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

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Prepared by:	Craig Ritchie, Miia Kivipelto, Alina Solomon, Sarah Gregory and Joseph Milne on behalf of the EPAD Consortium		

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

PROTOCOL SIGNATURE PAGE

Protocol details	
Study title:	**European Prevention of Alzheimer's Dementia Longitudinal Cohort Study**
Study name/acronym:	**EPAD LCS**
Protocol number:	**EPAD-UoE-001**

Protocol approved by:

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

Chief Investigator	
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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Requirements for reporting serious adverse events defined in Section 5.2 of this protocol.
- Terms outlined in the TDC Agreement.
- Responsibilities of the Investigator (covered in TDC agreement)

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted. File the original signature page in the study file at the site and send a copy of the signed and dated signature page to your CRA.

Signature of Principal Investigator Date

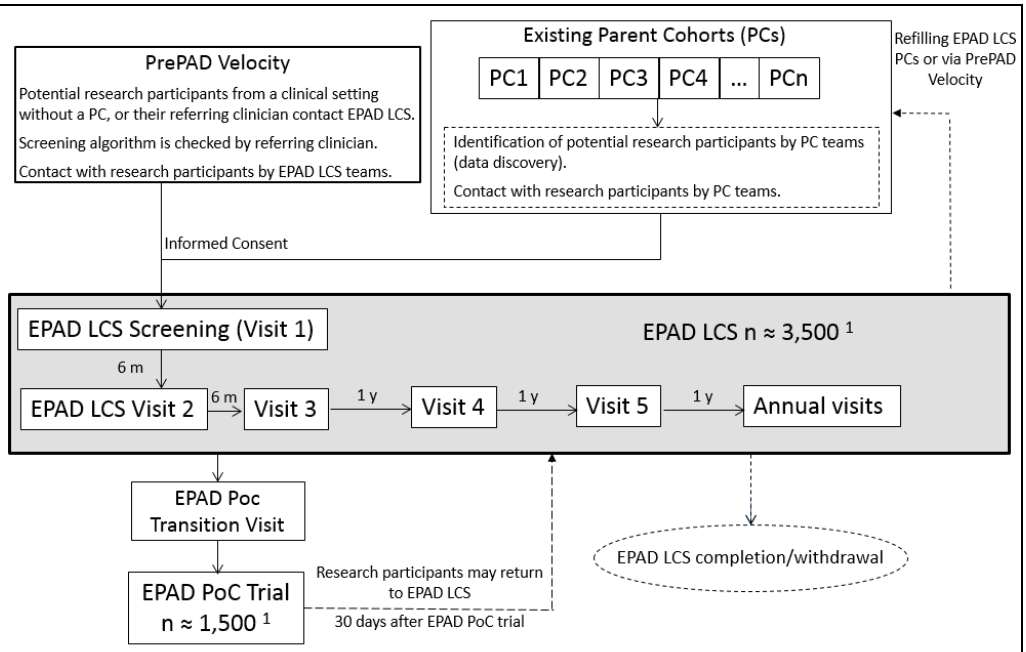
Principal Investigator Name (print or type)

Name of Facility and TDC number

Location of Facility (City, Country)

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 European Prevention of Alzheimer's Dementia (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 Longitudinal Cohort Study (LCS) in alignment with the adaptive design EPAD proof of concept (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. 3,500 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. 3,500 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 June 2020, 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.

[1] Once recruitment is completed, at any given time there should be approx. 3,500 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.

	• 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 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 principal investigator (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. Research participants may also be recruited from existing clinical or routine cohorts, (such as a memory clinic) therapeutic delivery centres may have access to. Research participants are identified by the appropriate team member at each centre from the appropriate clinical cohort database and contacted directly regarding possible participation in the EPAD LCS trial. If any participant is identified out with a database or cohort, the TDC should register the participant on the appropriate cohort or internal database before invitation into the study. 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. All informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task.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, checked and recorded at Screening (Visit 1) only, as well as fulfilling the criteria set by the balancing committee. • Fulfils the criteria set by the Balancing Committee [BC] • Able to read and write and with minimum 5 years of formal education, checked and recorded at screening (Visit 1) only. • 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; and [3] a flexible algorithm for selecting research participants after the EPAD LCS screening (considering parameters listed below) • All EPAD LCS research participants will have a CSF sample collected at V1 and V4 and then every second year. • Participants who score >1 on the CDR will not complete further MRI or CSF sampling, all other assessments will be completed annually. • If participants become unable to complete CSF sampling after baseline they will be invited to remain in the LCS cohort, but no further CSF sampling will be completed.
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, TREM-2, neurofilament light and neurogranin. • Neuroimaging parameters (MRI): hippocampal and whole brain volume; vascular burden (white matter lesion [WML], infarcts, lacunes, microbleeds, superficial siderosis) **Risk factors** • Apolipoprotein E (APOE) genotype • Family history of AD/dementia in first degree relatives • Sociodemographic factors: age, sex, education, marital status • Body mass index (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. National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] for AD; Lund Criteria for fronto-temporal dementia [FTD], McKeith Criteria for dementia with Lewy bodies [DLB], National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences [NINCDS-AIREN] Criteria for Vascular Dementia) • CDR ≥1 at screening (Visit 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 and localised prostate cancer in male subjects) • 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 diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 5 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 Trial Delivery Centre 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/positron emission tomography (PET) scan • Any contraindications for Lumbar Puncture at visit 1. • 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 of an investigational product (CTIMP) in the last 30 days[2]. Participation in a non-CTIMP or an observational arm of a CTIMP is not

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

	considered an exclusion criterion. Co-enrolment in the Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) Prognostic and Natural History Study (PNHS) is not considered to fall under this exclusion criteria. • Diminished decision-making capacity/not capable of consenting at screening visit • Unable to comply with protocol requirements in the opinion of the investigator
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. CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, except if biomarker status is disclosed. 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 (University College London/University of York.) - 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 - functional regional and network measures **CSF biomarker outcomes** TREM-2, neurofilament light, and neurogranin
OTHER MEASURES	Sociodemographic and lifestyle factors, family history of AD/dementia in first degree relatives, medical history, comorbidity, medication use, BMI, waist-hip ratio,

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

	blood pressure, CDR, Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), State-Trait Anxiety Inventory (STAI), Pittsburgh Sleep Quality Index (PSQI), 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): beta-amyloid, t-tau, p-tau, (neurofilament light, TREM 2, and neurogranin).
FOLLOW-UP	Research participants will be followed-up every 6 months during the first year, and then annually. All prodromal and preclinical participants who are eligible to join the PoC can leave the LCS after the baseline visit. Cognitive and clinical assessments will be conducted every 6 months during the first year, and then annually. CSF samples will be collected 2 years after baseline at V4 and then every second year. Structural MRI assessments will be performed 2 years after baseline at V4 and then every second year,and functional MRI assessments will be done in a sub-set of participants.
STUDY PERIOD	EPAD LCS will initially run until the end of June 2020. Extension of consent will be sought after 4 years. Research participants may leave EPAD LCS due to withdrawn consent, entry into the EPAD PoC trial, entry into another clinical trial of an investigational product (CTIMP) 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 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

