided to participants at LCS study recruitment to enable them to make an informed decision about whether they want to learn this information. Ongoing communication with research participants (described in section 6.6) will be used to address any stressful situations that may occur during recruitment and course of the study.

6.4. Procedures for Disclosing Incidental Findings

An incidental finding is a finding "concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study."[33] In EPAD LCS, incidental findings exclude

findings related to dementia or AD, as these are the variables of interest and are within the aims of the study. Although studies show that many research participants prefer incidental findings to be reported[34-36], participants are less interested in learning about findings of unclear clinical significance or that are not (very) relevant to health or reproductive issues.

Incidental findings may occur during the EPAD LCS assessments. Incidental findings with established clinical significance and requiring further monitoring and treatment will be disclosed to participants, and appropriate referrals to the participant's primary care or treating physician will be made. Potentially severe incidental findings will not be disclosed to participants without ensuring the provision of an acceptable level of care, support and guidance. Neuroimaging-related incidental findings will be managed according to the protocol established by the Rotterdam scan study or other locally used guidelines.

If the clinical significance of the finding is not fully clear, the investigator at the local TDC will consult a clinician with the relevant (oncological, neurological, neurosurgical, genetic etc.) expertise to confirm the finding or advise on the best course of action, in order to avoid false positives, concurrent costs and burdens of unnecessary follow-up and 'over-diagnosis'.

As part of the informed consent process, research participants will be asked to indicate their preferences with regard to the manner of communication of incidental findings and whether or not their primary care or treating physician should also be contacted in relation to such findings. The investigators at the local TDCs are responsible for the communication process to adhere to local or national legal and ethical requirements for the communication of incidental findings. Where possible, participants' preferences will be respected.

6.5. Privacy of Personal Data

EPAD LCS will ensure that data on research participants are appropriately managed, and research participant and study information are treated as confidential. The investigators at each TDCs should ensure that the research participant information will not be made publicly available. All research participant study records are identified by the research participant identification number to maintain research participants' confidentiality. Identification codes lists that link the research participants' names to the research participants' identification number must be stored in the Investigator Site File.

PCs are not required to share their data with EPAD. The data discovery process does not allow EPAD any access to individual-level data from PCs.

During the informed consent process, research participants will be asked if they consent to information from EPAD LCS assessments being returned to their respective PCs.

While EPAD LCS will have a policy of non-disclosure of overall probability of subsequent AD dementia, legal requirements may apply to returning personal data to participants in some countries. These requirements will be followed as appropriate.

6.6. Ongoing Communication with Research Participants

Communication between the EPAD team and research participants in EPAD LCS will be ongoing during recruitment and course of the study by phone and face-to-face meetings. Regular phone contact has been planned, and research participants will also have the

possibility to contact the EPAD team when needed. Participants' experiences of being in EPAD LCS, including potential effects on their mood and well-being will be assessed (e.g. clinical assessments include depressive symptoms, anxiety, sleep problems, self-rated health). Referrals to mental health professionals will be provided as needed, and appropriate support will be provided by the EPAD LCS teams at local TDCs. This should ensure that concerns that may emerge are explored and participants are supported in planning for the future. Additional support for family member's / study partners will be provided if research participants request it.

EPAD is also establishing a standing panel of research participants. The aims of this panel will be to provide feedback of the experience of study participation, to ensure that participant perspectives are represented in decision making about the future of the project and to advise local TDC and central EPAD LCS teams. The local panel will consist of 6-10 EPAD study participants at each TDC, and will meet at least twice annually. All EPAD participants at a TDC will be eligible to take part, and asked to join the panel for two years. A waiting list will be maintained of those who are interested if the panel is full. The panel meetings could be facilitated by a facilitator who is independent from the core EPAD TDC team. One member of the local panel will also be asked to attend the EPAD General Assembly, to contribute to discussions around study progress, governance and future plans.

Research participants will receive oral and written information during recruitment and in the course of EPAD LCS concerning communication of aggregate results from the study (e.g. newsletter, EPAD website where scientific publications will be listed and lay summaries posted).

6.7. Insurance and Incentives/Compensation for Research Participants

The Sponsor (University of Edinburgh) is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University of Edinburgh and collaborators. The University of Edinburgh has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University of Edinburgh.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

No financial compensation will be provided to research participants for participating in EPAD LCS, although out of pocket travel expenses will be covered and meals/refreshments provided as necessary.

7. STUDY ADMINISTRATION

7.1. Changes to the Protocol

Any changes and/or amendments to this protocol, will be prepared by the Sponsor. Protocol amendments will be submitted to the IEC/IRB in accordance with local regulatory requirements. Approval from the IEC/IRB must be obtained, before any implementation of changes, except for changes necessary to eliminate an immediate hazard to research participants. Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Sponsor and Chief Investigator.

Amendments to the protocol and associated documentation must be submitted in writing for appropriate ethical review and any additional local approval required. All amendments must receive requisite approvals prior to implementation.

7.2. Protocol Violations and Deviations

The investigator should document and explain any protocol violations. The investigator should promptly report any violations that might impact participant safety and data integrity to the Sponsor and to the IEC/IRB in accordance with established IEC/IRB policies and procedures.

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted for relevant approvals as detailed in section 8.1.

Protocol deviations will be recorded in a Protocol Deviation Log. Visit window deviations from the protocol guidance, or a single missed lumbar puncture sample will not be recorded as protocol deviations. Logs will be submitted to the Sponsor every 6 months by email to EPAD_LCS_TMF@ed.ac.uk. Instructions will be provided by the EPAD Clinical Trial Administrator.

Protocol violations will be reported to the Sponsor within 3 days of becoming aware of the violation. The relevant Protocol Violation Form must be used.

Completed logs and/or forms should be transmitted to the Sponsor by fax (+44 (0)131 242 9447) or email (researchgovernance@ed.ac.uk) and a copy sent to EPAD_LCS_TMF@ed.ac.uk.

7.3. Research Participants Identification and Enrolment

Independent Ethics Committee (IEC) or Institutional Review Board (IRB):

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the informed consent and all other forms of subject information related to the study

(e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to any activity with research participants at a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to the Sponsor

Ethical Conduct of the Study:

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

7.4. Source Documentation

Source documents (paper or electronic) are those in which research participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office chart, laboratory notes, memoranda, Participant Reported Outcomes, study partner reported outcomes, evaluation checklists, pharmacy dispensing record, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

An Investigator Site File will be held by the investigator, for retention of all study related documentation. A Delegation Log will be maintained by the investigator detailing all persons at the TDC involved in the LCS including the start and finish dates and details of the activities delegated to each person. The Delegation Log will be kept up to date and stored in the Trial Master File.

Before study initiation, data to be entered directly into the eCRFs (i.e. no prior written or electronic record of the data) and considered source data should be defined in the Source Data Agreement form.

The participating investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents as requested.

Informed Consent:

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved Informed Consent Form must be obtained from the research participant or their legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the research participant must be explained to them (or their legally authorized representative). The research participant must be given sufficient time to consider whether to participate in the study.

A copy of the signed and dated ICF must be given to the research participant, caregiver and/or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the research participant's medical record.

7.5. Case Report Form Completion

All CRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Principle Investigator or by medical qualified designee.

Case Report Forms (CRF) must be completed for each research participant enrolled in this study. These forms will be used to transmit information collected during the study to the EPAD consortium and designees and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by Quintiles and will be maintained in the Trial Master File at Quintiles.

The investigator will document subject data in his/her own subject files. These research participant files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by personnel from the EPAD LCS Clinical Research Organisation (CRO) Quintiles. EPAD consortium (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

7.6. Data Quality Control

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Quintiles will be responsible for the data management of this study, including quality check of the data. Data entered manually will be collected via electronic data capture (EDC) using eCRFs. Sites will be responsible for data entry into the EDC system. In the case of discrepant data, Quintiles will request data clarification from the sites, which thereby will resolve electronically in the EDC system.

Quintiles will produce a Data Quality Plan, which describes the quality checking to be performed on the data. External vendor data will be sent directly to Quintiles, using their standard procedures to handle and process the electronic transfer of these data.

The eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Quintiles and records retention for the study data will be consistent with their standard procedures. Data from the Quintiles Database will be sent on a regular basis to the Analytical Database hosted by Aridhia. Aridhia is a specialist company partner within EPAD and they will provide an analytical database solution for disease modelling work and assisting EPAD DOC with the data and summary data/reports for the balancing of the EPAD LCS.

7.7. Record Retention and Archiving

Records and documents pertaining to the conduct of this study, including eCRFs, ICFs, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study. Or for length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party, or moving them to another location.

7.8. Monitoring

The Sponsor's Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

Study monitors from Quintiles will perform ongoing source data verification to confirm that critical protocol data (i.e. source data) entered into the eCRFs, by authorized site personnel are accurate, complete and variable from source documents.

To facilitate source data verification, the investigator and institutions must provide the Sponsor, or associated partner (such as a CRO), direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IEC/IRB review. The investigator site must also allow inspection by applicable health authorities.

This trial will be monitored in accordance with the ICH GCP (ICH Topic E6, 1996). The site Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed CRFs and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

7.9. On-Site Audits

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participant's medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IECs/IRBs to inspect facilities and records relevant to this study.

