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The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol

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ABSTRACT

Introduction: The European Prevention of Alzheimer's Dementia (EPAD) project is funded initially by the Innovative Medicines Initiative and has been established to overcome the major hurdles hampering drug development for secondary prevention of Alzheimer's dementia, by conducting the EPAD Longitudinal Cohort Study (LCS) in alignment with the Bayesian adaptive designed EPAD Proof of Concept (PoC) trial.

Methods and analysis: EPAD LCS is an ongoing prospective, perpetual, multicentre, pan-European, longitudinal cohort study. Participants are recruited mainly from existing Parent Cohorts (PCs) across Europe to form a "probability-spectrum" population covering the entire continuum of anticipated probability for Alzheimer's dementia development. EPAD LCS will include at any one time approximately 6,000 research participants. This sample size will be maintained by continuous refilling from PCs. The primary objective of the EPAD LCS is to be a readiness cohort for the EPAD PoC trial though a second major objective is to generate the most comprehensive and largest data set ever for disease modelling of preclinical and prodromal Alzheimer's disease. This characterisation of cognitive, biomarker and risk factor (genetic and environmental) status of research participants over time will provide the necessary well-phenotyped population for developing accurate longitudinal models for Alzheimer's disease covering the entire disease course and concurrently create a pool of highly characterized individuals for the EPAD PoC trial.

Ethics and dissemination: The study has received the relevant approvals from numerous Institutional Review Boards across Europe. Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Regular and coordinated releases of EPAD LCS data will be made available for analysis to help researchers improve their understanding of early Alzheimer's disease stages, and facilitate collaborations.

Study registration number: NCT02804789.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Prospective, perpetual, multicentre, pan-European longitudinal cohort study with a large sample size recruited mainly from existing Parent Cohorts
- Well-phenotyped "probability-spectrum" population covering the entire continuum of probability for Alzheimer dementia development.
- Disease modelling based on four dimensions including cognitive and other clinical features, biomarkers, risk factors (fixed and modifiable), and trajectories of change in these over time.
- Readiness population for a Bayesian adaptive designed Proof of Concept trial, with high quality run in, pre-randomisation data against which the impact of various interventions will be measured.
- Complex design based on flexible algorithms for recruitment from both general populations and clinical settings, in order to meet the dual need for developing accurate longitudinal Alzheimer's disease models, and adequate infrastructure for facilitating clinical trials.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia globally.[1] As the population ages, the number of people with dementia will rise, and the economic burden of AD will increase dramatically from an already high baseline (~ €262 billion in 2015).[2] Clinical trials targeting populations with manifest dementia have so far failed.[3] There is now consensus that the genesis of AD predates dementia onset by over 20 years,[4] presenting an opportunity for early disease course modification. The key challenge is to accurately identify individuals with a high probability of subsequent AD dementia development, who are suitable for trial inclusion and willing to participate in secondary prevention studies. Secondary prevention populations can have e.g. evidence of AD pathology through relevant biomarker abnormalities, but without a clinical diagnosis of dementia.[5]

Current proposals for defining an individual's probability for dementia development have focused mainly on the AD stage proximal to dementia onset, and have relied on a very limited number of factors, e.g. cognition and amyloid or tau biomarkers.[6-10] Disease models and their phenotypic expression needed for probability estimation in earlier disease stages are currently less well defined. It is important to firstly develop accurate disease models for dementia onset or AD progression in early, asymptomatic or mildly symptomatic disease stages. These people need to be followed-up longitudinally, after which they could be recruited into trials designed to reduce early disease burden and therein decrease the probability of developing dementia. Moreover, the refined definition of populations at risk of dementia will provide data for the optimal stratification of these populations to match onto tailored disease modifying therapies as the basis for better personalised medicine.[11]

The European Prevention of Alzheimer's Dementia (EPAD) is a project to develop an environment for and then test multiple different interventions targeting the secondary prevention of AD dementia.[5] The EPAD project is ongoing across Europe with 38 partners from academia and the

commercial sector. EPAD is conducting a Longitudinal Cohort Study (EPAD LCS) in alignment with a Bayesian adaptive designed EPAD Proof-of-Concept (PoC) trial (Figure 1). This article presents the EPAD LCS study protocol.

OBJECTIVES OF EPAD LCS

EPAD LCS is a prospective, multicentre, pan-European, cohort study that will have a well phenotyped "probability-spectrum" population (covering the entire continuum of anticipated probability for dementia development) 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 potential recruitment into the EPAD PoC trial. EPAD LCS has four main 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 four different dimensions: cognitive and other clinical features; biomarkers; risk factors (fixed and modifiable); and trajectories of change in these over time.

3. To use disease models for assessing where and why participants fall in the overall probability continuum spectrum, and thereafter inform selection of participants into 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.

EPAD LCS STUDY DESIGN AND METHODS

Use of Parent Cohorts (PCs)

EPAD LCS participants will be recruited mainly from different types of existing Parent Cohorts (PCs) across Europe (Table 1) to ensure fast recruitment of a probability-spectrum population covering the entire continuum of probability for AD dementia development.

Table 1. Pathways for recruitment into EPAD LCS

Parent Cohorts	*Research cohorts*	• Observational study with participants from the general population • Observational study with participants recruited from other sources • Prevention trial • Pre-existing trial readiness cohort
	Clinical/routine care cohorts	• Memory clinic based • General practitioner/primary care based
	Cohort eligibility criteria	• Active cohorts including participants without dementia aged at least 50 years • Willingness of the Principal Investigator of the Parent Cohort to provide research participants for EPAD LCS and EPAD PoC trial • Existing consent from participants for re-contact by Parent Cohort team, or possibility to obtain consent to re-contact by Parent Cohort team
PrePAD Velocity	Research participants coming directly from a clinical setting without a Parent Cohort.	

PrePAD: Participant Register for EPAD

To ensure PC engagement, 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) and regional initiatives like the Dementias Platform UK (DPUK). Many other cohorts will also be included as needed.

Potential EPAD LCS research participants will be identified by each PC team based on data in their own PC. To ease the search process, a data discovery software tool will be provided to PCs by EPAD. This tool has been developed for EPAD by EPAD study partners working with EMIF and DPUK.[12] The Participant Register for EPAD (PrePAD) solution sits within a broader selection environment that also contains two other key elements – namely the Balancing Committee and Algorithm Running Committee.[13] A flexible search algorithm adapted to the types of data available in each PC will be used. Queries will be run that provide counts of participants according to the search algorithm which varies on the basis of several factors: available data in the PC; the

structure of the probability spectrum at any given time point in the EPAD LCS; the EPAD PoC trial's intervention pipeline; and the capacity at each EPAD LCS site to baseline and manage new participants.

PrePAD Velocity

Recruitment from existing PCs will be complemented with participants coming directly from a clinical setting (Table 1). In such cases, the participant or referring clinician will contact the local EPAD LCS site directly. The referring clinician will verify if potential participants match the aforementioned flexible algorithm, based on assessments available in the referring clinical setting. This will occur when amyloid status of the patient is known from their clinical work up – this mechanism therefore optimises the balance in the LCS towards as large a proportion as possible to be amyloid positive by existing thresholds.

EPAD LCS study population

EPAD LCS eligibility and exclusion criteria are listed in Table 2. Due to the variety of recruitment sources, some EPAD LCS participants will be e.g. memory clinic patients without dementia, while others will be e.g. PC participants without dementia from the general population.

Table 2. Criteria for selection of EPAD LCS participants.