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1. INTRODUCTION

1.1. Background

Alzheimer's disease (AD) is the leading cause of dementia globally affecting ~7 million 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 proof of concept (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 multiple 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 Longitudinal Cohort Study (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 3,500 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. 3,500 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 June 2020, 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:

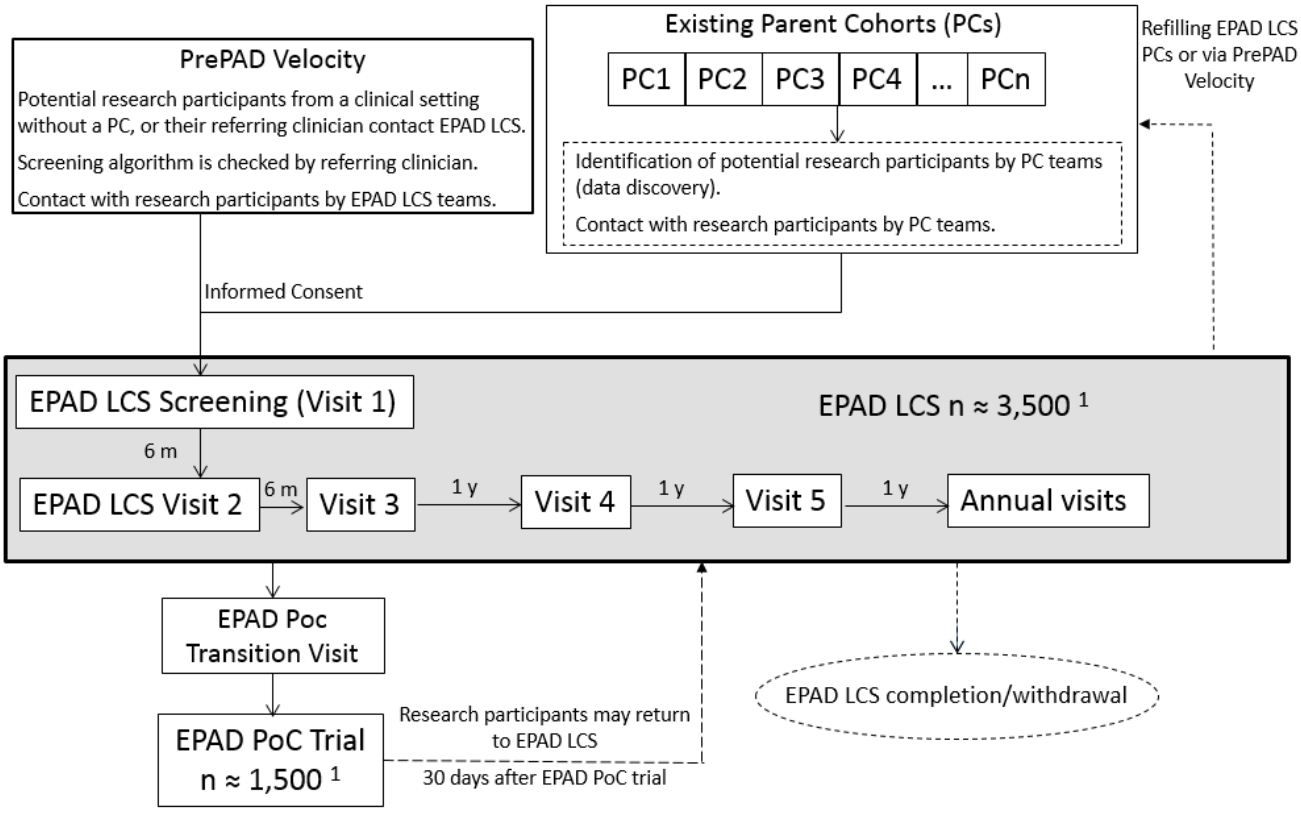
1. To provide a well-phenotyped population (readiness population) for the EPAD PoC trial to minimize trial screening failures
2. To provide a well-phenotyped probability-spectrum population for developing and continuously improving disease models for AD in individuals without dementia. The probability 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. 3,500 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 principal investigator (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. All informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task. Assessments and data collection for EPAD LCS will take place only after the Informed Consent Form (ICF) has been signed

3.2.1.1. Flow of Research Participants from Clinical or Routine Cohorts via PrePAD Velocity

Research participants may also be recruited from existing clinical or routine cohorts, (such as a memory clinic) trial delivery centres may have access to, as shown in Table 1.

Research participants are identified by the appropriate team member at each centre from the appropriate clinical cohort database and contacted directly regarding possible participation in the EPAD LCS trial. If any participant is identified out with a database or cohort, the TDC should register the participant on the appropriate cohort or internal database before invitation into the study.

At any point during the study TDCs may be given access to the PrePAD Velocity System (which is requested via IQVIA) to allow participants identified through the pathway described above to be allocated a unique identifying code created which is entered into the CRF.

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 are 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 or via PrePAD Velocity. The algorithm will be applied every three months by the EPAD BC, with variations by types of data available in different PCs. PrePAD Velocity allows sites to invite participants meeting the Velocity criteria. These criteria are flexible and change over time, and are also set by the balancing committee
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 Exclusion Criteria Population).

Participants may become unable for medical reasons to undergo the CSF sampling procedure. These participants will be allowed to remain in the study without completing CSF sampling future time-points. Participants who score >1 on the CDR will not complete further MRI or CSF sampling, all other assessments will be completed annually.

3.3. EPAD LCS Study Population

Once recruitment is completed, at any given time there should be approx. 3,500 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 end of June 2020, 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) 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, checked and recorded at Screening (Visit 1) only, as well as fulfilling the criteria set by the balancing committee.
2. Fulfils the criteria set by the BC
3. Able to read and write and with minimum 5 years of formal education, checked and recorded at Screening (Visit 1) only.
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 from the screening visit (Visit 1)

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 for face to face contact with the EPAD LCS staff at the local TDC or by video call. Prior to any EPAD LCS assessments with the participant, study partners will receive oral and written information about EPAD LCS and the overall EPAD project, and will sign an informed consent form (ICF). If a study partner is required to reconsent at any time when their relative or friend is a participant in the LCS, this can be done either at the TDC, or if this is not possible, via post . If the study partner has to be reconsented via the postal method, a member of the study team should forward 2 copies of the latest version(s) of the study partner consent form with a covering letter describing what has changed in the protocol and why the study partner is being asked to provide on-going consent to indicate their willingness to continue being their relative or friend's study partner. The consent forms will not contain the participant's name but will be instead contain their study number. The cover letter will indicate that the study partner should read the new consent form. A telephone number will be provided to allow the study partner to have any questions they may have answered by the research team at the TDC. If they agree to maintain their ongoing consent they should sign and date both copies A pre-paid envelope addressed to a member of the study staff at the TDC should also be provided in order that one of the signed forms can be returned. The other signed copy should be retained by the study partner for their own records.