7.10. Study Completion/Termination

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and Sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and the Sponsor. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to the Sponsor or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify the Sponsor to arrange alternative archiving options.

The Sponsor will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

7.11. Use of Information

All results from this study will be owned by the University of Edinburgh (UoE). Only UoE can publish these and when doing so needs to comply with the publication approval procedure in the EPAD Project Agreement.

8. REFERENCES

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LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Neither the participating physician nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor, and will be reviewed and approved in accordance with local regulations (see Section 7.1).

There are; 1 amendments to this protocol.

For all protocol amendments, include the standard protocol amendment table below to indicate the number and date of each amendment together with the changes and rationale for each change.
An example table is provided below;
Delete all the text below for initial protocols, but retain the heading and standard text above.

Details of the original protocol and amendments are provided below:

Protocol Version	Issue Date
Final Version 2.2	13 January 2016
Final Version 3.0	28 February 2017

Amendments are listed beginning with the most recent amendment.

Final Version 3.0 28 February 2017

The overall reason for the amendment: Correcting administrative errors in the protocol.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Applicable Section(s)	Description of Change(s)
Protocol Synopsis	Study objectives
	Study Diagram
	Study Description
	Recruitment Strategy and Procedures
	Selection of Parameters within EPAD LCS
	Exclusion Criteria
	Main Outcomes
	Exploratory Outcomes
	Other Assessments
List of Abbreviations	List of Abbreviations
Table of contents	Table of Contents
1.2	Overall Rationale for EPAD LCS
2	Objectives
3.1	Study Design and Rationale
3.2.1	Flow of Research Participants from PCs to EPAD LCS
3.2.2	Selection Process

Applicable Section(s)	Description of Change(s)
3.3.	EPAD LCS Study Population
3.3.1	Eligibility Criteria
3.3.2	Exclusion Criteria
3.3.3	Role of the Balancing Committee (BC) and Algorithm Running Committee (ARC)
3.4.1	Cognitive Outcomes
3.4.2	Other Clinical Outcomes
3.4.3	CSF Biomarker Outcomes
3.4.4	Neuroimaging Outcomes
3.4.6	Other Assessments
3.4.7	Biological Samples
3.4.8	Visit Windows
3.5	Study Completion or Withdrawal
4.1	Determination of Sample Size
4.3	Disease Modelling
4.4	Interim Analyses
5.2	Identification, Assessment, Recording and Reporting of (S)AEs
6.	Ethical and Regulatory Considerations
6.1	Independent Ethics Committee or Institutional Review Board
6.2	Informed Consent
6.3	Potential Disclosure of Risk Information
6.6	Ongoing Communication with Research Participants
6.7	Insurance and Incentives/Compensation for Research Participants
7.1	Changes to the Protocol
7.2	Protocol Violations and Deviations
7.4	Source Documentation
7.5	Case Report Form Completion
8. References	References
List of Attachments	List of Attachments
List of In-text Tables and Figures	List of In-text Tables and Figures
Protocol Amendments	Protocol Amendments
Data Collection Schedule	Data Collection Schedule

Applicable Section(s)	Description of Change(s)
Rationale: Correcting administrative errors in the protocol.	
Study Objectives	Changed wording of text regarding Study objectives
Study Diagram	Minor change to diagram to include research participants not recruited through a PC
Study Description	Added sentence regarding recruitment of participants who contact TDC's directly Minor change to the wording of research participants recruited from PC's
Recruitment Strategy and Procedures	Added a sentence regarding research participants who contact the TDC's directly without a PC Minor change to the wording of research participants recruited from PC's
Selection of Parameters within EPAD LCS	Additional sentence to include RBANS Total Scale Index Score
Exclusion Criteria	Deleted one criteria relating to the overall probability section Changed wording regarding exclusion due to Presenilin Changed the wording regarding medical conditions which might make the subject's participation in a drug trial unsafe. Changed previous re-vascularisation procedures from within 1 year to 6 months Added Investigator opinion of effect of intracranial pathology on cognition.
Main Outcomes	Divided into two sections; Primary Outcomes, and Secondary Outcomes Additional wording and footnote to describe RBANS total composite score as primary cognitive outcome Moved Secondary CSF Biomarker, and Neuroimaging outcomes into Secondary outcomes section Moved three cognitive outcomes from the exploratory outcomes to the secondary outcomes section with corrected test names and test owner names
Exploratory Outcomes	Added extra sub-heading for Cognitive Outcomes in secondary outcomes section Corrected owner of Four Mountains Test Changed description of Neuroimaging outcomes
Other Assessments	Changed name of section to Other Measures Moved GDS, STAI and the Pittsburgh Sleep Quality Index into this section from the Exploratory section Moved Vascular Burden from the Main Outcome section into this section
List of Abbreviations	Added four additional abbreviations to the list Deleted NART from the list
Table of Contents	Added section 3.3.3 Role of the Balancing Committee (BC) & Algorithm Running Committee (ARC) Changed the heading of section 3.4.2 from Other Clinical Outcomes to Other Clinical Outcome Assessments (COA)s Changed the heading of section 3.4.6 from Outcome Assessments to Outcome Measures Updates to page numbers
1.2	Minor changes to the wording of two sentences regarding recruitment from PC's Additional two sentences to describe contact of participants out with a PC Minor grammar correction Additional sentence to describe recruitment of participants out with a PC Changed the wording regarding extension of consent
2	Changed wording regarding point 4 of the objectives list
3.1	Change to figure 1 to include recruitment from clinics Changed the figure title to reflect inclusion of recruitment from clinics
3.2.1	Minor change to the wording of research participants recruited from PC's Additional two sentences regarding recruitment of participants out with a PC
3.2.2	Changed wording from the EPAD Data Oversight Committee to the Balancing Committee (BC)
3.3.	Minor Grammar correction
3.3.1	Minor change in wording of criterion 2 Changed formatting from bullet points to numbers

Applicable Section(s)	Description of Change(s)
3.3.2	Changed formatting from bullet points to numbers Changed wording regarding exclusion due to Presenilin / APP mutation Deletion of the wording for UBACC Minor spelling correction Deleted exclusion criterion "Deemed as not contributing to the overall probability spectrum Changed the wording regarding medical conditions which might make the subject's participation in a drug trial unsafe. Changed previous re-vascularisation procedures from within 1 year to 6 months Added Investigator opinion of effect of intracranial pathology on cognition.
3.3.3	Created section 3.3.3 Role of the Balancing Committee (BC) & Algorithm Running Committee (ARC) title. Added text to explain the involvement of the Balancing Committee in selection/deselection of participants
3.4.1	Addition of footnote in table 2 Deleted a sentence regarding primary and secondary collection measures Additional paragraph to describe primary outcome measures Additional paragraph to describe secondary and exploratory outcome measures Additional paragraph to explain compliance of computerised tests with GCP Changed test name from List Learning to List Learning/ Recall Additional wording and sentence to describe List Learning/ Recall test procedure Changed wording to describe Line Orientation task procedure Addition of category examples in the Semantic Fluency task procedure description Corrected description of Digit Span procedure Corrected the description of the RBANS Coding task Corrected the name of the Dot Counting task test owner Corrected the name of the Flanker task test owner Minor change to Flanker task description Changed test name from Name-Face Pairs to Favourites in table 2 Changed test name from Name-Face Pairs to Favourites in text heading Changed wording in the Name-Face Pairs (Favourites) paragraph Corrected the name of the Four Mountains task test owner Changed the order of tests to match Table 2
3.4.2	Changed the title of the section to Other Clinical Outcome Assessments (COAs) Added text to specify that The Amsterdam Instrumental Activities of Daily Living Questionnaire is recorded by a clinician Changed the wording of clinical outcomes to COAs Removed, GDS, STAI and the Pittsburgh Sleep Quality index to section 3.4.6 Additional sentence regarding frequency of COA's
3.4.3	Minor change to the name of the central lab Changed the duration of prior CSF sample from 6months to 12 months
3.4.4	Deletion of table 4 – Neuroimaging Assessments and Outcomes Changed location of outcomes from table 4 into the main text Changed wording of exploratory outcomes Additional section added to outcomes 'Other Measures' Moved Vascular burden from secondary outcomes to other measures Deletion of sentence referring to Structural and Functional imaging modalities Additional section explaining Core and Advanced image acquisition Change of Structural Imaging section to Core MRI Imaging Additional two sentences to explain why the Core examinations are performed Deletion of a sentence referring to anatomic 3D- T1, 3D FLAIR, 2D-T2 and 2D and 3D-SWI and their purpose Minor change to the core MRI time Deletion of DTI and ADNI descriptions Addition of Advanced MRI Imaging section, including type and timing Deletion of Functional Imaging section