Eligibility criteria	• Age at least 50 years • Characterisation of cognitive, biomarker and risk factors (genetic, environmental) status of research participants based on data collected at the EPAD screening/baseline visit, so that decisions on selection/deselection can be made with reference to the dual needs of having sufficient heterogeneity across the entire probability-spectrum population for disease-modelling work, and suitable research participants for the EPAD PoC trial (Balancing Committee decision, Table 3) • Able to read and write and with minimum 7 years of formal education • Willing in principle to participate in the EPAD PoC trial subject to further informed consent • Have a study partner or can identify someone willing in principle to be a study partner (e.g. relative or friend who is at least 18 years old, may or may not live together with the participant, and is available either for face to face or telephone contact with the

	EPAD LCS team). As EPAD LCS participants do not have dementia, have no or only slight impairment (i.e. Clinical Dementia Rating, CDR 0 or 0.5), and are fully capable of providing informed consent (as per Exclusion criteria), the primary role of the study partner in EPAD LCS will be as informant.
Exclusion criteria	• Research participants who fulfil diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLB, NINCDS-AIREN Criteria for Vascular Dementia) • CDR>=1 • Known carriers of a PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD or any other neurodegenerative disease • Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse; or major psychiatric disorders including current major depressive disorder, schizophrenia, schizoaffective or bipolar disorder. • Any cancer or history of cancer in the preceding 5 years (excluding cutaneous basal or squamous cell cancer resolved by excision) • Any current medical conditions that are clinically significant and might make the subject's participation in an investigational trial unsafe, e.g., uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including revascularisation procedures; severe renal or hepatic failure; unstable or poorly controlled diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in men); any clinically relevant abnormalities in blood parameters included in local routine assessments; severe loss of vision, hearing or communicative ability; or any conditions preventing co-operation or completion of the required assessments in the trial, as judged by the investigator • Any contraindications for MRI/PET scan • Any contraindications for Lumbar Puncture • Any evidence of intracranial pathology which, in the opinion of the investigator, may affect cognition including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. 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. • Participation in a Clinical Trial of an Investigational Product (CTIMP) in the last 30 days (continued participation in the parent cohort is expected). Participation in a non-CTIMP is not an exclusion criterion • Diminished decision-making capacity/not capable of consenting at the screening or 6-month visit. If at a subsequent annual EPAD LCS visit health professionals suspect diminished consent capacity according to local 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). 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. Capacity will be assessed at each study visit using the correct legal framework.

AD: Alzheimer's disease; APP: amyloid precursor protein; DLB: dementia with Lewy bodies; FTD: fronto-temporal dementia; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (now Alzheimer's Association); NINCDS-AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PSEN: presenilin; MRI: magnetic Resonance Imaging; PET: Positron Emission Tomography

At any given time after initial overall recruitment target is achieved, there should be approximately 6,000 participants in the EPAD LCS. Population size will be maintained over time by continuous refilling from the PCs or via PrePAD Velocity. Initial duration of EPAD LCS will be 4 years to December 2019 (which represents the duration of Innovative Medicines Initiative-IMI funding), and after that extension of consent will be asked from participants who are still eligible for EPAD LCS. EPAD LCS participants will not be asked to leave their PCs, and those who participate in the EPAD PoC trial (approximately 1,500 participants at any one time with at least 6 months' follow-up in EPAD LCS) and 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.

EPAD LCS participant selection process

Interventions must start early in the course of AD, but accurate disease models covering the entire disease course before dementia onset are lacking. As one objective of the EPAD LCS is for disease modelling, selection bias needs to be minimised by not over-specifying criteria for EPAD LCS inclusion. 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 and changes in these factors over time). 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).

The tools used to maintain the probability-spectrum population in EPAD LCS, and parameters considered for estimating an individual's overall probability of developing AD dementia are listed in Table 3. 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 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. The 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 resides with the EPAD Balancing Committee, made up of biostatisticians, data managers and LCS senior investigators.

EPAD LCS research participants may be deselected after the screening visit if they do not contribute to the overall probability spectrum. Deselection will be managed by the EPAD LCS Balancing Committee, and investigators will be blinded to which dimensions/components do not contribute to the overall probability spectrum in individual participants in order to avoid an implicit disclosure. This is necessary because investigators will be blinded to results of new data collected in the EPAD LCS, namely CSF biomarkers of tau and amyloid, imaging results and apolipoprotein E (APOE) ε4 allele carrier status, to limit biases in clinical assessments that may affect disease modelling work in EPAD LCS. This blinding is only compromised if a research participant enters LCS via PrePAD with known and disclosed biomarker status or if the research participant enters an arm of the EPAD PoC which requires only amyloid (or other biomarker) positive individuals.

Table 3. EPAD LCS participant selection process - novel approach based on flexible algorithms instead of simple cut-offs.

The three main tools for maintaining the probability-spectrum population
1. *Flexible algorithm for identification of potential participants by Parent Cohort teams and clinical settings using PrePAD Velocity*. Variations in the algorithm will be determined by types of data available in different Parent Cohorts. The algorithm will be applied potentially every month by the EPAD LCS Balancing Committee, and the output will be provided to each Parent Cohort by the Algorithm Running Committee. For PrePAD Velocity, the algorithm will be agreed upon by the Balancing Committee based on information about assessments available in each referring clinical setting. The Algorithm Running Committee will provide a checklist to the referring clinician for verifying eligibility before contacting the local EPAD LCS site. 2. *Oversampling or under-sampling from different types of Parent Cohorts and clinical settings*. Decisions will be made by the Balancing Committee based on EPAD LCS cognitive, biomarker and risk factor parameters, as well as types of data/assessments available in different Parent Cohorts, and clinical settings using PrePAD Velocity. 3. *Flexible algorithm for deselecting research participants after the EPAD LCS screening visit.* The Balancing Committee will agree on the use of EPAD LCS cognitive, biomarker and risk factor parameters for deselecting research participants.
EPAD LCS parameters considered for estimating overall probability of developing AD dementia
Cognitive parameters These will be based on the following Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) parameters which in combination 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* • Cerebrospinal fluid (CSF) biomarkers: beta-amyloid, total tau, phosphorylated tau • Neuroimaging parameters: hippocampal and whole brain volume; vascular burden (white matter lesions, 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 • 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

EPAD LCS outcomes and other assessments

EPAD LCS outcomes, other assessments and the data collection schedule are detailed in Table 4 and Table 5. The assessments are based on recommendations developed by the five EPAD Scientific Advisory Groups (SAGs) (Clinical and Cognitive Outcomes, Epidemiology, Fluid Biomarkers, Genetics, and Imaging). SAGs recommendations were based on reviewing the current literature, following widely accepted practices, and minimizing participant burden.

Table 4. EPAD LCS outcomes and other assessments.

Primary cognitive outcome	The *RBANS Total Scale Index Score* based on: • 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
Secondary outcomes	*Cognitive outcomes* • Working memory: Dot counting (NIH EXAMINER,[19, 20]) • Choice reaction time and set shifting: Flanker (NIH EXAMINER) • Paired associate learning: Favourites (University of California, San Francisco,[21]) *CSF biomarkers* • Beta-amyloid, total tau, phosphorylated tau *Neuroimaging outcomes (MRI)* • Hippocampal and whole brain volume
Exploratory outcomes	*Cognitive outcomes* • Allocentric Space: Four Mountains Task (Cambridge University, [22]) • Navigation in Egocentric Space: Virtual Reality Supermarket Trolley (University College London, [23]) *Other clinical outcomes* • Amsterdam Instrumental Activities of Daily Living Questionnaire [24, 25] *Neuroimaging outcomes* • Multi-region structural MRI analysis • Functional regional and network measures
Other assessments	• *Sociodemographics*: date of birth, sex, ethnicity, years of formal education, marital status • *Family history of AD* (first degree relatives) • *APOE* genotype, Polygenic Scores • *Medical history* (yes/no): stroke, diabetes mellitus (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 (Brain Injury Screening Questionnaire (BISQ, [26]), Mild Cognitive Impairment, other conditions • *Current medication*: name of drugs; treatment duration (<1year / 1-5years / >5years)

	• *Physical examination*, including e.g. neurological examination, blood pressure, pulse, weight, height, and hip-waist circumference measurements • *Handedness* • *Lifestyle factors*: - Smoking (never / past / current) - Alcohol consumption (units/week) - Drug abuse/misuse (never / past / current) - Diet (questionnaire, Healthy Ageing through Internet Counselling in the Elderly, HATICE [27]) - Physical activity: leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating. Frequency 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 [28, 29] - Life events (brief questionnaire based on the Swedish National study on Aging and Care, SNAC [30]) - Self-rated health and self-rated fitness (Likert-type questions with response options very good / good / satisfactory / relatively poor / very poor [29]) • *MMSE*, Mini-Mental Status Exam [15] • *CDR*, Clinical Dementia Rating Scale [16] • *GDS*, 30-item Geriatric Depression Scale [31, 32] • *STAI,* State-Trait Anxiety Inventory [33] • *Pittsburgh Sleep Quality Index* [34] • *Dementia* diagnosed by the participant's physician, including type and date of diagnosis • *Collection of CSF and blood, urine & saliva samples* for future biomarker assessments (emerging AD biomarkers)