3.3.2. Exclusion Criteria

1. Research participants who fulfil diagnostic criteria for any type of dementia at Screening (Visit 1) (e.g. National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] for AD; Lund Criteria for fronto-temporal dementia [FTD], McKeith Criteria for dementia with Lewy bodies [DLB], National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences [NINCDS-AIREN] Criteria for Vascular Dementia)
2. CDR ≥1 at Screening (Visit 1) only.
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 and localized prostate cancer in male subjects)
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 diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 5 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/positron emission tomography (PET) scan
8. Any contraindications for Lumbar Puncture at visit 1 (including refusal of lumbar puncture procedure to collect sample)
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[7]. Participation in a non-CTIMP or an observational arm of a CTIMP is not considered an exclusion criterion. Co-enrolment in the Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) Prognostic and Natural History Study (PNHS) is not considered to fall under this exclusion criteria.
11. Diminished decision-making capacity/not capable of consenting at Visit 1.
12. Unable to comply with protocol requirements in the opinion of the investigator

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 lose capacity.

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

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.

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

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 Cognitive Outcomes) 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

- Biomarkers: beta-amyloid, t-tau, p-tau, currently assessed. Additional biomarkers TREM-2 neurofilament light, neurogranin will be included.
- Neuroimaging parameters (MRI, details in Section 3.4.4 Neuroimaging Outcomes): hippocampal and whole brain volume; vascular burden (white matter lesion [WML], infarcts, lacunes, microbleeds, superficial siderosis)

c. Risk factors

- Apolipoprotein E (APOE) genotype
- Family history of AD/dementia in first degree relatives
- Sociodemographic factors: age, sex, education, marital status
- Body mass index (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 Other Measures)

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 BC will check on a 3 monthly basis that recruited participants to EPAD LCS are suitable for the Proof of Concept Trial and suitable run-in data can be provided. They will also check that the data are suitable for disease modelling and also for risk stratification. Thus the main task of the BC is to achieve a suitable study cohort which is trial ready and can be utilised for disease modelling and risk stratification by means of a flexible algorithm. This algorithm can be adjusted as necessary.

The Algorithm Running Committee will forward the algorithm to the TDCs whenever it is updated.

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

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. CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, except if biomarker status is disclosed. Overall probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy of current disease models, but will be disclosed at participant's request. 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 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[8]

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 (Learning, Delay & 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 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 Good Clinical Practice (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

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

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 (University College London/University of York)[21,38]

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 Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (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

All participants will have a lumbar puncture performed at baseline (Visit 1) and at 2 years (Visit 4) and every second year thereafter We believe that a CSF collection every two years will be sufficient to reflect any changes in the biomarkers associated with AD related biomarkers.

If an attempt(s) at collecting the sample (CSF) is made at Visit 1, and no sample is obtained, then approval should be sought from the Medical Monitor on the participant's continuation in the trial. Attempts should be made at Visit 2 or Visit 3 to collect a sample from the participant. If no sample is obtained in these future visits, then there should be further discussion with the Medical Monitor. Participants may remain in the study despite being unable to provide a CSF sample as they are still contributing valuable biological samples, images and cognitive data all of which will advance the understanding of Alzheimer's Disease.

Participants may become unable for medical reasons to undergo a lumbar puncture after the baseline visit. These participants will be allowed to remain in the study without completing lumbar punctures at future time-points. Participants who score >1 on the CDR will remain in the cohort and will not complete further lumbar punctures or MRI sampling at Visit 4 or any other future visits.

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), neurofilament light, TREM 2, and neurogranin and this data will be used for disease modelling and for staging of disease pathology. All details of CSF sampling will be provided in the accompanying laboratory manual.

If an individual participant has had a lumbar puncture and CSF sample collected and stored according to the CSF sampling manual procedure (included in the laboratory manual) within 12 months prior to Visit 1, then this sample can be provided for analysis for the Visit 1 baseline data. Those participants who qualify for EPAD LCS and who have had a previous lumbar puncture performed within 12 months prior to the baseline visit, are still required to have a baseline MRI scan unless they have had an MRI performed to the specifications in the Core EPAD scanning protocol in the 12 months prior to Visit 1 as per section 3.4.4. of the protocol. If a participant has had a PET amyloid scan in the last 12 months, with results available to EPAD TDC for review and the participant is aware of PET results, they may choose to defer the baseline lumbar puncture to the 12 month visit. All participants are expected to have at least one lumbar puncture performed as part of the EPAD LCS.

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 (WMLs, 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.

Investigators that have concerns over a participant's safety undergoing an MRI scan can conduct any safety measures at their discretion (for example, an x-ray to identify metal fragments). The outcome of any safety tests should be recorded in the participant's study notes but will not be reported in the study data. If any safety examinations show a participant cannot undergo an MRI scan, then the participant should be deemed ineligible for the study.

Core MRI Imaging

MRI was chosen because compared to computed tomography 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.

All participants will be required to complete baseline core MRI imaging. Core MRI imaging will be repeated at 2 years (Visit 4) and then every second year for all EPAD research participants. Following visit 1, the MRI scans are scheduled every two years to coincide with the collection of the two yearly CSF sample. The MRI scan precedes the CSF collection as a safety procedure prior to undertaking the lumbar puncture. 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. Alzheimer's Disease Neuroimaging Initiative (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 approximately 45–60 minutes.

If an individual participant has had an MRI to the specification in the Core EPAD Scanning protocol in the 12 months prior to Visit 1, then this scan can be provided for analysis for the Visit 1 baseline data. It can also apply to subsections of the protocol as long as the specifications are similar to the EPAD Imaging protocol.

3.4.5. Genetic Assessments

The primary genetic assessment will include APOE genotype. Further genetic analysis will also be carried out in UoE. 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
- *Electrocardiogram (ECG)* will be recorded if any finding within the physical exam indicates its necessity. Data/findings and traces will be kept within the participant's study notes.
- *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. SNAC questionnaires are not required to be completed if there are no change in reported events from the previous visit (e.g. at screening visit). Only changes (new events) from the previous visit should be reflected in the next completed SNAC 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 face to face 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. Raters that conduct the CDR assessment on a particular research participant cannot rate any other assessments for that participant. 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 The Charles F. and Joanne Knight Alzheimer's Disease Research Center [Knight ADRC]), the CDR sum of boxes (CDR-sb, the sum of all six domains), and a CDR rating for each domain. CDR raters, where possible, should be blinded, as far as possible, to all other cognitive and clinical assessments, except if biomarker status is disclosed. The rationale for the CDR rater remaining blinded is that if they know the status of the biomarker tests, or result of any other tests this could potentially influence how they score participants undertaking a CDR test.