Applicable Section(s)	Description of Change(s)
	Addition of text to describe when a previous MRI scan can be used for EPAD LCS baseline
3.4.6	Changed the tile of the heading from Other Assessments to Other Measures Addition of instruction for Date of birth collection Added Age Added instruction to Ethnicity collection Added 'Handedness' to Medical History section Added 'Mild Cognitive Impairment' to Medical History section Deleted a sentence referring to CDR in MMSE Added text to CDR Rater to indicate that they are blinded, independent Raters Moved the Depression, Anxiety, and Sleep measures into this section Added text to specify that the GDS is recorded by a clinician
3.4.7	Changed naming of Laboratory Manual to EPAD Sample Instruction Manual Minor change to wording of instructions within laboratory manual
3.4.8	Changed the visit window for follow up visits from ±14 to ±21 days Changed the 28 day visit window for follow up visits from 28 days to 42.
3.5	Minor grammar corrections Changed the wording regarding timing of extension of consent
4.1	Changed the estimated number of participants to be recruited by the end of 2019 Deleted the assumptions
4.3	Changed the description of the analysis of cognitive outcomes
4.4	Minor change to the wording of aim 1 of the interim analyses
5.2	Minor grammar correction
6.	Deletion of reference to cohort studies
6.1	Addition of EPAD and Amyloid information videos
6.2	Minor grammar correction Addition of the word 'Form'
6.3	Addition of a sentence to describe educational materials for disclosure Changed reference to section 7.6 to section 6.6
6.6	Additional paragraph to explain the EPAD Participant panel Minor grammar correction x2 Addition of lay summaries to the list of oral and written information participants will receive
6.7	Minor grammar correction
7.1	Minor grammar correction
7.2	Additional instruction for the submission of protocol deviations and violations
7.4	Changed the name of the file held by the investigator on site Minor grammar correction
7.5	Minor grammar correction Minor addition to clarify type of investigator
8. References	Deletion of reference 32 and subsequent renaming of 33-37 Change in location of reference 15 and subsequent renaming of references 16-21 Additional Reference added
List of Attachments	Additional attachments to include protocol amendment
List of In-Text Tables and Figures	Deleted Tables three and four Updated page numbers Minor change to wording of Figure 1.
Protocol Amendments	Addition of Amendment
Data Collection Schedule	Changed test name from Name-Face Pairs to Favourites (Delay, Learning and Recognition) Minor spelling changes Minor grammar corrections Corrected order of procedures to match the protocol Added BISQ with Medical History Added BISQ, HATICE and SNAC to the acronym list Deleted NART, FLAIR, SWI, DTI, rs-fMRI and ASL from the acronym list Removal of the following biomarkers; Structural MRI protocol (DTI),

Applicable Section(s)	Description of Change(s)
	Functional MRI Imaging Protocol (ASL), Functional MRI Imaging Protocol (rs-fMRI) Additional Biomarker added; Advanced MRI sequences Change to the name of the standard structural MRI protocol biomarker to Core MRI sequences Corrected test owner names for; Dot Counting, Flanker, Four Mountains Task Changed the visit windows for follow up visits from ±14 to ±21 days

DATA COLLECTION SCHEDULE

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
Eligibility criteria	X	X	X	X	X	X
Research participant consent[b]	X					
Cognitive outcomes (ENE battery)						
RBANS	X	X	X	X	X	X
Dot Counting (NIH EXAMINER)	X	X	X	X	X	X
Flanker (NIH EXAMINER)	X	X	X	X	X	X
Favourites (Delay, Learning & Recognition) (University of California, San Francisco)	X	X	X	X	X	X
Four Mountains Task (Cambridge University)	X	X	X	X	X	X
Virtual Reality Supermarket Trolley (University College London)	X	X	X	X	X	X
Clinical outcomes						
GDS	X		X	X	X	X
STAI	X		X	X	X	X
Pittsburgh Sleep Quality Index	X		X	X	X	X
Amsterdam Instrumental Activities of Daily Living Questionnaire	X		X	X	X	X
Biomarkers						
Core MRI sequences	X		X	X	X	X
Advanced MRI sequences	X (subset)		X (subset)	X (subset)	X (subset)	X (subset)
CSF Sampling	X		X	X	X	X
Blood, urine & saliva sampling	X		X	X	X	X
Other assessments						
Socio-demographics (date of birth, sex, ethnicity, education, marital status)	X					
Family history of AD	X					

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
Height	X					
Weight, hip-waist circumference	X		X	X	X	X
Medical history inc. BISQ	X		X	X	X	X
Current medication	X	X	X	X	X	X
Lifestyle factors inc. HATICE & SNAC	X		X	X	X	X
Dementia diagnosed by the participant's physician	X	X	X	X	X	X
MMSE	X		X	X	X	X
CDR	X	X	X	X	X	X
Physical exam	X		X	X	X	X
Blood pressure	X		X	X	X	X
Ongoing research participant safety assessment						
Adverse events[c]	X	X	X	X	X	X

[a] Visit assessments will be completed within a 28-day window of the planned visit date tethered to the first assessment of Visit 1

[b] Before the start of data collection in this study, all research participants must sign a participation agreement/Informed Consent Form (ICF) allowing data collection and source data verification in accordance with local requirements.

[c] All adverse events deemed by clinical judgement to be at least possibly related to EPAD LCS study procedures are to be recorded in the CRF. Adverse event collection should start with the first EPAD LCS procedure and will apply to all adverse events that occur within 30 days after a research participant's last study visit/procedure.
When an enrolled participant completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s).

ENE - EPAD Neuropsychological Examination; RBANS - Repeatable Battery for the Assessment of Neuropsychological Status; NIH EXAMINER - National Institutes of Health-Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research; GDS - Geriatric Depression Scale; STAI - State-Trait Anxiety Inventory; MRI - Magnetic Resonance Imaging; CSF - Cerebrospinal fluid; AD - Alzheimer's disease; Hatice – Healthy Ageing through Internet Counselling in the Elderly; SNAC – Swedish National study on Aging and Care; BISQ – Brain Injury Screening Questionnaire; CDR - Clinical Dementia Rating; MMSE - Mini Mental State Exam

Attachment 1: EPAD LCS Participant Information Sheet

[Insert local details]

Information sheet for participants:

European Prevention of Alzheimer's Dementia Longitudinal Cohort Study

(EPAD LCS)

Research Ethics Committee Reference:

You are being invited to take part in a research study.
Please take time to read the following information carefully.
Discuss with friends, relatives or your doctor if you wish.

Who are we?

Principal Investigator: [Insert local details]

Contact details: [Insert local details]

Telephone: [Insert local details]

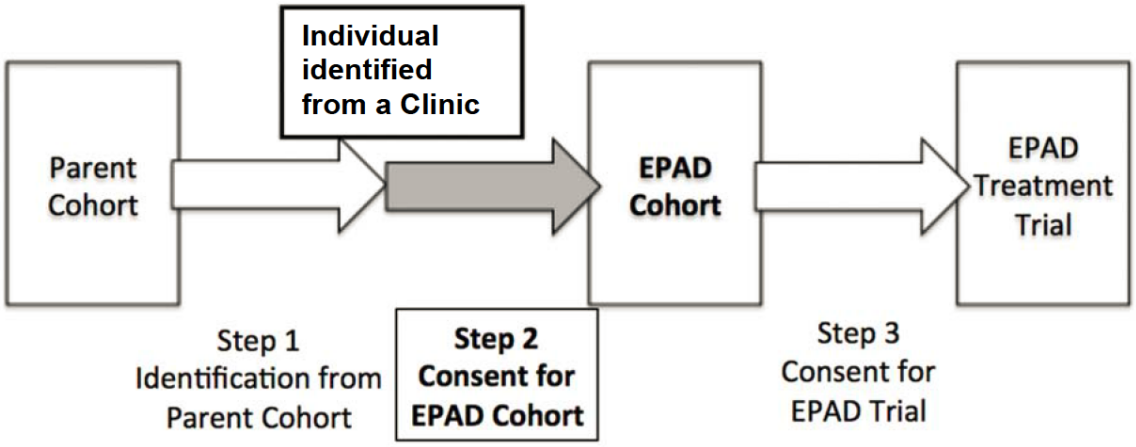
What is EPAD?

The European Prevention of Alzheimer's Dementia (EPAD) Project is an international study on-going in several European countries. The study is managed and sponsored by the University of Edinburgh in Scotland, UK.

The aims of EPAD are

1. To learn and understand better the factors involved in developing Alzheimer's dementia.
2. To develop new treatments more quickly which are hoped to prevent Alzheimer's dementia.

The project has several parts. One of the main parts is called the EPAD Longitudinal Cohort Study (EPAD LCS) which we will refer to throughout this document for clarity as 'EPAD Cohort' and this is what you are being invited to join. There are 3 main steps in being part of EPAD shown in the diagram below.



The consent we are asking for in this document is 'Step 2' above to join the EPAD Cohort.

A cohort is a group of people who are observed over time for changes in various factors. The main reasons for the EPAD cohort are to help us understand more about what happens to people who might develop Alzheimer's dementia. Some people in the EPAD Cohort will develop Alzheimer's dementia and others will not. It is important that we have a wide range of people with different risks of Alzheimer's dementia in the EPAD Cohort. The second reason for the cohort is to find people more quickly who would be suitable to be approached for the EPAD treatment trials of many new treatments expected to prevent dementia. We call this a 'readiness cohort' because the people are 'ready' to join the trial. It is important to highlight and emphasise that by agreeing to enter the EPAD Cohort you are not consenting or committing to be in the EPAD trial; if you are invited to participate in a trial evaluating a treatment that would require subsequent consent. However, you need to be comfortable with the idea that you may be considered for joining the trial in the future. If you never want to be involved in treatment studies, you should not consent to take part in the EPAD Cohort.