Table 5. Data collection schedule.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
Eligibility criteria	X	X	X	X	X	X
Research participant consent[b]	X					
Cognitive outcomes (ENE battery)						
RBANS	X	X	X	X	X	X
Dot Counting (NIH EXAMINER)	X	X	X	X	X	X
Flanker (NIH EXAMINER)	X	X	X	X	X	X
Favourites (University of California, San Francisco)	X	X	X	X	X	X
Four Mountains Task (Cambridge University)	X	X	X	X	X	X
Virtual Reality Supermarket Trolley (University College London)	X	X	X	X	X	X
Clinical outcomes						
Amsterdam Instrumental Activities of Daily Living Questionnaire	X		X	X	X	X
Biomarkers						
*Core MRI sequences	X		X	X	X	X
Advanced MRI sequences	X (subset)		X (subset)	X (subset)	X (subset)	X (subset)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
**CSF sampling	X		X	X	X	X
Blood, urine & saliva sampling	X		X	X	X	X
Other assessments						
Socio-demographics (date of birth, sex, ethnicity, education, marital status)	X					
Family history of AD	X					
Medical history	X		X	X	X	X
Current medication	X	X	X	X	X	X
GDS	X		X	X	X	X
STAI	X		X	X	X	X
Pittsburgh Sleep Quality Index	X		X	X	X	X
Lifestyle factors	X		X	X	X	X
Dementia diagnosed by physician	X	X	X	X	X	X
CDR	X	X	X	X	X	X
MMSE	X		X	X	X	X
Physical exam	X		X	X	X	X
Height	X					
Weight, hip-waist circumference	X		X	X	X	X
Blood pressure	X		X	X	X	X
Ongoing research participant safety assessment						
Adverse events[c]	X	X	X	X	X	X

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

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

[c] All adverse events deemed by clinical judgement to be at least possibly related to EPAD LCS study procedures are to be recorded in the CRF. Adverse event collection should start with the first EPAD LCS procedure and will apply to all adverse events that occur within 30 days after a research participant's last study visit/procedure.
When an enrolled participant completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s).
* If an individual participant has had an MRI to the specifications in the Core EPAD Scanning protocol within 12 months of the Visit 1 first assessment of the EPAD LCS then this scan can be provided for analysis for the Visit 1 baseline data.
** If an individual participant refuses a lumbar puncture at Visit 3 or a subsequent annual visit this will be defined as missing data. If the participant refuses a lumbar puncture at two sequential visits, then they will be withdrawn from the EPAD LCS as a non-compliant participant.
If an individual participant has had a lumbar puncture and CSF sample collected and stored according to the CSF sampling manual procedure within 12 months of the Visit 1 first assessment of the EPAD LCS then this sample can be provided for analysis for the Visit 1 baseline data.

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; CDR - Clinical Dementia Rating; MMSE - Mini Mental State Exam.

Cognitive Outcomes

The selection process for EPAD LCS cognitive outcome measures has been described in detail elsewhere.[14] The final EPAD Neuropsychological Examination (ENE) battery (Table 4) was chosen to adequately cover all relevant cognitive domains, with greatest possible sensitivity to early-stage changes. 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.

For LCS purposes, primary outcomes include anchor or criterion measure(s) that have been accepted by regulatory authorities in previous registration trials. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will serve as the criterion measure for this study.[14] For statistical purposes, the RBANS Total Scale Index Score (Table 4) will serve as the primary outcome. Secondary cognitive outcomes are those either in need of additional psychometric validation, validation of alternative forms and/or lack normative data. Exploratory cognitive outcomes are those untested in large population-based studies and/or in need of psychometric validation. 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.

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 conducted in

compliance with GCP, including the primary outcome, the computerized secondary and exploratory measures are undergoing additional validation in EPAD LCS and, thus, do not yet fully meet GCP.

CSF biomarker outcomes

Measurements will include AD-related markers (beta-amyloid, total tau and phosphorylated tau), and this data will be used for disease modelling and for staging of disease pathology. CSF sampling follows a harmonised preclinical protocol and analyses take place using the fully automatized Roche Elecsys System in a single laboratory (University of Gothenburg). Additional CSF is stored in the EPAD BioBank at the Roslin Research Institute, University of Edinburgh with all other fluid samples.

Neuroimaging outcomes

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 APOEε4 allele. 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.

The Magnetic Resonance Imaging (MRI) acquisition is divided into:

[1] Core image acquisition, conducted in all LCS participants to assess study eligibility, for baseline assessment that can be used for subsequent safety monitoring in the EPAD PoC trial, and for

quantitative analysis of brain structure and vascular lesions. ADNI-like protocols and quality control will be used to ascertain precision in measuring change.

[2] Advanced image acquisition, which only a sub-set of sites with suitable equipment and experience will acquire. This may include on or more of the following types of acquisition: 3D-Susceptibility Weighted Imaging or 3D-T2*, Diffusion Tensor Imaging, Arterial Spin Labelling, and resting state functional MRI.

Genetic Assessments

The primary genetic assessment will include APOE genotype. The samples may also be sequenced when additional resources become available. Genetic variants with strong effect (e.g. 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 individuals with early onset AD, and are therefore unlikely to be included in the EPAD LCS.

Other assessments

A broad range of sociodemographic, medical and lifestyle-related data will be collected (Tables 4 and 5). Mini-Mental Status Exam (MMSE) [15] and Clinical Dementia Rating scale (CDR) [16] will be used given their utility principally as clinical descriptors. Biological samples will include blood, urine and saliva (e.g. for cortisol measurements) stored under optimal conditions in the central EPAD Biobank.

Data Sources, collection and monitoring

The only data source for this study will be the data collected as part of the EPAD LCS. Electronic data capture will be used as appropriate, e.g. for cognitive and imaging data. Central laboratories will be used for all CSF (University of Gothenburg) and genetic (University of Edinburgh)

assessments, and central reading of all neuroimaging will be undertaken. A common pre-analytical procedures schedule for sample collection, storage and shipment will be used at all EPAD LCS sites. The study will be monitored in accordance with the ICH GCP (ICH Topic E6, 1996).

STATISTICAL ANALYSIS

Sample Size

A constant sample size of approximately 6,000 participants for the EPAD LCS is considered sufficient for a readiness cohort that should provide approximately 1,500 participants for the EPAD PoC trial. The EPAD LCS sample size will be maintained through continuous recruitment from the PCs and via PrePAD Velocity. Strategies for motivation and engagement, as well as improving the research experience for participants will be developed, including e.g. newsletters, websites and telephone contact from the study sites.

Disease modelling principles

As EPAD LCS research 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 and pre-defined intermediate disease states (e.g. decline in cognitive function or increase in amyloid burden). 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 participants from the EPAD LCS into subsequent arms of the EPAD PoC trial. As data accrues in the EPAD LCS, soft data locks and releases will occur after 500, 1000, 2000 (and by intervals of 1,000 thereafter) and by stage of follow up e.g.

baseline, 1 year, 2 year etc. to inform selection algorithms for EPAD LCS; provide updated information for improving selection into the EPAD PoC trial; and provide updated disease models. These updated models will be submitted for peer-reviewed publication.

SAFETY

As EPAD LCS is not a Clinical Trial of Investigational Medicinal Product (CTIMP), only adverse events (AE) and serious adverse events (SAE) potentially related to EPAD LCS study procedures (e.g. lumbar puncture for CSF sampling) will be recorded and reported as appropriate. An AE is defined as any untoward medical occurrence in a 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. Information to be collected includes type of event, onset date, severity, date of resolution as well as treatment required, investigations needed and outcome. The severity assessment will be made by the investigator: 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).
(S)AEs will be recorded throughout the study from the time a participant undergoes the first EPAD LCS procedure until 30 days after the participant has completed the EPAD LCS (last procedure).

ETHICAL ASPECTS

The 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. EPAD LCS has received ethical approval from numerous institutional review boards (IRBs) across Europe.