- *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
- 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; cortisol samples will not be collected for participants taking steroidal preparations e.g. oral, cream, ointment, inhaled or drops, these participants will be eligible to continue in the study and complete all other assessments including drool saliva collection)

Detailed instructions for the documentation, collection and management of the biological samples will be provided in a separate EPAD Sample Instruction Manual. Blood, urine and saliva samples will be collected annually in all EPAD LCS participants and CSF every 2 years for potential future

analyses of emerging AD biomarkers. Cortisol samples will be collected at baseline (Visit 1) and at 2 years (Visit 4) and then every second year. All biological samples will be stored at UoE, UK with reference to appropriate regulatory procedures.

3.4.8. 4-Monthly Telephone Contact

Participants will be contacted every 4 months throughout the duration of the study by telephone. However, if a 4-month call falls at the same time as a visit (i.e. months 12, 24, 36) this discussion will be done in person. This telephone call will serve as a reminder that participants are in a readiness cohort and may be invited to PoC trials in the future. Participants will be asked to indicate if they remain willing in principle to participate in these trials. Continued willingness to participate in PoC will be indicated in source data. If a participant responds that they are not willing to participate in the PoCs during a 4-month phone call, but had previously been willing in principle to participate when they were asked at baseline, as evidenced by a signed consent form, they will be eligible to remain in the LCS completing scheduled assessments and will continue to receive 4-monthly calls. Adverse events (AEs) related to study procedures from previous visits, changes to general health and medication use will also be checked during the 4 month phone call. There will be window of +/- 14 days surrounding the date of each 4 month phone call during which it can be performed. The 4-monthly point of contact should preferably be in the form a phone call, but if a participant prefers to be contacted by email then this is permitted as an alternative form of contact. Sites who contact their participants by email must do so as per their local email policy.

3.4.9. 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, except the MRI associated with the visit which should be completed within ± 42 days. This provides an 84-day window for each visit following Visit 1. Assessments that take place outside of these windows will be collected and included in the analysis but must be reported as a protocol deviation.

3.5. Study Completion or Withdrawal

The initial duration of EPAD LCS will be from April 2016 to June 2020, and extension of consent will be asked for prior to end of June 2020 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 ICF).
- They enter another clinical trial (continued participation in the parent cohort is expected)
- Safety reason or research participant not compliant with protocol procedures

- Sponsor's decision to stop the study
- Decision by Balancing Committee to select/deselect individual participants. The Algorithm Running Committee will provide the output for the PCs.

For research participants selected for the EPAD PoC trial, the transition 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. Research participants who fail to meet the entry criteria for the EPAD PoC trial may return to EPAD LCS if they wish to at their next scheduled visit. The LCS visits for the returning research participants from PoC will be scheduled for the same time as their normal, annual LCS visit would have been due.

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 AEs potentially related to study procedures, follow-up must be reported until the AE has abated, or until a stable situation has been reached, with findings being recorded in the eCRF.

3.5.1. Participant Re-Screening

If a participant screen fails for a reason that the Investigator deems resolvable then it is possible to rescreen the participant at a later date, with prior approval from the Chief Investigator. In the event of a re-screen the participant should be given a new study identification number and it should be clearly marked within the study data that the participant previously screen failed. If the participant screen fails on a second occasion, then there should be no attempt to include them further in the study. It should be under the investigators guidance and best interests of the participant if any action is taken to re-screen for the study (i.e. withdrawal from an active CTIMP to re-screen).

3.5.2. Lost to Follow up

An individual may be considered as lost to follow up when the TDC has conducted 3 follow up attempts to schedule a study visit with any participant that is not responsive. All attempts should be documented in source documentation at the TDC which should include the date, time and outcome.

4. STATISTICAL ANALYSIS METHODS

4.1. Determination of Sample Size

A constant sample size of approximately 3,500 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 June 2020 is 3,500.

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 BC 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 CTIMP, only AEs 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 UoE. 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 UoE 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

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

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. All informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task.

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. All informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task.

c. *Transition into EPAD PoC Trial*

A transition visit will take place for research participants who are invited to participate in the EPAD PoC trial. Research participants who are potentially eligible for entry into the EPAD PoC trial will be contacted by EPAD LCS staff. The participant will be informed that they may be eligible to join the EPAD PoC trial and will be invited to attend the site with their study partner for further discussions and to complete some brief assessments. Disclosure discussions about reasons for eligibility to join EPAD PoC trial may be completed during the initial telephone call, during a face to face visit or both, and can be supplemented with additional calls as required by participant to ensure understanding. At the transition visit the participant will receive an overview of the PoC trial design including the potential allocation arms and, if willing in principle to be allocated to any and all open arms, provide consent to be randomly allocated to one of the ongoing appendices in the EPAD PoC trial. The participant will be informed of the outcome of this allocation and provided with detailed written information concerning potential participation in the Appendix, i.e. that allocation to the Appendix does not automatically imply eligibility for the Appendix, and that participation is subject to separate informed consent and subsequent screening procedures.

d. Identification of study partners

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 for face to face contact with the EPAD LCS staff at the local TDC. Study partners must sign and ICF before any study procedures can take place with the study participant.

EPAD LCS will recruit participants with no or only minor cognitive impairments, and therefore will not include participants at baseline visit who do not have the capacity to provide informed consent. The study partner has the role of an informant. If a participant loses capacity during the study they will be eligible to continue in the LCS. When re-consent becomes necessary, due to updated study information or regulatory requirements to re-consent at loss of capacity, this can be done using a legal representative consent form. The legal representative may or may not be the study partner and local regulations will apply on who can act as the legal representative.

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 without explanation. During scheduled EPAD LCS visits the research participants and study partners will be informed about new developments within the EPAD project and given a refresher on existing study information, 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. Research participants can be withdrawn from EPAD LCS for safety reasons or if the research participant is not compliant with protocol procedures, or if the Sponsor decides to stop the study. Research participants may also be deselected from the study by recommendation of the Balancing Committee and the agreement of their PI.

EPAD LCS research participants and study partners may withdraw consent at any time without explanation. Withdrawal will result in the research participant not being re-contacted by EPAD any further (this implies not to have new data collected), while allowing for the further use of already collected data.

If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. If a participant is de-selected this following recommendation by the Balancing Committee and discussion with their PI, this would not be considered a deviation should the PI be unblinded to the results.

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. If a study partner is required to re-consent at any time when their relative or friend is a participant in the LCS, this can be done either at the TDC or via post.

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. Disclosure will take place in case this is specifically requested by a participant i.e. results can be made available to a participant on their request. CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, even if biomarker status is disclosed.

Investigators cannot be blinded to results of some 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 ≥1 represent exclusion criteria at baseline. 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 ≥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 Ongoing Communication with Research Participants) 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. Data Protection

All investigators, TDC study site staff and other parties involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation) with regard to the collection, storage, processing and disclosure of personal information. Computers used to collect the data will have limited access measures via user names and passwords.