We are now asking you if you are interested to participate in the EPAD Cohort.

What is the difference between Alzheimer's disease and Alzheimer's dementia?

Throughout this information sheet we use the terms Alzheimer's disease and Alzheimer's dementia. These are not the same things. When we talk about Alzheimer's disease we mean

the changes in the brain that can lead to Alzheimer's dementia. When we talk about Alzheimer's dementia we talk about the clinical syndrome where memory and thinking are impaired to the extent that day-to-day functioning of the individual is affected.

Why are we doing this research?

Changes in the brain may precede symptoms of Alzheimer's dementia by many years if not decades. Such changes suggest that a very early Alzheimer's disease process has started well before people start developing the typical symptoms of Alzheimer's dementia like memory loss. If this is the case, then we may be able to identify Alzheimer's disease at a very early stage, and prevent or delay the disease from developing into dementia. However, with current knowledge doctors can only diagnose Alzheimer's disease in people who already have dementia or are very close to developing dementia. Available treatments are helpful but cannot fully stop the disease from progressing. We hope to be able to identify Alzheimer's disease before the occurrence of symptoms when in theory treatments are most likely to be successful in preventing further spread of the disease in the brain.

The brain changes as we age, even in people who never develop dementia. Such brain changes may be seen on brain scans, in the spinal fluid or in the blood. It is still not fully clear what different brain changes mean for the longer-term likelihood of developing Alzheimer's dementia. We suspect that certain interventions will work best in people who share a small number of characteristics rather than everyone at risk of developing Alzheimer's dementia. In the EPAD Cohort we will be able to match the people most likely to respond to a particular treatment and invite them to enter that treatment trial. In the EPAD trial we will test whether that proved to be the case and if not we can maybe find people in the EPAD Cohort who we have learnt are most likely to benefit. This is one of the main reasons why the EPAD Cohort and EPAD Trial are run together in the same research programme.

If you are invited to join the EPAD trial you may learn about your risk of developing Alzheimer's Dementia, and we would like you to consider this before you decide to join EPAD. The videos and leaflet accompanying this information sheet tell you more about what this would mean. If we do ask you later about participating in the EPAD Trial, you will be asked if you wish to consent to participate. We would like to re-emphasise that participating in the EPAD Cohort does not automatically mean you will be eligible for the EPAD trial and there is a possibility that you will never be invited to enter the EPAD trial. However, if you currently have no interest in being part of the EPAD trial you should not consent to being part of the EPAD Cohort.

Why have I been approached?

You have been approached because

1. You expressed interest in participating in research studies
2. You are over 50 years old
3. You do not suffer from dementia

You may already be part of a research Cohort. The EPAD project has been collaborating with the academic leaders of the cohort study you are already in. From the data already held on you we discovered that you might be suitable for the EPAD Cohort. That is why the Principal Investigator or one of their researchers contacted you to speak to us about the EPAD Project.

You also may have been identified by the clinician seeing you about memory complaints when you were seen in their clinic, and they will have spoken to you about the EPAD Project. With your agreement they passed your details to this EPAD Research Centre.

To find out which factors are good predictors of the risk of Alzheimer's dementia, we need a broad range of people with different likelihoods of developing Alzheimer's dementia. We do not know in advance who will develop dementia and who will not. This means we need to include in the EPAD Cohort people who are possibly at high risk, at low risk and everywhere in between. As we follow all the people in the EPAD Cohort in the years ahead, we will learn which factors predict risk. Only by including such a wide range of people can we calculate who is most at risk for development of Alzheimer's dementia.

Do I have to take part?

No. Your participation in this study is entirely voluntary. It is up to you to decide whether or not you take part,

Can I withdraw from the study?

You are free to withdraw your consent and withdraw from the study at any time after you have signed the consent form and will not be asked to justify your decision. Whatever you decide it won't affect any health or social care that you or anyone you care for receives.

What will happen to me if I would like to take part?

1. The EPAD study team will be in contact with you either by phone, e-mail or letter (depending on what suits you best and what you have told the investigator from your parent cohort or your treating clinician) to answer any questions you may have and to see whether you would like to join the study.
2. You will also be asked to identify a relative or friend who knows you well, who would be willing to be your study partner. Your study partner will be asked to answer some standard questionnaires about daily life/activities on rating scales designed to be completed by an informant. She/he would need to come to the research centre to answer the questionnaires. If this is not possible, it is important that we can talk to your study partner by phone. Personal information you give us as part of the study will not be shared or disclosed to your study partner, without your consent.
3. Once you have read through the information sheet and information about Alzheimer's risk, and watched the associated EPAD videos then the research team will be able to arrange your study visits and start undertaking the study procedures listed later in this document. Your study partner will also receive an information sheet.
4. On the day of your visit one of the senior researchers will discuss the information with you again, and answer any questions you might have.
5. You will then be asked if you wish to participate in the EPAD LCS, and you will be asked to sign a consent form. One of the senior researchers in the research centre will then countersign the form. You will be asked to stay in the research centre to complete your first visit which is called your 'screening visit'. This is where the researchers can double check that you are suitable to enter the EPAD Cohort.

How many study visits do I need to make?

The current study will end in December 2019, as this is when the funding will run out; however, we plan to get additional funding to keep the study going indefinitely. You are free to withdraw consent at any time but if you do not we will ask you to reconsent every 4 years. After the initial study visit and assessments, additional visits will be planned for you after 6 months, 1 year, 2 years, 3 years, and 4 years. We need to do follow up visits to make sure that your health hasn't changed and also to be able to measure changes in certain tests that may or may not be related to Alzheimer's disease.

The duration of your participation in the EPAD Cohort Study may vary and depends upon four factors:

1. Whether you wish to continue participating in the study.
2. Whether you develop any health conditions that may affect your participation in the study. If you do develop dementia during the course of the EPAD Cohort Study, you will not be part of the EPAD Cohort any longer but you will be offered the chance to continue to be followed-up by the EPAD research team and have all the same tests undertaken. Your own doctor and the EPAD research team can discuss these with you if the need arises and if you would welcome this. However, if you do develop dementia, you would no longer be eligible for the EPAD trial as this is aiming to prevent dementia. There may be other studies though that you may be suitable for and your own doctor and EPAD researchers can discuss these with you. Any new study would require you to give separate consent.
3. The EPAD Cohort Study is running across Europe and will involve several thousands of people. There may come a time when people at certain risk of developing Alzheimer's dementia are over-represented in the whole cohort. If this happens we would wish to stop following some participants after their Year 1 visit. Being asked to leave the EPAD Cohort study does not imply any specific risk for developing Alzheimer's dementia and your own research team will not know why you have been asked to leave either as they do not know your risk of getting Alzheimer's dementia. The decision to ask you to leave is made by people working centrally in EPAD who do not know you and have no means of identifying you from the data they are looking at.
4. If you are suitable or eligible for the EPAD trial then the EPAD Research Team will contact you. Eligible persons who later on decide and give separate consent to participate in the EPAD trial may return to EPAD LCS after the end of the trial if they wish to and provided that they are still eligible for EPAD LCS.

What will happen at the study visits?

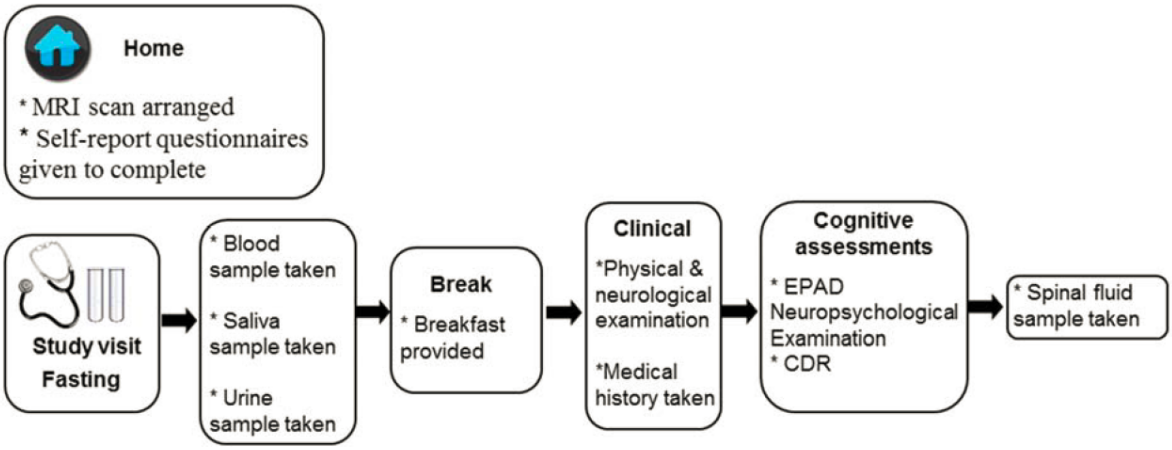
There are several assessments that are necessary. These can be spread over several visits to the research centre to make this as convenient for you as possible.