EPAD has an Ethics Workgroup examining the complex ethical considerations involved in the project, and providing appropriate recommendations.[17, 18]

Informed consent

As the EPAD project is extended over time and multi-staged, staged consent will be used as decision making model.[17] Staged consent feeds relevant/indispensable/'material' information – bit by bit, extended over time - to participants and study partners, and asks informed consent at every moment in which important decisions need to be made by 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 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. Within the EPAD programme a series of videos have been created (http://ep-ad.org/) to compliment written information, and these videos form a fundamental part of the entire EPAD consent process. Recruitment from PCs is conditioned by existing consent from participants for re-contact by PC teams, or possibility to obtain consent to re-contact by PC teams according to local regulations. Written informed consent for EPAD LCS is obtained from participants and study partners before the screening/baseline visit. This does not imply consent for the EPAD PoC trial, which is subject to separate informed consent. EPAD LCS consent procedures make it clear that consent can be refused at any stage, and participants and study partners can withdraw from the study at any time.

Potential Disclosure of Risk Information

Overall estimated probability for developing Alzheimer's dementia will not be disclosed to research participants due to insufficient accuracy/robustness of current disease models. However, findings with established clinical relevance and requiring further monitoring and treatment will be disclosed to research participants and, with their consent, appropriate referrals to the primary care or treating physician will be made. AD-related CSF biomarkers may be disclosed if progression to AD dementia is suspected during EPAD LCS or where it is considered relevant to an individual's ongoing clinical management.

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 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 recruitment to enable them to make an informed decision about whether they want to learn this information. Ongoing communication with participants will be used to address any stressful situations that may occur during recruitment and course of the study.

Privacy of Personal Data

EPAD LCS will ensure that data on participants are appropriately managed, and participant and study information are treated as confidential. All participant study records are identified by the participant identification number to maintain participants' confidentiality.

PCs are not required to share their data with EPAD. The data discovery process does not allow EPAD any access to individual-level data from PCs. During the informed consent process, participants will be asked if they consent to information from EPAD LCS assessments being returned to their respective PCs.

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

EPAD Research Participants Panel

The Panel has been established to provide feedback of the experience of research participation, to ensure that participant perspectives are represented in decision making about the future of the project and to advise local and central EPAD LCS teams. The local panel will consist of 6-10 EPAD LCS participants at each site, and will meet at least twice annually. All EPAD LCS participants at a site 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. 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.

DISSEMINATION PLAN

Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Types of communication will include scientific publications, conference presentations, press releases, interviews and other media communications (including social media), meetings etc. Information and regular updates are posted on the EPAD project website (www.ep-ad.org).
Data collected from EPAD LCS will be made available for analysis to help researchers everywhere improve their understanding of the early, pre-dementia phase of AD, and facilitate collaborations.

DISCUSSION

The EPAD project has been established to overcome the major hurdles hampering drug development for the secondary prevention of AD dementia, by conducting the EPAD LCS in alignment with the Bayesian adaptive designed EPAD PoC trial. 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 participants and clinical trial recruitment. EPAD LCS thus takes a novel approach to dementia prevention, reflected in several key design elements.

Closing the previous gap between prediction and prevention

While several Alzheimer's dementia/disease prediction models have already been developed, very few have been validated, and none has been tested in a drug trial. Disease modelling work and Alzheimer's dementia probability estimations in EPAD LCS are designed in alignment with the adaptive EPAD PoC trial, thus ensuring a close link between prediction and prevention. The inclusion of participants from several European countries will also ensure the validity of disease and prediction models beyond selected single-country populations.

Well-phenotyped probability-spectrum readiness population

The EPAD LCS population will be selected mainly from different types of already existing PCs across Europe (e.g. memory clinic-based, population-based). 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. 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.

Novel selection process - from simple cut-offs to flexible algorithms

Alzheimer's disease is a complex condition, and is most likely the result of multiple contributing factors. Multiple dimensions will be taken into account in EPAD LCS disease modelling work, e.g. cognition, biomarkers, traditional risk factors - genetic and environmental, and changes in these factors over time. This will allow any given individual to be placed somewhere on a probability spectrum from low to high. Because different contributions from various components in each dimension may result in similar overall probability, flexible algorithms are more suitable than simple cut-offs for identifying a probability-spectrum population adequate for both disease modelling and for providing a sufficient number of potential trial participants. Moreover, the drivers of an individual's probability can be then targeted for tailored and optimal effect.

Pan-European AD dementia network

Both EPAD LCS and EPAD PoC trial will be run in an exclusive network of highly selected, expert sites (Trial Delivery Centres) selected on the basis of strictly applied criteria to ensure the highest possible data quality, successful recruitment and adherence to the EPAD principles.

The EPAD project does not operate alone. Together with IMI's EMIF-AD, Amyloid imaging to prevent Alzheimer's disease (AMYPAD), Real world outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP), and Organising Knowledge about Neurodegenerative Disease Mechanisms for the Improvement of Drug Development and Therapy (AETIONOMY) projects, it forms a key and major part of the IMI-AD platform. It is also working closely with other, similar initiatives worldwide, including the US-based Global Alzheimer's Platform. The multi-national approach and academia-industry collaborations are essential for advancing knowledge on the entire spectrum of AD, and for finding effective therapies to prevent the onset of dementia.

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Contributors: CWR is the Chief Investigator; AS, MK, JLM are Coordinating Investigators; BT is the coordinating biostatistician. All authors have contributed to the writing of the study protocol and have approved the final version of this manuscript.

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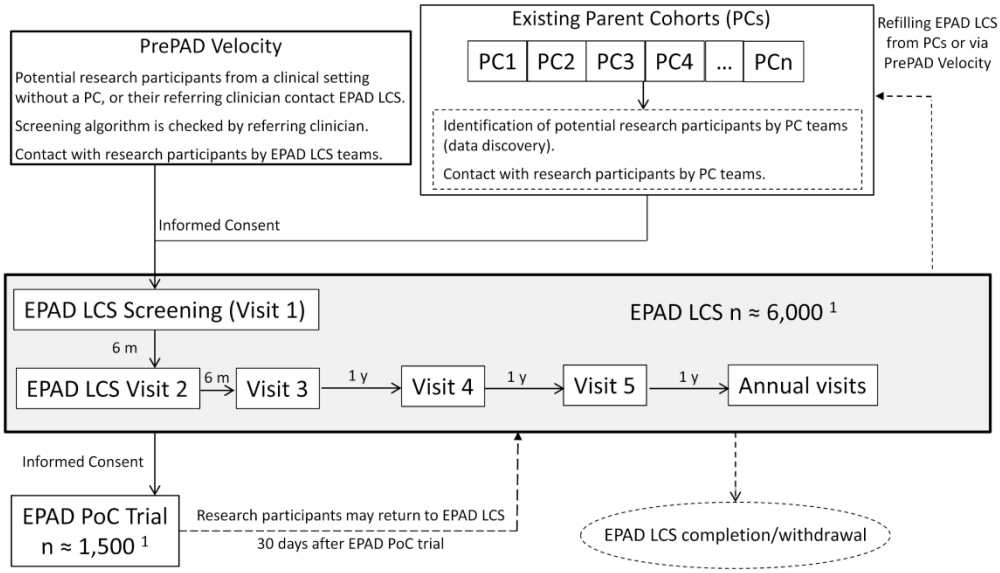
Figure 1. Flow of participants to EPAD LCS and into the EPAD Proof of Concept (PoC) trial



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

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The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol

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The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol

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ABSTRACT

Introduction: The European Prevention of Alzheimer's Dementia (EPAD) project is funded initially by the Innovative Medicines Initiative and has been established to overcome the major hurdles hampering drug development for secondary prevention of Alzheimer's dementia, by conducting the EPAD Longitudinal Cohort Study (LCS) in alignment with the Bayesian adaptive designed EPAD Proof of Concept (PoC) trial.

Methods and analysis: EPAD LCS is an ongoing prospective, perpetual, multicentre, pan-European, longitudinal cohort study. Participants are recruited mainly from existing Parent Cohorts (PCs) across Europe to form a "probability-spectrum" population covering the entire continuum of anticipated probability for Alzheimer's dementia development. EPAD LCS will include at any one time approximately 6,000 research participants. This sample size will be maintained by continuous refilling from PCs. The primary objective of the EPAD LCS is to be a readiness cohort for the EPAD PoC trial though a second major objective is to generate the most comprehensive and largest data set ever for disease modelling of preclinical and prodromal Alzheimer's disease. This characterisation of cognitive, biomarker and risk factor (genetic and environmental) status of research participants over time will provide the necessary well-phenotyped population for developing accurate longitudinal models for Alzheimer's disease covering the entire disease course and concurrently create a pool of highly characterized individuals for the EPAD PoC trial.