6.5.1. Personal Data

Depending on country regulation and TDC requirements, personal information (including participant name, date of birth, gender, ethnicity, race, contact details, gender, health provided/social identification number) and other information relating to the social identity of a participant may be recorded in the TDC medical records/source data notes.

Personal information will be stored by the TDC staff working on the project in a secure location, which is only accessible to TDC staff working within the project.

The relevant data controller will ensure that research participants' personal information is appropriately managed, and research participant and study information are treated as confidential. The investigators at each TDCs will ensure that the research participant personal 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 shall be stored in the Investigator Site File.

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 research participants in some countries. These requirements will be followed as appropriate.

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.

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.

6.5.2. Transfer of Data

Data collected or generated by the study will be transferred to IQVIA, ARIDHIA and other relevant third parties to manage on behalf of UoE.

6.5.3. Data Controller

UoE shall be a data controller along with any other entities involved in delivering EPAD LCS that may be a data controller in accordance with applicable laws (e.g. relevant TDCs).

6.5.4. Data Breaches

Any data breaches will be reported to the UoE Data Protection Officer who will report to the relevant local authority according to the appropriate timelines if required. Any data breaches will be reported in accordance with applicable laws.

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 e-mail (as per local policy). Regular phone and/or email contact has been planned, and research participants will also have the opportunity 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 members/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 (UoE) 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 UoE and collaborators. UoE has insurance in place (which includes no-fault compensation) for negligent harm caused by protocol design by the Chief Investigator and researchers employed by the UoE.
- 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. UoE 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. Travel expenses and meal/refreshments may be covered as necessary as per local TDC policies.

7. STUDY ADMINISTRATION

7.1. Protocol Amendments

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 Chief Investigator and Sponsor.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB), Regulatory Authority and local R&D (if applicable) for approval prior to implementation.

7.2. Protocol Violations and Deviations

7.2.1. Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

7.2.2. Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented.

7.2.3. Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. Deviation logs / violation forms will be transmitted via email to QA@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

7.3. Serious Breach Requirements

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief Investigator, Principal Investigator or delegates, the Sponsor (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to the IEC/IRB as necessary.

7.4. 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.

7.5. 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 Documents.

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.

7.6. 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 IQVIA and will be maintained in the Trial Master File atUoE.

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) IQVIA. 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.

7.7. 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.

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

IQVIA 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 IQVIA, 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 IQVIA and records retention for the study data will be consistent with their standard procedures. Data from the IQVIA 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.

7.8. 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 the 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.

7.9. 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. 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 IQVIA 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.

7.10. 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.

7.11. 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.

7.12. Use of Information

All results from this study will be owned by UoE. Only UoE can publish these and when doing so needs to comply with the publication approval procedure in the EPAD Project Agreement. Published results will not contain any personal data that could allow identification of individual participants.

8. STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 Study Management Group

The trial will be coordinated by a Project Management Group within UoE, known as the Chief Investigator's Office (CI Office). This group consists of the Chief Investigator and Principal Investigator in Edinburgh,the Global Trial Lead and the Depute Global Trial Lead. This group has oversight of the LCS study

The Depute Global Trial Lead will oversee the study and will be accountable to the Chief Investigator and Global Trial Lead. Any queries will be resolved by the Chief Investigator or delegated member of the trial team.

A Contract Research Organisation (CRO), IQVIA, has been appointed by UoE, to manage and oversee responsibilities delegated to them by UoE. The CI Office and CRO meet regularly, and in addition also meet monthly with the Sponsor to discuss study progress. The UoE legal team also attend progress meetings with the CI Office and the Study Sponsor.

8.2 Study Oversight Meetings

Although EPAD LCS does not have a traditional Trial Steering Committee, EPAD LCS has a number of management groups which are responsible for overseeing the conduct and progress of the LCS study.

1. **Clinical Development Executive (CDEx)** – CDEx oversees activities related to operationalising EPAD LCS and is responsible for decision making on most issues related with the LCS. Such decisions involve technological decisions, and setting up of Task Forces to study/resolve specific issues. The main aim of CDEx is to provide a forum for all parties involved working in EPAD LCS to discuss activities in an efficient and collaborative manner. CDEx meets monthly.
2. **LCS Recruitment Task Force (RTF)** – The purpose of the recruitment task force is to meet more regularly than CEDEx and to ensure that recruitment is running smoothly and efficiently. Recruitment progress and resolving any issues which may be limiting recruitment are the main focus of this meeting.
3. **LCS Recruitment Core Team (RCT)** - The recruitment core team is a sub-set of the recruitment task force. The RCT concentrates on working at site level to improve issues at trial delivery centres and enhance recruitment.
4. **Research Participant Panel Meeting** - EPAD LCS has active research participant panel groups which meet every 6 months. These meeting are attended by the representatives of the participant's panel, the CI, and study co-ordinators. Representatives from the participant's panel are also invited to attend the annual EPAD general assembly meeting which is an opportunity for members from all disciplines who are working on EPAD LCS to meet.
5. **Edinburgh Project Operations Group** – EDPOG This local monthly meeting involves members from the CI Office, IQVIA, Sponsor Office and the Bioresource PI meeting to discuss the progress of EPAD LCS.
6. **Bioresource Meetings** - The Bioresource Team hold regular meetings with the CRO, CI Office and Study Sponsor to discuss sample collection, processing, returns, storage, transfer, site training and availability of results.
7. **Balancing Committee** - Meets monthly to check that recruited participants to EPAD LCS are suitable for the Proof of Concept Trial and can provide run-in data, suitable for disease modelling and suitable for risk stratification. Main focus is to provide a flexible algorithm for the TDCs, ensure it is providing sutable and adjust this as necessary.
8. **The Algorithm Running Committee** –Forwards the flexible algorithm to the TDCs.

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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 **Error! Reference source not found.**).

Details of the original protocol and amendments are provided below:

Protocol Version	Issue Date
Final Version 2.2 (Original protocol)	13 January 2016
Final Version 3.0	28 February 2017
Final Version 4.0	18 September 2018
Final Version 5.0	10 September 2019

Amendments are listed beginning with the most recent amendment.