In the first instance, you will be required to attend the annual (Baseline, Year 1, Year 2, Year 3 and Year 4) study visits fasted so that fasting blood samples can be taken. You do not need to come in a fasting state to the 6-month visit.

On your arrival at the research centre for the first screening visit, you will have the opportunity to ask any further questions. Once you are happy with your involvement in the study, your consent form will be signed by you and countersigned by one of the research team. Once you have signed a consent form, you will then be asked to complete a number of forms and take part in interviews with the study doctor, nurse and psychologist. These forms

and interviews will gather details as specified below. As stated above, this can take place over one or several visits to the study site, to be agreed between you and the study team – though all data should ideally be collected within a 1-month period. It is important that your participation in this research does not inconvenience you more than is necessary and we will do everything we can to fit into your schedule and be as flexible as possible.

Below is a diagram detailing the activities that will be carried out on your annual study visit, although the activities at your visit may not be performed in the same order. Not all of the assessments will happen on the same day. Your EPAD Researchers will be able to tell you exactly when each activity will take place. All assessments listed are compulsory for participation in the EPAD Cohort study:



If during any of the testing we note any health issues, we will discuss these with you and provide help in planning potential next steps. In the EPAD Cohort study the doctors do not undertake a full and thorough physical examination so there is the potential that some health conditions may be missed. If we do though notice any problems, with your consent, then we may wish to contact with your primary care doctor or other relevant physician as is needed.

Study visit procedures

The assessments are divided into 4 main areas:

1. Brain Scans
2. Clinical and cognitive assessments,
3. Blood, Saliva, Spinal Fluid and Urine tests
4. Other assessments.

Brain scans

Magnetic Resonance Imaging (MRI) is an established, widely accepted medical way to look in detail at the structure of the brain. We can determine whether certain brain areas of interest are smaller than usual, or whether there is any evidence that blood supply to the brain isn't ideal. Brain activity can also be measured and this is called functional Magnetic Resonance Imaging (fMRI). MRI and fMRI are painless. However, you do need to lie still in the scanner for up to 80 minutes. Some people can find this claustrophobic. The scanner is also quite noisy, although you will be wearing ear protection. The scanners we will use and the radiographers who operate them are very experienced and very good at explaining all the procedures on the day and making sure that you are as relaxed as possible for the scan. Some people with metal implants or pacemakers cannot have an MRI scan. This will be checked

thoroughly before having a scan and will also be asked for when you enter the EPAD Cohort study specifically.

If the scan results show anything which are known to be clinically relevant that is they show there is an illness or problem that can be managed by you or your doctor to improve your health, then your study team will let you know and work with you on how best to follow up on these findings. This may involve discussion with your GP or other appropriate doctor.

The brain scan will be conducted annually while you participate in the study. At your first visit, if you have had an MRI scan in the previous year of suitable quality for EPAD, you may not need to undergo another scan as we may be able to use the previous results.

Clinical and Cognitive Tests

Physical examination and medical history

The examination will include measurement of your blood pressure, height, weight, hip and waist circumference. The study doctor will also do a full neurological (senses, power, coordination and reflexes) and cardiac examination.

You will also be asked to provide information about your medical history, including family history of dementia, and your current medication(s). We would also like your permission to contact your primary care doctor and other doctors you may be seeing for further medical information should this be required.

The physical examination will be conducted annually while you participate in the study.

Cognitive assessments

These will be undertaken using a computerised neuropsychological examination lasting about 2 hour assessing your reaction time, function, language skills, memory and attention. You can have a break between certain tests in this evaluation. These tests are all measures of cognition. All the tests are on an electronic tablet, which the research team will help you to use. Using tablets, to measure cognitive function has been shown to be a very accurate way of assessing cognition. The study psychologist or research nurse will provide clear instructions on how to complete the assessments. One of the tests needs your study partner to be interviewed too.

The cognitive tests will be conducted at the initial study visit, after six months, and then annually, while you participate in the study.

Blood, Saliva, Spinal Fluid and Urine Tests

We will look in 4 body fluids for Biomarkers and other evidence of changes or abnormalities that may be relevant for you or for the study itself. 'Biomarkers' are literally Biological Markers and we will use them to determine if some changes in the brains of people with Alzheimer's disease can be measured in blood, saliva, spinal fluid or urine. Below we list what we do with the samples. All samples will also be stored for future use. This means that we will be able to look at your samples in the future for genes or Biomarkers that future scientific developments may consider to be relevant. All your samples will be shipped to and stored in laboratories in the University of Edinburgh. EPAD has developed a 'Sample Access Committee', which will decide exactly what the samples are used for in the future. There may be occasions where samples are shipped to other laboratories elsewhere in the world for specific analyses. At the outset, some of the Spinal Fluid collected will be sent to the University of Gothenburg (Sweden) for analysis.

Blood sample

A blood sample (about 50ml) will be taken. We would like to take fasting blood samples, and therefore require that you come to your clinic visit fasted. We will ensure your blood sample is the first procedure to be completed and then provide you with some breakfast before continuing with the other assessments.

The blood sample will be stored to identify biomarkers, to undertake genetic analysis and to look at standard biochemical and haematological tests (your research team will be able to give you a full list of what these are), that will tell us more about your general health.

If any blood tests come back which are known to be clinically relevant that is they show there is an illness or problem that can be managed by you or your doctor to improve your health, then your study team will let you know and work with you on how best to follow up on these findings. This may involve discussion with your GP or other appropriate doctor.

The blood sample will be taken annually while you participate in the study.

Saliva sample

You will, according to the instructions of the study team at the research centre, be asked to provide one saliva sample during the visit (of about 1-2 ml), and take a set of samples home with you to take over a two day period. This can be used to look at Biomarkers especially hormones related to stress – for example cortisol – which are thought to be related to the risk of developing Alzheimer's dementia.

Prior to giving the saliva sample, you should not drink coffee, tea or other caffeinated drinks (such as Coca-Cola, Pepsi etc.), and you should not smoke or use tobacco. You will also be asked to rinse your mouth with water before giving the saliva sample.

The saliva sample will be taken annually while you participate in the study.

Spinal Fluid

Spinal fluid is collected via a procedure called a Lumbar Puncture. The spinal fluid connects with the spaces within and around the brain so is a very good source of information about what is happening in the brain. This is a commonly conducted test in both research and clinical practice in many parts of Europe in people with dementia or those with cognitive complaints but no dementia.

The procedure takes about 1 hour in total. You will normally be lying on your side, with your legs pulled up and your chin tucked in, but the procedure can also be carried out while you're seated and leaning forwards. Under local anaesthetic, a hollow needle is inserted in the lower part of your back and about 5 ml (about a teaspoon) of spinal fluid is collected. The lumbar puncture usually takes around 30-45 minutes to complete. After the procedure participants are asked to rest for approximately 30 minutes.

The spinal fluid sample will be taken annually, while you participate in the study. At your first visit, if you have had a Lumbar Puncture in the previous year you may not need to undergo another at this visit as we may be able to use your previous results.

Urine sample

You will, according to the instructions of the study team at the research centre, be asked to provide a urine sample at the clinic. These can be used to detect biomarkers as well as check on your general health, in particular for bladder or kidney disease.

The urine sample will be taken annually while you participate in the study.

Other Assessments

Self-report questionnaires

During the initial study visit we will provide you with a number of self-report questionnaires to be completed. You can complete the questionnaires during the study visit, or you can choose to take them home and complete them at your own pace. You will be provided with a pre-stamped and pre-labelled envelope for sending the completed questionnaires back to the study site by post.

All these questionnaires will be completed annually while you participate in the EPAD Cohort.

The self-report questionnaires include questions about lifestyle:

- Lifestyle – (e.g. marital status, education, alcohol and tobacco use, diet and physical activity. There is also a list of upsetting or stressful life events, and you will be asked if you have experienced any of these events in your life.

Other assessments using the EPAD Tablet

All the questionnaires below will be completed annually while you participate in the EPAD Cohort

- Symptoms of anxiety - these are questions meant to assess your level of anxiety.
- Assessment of sleep quality - you will be asked questions about the quality of your sleep during the past month.
- Symptoms of depression - you will be asked questions to determine if you experience any depressive feelings or behaviours.

In summary:

Not all assessments have to be done on the same day, but ideally they need to be done within a maximum of one month time period for the screening visit and 6 weeks for all follow up visits. The study team will contact you in advance to plan the visits and we will take your availability into account. You will also have the possibility to contact the study team by phone or email if you have any questions. We will do all we can to work around your schedule to minimise the inconvenience that being part of this study may cause.

- The visit to the research centre could take up to about 5 hours in total.
- The brain scan can take between 30-60 minutes. Including the time to get ready for the scan, you will be expected to be at the imaging facility for a total visit time of 2 hours.
- While you participate in the study, the same tests will be repeated every year after your initial study visit. Cognitive assessments will additionally be conducted 6 months after the initial study visit.
- If an intervention study is started from within the EPAD programme, which we think you may be suitable for, we will also contact you. This may be before your 1-year follow up visit but NOT before your 6-month visit.
- We would like to re-emphasise that if any of the tests we do show anything which shows there is an illness or problem that can be managed by you or your doctor to improve your health, then your study team will let you know and work with you on how best to follow up on these findings. This may involve discussion with your GP or

other appropriate doctor. Such findings we would refer to as being 'clinically relevant'.