Ethics and dissemination: The study has received the relevant approvals from numerous Institutional Review Boards across Europe. Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Regular and coordinated releases of EPAD LCS data will be made available for analysis to help researchers improve their understanding of early Alzheimer's disease stages, and facilitate collaborations.

Study registration number: NCT02804789.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Prospective, perpetual, multicentre, pan-European longitudinal cohort study with a large sample size recruited mainly from existing Parent Cohorts
- Well-phenotyped "probability-spectrum" population covering the entire continuum of probability for Alzheimer dementia development.
- Disease modelling based on four dimensions including cognitive and other clinical features, biomarkers, risk factors (fixed and modifiable), and trajectories of change in these over time.
- Readiness population for a Bayesian adaptive designed Proof of Concept trial, with high quality run in, pre-randomisation data against which the impact of various interventions will be measured.
- Limitations: alignment of the cohort with the Proof of Concept trial means that this is not a traditional epidemiologically selected real-life population.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia globally.[1] As the population ages, the number of people with dementia will rise, and the economic burden of AD will increase dramatically from an already high baseline (~ €262 billion in 2015).[2] Clinical trials targeting populations with manifest dementia have so far failed.[3] There is now consensus that the genesis of AD predates dementia onset by over 20 years,[4] presenting an opportunity for early disease course modification. The key challenge is to accurately identify individuals with a high probability of subsequent AD dementia development, who are suitable for trial inclusion and willing to participate in secondary prevention studies. Secondary prevention populations can have e.g. evidence of AD pathology through relevant biomarker abnormalities, but without a clinical diagnosis of dementia.[5]

Current proposals for defining an individual's probability for dementia development have focused mainly on the AD stage proximal to dementia onset, and have relied on a very limited number of factors, e.g. cognition and amyloid or tau biomarkers.[6-10] Disease models and their phenotypic expression needed for probability estimation in earlier disease stages are currently less well defined. It is important to firstly develop accurate disease models for dementia onset or AD progression in early, asymptomatic or mildly symptomatic disease stages. These people need to be followed-up longitudinally, after which they could be recruited into trials designed to reduce early disease burden and therein decrease the probability of developing dementia. Moreover, the refined definition of populations at risk of dementia will provide data for the optimal stratification of these populations to match onto tailored disease modifying therapies as the basis for better personalised medicine.[11]

The European Prevention of Alzheimer's Dementia (EPAD) is a project to develop an environment for and then test multiple different interventions targeting the secondary prevention of AD dementia.[5] The EPAD project is ongoing across Europe with 38 partners from academia and the

commercial sector. EPAD is conducting a Longitudinal Cohort Study (EPAD LCS) in alignment with a Bayesian adaptive designed EPAD Proof-of-Concept (PoC) trial (Figure 1). This article presents the EPAD LCS study protocol.

OBJECTIVES OF EPAD LCS

EPAD LCS is a prospective, multicentre, pan-European, cohort study that will 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 potential recruitment into the EPAD PoC trial. EPAD LCS will have a well phenotyped "probability-spectrum" population, i.e. covering the entire continuum of probability for dementia development, from low to high and everywhere in between. EPAD LCS has four main 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. Probability for subsequent dementia will consider four different dimensions: cognitive and other clinical features; biomarkers; risk factors (fixed and modifiable); and trajectories of change in these over time.

3. To use disease models for assessing where and why participants fall in the overall probability continuum, and thereafter inform selection of participants into 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.

EPAD LCS STUDY DESIGN AND METHODS

Recruitment sources for EPAD LCS

EPAD LCS participants will be recruited mainly from existing Parent Cohorts (PCs) across Europe. These can be research cohorts (e.g. observational studies with participants from the general population or other populations; prevention trials; or pre-existing readiness cohorts), or clinical/routine care cohorts (memory clinic or general practitioner/primary care-based). Cohort eligibility criteria are: active cohorts including participants without dementia aged at least 50 years; willingness of the Principal Investigator of the Parent Cohort to provide research participants for EPAD LCS and EPAD PoC trial; and existing consent from participants for re-contact by Parent Cohort team, or possibility to obtain consent to re-contact by Parent Cohort team.

To ensure PCs engagement, 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) and regional initiatives like the Dementias Platform UK (DPUK). Many other cohorts will also be included as needed.

Recruitment from existing PCs will be complemented with participants coming directly from clinical settings without a PC.

The involvement of existing PCs and clinics where some data is already available on potential participants will facilitate fast recruitment. In addition, the variety of recruitment sources (from general populations to memory clinics) will provide a probability-spectrum population covering the entire continuum of probability for AD dementia development.

EPAD LCS study population

EPAD LCS eligibility and exclusion criteria are listed in Table 1.

Table 1. Criteria for selection of EPAD LCS participants.

Eligibility criteria	• Age at least 50 years • Completing all EPAD LCS screening/baseline assessments • Able to read and write and with minimum 7 years of formal education • Willing in principle to participate in the EPAD PoC trial subject to further informed consent

	• Have a study partner or can identify someone willing in principle to be a study partner*.
Exclusion criteria	• Research participants who fulfill diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLB, NINCDS-AIREN Criteria for Vascular Dementia) • CDR>=1 • Known carriers of a PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD or any other neurodegenerative disease • Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse; or major psychiatric disorders including current major depressive disorder, schizophrenia, schizoaffective or bipolar disorder. • Any cancer or history of cancer in the preceding 5 years (excluding cutaneous basal or squamous cell cancer resolved by excision) • Any current medical conditions that are clinically significant and might make the subject's participation in an investigational trial unsafe, e.g., uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including revascularisation procedures; severe renal or hepatic failure; unstable or poorly controlled diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in men); any clinically relevant abnormalities in blood parameters included in local routine assessments; severe loss of vision, hearing or communicative ability; or any conditions preventing co-operation or completion of the required assessments in the trial, as judged by the investigator • Any contraindications for MRI/PET scan • Any contraindications for Lumbar Puncture • Any evidence of intracranial pathology which, in the opinion of the investigator, may affect cognition including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. 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. • Participation in a Clinical Trial of an Investigational Product (CTIMP) in the last 30 days (continued participation in the parent cohort is expected). Participation in a non-CTIMP is not an exclusion criterion • Diminished decision-making capacity/not capable of consenting at the screening or 6-month visit. If at a subsequent annual EPAD LCS visit health professionals suspect diminished consent capacity according to local 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). 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. Capacity will be assessed at each

	study visit using the correct legal framework.

AD: Alzheimer's disease; APP: amyloid precursor protein; DLB: dementia with Lewy bodies; FTD: fronto-temporal dementia; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (now Alzheimer's Association); NINCDS-AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PSEN: presenilin; MRI: magnetic Resonance Imaging; PET: Positron Emission Tomography

* A study partner is e.g. relative or friend who is at least 18 years old, may or may not live together with the participant, and is available either for face to face or telephone contact with the EPAD LCS team. As EPAD LCS participants do not have dementia, have no or only slight impairment (i.e. Clinical Dementia Rating, CDR 0 or 0.5), and are fully capable of providing informed consent (as per Exclusion criteria), the primary role of the study partner in EPAD LCS will be as informant.

At any given time after initial overall recruitment target is achieved, there should be approximately 6,000 participants in the EPAD LCS. Population size will be maintained over time by continuous refilling from the PCs or clinical settings as participants move into the PoC trial or drop out. Initial duration of EPAD LCS will be from May 2016 (start of recruitment) to December 2019 (end of current Innovative Medicines Initiative-IMI funding), and after that extension of consent will be asked from participants who are still eligible for EPAD LCS. EPAD LCS participants will not be asked to leave their PCs. Participants recruited into the EPAD PoC trial may return to EPAD LCS at least 30 days after trial completion, if they wish to and if they are still eligible for EPAD LCS. The current status of the LCS can be followed on the EPAD website (http://ep-ad.org/) where updates are continuously posted as new research participants, recruiting sites and countries join the project.