Final Version 5.0 10 September 2019

The overall reason for the amendment: Added 3 new biomarkers, deleted EPAD Mini Process, and updated visit details and procedures for CSF sample collection and MRI assessments, updated collection of cortisol samples, modified blinding details of investigators and CDR, updated that study partners can be re-consented by post, updated that study partners can communicate by video call and changed the end of study date,

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)
Cover Page	Added EudraCT Number 2018-004617-41
Investigator Agreement	Removed ‘and package insert’
Protocol Synopsis	Study Description
	Recruitment Strategy and Procedures
	Selection Process
	Selection Parameters within EPAD LCS
	Data Sources and Collection
	Secondary Outcomes
	Other Measures
	Follow-up
	Study Period
List of Abbreviations	Removed EPAD DOC.
Table of contents	Table of contents

Applicable Section(s)	Description of Change(s)
1.2	Overall Rationale for EPAD LCS
3.2.1	Flow of Research Participants for PCs to EPAD LCS
3.2.3	EPAD LCS Mini
3.3	EPAD LCS Study Population
3.3.1	Eligibility criteria
3.3.3	Role of the Balancing Committee (BC) & Algorithm Running Committee (ARC)
3.4	EPAD LCS Data Sources and Collection
3.4.3	CSF Biomarker Outcomes
3.4.4	Neuroimaging Outcomes
3.4.5	Genetic Assessments
3.4.6	Other Measures
3.4.7	Biological Samples
3.4.8	4-Monthly Telephone Contact
3.4.9	Visit Windows
3.5	Study Completion or Withdrawal
6.2	Informed Consent
6.3	Potential Disclosure of Risk Information
6.6	Ongoing Communication with Research Participants
7.2.3	Management of Deviations and Violations
7.6	Case Report Form Completion
8.	Study Management and Oversight Procedures
8.1	Study Management Group
8.2	Study Oversight Meetings
9.	Addition of reference 38.
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)
Investigator Agreement Protocol Synopsis	Removed 'and package insert' Study Description: Changed the end of study date from Dec 2019 to end of June 2020 Recruitment Strategy and Procedures – Update information on informed consents. Selection Process: Updated the visit details for CSF sample collection to V1 and V4 and then every second year. Also added participants who score >1 on the CDR will not complete further MRI or CSF sampling, all other assessments will be completed annually. Removal of Data Oversight Committee. Selection Parameters within EPAD LCS: Added 3 new biomarkers 'TREM-2, neurofilament light and neurogranin' Data Sources and Collection: Deleted the statement that investigators will be blinded to results from genetic biomarker and neuroimaging assessments and added that CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, except if biomarker status is disclosed.. Secondary Outcomes: Added 3 new biomarkers 'TREM-2, neurofilament light and neurogranin' Exploratory Outcomes: Changed Cambridge University to University College London/University of York) to reflect IP ownership and agreement for the Four Mountains Test. Other Measures: Added 3 new biomarkers 'TREM-2, neurofilament light and neurogranin' Follow-up: Deleted the statement (to ensure a minimum of two cognitive assessments before potential recruitment into the EPAD PoC trial). Updated that CSF sample collection will be collected 2 years after baseline at V4 and then every second year and MRI assessments will be performed 2 years after baseline at V4 and then every second year. Added that all prodromal and preclinical participants who are eligible to join the PoC can leave the LCS after the baseline visit. Study Period: Changed the end of study date from Dec 2019 to end of June 2020 and removed the statement that research participants will have to have at least 6 months of participation in the EPAD LCS prior to recruitment in the EPAD PoC trial.
Table of contents	Updated Table of contents to include/deleted sections
1.2	Overall Rationale for EPAD LCS: Changed the end of study date from December 2019 to end of June 2020
3.2.1	Added that all informed consents should be taken by Principal Investigator or medical practitioner
3.2.3	EPAD LCS Mini was removed from the protocol

3.3	EPAD LCS Study Population: Changed the end of study date from December 2019 to end of June 2020 and removed the statement that research participants will have to have at least 6 months of participation in the EPAD LCS prior to recruitment in the EPAD PoC trial.
3.3.1	Eligibility criteria: Modified the eligibility criterion regarding age to 'Age at least 50 years, checked and recorded at Screening (Visit 1) only, as well as fulfilling the criteria set by the balancing committee'. Added that study partner is required to reconsent at any time when their relative or friend is a participant in the LCS, this can be done either at the TDC or via post. Provided logisitics for postal method. Added that study partner can be contacted by video.call.
3.3.3	Role of the Balancing Committee (BC) & Algorithm Running Committee (ARC): Added 3 new biomarkers 'TREM-2, neurofilament light and neurogranin' Expanded on role of BC and ARC.
3.4	EPAD LCS Data Sources and Collection: Deleted the statement that investigators will be blinded to results from genetic biomarker and neuroimaging assessments and added that CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, except if biomarker status is disclosed.. Added that overall probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy of current disease models, but will be disclosed at participant's request
3.4.1	Allocentric Space: Four Mountains Task (Cambridge University) replaced with Four Mountains Task (University College London/University of York).
3.4.3	CSF Biomarker Outcomes: Added that CSF sample will be collected at baseline (V1) and 2 years (V4) and then every second year as collection every 2 years should relect changes in AD related markers.. Modified the procedure for CSF sampling and MRI. Added if CSF can't be obtained at Visit 1 the Medical Monitor should be contacted and also if can't be obtained at either Visit 2 or Visit 3 the Medical Monitor should also be contacted. Added 3 new biomarkers 'TREM-2, neurofilament light and neurogranin'. However, these biomarkers will not be analysed at University of Gothenburg. Section number was added.
3.4.4	Neuroimaging Outcomes: Modified the procedure for CSF sampling and MRI. Added that Core MRI imaging will be repeated at 2 years and then every second year for all EPAD research participants. Added explanation to indicate why MRI should be taken every 2 years. Added a statement that it can also apply to subsections of the protocol as long as the specifications are similar to the EPAD Imaging protocol. Section number was changed.
3.4.5	Genetic Assessments: Section number was changed
3.4.6	Added that CDR raters, where possible, should be blinded, as far as possible, to all other cognitive and clinical assessments, except if biomarker status is disclosed. Rationale added as to why CDR raters should remain blinded.Section number was changed.
3.4.7	Biological Samples: Annual CSF sampling procedure for participants was removed. Changed steroidal anti-inflammatory drugs to steroidal preparations e.g. oral, cream, ointment, inhaled or drops. Added that CORTISOL samples will be collected at baseline (Visit 1) and at 2 years (Visit 4) and then every 2 years...Section number was changed.