Will I be made aware of any test results?

We have a duty of care to share with you the results of any investigation if they are known to be abnormal and clinically relevant. However, we do not yet know if some of the data we are gathering can be used as a predictor of dementia so, by definition, we are not sure what represents an abnormal value and what the implications of some of the tests are. You will therefore not, as a matter of course, receive this feedback.

If the study team receives any clinically relevant abnormal values, or if new information becomes available that means previous test results are then considered clinically relevant; the study team will contact you to arrange for you to discuss these with one of the study doctors. Again, at this point we would at this point ask your permission to also let your GP or other treating doctor know.

To make sure that our analyses are not affected by either your or the researchers' personal opinions or perceptions, measurements of brain scans, blood, urine and spinal fluid biomarkers during the study will not be known by the study team or yourself. During the EPAD Cohort study they will also not know any of the results of your genetic tests. Other test results will be known straight away, for example your cognitive tests, however these test scores need a lot of analyses by statisticians before their meaning is fully understood therefore there is very limited feedback that your researcher can give you about how well you have done in the tests.

What's in this for me?

You should not expect to benefit medically from being involved in this project; however, you may derive benefits from your involvement in detailed clinical assessments and consultation, over and above your standard clinical care. In cohort studies such assessments may identify clinically relevant problems that would benefit from early intervention. Previous research in people involved with research has noted the benefit that research participants may gain in the knowledge that they are helping to advance scientific knowledge and understanding of disease. The analysis of data held on participants will help researchers and clinicians to treat dementia and symptoms of cognitive disorders in the future. As part of a very large group of participants across Europe and thanks to the data collected, we will be able to make substantial steps forward in our understanding of Alzheimer's disease.

You will also receive information about EPAD intervention studies that you may be suitable for. Any intervention studies will be subject to separate ethical approval and separate consent and there is no guarantee that you will be suitable for any intervention study in the future within the EPAD programme.

You should be aware that as you were identified from a pre-existing cohort study or register, we do not expect you to leave that research due to being a part of the EPAD Cohort. We are happy that you, as long as possible, are in both studies at the same time.

What are the possible disadvantages and risks of taking part in the study?

The main disadvantages and risks we recognise are in 4 areas: the time commitment, blood sampling, CSF sampling and having a brain scan.

- Time commitment: while we will do all we can to make your study visits as comfortable as possible, we do appreciate that we are asking a lot of you and of your time (about 8 hours in total).
- Taking blood samples: you may experience slight discomfort and pain, and there is a small risk of bruising and/or infection at the place where the needle is inserted. If you have experienced problems before, please let the study doctor or nurse know.
- Lumbar puncture: this is generally safe and the risk of serious complications such as severe headache or infection is very low. You may experience some discomfort and pain when the sample is taken. Serious side effects are generally uncommon, although some people experience headaches. Lying down, drinking plenty of fluids and taking simple painkillers can usually relieve the headaches you might experience.
- MRI scan: this is a painless and safe procedure, but you may find it uncomfortable if you have claustrophobia (fear of enclosed spaces). Most people find this manageable, with support from the radiographer.

What if something goes wrong in the study?

If you have a concern about this study, you can speak to the researchers who will do their best to answer your questions. However, if you are still unhappy with the answers given and wish to complain, you can do this through the [local complaints procedure]: [address, telephone, email].

Will my taking part in the study be kept confidential?

Yes, all the data we collect from you (clinical, cognitive, imaging and biomarker (including genetic)) in this study will be kept confidential. All the data will be de-identified. 'De-identified' means that anyone seeing the data will not be able to link it to you. We do this by giving every participant a unique ID number. This ID number is attached to all your test results, but the link between the ID number and your name and personal details (address etc.) is kept securely with exclusive access by the [local TDC name]. This list is very securely stored and only the principal investigator, or researchers given authority by him or /her, will have access.

All data capture, transfer, storage and analyses are being managed by a group within EPAD called the EPAD Data Oversight Committee and will be compliant with all local information governance regulations in the regions where the study is being conducted. The overall EPAD Cohort Chief Investigator who represents the University of Edinburgh who are the sponsors of the EPAD Cohort Study chairs the EPAD Data Oversight Committee.

We will publish our findings in scientific journals as well as present our findings at national and international conferences. However, we only present general conclusions made from result(s) from all or very large sub-groups of the participants, and it will not be possible to identify any particular individuals in what we present or publish publicly.

We will also produce lay summaries so the general public can understand all of our findings and these will be posted on the EPAD website and shared through other media channels like other social media, print, radio and television. In this regard, we are working with our partner, Alzheimer Europe, to ensure that all communications about the study, to the public as a whole and to research participants specifically, are comprehensive and appropriate.

If you consent to join the EPAD Cohort, we will tell your GP of your participation and if any abnormal clinically significant test results are found, we would, after obtaining your permission to do so, like to be able to discuss these with your GP.

What will happen to the samples that I give?

The samples you provide will be stored and used by our own and other scientists for additional research in the future. The EPAD Sample Access Committee will manage the use of these samples. The Sample Access Committee has been established to ensure that any analyses undertaken are of the highest scientific rigour and in line with the aims of EPAD. The Sample Access Committee is managed by The University of Edinburgh. The new information that could be obtained from the analysis of your samples may be used scientifically and may be used in other research. The analysis of your samples may contribute to the creation of new diagnostic tests, new medicines or other uses. You will receive no financial benefits and may not receive any health-related benefits from such developments. The samples and data are linked through your unique ID number and no analyses of samples or use of data by researchers can be linked to you as an individual. Any new knowledge gained from the use of your samples given in the EPAD Cohort Study that leads to new inventions or tests, which lead to commercial benefit, will see that commercial benefit shared between all the EPAD Partners who agreed to the EPAD Project Agreement. There are both academic and commercial partners in EPAD and your research team can provide a full list to you.

Are research participants represented in the organisation of the study?

Yes. A panel of EPAD participants at each EPAD centre provide feedback on the experience of taking part in research, review information sent out to participants and will be involved in making decisions about future directions for EPAD research. This group of 6-10 people meets twice a year, and all EPAD participants and study partners are eligible to be involved. If you would like to be involved and there are no current vacancies on the panel, we can add your name to the waiting list.

Who is funding and organising this research?

The research is being organised in several European countries, under the leadership of the University of Edinburgh, Scotland, UK. The European Commission and the European Federation of the Pharmaceutical Industry Association (EFPIA) under the auspices of the Innovative Medicines Initiative Joint Undertaking (IMI JU) fund EPAD. Over time other sources of funding will be sought, to grow and maintain the EPAD cohort of participants.

Who has reviewed the study?

This study has been looked at by the [local Research Ethics Committee] to protect and ensure participants' safety, rights, wellbeing and dignity.

Thank you for considering your involvement in this project and taking time to read this information sheet.

Attachment 2: EPAD LCS Informed Consent Form for Research Participants

[Local Headed Paper]

EPAD LCS Informed Consent Form for Research Participants

Compulsory statements (if you do not agree with one of the statements below you cannot participate):

- I have received oral and written information about the *European Prevention of Alzheimer's Disease Longitudinal Cohort Study (EPAD LCS).* I had the opportunity to ask questions. These questions have been answered to my satisfaction. I had enough time to decide if I want to participate.
- I know that participation is voluntary.
- I understand that I have the right to withdraw my consent to participate in the study at any time and without having to explain or justify my decision. I understand that if I decide to withdraw my consent to participate in the study, this will not affect my current or future medical treatment and care
- I agree to my GP/treating physician/PI of PC being notified about my participation in this study
- I agree to the use of my data for the goals described in the information sheet
- I agree to the use of my data/samples to test for new biomarkers which weren't mentioned in the information sheets, during EPAD, without further/separate consent being requested from me.
- I agree to the storage of my research data for 15 years after the completion of this study
- I agree to be contacted during my participation in EPAD LCS about the possibility of participating in an EPAD drug trial. (you will only be contacted if you are eligible).
- I am aware that an invitation into such an EPAD drug trial will be based on factors associated with Alzheimer's Dementia risk and agree to possibly learning about carrying such factors.
- I have read and/or watched the provided materials related to learning my amyloid status and have had the opportunity to discuss this information
- I want to participate in this study

Optional statements (if you do not agree with one of the statements this does not affect your ability to participate):

- ☐ I agree to receive information about clinically relevant incidental findings not related to Alzheimer's disease.
- ☐ I agree to my GP/treating physician being contacted in relation to these clinically relevant incidental findings not related to Alzheimer's disease.
- ☐ I agree to the researchers contacting my GP and other relevant doctors I am seeing for further medical information if this is required.