EPAD LCS participant selection process

Selection from Parent Cohorts (PrePAD)

Potential EPAD LCS research participants will be identified by each PC team based on data in their own PC. Individual-level PC data does not have to be shared with EPAD. To ease the search process, a data discovery software tool is provided to PCs by EPAD. The Participant Register for EPAD (PrePAD) solution has been developed by EPAD study partners working with EMIF and DPUK.[12] PrePAD queries will be run that provide counts of participants, without giving EPAD LCS access to individual-level data. Only the PC team will be able to identify the selected PC

research participants and contact them. Those who express interest in EPAD LCS participation are then referred to the local LCS site.

As of March 2018, 10 different cohorts with a total of 17500 participants aged >50 years and without dementia have been included in PrePAD [12]. New cohorts are continuously added.

Selection from clinical settings (PrePAD Velocity)

The participant or referring clinician will contact the local EPAD LCS site directly. The referring clinician will verify eligibility using a checklist based on assessments available in each referring clinical setting.

Novel flexible approach to selection

EPAD LCS will provide a probability-spectrum population, i.e. where the entire continuum from low to high probability of subsequent dementia is represented at any time during the study. Probability of developing dementia is determined by multiple dimensions, e.g. cognition, biomarkers, traditional risk factors (genetic and environmental). However, no disease model covering all these dimensions is currently available to determine where an individual is located on the probability continuum. In addition, an individual may move across the continuum over time due to changes in these dimensions.

EPAD LCS needs to ensure that at any time (i) the entire probability continuum is represented, and (ii) there are enough participants potentially eligible for an adaptive designed trial, where multiple active experimental drugs may be assessed concurrently with a shared placebo arm, and interim analyses may affect participant accrual or stopping/continuing trial arms. For this purpose, a flexible approach to selection will be used (Table 2). This will allow for adjustments over time as data accumulate, disease models improve, and the needs of the EPAD PoC trial's intervention pipeline change.

To guarantee a well-organized selection process, EPAD LCS has a Balancing Committee (biostatisticians, data managers and LCS senior investigators) responsible for data monitoring and algorithm adaptations, and an Algorithm Running Committee responsible for algorithm documenting, and sending outputs to PCs or clinics in PrePAD Velocity.[13]

This centralized selection process was also set up because investigators will be blinded to results of new data collected in the EPAD LCS, namely CSF biomarkers of tau and amyloid, imaging results and apolipoprotein E (APOE) ε4 allele carrier status, to limit biases in clinical assessments that may affect disease modelling work in EPAD LCS. This blinding is only compromised if a research participant enters LCS via PrePAD Velocity with known and disclosed biomarker status or if the research participant enters an arm of the EPAD PoC which requires only biomarker-positive individuals.

Table 2. Novel flexible approach to participant selection

Flexible algorithm for identification of potential participants from Parent Cohorts
• For example, probability of subsequent dementia (and the selection algorithm) may be initially based on age, absence of dementia diagnosis, and family history of AD in a PC with less extensive assessments; or age, cognitive performance, and APOE genotype in another PC with more detailed assessments; or age, cognitive performance, MRI and CSF biomarkers in a PC where such data are available • The PrePAD queries of PCs will be conducted potentially every month and may be adjusted depending on several factors: types of available data in the PC; the structure of the probability spectrum at any given time point in EPAD LCS; the EPAD PoC trial's intervention pipeline; and the capacity at each EPAD LCS site to baseline and manage new participants • The flexible algorithm will be agreed upon and applied by the EPAD LCS Balancing Committee, and the output will be provided to each Parent Cohort by the Algorithm Running Committee
Oversampling or under-sampling from different types of Parent Cohorts
• For example, if some PCs are more likely to provide participants with a profile suitable for a certain PoC trial arm, oversampling from such cohorts and under-sampling from others may occur before and during the trial recruitment period.
Flexible algorithm and over/under-sampling for PrePAD Velocity
• For similar reasons, a central element of PrePAD Velocity will be that the AD biomarker status of referred patients should be known from their regular clinical assessments. • The selection algorithm will be agreed upon by the Balancing Committee based on information about assessments available in each referring clinical setting. The Algorithm Running Committee will provide a checklist to the referring clinician for verifying eligibility before contacting the local EPAD LCS site.

Flexible algorithm for refilling EPAD LCS over time
• The aforementioned procedures will be applied for both establishing and refilling the EPAD LCS. • The structure of the probability spectrum in LCS may change over time because participants (i) move into the PoC trial; (ii) drop out; or (iii) their characteristics (e.g. cognition, biomarkers, risk factors) change. • Depending on the structure of the probability spectrum at any given time point in LCS, participants coming in may or may not need to match participants moving out.

EPAD LCS outcomes and other assessments

EPAD LCS outcomes, other assessments and the data collection schedule are detailed in Table 3 and Table 4. The assessments are based on recommendations developed by the five EPAD Scientific Advisory Groups (SAGs) (Clinical and Cognitive Outcomes, Epidemiology, Fluid Biomarkers, Genetics, and Imaging). SAGs recommendations were based on reviewing the current literature, following widely accepted practices, and minimizing participant burden.

Table 3. EPAD LCS outcomes and other assessments.

Primary cognitive outcome	The *RBANS Total Scale Index Score* based on: • 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
Secondary outcomes	*Cognitive outcomes* • Working memory: Dot counting (NIH EXAMINER,[14, 15]) • Choice reaction time and set shifting: Flanker (NIH EXAMINER) • Paired associate learning: Favourites (University of California, San Francisco,[16]) *CSF biomarkers* • Beta-amyloid, total tau, phosphorylated tau *Neuroimaging outcomes (MRI)* • Hippocampal and whole brain volume
Exploratory outcomes	*Cognitive outcomes* • Allocentric Space: Four Mountains Task (Cambridge University, [17]) • Navigation in Egocentric Space: Virtual Reality Supermarket Trolley (University College London, [18]) *Other clinical outcomes* • Amsterdam Instrumental Activities of Daily Living Questionnaire [19, 20] *Neuroimaging outcomes*

	• Multi-region structural MRI analysis • Functional regional and network measures
Other assessments	**Clinical:** • *Dementia* diagnosed by the participant's physician, including type and date of diagnosis • *MMSE*, Mini-Mental Status Exam [21] • *CDR*, Clinical Dementia Rating Scale [22] • *GDS*, 30-item Geriatric Depression Scale [23, 24] • *STAI,* State-Trait Anxiety Inventory [25] • *Pittsburgh Sleep Quality Index* [26] • *Physical examination*, including e.g. neurological examination, blood pressure, pulse, weight, height, and hip-waist circumference measurements • *Medical history* (yes/no): family history of AD (first degree relatives), stroke, diabetes mellitus (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 (Brain Injury Screening Questionnaire (BISQ, [27]), Mild Cognitive Impairment, other conditions • *Current medication*: name of drugs; treatment duration (<1year / 1-5years / >5years) **Biomarkers:** • *Collection of CSF and blood, urine & saliva samples* for future biomarker assessments (emerging AD biomarkers) • *APOE* genotype, Polygenic Scores **Other:** • *Sociodemographics*: date of birth, sex, ethnicity, years of formal education, marital status • *Lifestyle factors*: - Smoking (never / past / current) - Alcohol consumption (units/week) - Drug abuse/misuse (never / past / current) - Diet (questionnaire, Healthy Ageing through Internet Counselling in the Elderly, HATICE [28]) - Physical activity: leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating. Frequency 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 [29, 30] - Life events (brief questionnaire based on the Swedish National study on Aging and Care, SNAC [31]) - Self-rated health and self-rated fitness (Likert-type questions with response options very good / good / satisfactory / relatively poor / very poor [30]) • *Handedness*

Table 4. Data collection schedule.