3.4.8	4-Monthly Telephone Contact: Deleted the procedure of informing the participants about current portfolio of open trials. Added that there will be window of +/- 14 days surrounding the date of each 4-month phone call during which it can be performed. The 4-monthly point of contact should preferably be in the form a phone call, but if a participant prefers to be contacted by email then this is permitted as an alternative form of contact. Sites who contact their participants by email must do so as per their local email policy. Section number was changed.
3.4.9	Visit Windows: Section number was changed
3.5	Study Completion or Withdrawal: Changed the end of study date from December 2019 to June 2020 and removed the statement that research participants will have to have at least 6 months of participation in the EPAD LCS prior to recruitment in the EPAD PoC trial. Also removed the statement 'Due to investigator's decision, e.g. research participant considered as not contributing to the overall probability spectrum.' Added decision by Balancing Committee to select/deselect individual partiicpants and the Algorithm Running Committee will provide the output for the PCs.
3.5.2	Participants Lost to Follow-up: Modified the section to 'An individual may be considered as lost to follow up when the TDC has conducted 3 follow up attempts to schedule a study visit with any participant that is not responsive. All attempts should be documented in source documentation at the TDC which should include the date, time and outcome.'
6.2	Informed Consent-Removed 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 Study Population). Added that research participants can be withdrawn from EPAD LCS for safety reasons or if the research participant is not compliant with protocol procedures, or if the Sponsor decides to stop the study. Also added that research participants may also be deselected from the study by recommendation of the Balancing Committee and the agreement of their PI. Also added if a participant is de-selected this following recommendation by the Balancing Committee and discussion with their PI, this would not be considered a deviation should the PI be unblinded to the results. Added that if a study partner is required to consent at any time when their relative or friend is a participant in the LCS, this can be done either at the TDC or via post. Added that all informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task.
6.2.b	Added that all informed consents must be taken by either the Prinicipal Investigator or another medical practitioner who has been delegated this task.
6.3	Potential Disclosure of Risk Information: Added that disclosure will take place in case this is specifically requested by a participant. Deleted the statement that investigators will be blinded to results from genetic biomarker and neuroimaging assessments and added that CDR raters, where possible, should be blinded to all other cognitive and clinical assessments, even if biomarker status is disclosed.
6.6	Ongoing Communication with Research Participants: Added an option for e-mail (as per local policy)

6.7	Insurance and Incentives/Compensation for Research Participants: Reworded the section to 'No financial compensation will be provided to research participants for participating in EPAD LCS. Travel expenses and meal/refreshments may be covered as necessary as per local TDC policies.'
7.2.3	Management of Deviations and Violations: Decreased the time of submission of protocol deviation logs from 6 months to quarterly (4 months)..
7.5	Source data agreement changed to source data documents.
7.6	Changed that Trial Master held is by UoE rather than IQVIA.
8	Insertion of section titled "Study Management and Oversight Arrangements".
8.1	Addition of details of the Study Management Group.
8.2	Addition of details of Study Oversight Meetings.
9	Addition of reference 38.
List of In-Text Tables and Figures	Updated the list of In-Text Tables and Figures
Protocol Amendments	Protocol Amendments: Added summary of changes table for version 5.0
Data Collection Schedule	Data Collection Schedule: Table and Footnotes Footnote a. Added -if a participant develops a condition listed in exclusion criteria e.g. cancer during the follow up period (from visit 2 onwards), the participant may continue in the trial if treating physician and participant agree. Added to footnote b that informed consent must be taken by the Principal Investigator or medical practitioner who has been delegated to do so. Previous footnote g now renamed as footnote f. Removed previous footnote h i.e. CDR and MRI was removed. Previous footnote i now becomes renamed as footnote g: Footnote g changed to allow participant to choose to defer the baseline lumbar puncture to the 12 month visit. Previous footnote j renamed as footnote h and CSF sampling schedule relating to CDR score 0 is now removed. Also added to footnote h 'Participants may become unable for medical reasons to undergo the CSF sampling procedure. These participants will be allowed to remain in the study without completing CSF sampling at future time-points. Participants who score >1 on the CDR will not complete further MRI of CSF sampling, all other assessments will be completed annually MRI scan is performed at V1, V4, and then every second year following V4. Therefore MRI scan and LP at V5 was removed as it is only one year after V4. A footnote i was added to indicate that MRI scan and LP should be collected this year, and then every second year. Another footnote j was added to indicate that cortisol samples will be collected at baseline (Visit 1) and at 2 years (Visit 4) and then every second year. Footnote k added: if a lumbar puncture is performed at Visit 1 and no CSF can be obtained, then approval should be sought from the Medical Monitor on the participant's continuation in the trial. Attempts should be made at Visit 2 or Visit 3 to collect a sample from the participant. If no sample is obtained in these future visits then further discussion with the medical monitor should occur. Modified the Data Collection Schedule for Core MRI sequence, Advanced MRI sequence, and CSF sampling. Four Mountains Task (Cambridge University) replaced with Four Mountains Task (University College London/University of York.)

Final Version 4.0 18 September 2018

The overall reason for the amendment: Correcting administrative errors in the protocol, adding information on PrePAD Velocity, EPAD Mini and extending visit procedure window for MRI

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)	Section Title
Investigator Signature Page	Added signature page
Protocol Synopsis	Study Diagram
	Study Description
	Recruitment Strategy and Procedures
	Eligibility Criteria
	Selection Process
	Exclusion Criteria
	Follow up
	Study Period
Table of contents	Table of Contents
1.2	Overall Rationale for EPAD LCS
3.1	Study Design and Rationale
3.2.1.1	Flow of Research Participants from Clinical or Routine Cohorts
3.2.2	Selection Process
3.2.3	EPAD Mini
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)
3.4.3	CSF Biomarker Outcomes
3.4.4	Neuroimaging Outcomes
3.4.6	Other Measures
3.4.7	Biological Samples
3.4.8	3 Monthly Telephone Contact

Applicable Section(s)	Section Title
3.4.9	Visit Windows
3.5	Study Completion or Withdrawal
3.5.1	Participant Re-Screening
3.5.2	Participant Lost to Follow Up
4.1	Determination of Sample Size
6.1	Independent Ethics Committee or Institutional Review Board
6.2	Informed Consent
6.3	Potential Disclosure of Risk Information
6.5	Privacy of Personal Data
6.5.1	Personal Data
6.5.2	Transfer of Data
6.5.3	Data Custodian
6.5.4	Data Controller
7.1	Changes to the Protocol
7.2	Protocol Violations and Deviations
7.5	Case Report Form Completion
7.6	Data Quality Control
7.8	Monitoring
7.11	Use of Information
7.12	Data Protection
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	Description of Change
Investigator Signature Page	Added Signature page for PI’s acceptance of the Protocol
Protocol Synopsis	

	Study Diagram: updated to include new PoC transition visit, recruitment out with a parent cohort and updated participant numbers Study Description: updated target participant numbers Recruitment Strategy and Procedures: Added details around PrePAD Velocity participant identification and enrolment pathway Eligibility Criteria: Minor corrections around age, years of education and eligibility set by balancing committee Selection Process: Updated to include new imagining and CSF sampling schedule for participants with CDR score of 0 at baseline Exclusion Criteria: Updated wording around criteria of participation in other clinical trials and added exclusion criteria related to investigators opinion if the participant cannot follow the protocol requirements Follow up: Updated to include new imaging and CSF sampling schedule for participants with CDR score of 0 at baseline Study Period: updated to include clarifications around a participant's involvement in other clinical trials at the same time as this study
Table of contents	Updated Table of Contents to include new sections/page numbers
1.2	Updated number of participants expected to participate in the study
3.1	Updated to include new PoC transition visit, recruitment out with a parent cohort and updated participant numbers
3.2.1.1	Additional section to describe recruitment through clinical databases at TDCs (PrePAD Velocity)
3.2.2	Updated to include clarity on recruitment through Velocity
3.2.3	New section to detail EPAD mini – reducing the yearly imaging and CSF sampling requirements for participants with a CDR score of 0 at baseline. This reduces burden on participant and TDC
3.3.	Updated number of participants expected to participate in the study
3.3.1	Several clarifications added to eligibility criteria
3.3.2	Several clarifications added to exclusion criteria
3.3.3	Updated wording for sense and corrected reference to other sections within the protocol
3.4.3	Updated to include reduced CSF sampling regime within the study for CDR 0 participants at baseline. Added details if Amyloid PET scan results are available for the participant, they may defer CSF sampling to Visit 3. This reduces burden on participant and TDC.
3.4.4	Updated to reduce requirement for MRI on participants with a CDR score of 0 to a scan every 2 years. This reduces burden on participant and TDC.