[Local Headed Paper]

- ☐ I agree to data previously collected in < the original PC > being exported and used in this study
- ☐ I agree to data collected from me during this study may be returned to <the PI of the original PC>
- ☐ I agree to the storage of my material for 15 years after the end of this study, so that it can be used for future research
- ☐ I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
- ☐ I agree to be re-contacted about future research with the same objective
- ☐ I agree to be re-contacted about future research with other objectives

*Full name of participant:*_____

Signature: *Date:*

I declare I have fully informed this person about the study.

If, during the study, information becomes known that could influence the participants' decision, I will inform them in a timely manner.

*Full name of researcher (or his representative):*_____

Signature: *Date:*

[When completed, 1 for participant; 1 (original) for researcher site file]

Attachment 3: EPAD LCS Information Sheet for Study Partners

[Insert local details]

Information sheet for study partners of participants:

European Prevention of Alzheimer's Dementia Longitudinal Cohort Study

(EPAD LCS)

Research Ethics Committee Reference:

You are being invited to take part in a research study.
Please take time to read the following information carefully.
Discuss with friends, relatives or your doctor if you wish.

Who are we?

Principal Investigator: [Insert local details]

Contact details: [Insert local details]

Telephone: [Insert local details]

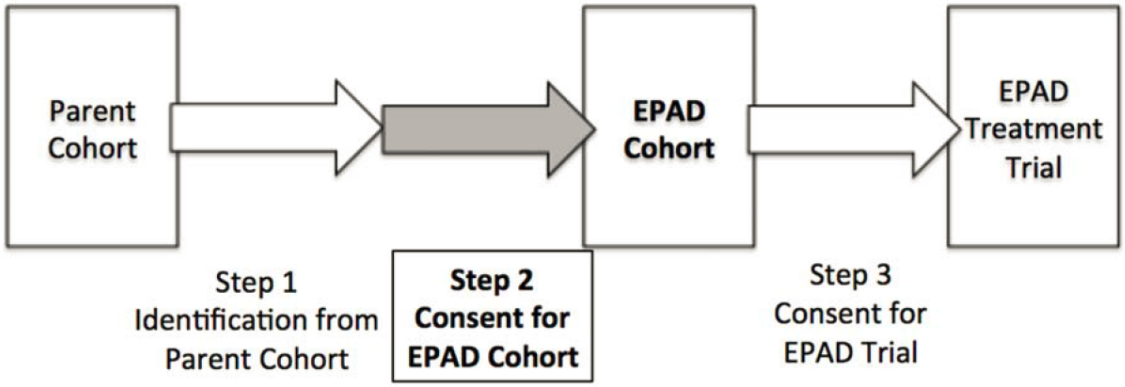
What is EPAD?

The European Prevention of Alzheimer's Dementia (EPAD) Project is an international study on-going in several European countries. The study is managed and sponsored by the University of Edinburgh in Scotland, UK.

The aims of EPAD are

1. To learn and understand better the factors involved in developing Alzheimer's dementia.
2. To develop new treatments more quickly which are hoped to prevent Alzheimer's dementia.

The project has several parts. One of the main parts is called the EPAD Longitudinal Cohort Study (EPAD LCS) which we will refer to throughout this document for clarity as 'EPAD Cohort' and this is what you are being invited to join as a study partner for your relative/friend who has expressed interest in being an EPAD Cohort participant. There are 3 main steps in being part of EPAD shown in the diagram below.



The consent we are asking for in this document is 'Step 2' above, to be a study partner for an EPAD Cohort participant.

A cohort is a group of people who are observed over time for changes in various factors. The main reasons for EPAD developing a cohort are to help us understand more about what happens to people who might develop Alzheimer's dementia. Some participants in the EPAD Cohort will develop Alzheimer's dementia and others will not. It is important that we have a wide range of people with different risks of Alzheimer's dementia in the EPAD Cohort. The second reason for the cohort is to find people more quickly who would be suitable to be approached for the EPAD treatment trials of many new treatments expected to prevent dementia. We call this a 'readiness cohort' because the people are 'ready' to join the trial. It is essential that each participant has a study partner (e.g. a relative or friend) who can provide additional information about the participant that is very relevant for our research.

It is important to highlight and emphasise that by agreeing to be a study partner for your relative/friend who participates in the EPAD Cohort, you are not consenting or committing to be a study partner in the EPAD trial. If your relative/friend is invited to participate in a trial evaluating a treatment, that would require subsequent consent for both her/him and you as a study partner.

We are now asking you if you are interested to be a study partner for your relative/friend participating in the EPAD Cohort.

What is the difference between Alzheimer's disease and Alzheimer's dementia?

Throughout this information sheet we use the terms Alzheimer's disease and Alzheimer's dementia. These are not the same things. When we talk about Alzheimer's disease we mean the changes in the brain that can lead to Alzheimer's dementia. When we talk about Alzheimer's dementia we talk about the clinical syndrome where memory and thinking is impaired to the extent that day-to-day functioning of the individual is affected.

Why are we doing this research?

Changes in the brain may precede symptoms of Alzheimer's dementia by many years if not decades. Such changes suggest that a very early Alzheimer's disease process has started well before people start developing the typical symptoms of Alzheimer's dementia like memory loss. If this is the case, then we may be able to identify Alzheimer's disease at a very early stage, and prevent or delay the disease from developing into dementia. However, with current knowledge doctors can only diagnose Alzheimer's disease in people who already have dementia or are very close to developing dementia. Available treatments are helpful but cannot fully stop the disease from progressing. We hope to be able to identify Alzheimer's disease before the occurrence of symptoms when in theory treatments are most likely to be successful in preventing further spread of the disease in the brain.

The brain changes as we age, even in people who never develop dementia. Such brain changes may be seen on brain scans, in the spinal fluid or in the blood. It is still not fully clear what different brain changes mean for the longer-term likelihood of developing Alzheimer's dementia. We suspect that certain interventions will work best in people who share a small number of characteristics rather than everyone at risk of developing Alzheimer's dementia. In the EPAD Cohort we will be able to match the people most likely to respond to a particular treatment and invite them to enter that treatment trial. In the EPAD trial we will test whether that proved to be the case and if not we can maybe find people in the EPAD Cohort who we have learnt are most likely to benefit. This is one of the main reasons why the EPAD Cohort and EPAD Trial are run together in the same research programme.

We would like to re-emphasise that participating in the EPAD Cohort does not automatically mean your relative/friend will be eligible for the EPAD trial and there is a possibility that she/he will never be invited to enter the EPAD trial; in this case you will not be asked to be a study partner in the EPAD trial. If we do later ask your relative/friend about participating in the EPAD Trial with you as study partner, both of you will receive detailed information about it and both of you will be asked if you wish to consent to participate.

Why have I been approached?

You have been approached because you were identified by your relative/friend as a potential study partner in the EPAD Cohort. Your relative/friend was approached for participation in the EPAD Cohort because she/he has previously taken part in another research study or consented to their data being used for research.

To find out which factors are good predictors of the risk of Alzheimer's dementia, we need a broad range of participants with different likelihoods of developing Alzheimer's dementia. It

is also important that each participant has a study partner who can provide additional information about the participant.

We do not know in advance who will develop dementia and who will not among the EPAD Cohort participants. This means we need to include in the EPAD Cohort people who are possibly at high risk, at low risk and everywhere in between. As we follow all the people in the EPAD Cohort in the years ahead than we will learn which factors predict risk. Only by including such a wide range of people can we calculate who is most at risk for development of Alzheimer's dementia. The information you provide about the daily life/activities of your relative/friend by filling in standard questionnaires will help us refine these calculations.

Do I have to take part?

No. Your participation as a study partner to your relative/friend in the EPAD Cohort is entirely voluntary. It is up to you to decide whether or not you become a study partner.

Can I withdraw from the study?

You are free to withdra`w your consent and withdraw from the study at any time after you have signed the consent form and will not be asked to justify your decision. Whatever you decide it won't affect any health or social care that you, your relative/friend or anyone you care for receive.

What will happen to me if I would like to take part?

1. The EPAD study team will be in contact with you either by phone, e-mail or letter (depending on what suits you best) to answer any questions you may have and to see whether you would like to become a study partner for your relative/friend.
2. Once you have read through the information sheet please complete the consent form. One of the senior researchers in the research centre will then countersign the form. Your relative/friend will also receive an information sheet, and will be asked to sign their own consent form.
3. After you and your relative/friend sign the consent forms, the research team will be able to arrange your study visits. It is preferable that you come to the research centre. If this is not possible, it is important that we can talk to you by phone.You will be asked to answer some standard questionnaires about daily life/activities of your relative/friend on rating scales designed to be completed by an informant. You will not undergo any medical assessments or tests as part of the EPAD Cohort.
4. Your relative/friend will undergo several study procedures (summarized later in this document). Personal information she/he gives us as part of the study will not be shared or disclosed to you, without her/his consent.

How many study visits do I need to make?

The current study will end in December 2019, as this is when the funding will run out; however, we plan to get additional funding to keep the study going indefinitely. You are free to withdraw consent at any time but if you do not we will ask you to reconsent every 4 years. After the initial study visit and questionnaires, additional visits will be planned for you after 6

months, 1 year, 2 years, 3 years, and 4 years. We need to do follow up visits to be able to measure changes in your answers to the questionnaires.