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Annual visits**
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
Eligibility criteria	X	X	X	X	X	X
Research participant consent[b]	X					
Cognitive outcomes (ENE battery)						
RBANS	X	X	X	X	X	X
Dot Counting (NIH EXAMINER)	X	X	X	X	X	X
Flanker (NIH EXAMINER)	X	X	X	X	X	X
Favourites (University of California, San Francisco)	X	X	X	X	X	X
Four Mountains Task (Cambridge University)	X	X	X	X	X	X
Virtual Reality Supermarket Trolley (University College London)	X	X	X	X	X	X
Clinical outcomes						
Amsterdam Instrumental Activities of Daily Living Questionnaire	X		X	X	X	X
Biomarkers						
*Core MRI sequences	X		X	X	X	X
Advanced MRI sequences	X (subset)		X (subset)	X (subset)	X (subset)	X (subset)
**CSF sampling	X		X	X	X	X
Blood, urine & saliva sampling	X		X	X	X	X
Other assessments						
Socio-demographics (date of birth, sex, ethnicity, education, marital status)	X					
Family history of AD	X					
Medical history	X		X	X	X	X
Current medication	X	X	X	X	X	X
GDS	X		X	X	X	X
STAI	X		X	X	X	X
Pittsburgh Sleep Quality Index	X		X	X	X	X
Lifestyle factors	X		X	X	X	X
Dementia diagnosed by physician	X	X	X	X	X	X
CDR	X	X	X	X	X	X
MMSE	X		X	X	X	X
Physical exam	X		X	X	X	X
Height	X					
Weight, hip-waist circumference	X		X	X	X	X
Blood pressure	X		X	X	X	X
Ongoing research participant safety assessment						
Adverse events[c]	X	X	X	X	X	X

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

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

[c] All adverse events deemed by clinical judgement to be at least possibly related to EPAD LCS study procedures are to be recorded in the CRF. Adverse event collection should start with the first EPAD LCS procedure and will apply to all adverse events that occur within 30 days after a research participant's last study visit/procedure.

When an enrolled participant completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s).
* If an individual participant has had an MRI to the specifications in the Core EPAD Scanning protocol within 12 months of the Visit 1 first assessment of the EPAD LCS then this scan can be provided for analysis for the Visit 1 baseline data.
** If an individual participant refuses a lumbar puncture at Visit 3 or a subsequent annual visit this will be defined as missing data. If the participant refuses a lumbar puncture at two sequential visits, then they will be withdrawn from the EPAD LCS as a non-compliant participant.
If an individual participant has had a lumbar puncture and CSF sample collected and stored according to the CSF sampling manual procedure within 12 months of the Visit 1 first assessment of the EPAD LCS then this sample can be provided for analysis for the Visit 1 baseline data.

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; CDR - Clinical Dementia Rating; MMSE - Mini Mental State Exam.

Cognitive Outcomes

The selection process for EPAD LCS cognitive outcome measures has been described previously.[32] The EPAD Neuropsychological Examination (ENE) battery (Table 4) was chosen to cover all relevant cognitive domains, with greatest possible sensitivity to early-stage changes. The ENE 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, component tasks will have four alternative forms for retesting.

For LCS purposes, primary outcomes include anchor or criterion measure(s) accepted by regulatory authorities in previous registration trials. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will serve as the criterion measure for this study.[32] For statistical purposes, the RBANS Total Scale Index Score (Table 4) will serve as the primary outcome. LCS will also help validate the secondary and exploratory cognitive outcome measures against a known and accepted criterion measure. Although the EPAD LCS is conducted in compliance with Good Clinical Practice (GCP), including the primary outcome, the computerized secondary and exploratory cognitive measures are undergoing additional validation in EPAD LCS and, thus, do not yet fully meet GCP (Title 21 CFR Part 11/European Union Annex 11).

CSF biomarker outcomes

Measurements will include AD-related markers (beta-amyloid, total tau and phosphorylated tau), and this data will be used for disease modelling and for staging of disease pathology. CSF sampling follows a harmonised preclinical protocol and analyses take place using the fully automatized Roche Elecsys System in a single laboratory (University of Gothenburg). Additional CSF is stored in the EPAD BioBank at the Roslin Research Institute, University of Edinburgh with all other fluid samples.

Neuroimaging outcomes

The selection process for the neuroimaging measures included in the LCS protocol was based on evidence from available studies with an emphasis on secondary prevention of AD. Other considerations were usefulness of imaging data for the EPAD PoC trial, participant burden, implementation and costs, and avoiding redundancies between imaging and non-imaging measures.

The Magnetic Resonance Imaging (MRI) acquisition is divided into:

[1] Core image acquisition, conducted in all LCS participants to assess study eligibility, for baseline assessment that can be used for subsequent safety monitoring in the EPAD PoC trial, and for quantitative analysis of brain structure and vascular lesions. ADNI-like protocols and quality control will be used to ascertain precision in measuring change.

[2] Advanced image acquisition, which only a sub-set of sites with suitable equipment and experience will acquire. This may include one or more of the following types of acquisition: 3D-Susceptibility Weighted Imaging or 3D-T2*, Diffusion Tensor Imaging, Arterial Spin Labelling, and resting state functional MRI.

Genetic Assessments

The primary genetic assessment will include APOE genotype. The samples may also be sequenced when additional resources become available. Genetic variants with strong effect (e.g. 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 individuals with early onset AD and are therefore unlikely to be included in the EPAD LCS.

Other assessments

A broad range of sociodemographic, medical and lifestyle-related data will be collected (Tables 4 and 5). Mini-Mental Status Exam (MMSE) [21] and Clinical Dementia Rating scale (CDR) [22] will be used given their utility principally as clinical descriptors. Biological samples will include blood, urine and saliva (e.g. for cortisol measurements) stored under optimal conditions in the central EPAD Biobank.

EPAD LCS-MINI protocol for participants who maintain a low likelihood of trial inclusion

During EPAD LCS it may become clear that some participants maintain a low likelihood of being invited to the PoC trial. This may happen for several reasons, e.g. developing health conditions that preclude trial participation, or showing no impairment/decline in cognition and AD biomarkers. Starting from their third visit (one year after baseline), such participants may have the possibility to continue with a lower-burden protocol, i.e. without the yearly MRI and CSF sampling.

Data Sources, collection and monitoring

The only data source for this study will be data collected as part of the EPAD LCS. Electronic data capture will be used as appropriate, e.g. for cognitive and imaging data. Central laboratories will be used for all CSF (University of Gothenburg) and genetic (University of Edinburgh) assessments, and central reading of all neuroimaging will be undertaken (University of Edinburgh, VU

University Medical Center Amsterdam). A common pre-analytical procedures schedule for sample collection, storage and shipment will be used at all EPAD LCS sites. The study will be monitored in accordance with the ICH GCP (ICH Topic E6, 1996).

STATISTICAL ANALYSIS

Sample Size

A constant sample size of approximately 6,000 participants for the EPAD LCS is considered sufficient for a readiness cohort that should provide approximately 1,500 participants for the EPAD PoC trial. The EPAD LCS sample size will be maintained through continuous recruitment from PCs and via PrePAD Velocity. Strategies for motivation and engagement, as well as improving the research experience for participants will be developed, including e.g. newsletters, websites and telephone contact from the study sites.

Disease modelling

AD is a complex condition, and an individual's probability of developing dementia is most likely the result of multiple contributing factors.[1, 3] In EPAD LCS, participants may fall on a continuum of overall probability for subsequent dementia driven by several underlying dimensions: cognition; AD-related biomarkers; traditional risk factors (genetic and environmental); and their longitudinal changes. These dimensions may be continuous in nature. Treating them as such rather than dichotomizing or categorizing them 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. This is especially important as participants with similar overall probability may have different contributions from the various dimensions. Interrogating the underlying dimensions in addition to the overall predicted probability will also facilitate decisions on participant stratification considering the drivers and needs related to compounds to be tested in the EPAD PoC trial.

Longitudinal modelling of cognitive outcomes, biomarkers and risk factors will be used to characterise these dimensions dynamically and relate their trajectories to the probability of AD dementia development or other meaningful intermediate disease states. Modelling will identify and rank strata of sub-populations of different probability. Each sub-population will have a cognitive, biomarker and risk factors profile, and this stratification will be used to identify potential interventions, the size of a potential intervention effect, and to guide the flow of participants from EPAD LCS into subsequent arms of the PoC trial.

The starting point of the modelling will be mixed-effects models for the cognitive outcomes, biomarkers and risk factors, especially as dementia events are expected to be rare in the first few years of follow-up of participants. Complexity of investigated models will subsequently increase and focus on (multivariate) latent trajectory/class mixed models for the longitudinal outcomes and biomarkers; survival and more general event history models for progression to AD dementia and joint models linking these longitudinal outcomes and biomarkers to AD dementia. The longitudinal models will initially be developed for each cognitive outcome and biomarker separately and then combined to ultimately maximise the prediction of probability for subsequent dementia.