Applicable Section	Description of Change
3.4.6	Added ECG requirement during physical exam if investigator deems necessary. Updated that the SNAC questionnaire does not need recompletion at follow up visits if the participant indicates there is no change to the answers previously given and updated for clarity that a rater who does CDR score for a participant should not rate any other scales on that individual.
3.4.7	Removed requirement for overnight fasting as there is no scientific rationale for this on these samples. Included clarity that no cortisol samples will be taken from participants taking steroidal anti-inflammatory drugs
3.4.8	Added section to include requirement for TDCs to do quarterly calls with all involved participants. To provide additional contact for each participant.
3.4.9	Updated to include ±42 day window for MRI on follow up visits to reduce TDC burden
3.5	Updated to include details of PoC transition visit and return to LCS after PoC Participation
3.5.1	Added section detailing guidance on participant re-screening.
3.5.2	Added section to include details of participants considered lost to follow up
4.1	Updated number of participants expected to participate in the study
6.1	Updated wording to simplify existing text to ensure all required country approvals are in place prior to starting study
6.2	Updated to include details of PoC transition visit and consent which will be taken at that time. Updated wording for Study partners, removing telephone contact and added wording on consent and procedure in the event of an active participant losing capacity
6.3	Updated to remove section on deselection of participants. Included wording to clarify procedure if participant develops a CDR score of greater than one.
6.5	Added section detailing Privacy of Personal data so protocol complies with General Data Protection Regulations
6.5.1	Added section detailing what personal data is collected from participants, data storage and use
6.5.2	Added section detailing data is transferred to IQVIA as CRO
6.5.3	Added section identifying the Chief Investigator as data custodian
6.5.4	Added section identifying UoE as Data controller
7.1	Updated to include clarification on amendment implementation and approvals required to actively use an amendment at TDC level.
7.2	Updated wording to comply with Sponsor SOPs on deviation/violation reporting.
7.5 & 7.6 & 7.8	Updated to updated all ‘Quintiles’ references to ‘IQVIA’ Changed
7.11	Updated to clarify all personal data will not be published in study results
7.12	Added section on how participant data is collected and how the study complies with GDPR
List of Attachments	Removed section
List of In-text Tables and Figures	Added Figure 2 relating to EPAD Mini

Protocol Amendments	Including section for Protocol V4.0
Data Collection Schedule	Added quarterly telephone contact visit Added PoC Transition visit with associated footnotes Added footnote to extend visit window for MRI to ±42 days Added footnotes to detail reduced MRI and CSF schedule for participants with CDR score of 0 at Baseline Added footnote regarding SNAC requirement

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
3.3.	EPAD LCS Study Population
3.3.1	Eligibility Criteria
3.3.2	Exclusion Criteria

Applicable Section(s)	Description of Change(s)
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

Applicable Section(s)	Description of Change(s)
	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
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

Applicable Section(s)	Description of Change(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 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

Applicable Section(s)	Description of Change(s)
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), 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

DATA COLLECTION SCHEDULE	Visit 1	Telephone contact	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits	PoC Transition Visit
Procedure	**Screening / Baseline**	**Every 4 months from date of Visit 1 ± 14 days**	**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[a]	X		X	X	X	X	X	
Research participant consent[b]	X							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 (Learning, Delay & Recognition) (University of California, San Francisco)	X		X	X	X	X	X	
Four Mountains Task (University College London/University of York))	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[i]	X				X		X[i]	
Advanced MRI sequences	X (subset)				X (subset)		X (subset)	

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CSF Sampling [g, k, h, i]	X[g, k]				X[h]		X[h, i]	
Blood, urine & saliva sampling[j]	X[j]			X	X[j]	X	X[j]	
Blood sample for Genetic Analysis (APoE)	X[e]							
Other assessments								
Socio-demographics (date of birth, sex, ethnicity, education, marital status)	X							
Family history of AD	X							
Height	X							
Weight, hip-waist circumference	X			X	X	X	X	
Medical history inc. BISQ	X			X	X	X	X	X[d]
Current medication	X		X	X	X	X	X	X
Lifestyle factors inc. HATICE & SNAC[f]	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	
Ongoing research participant safety assessment								
Adverse events [c]	X	X	X	X	X	X	X	X
Participant education								
Discussion about readiness cohort and Proof of Concept trials		X	X	X	X	X	X	

DATA COLLECTION SCHEDULE	Visit 1	Telephone contact	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits	PoC Transition Visit
Procedure	**Screening / Baseline**	**Every 4 months from date of Visit 1 ± 14 days**	**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]	
Willingness to participant in principle in Proof of Concept trials	X	X	X	X	X	X	X	

[a] Visit assessments will be completed within a 21-day window of the planned visit date tethered to the consent form signature date of Visit 1, with the exception of the MRI associated with the visit which should be completed within ± 42 days. The Eligibility will be checked fully at the baseline/visit 1 If a participant develops a condition listed in exclusion criteria e.g. cancer during the follow up period (from visit 2 onwards), the participant may continue in the trial if treating physician and participant agree.

[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. All informed consents must be taken by the Principal Investigator or medical practitioner who has been delegated to do so.

[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).

[d] Check for changes since last visit; do not repeat BISQ.

[e] Sample to be taken at baseline visit

[f] For SNAC : Participants only report recent events since last visit

[g] If participant has had a PET amyloid scan in the last 12 months , with results available to EPAD TDC for review and participant is aware of PET results they may choose to defer the baseline lumbar puncture to the 12 month visit. All participants are expected to have at least one lumbar puncture as part of the EPAD LCS cohort.

[h] Participants may become unable for medical reasons to undergo the CSF sampling procedure. These participants will be allowed to remain in the study without completing CSF sampling future time-points. Participants who score >1 on the CDR will not complete further MRI or CSF sampling, all other assessments will be completed annually.

[i]. MRI scan and LP should be collected this year, and then every second year

[j] Cortisol samples will be collected at baseline (Visit 1) and at 2 years (Visit 4) and then every second year.

[k] If a lumbar puncture is performed at Visit 1 and no CSF can be obtained, then approval should be sought from the Medical Monitor on the participant's continuation in the trial. Attempts should be made at Visit 2 or Visit 3 to collect a sample from the participant. If no sample is obtained in these future visits then further discussion with the medical monitor should occur.

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