The duration of your participation as a study partner in the EPAD Cohort may vary and depends upon five factors:

1. Whether you wish to continue being a study partner.
2. Whether your relative/friend wishes to continue participating the EPAD Cohort.
3. Whether your relative/friend develops any health conditions that may affect her/his participation in the study. If she/he develops dementia during the course of the EPAD Cohort Study, neither of you will continue to be part of the EPAD Cohort but your relative/friend (with you as study partner) will be offered the chance to continue to be followed-up by the EPAD research team. You can discuss these issues with your relative/friend and the EPAD research team if the need arises and your relative/friend would welcome this. However, if your relative/friend does develop dementia, she/he would no longer be eligible for the EPAD trial as this is aiming to prevent dementia.
4. The EPAD Cohort Study is running across Europe and will involve several thousands of people. There may come a time when people at certain risk of developing Alzheimer's dementia are over-represented in the whole cohort. If this happens we would wish to stop following some participants and their study partners after their Year 1 visit. Being asked to leave the EPAD Cohort study does not imply any specific risk for developing Alzheimer's dementia and the research team will not know why your relative/friend has been asked to leave either as they do not know her/his risk of getting Alzheimer's dementia. The decision to ask a participant and their study partner to leave is made by people working centrally in EPAD who do not know your relative/friend or you and have no means of identifying either of you from the data they are looking at.
5. If your relative/friend is suitable or eligible for the EPAD trial then the EPAD Research Team will contact you as a study partner. Eligible persons and their study partners who later on decide and give separate consent to participate in the EPAD trial may return to EPAD LCS after the end of the trial if they wish to and provided that they are still eligible for EPAD LCS.

What will happen at my study visits?

On your arrival at the research site for the first visit, you will have the opportunity to ask any further questions. Once you are happy with your involvement in the study, your consent form will be signed by you and countersigned by one of the research team. Once you have signed a consent form, you will then be asked to complete two questionnaires.

It is preferable that you come to the research centre for your study visits. If this is not possible, it is important that we can talk to you by phone. You should need about one hour per visit. You may accompany your relative/friend to their study visits if both of you wish to do so, and we can arrange your study visits separately if that is more convenient.

You will be asked to fill in two standard questionnaires about the daily life/activities of your relative/friend, including questions about her/his memory and thinking, ability to perform household tasks, community affairs and social functions, and whether these have changed in any way recently. One questionnaire is called Clinical dementia Rating (CDR), and you will answer these questions at each visit in a discussion with a member of the EPAD research

team. The other questionnaire is called Amsterdam Instrumental Activities of Daily Living, and will have to be filled in annually.

You will not undergo any medical assessments or procedures during the EPAD Cohort study.

What will happen at my relative's/friend's study visits?

Your relative/friend will also have the opportunity to ask any questions about the study. At the first screening visit, once your relative/friend is happy with her/his involvement in the study, she/he will sign a consent form, which will then be countersigned by one of the research team. Once your relative/friend has signed a consent form, the assessments can start.

There are several assessments that are necessary, divided into 4 main areas: brain scans; clinical and cognitive assessments; blood, saliva, spinal fluid and urine tests; and other assessments including self-report questionnaires. These can be spread over several visits to the research centre to make this as convenient for your relative/friend as possible – though all data should ideally be collected within a 1-month period. Visits for your relative/friend will be planned annually, and there will also be a study visit 6 months after baseline.

If during any of the testing we note any health issues, we will discuss these with your relative/friend and provide help in planning potential next steps. In the EPAD Cohort study the doctors do not undertake a full and thorough physical examination so there is the potential that some health conditions may be missed. If we do though notice any problems, with your relative/friend's consent, then we may wish to contact with her/his primary care doctor or other relevant physician as is needed. We will not discuss these issues with you unless your relative/friend has given consent for this.

In summary:

- You will need about one hour to complete the questionnaires for study partners. You can do this either at the research centre, or by phone. The study team will contact you in advance to plan the visits and we will take your availability into account. You will also have the possibility to contact the study team by phone or email if you have any questions. We will do all we can to work around your schedule to minimise the inconvenience that being part of this study may cause.
- While you are a study partner for your relative/friend participating in the EPAD Cohort study, you will need to answer the questionnaires 6 months after your initial study visit, 1 years after your initial study visit, and then annually.
- If an intervention study is started from within the EPAD programme, which we think your relative/friend may be suitable for, we will also contact you as a study partner. This may be before the 1-year follow up visit but NOT before the 6-month visit.

Will I be made aware of any test results?

We have a duty of care to share with your relative/friend the results of any investigation if they are known to be abnormal and clinically relevant. However, we do not yet know if some of the data we are gathering can be used as a predictor of dementia so, by definition, we are not sure what represents an abnormal value and what the implications of some of the tests are. Your relative/friend will therefore not, as a matter of course, receive this feedback.

If the study team receives any clinically relevant abnormal values, or if new information becomes available that means previous test results are then considered clinically relevant; the study team will contact your relative/friend to arrange for her/him to discuss these with one of the study doctors.

Test results that may be discussed with your relative/friend will not be discussed with you unless she/he gives consent for this.

What's in this for me?

You should not expect to benefit medically from being involved in this project. Previous research in people involved with research has noted the benefit that research participants may gain in the knowledge that they are helping to advance scientific knowledge and understanding of disease. The analysis of data held on participants will help researchers and clinicians to treat dementia and symptoms of cognitive disorders in the future. As part of a very large group of participants across Europe and thanks to the data collected, we will be able to make substantial steps forward in our understanding of Alzheimer's disease.

What are the possible disadvantages and risks of taking part in the study?

The main disadvantage we recognise for you is your time commitment. While we will do all we can to make your study visits as comfortable as possible, we do appreciate that we are asking you to dedicate part of your time to the EPAD Cohort study.

What if something goes wrong with me or my relative/friend in the study?

If you have a concern about this study, you can speak to the researchers who will do their best to answer your questions. However, if you are still unhappy with the answers given and wish to complain, you can do this through the [local complaints procedure]: [address, telephone, email].

Will my and my relative's/friend's taking part in the study be kept confidential?

Yes, all the data we collect from you and your relative/friend in this study will be kept confidential. All the data will be de-identified. 'De-identified' means that anyone seeing the data will not be able to link it to you. We do this by giving every participant (and their study partner) a unique ID number. This ID number is attached to all test results, but the link between the ID number and your or your relative/friend's name and personal details (address etc.) is kept securely with exclusive access by the [local TDC name]. This list is very securely stored and only the principal investigator, or researchers given authority by him or /her, will have access.

All data capture, transfer, storage and analyses are being managed by the EPAD Data Oversight Committee and will be compliant with all local information governance regulations in the regions where the study is being conducted. The overall EPAD Cohort Chief Investigator who represents the University of Edinburgh who are the sponsors of the EPAD Cohort Study chairs the EPAD Data Oversight Committee.

We will publish our findings in scientific journals as well as present our findings at national and international conferences. However, we only present general conclusions made from

result(s) from all or very large sub-groups of the participants, and it will not be possible to identify any particular individuals in what we present or publish publicly.

We will also produce lay summaries so the general public can understand all of our findings and these will be posted these on the EPAD website and shared through other media channels like print, radio and television. In this regard, we are working with our partner, Alzheimer Europe, to ensure that all communications about the study, to the public as a whole and to research participants and study partners specifically, are comprehensive and appropriate.

Who is funding and organising this research?

The research is being organised in several European countries, under the leadership of the University of Edinburgh, Scotland, UK. The European Commission and the European Federation of the Pharmaceutical Industry Association (EFPIA) under the auspices of the Innovative Medicines Initiative Joint Undertaking (IMI JU) fund EPAD. Over time other sources of funding will be sought, to grow and maintain the EPAD cohort of participants.

Who has reviewed the study?

This study h`as been looked at by the [local Research Ethics Committee] to protect and ensure participants' safety, rights, wellbeing and dignity.

Thank you for considering your involvement in this project and taking time to read this information sheet.

Attachment 4: EPAD LCS Informed Consent Form for Study Partners

EPAD LCS Informed Consent Form for Study Partners

I have received oral and written information about the *European Prevention of Alzheimer's Disease Longitudinal Cohort Study (EPAD LCS)* and the role of a Study Partner. I had the opportunity to ask questions. These questions have been answered to my satisfaction. I had enough time to decide if I want to participate as a Study Partner.

I confirm that I have read and understand the information sheet (Version X.X Date XXXXXXXXX) for the above named research project, I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I have the right to withdraw my consent to participate in the study at any time and without having to explain my decision. I understand that if I decide to withdraw my consent to participate in the study, this will not affect my current or future medical treatment and care. ☐

I agree to the use of the data I provide for the goals described in the information sheet ☐

I agree to data collected from me during this study being returned to *<the PI of the original PC>* ☐

I agree to the storage of the research data I provide for 15 years after the end of this study. ☐

I want to participate in this study as a Study Partner for: ☐

*Full name of Study Participant:*_____

*Full name of Study Partner:*_____

Signature: *Date:*

*Full name of researcher (or his representative):*_____

Signature: *Date:*

[When completed, 1 for participant; 1 (original) for researcher site file]

LAST PAGE