Analyses of cognitive outcomes will be carried out at both the individual cognitive domain and composite score (RBANS Total Scale Index) levels. Robustness of models developed will be evaluated using cross-validation.

As data accrues in the EPAD LCS, soft data locks and releases will occur after 500, 1000, 2000 participants (and by intervals of 1,000 thereafter) and by stage of follow up e.g. baseline, 1 year, 2 year etc. to inform selection algorithms for EPAD LCS; provide updated information for improving selection into the EPAD PoC trial; and provide updated disease models.

ETHICAL ASPECTS

The 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. EPAD LCS has received ethical approval from numerous institutional review boards (IRBs) across Europe.

EPAD has an Ethics Workgroup examining the complex ethical considerations involved in the project, and providing appropriate recommendations.[33, 34]

Informed consent

As the EPAD project is multi-staged, staged consent will be used as decision making model.[17] Staged consent feeds relevant information – bit by bit, extended over time - to participants and study partners, and asks informed consent at every step when they need to make important decisions. Although informed consent is given for a specific stage of EPAD (e.g. consent for LCS does not imply consent for the PoC trial), information about the 'totality of EPAD' will always and explicitly be made available.

Potential Disclosure of Risk Information

Overall estimated probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy/robustness of current disease models. However, findings with established clinical relevance and requiring further monitoring and treatment will be disclosed to participants, and appropriate measures will be taken. AD-related CSF biomarkers may be disclosed if progression to AD dementia is suspected during EPAD LCS, or where it is considered

relevant to an individual's ongoing clinical management, or if a participant is later invited to the PoC trial.

Privacy of Personal Data

EPAD LCS will ensure that data on participants are appropriately managed, and participant and study information are treated as confidential. All participant study records are identified by the participant identification number to maintain participants' confidentiality.

RESEARCH PARTICIPANT INVOLVEMENT

EPAD has established a Research Participants Panel to provide feedback of the experience of research participation, to ensure that participant perspectives are represented in decision making about the future of the project and to advise local and central EPAD LCS teams. The local panel will consist of 6-10 EPAD LCS participants at each site and will meet at least twice annually. All EPAD LCS participants at a site 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. 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.

DISSEMINATION PLAN

Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Types of communication will include scientific publications, conference presentations, press releases, interviews and other media communications (including social media), meetings etc. Information and regular updates are posted on the EPAD project website (www.ep-ad.org).
Data collected from EPAD LCS will be made available for analysis to help researchers everywhere improve their understanding of the early stages of AD and facilitate collaborations.

DISCUSSION

The EPAD project has been established to overcome the major hurdles hampering drug development for the secondary prevention of AD dementia, by conducting the EPAD LCS in alignment with the Bayesian adaptive designed EPAD PoC trial. This set-up addresses the dual need for (i) developing accurate longitudinal models for AD covering the entire disease course, and (ii) developing an adequate infrastructure for facilitating identification of participants and clinical trial recruitment. While several dementia prediction models have already been developed, very few have been validated, and none has been tested in a drug trial. The alignment of a longitudinal cohort study with an adaptive trial design within the same project [5] is a novel approach that closes the previous gap between dementia prediction and prevention. This design aspect differentiates EPAD LCS from other international networks of observational studies, e.g. the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) [35], the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA/Maelstrom) [36], or Stroke and Cognition consortium (STROKOG) [37]. Other novel solutions for facilitating trial recruitment include e.g. online Brain Health Registers [38, 39], but they require older populations with significant internet literacy, and outcome measures cannot yet be aligned between the online observational cohorts and clinical trials.

EPAD LCS recruitment relies on existing cohorts across Europe. The variety of recruitment sources, i.e. from general populations to memory clinics, will ensure that the EPAD LCS probability-spectrum population can cover the entire continuum of probability for AD dementia development. The yearly EPAD LCS follow-up with comprehensive cognitive, clinical and biomarker assessments will provide a well-phenotyped 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 novel flexible

approach to participant selection is designed to balance the disease modelling and adaptive trial design needs.Both EPAD LCS and EPAD PoC trial will be run in an exclusive network of highly selected, expert sites (Trial Delivery Centres) selected on the basis of strictly applied criteria to ensure the highest possible data quality, successful recruitment and adherence to the EPAD principles.

The EPAD project does not operate alone. Together with IMI's EMIF-AD, Amyloid imaging to prevent Alzheimer's disease (AMYPAD), Real world outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP), and Organising Knowledge about Neurodegenerative Disease Mechanisms for the Improvement of Drug Development and Therapy (AETIONOMY) projects, it forms a key and major part of the IMI-AD platform. It is also working closely with other, similar initiatives worldwide, including the US-based Global Alzheimer's Platform. The multi-national approach and academia-industry collaborations are essential for advancing knowledge on the entire spectrum of AD, and for finding effective therapies to prevent the onset of dementia.

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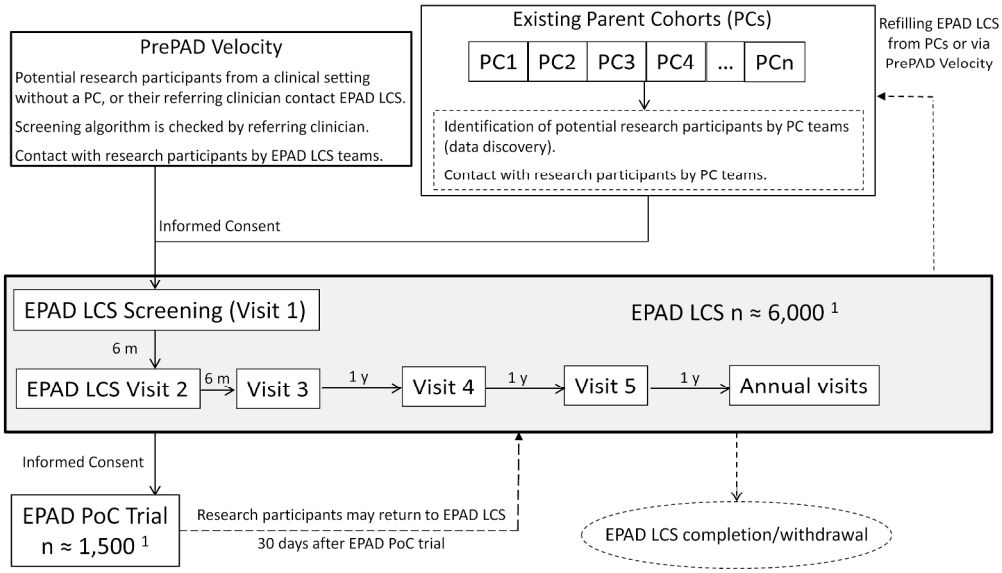
Figure 1. Flow of participants to EPAD LCS and into the EPAD Proof of Concept (PoC) trial



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

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The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol

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ABSTRACT

Introduction: The European Prevention of Alzheimer's Dementia (EPAD) project is funded initially by the Innovative Medicines Initiative and has been established to overcome the major hurdles hampering drug development for secondary prevention of Alzheimer's dementia, by conducting the EPAD Longitudinal Cohort Study (LCS) in alignment with the Bayesian adaptive designed EPAD Proof of Concept (PoC) trial.

Methods and analysis: EPAD LCS is an ongoing prospective, multicentre, pan-European, longitudinal cohort study. Participants are recruited mainly from existing Parent Cohorts (PCs) across Europe to form a "probability-spectrum" population covering the entire continuum of anticipated probability for Alzheimer's dementia development. The primary objective of the EPAD LCS is to be a readiness cohort for the EPAD PoC trial though a second major objective is to generate a comprehensive and large data set for disease modelling of preclinical and prodromal Alzheimer's disease. This characterisation of cognitive, biomarker and risk factor (genetic and environmental) status of research participants over time will provide the necessary well-phenotyped population for developing accurate longitudinal models for Alzheimer's disease covering the entire disease course and concurrently create a pool of highly characterized individuals for the EPAD PoC trial.

Ethics and dissemination: The study has received the relevant approvals from numerous Institutional Review Boards across Europe. Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Regular and coordinated releases of EPAD LCS data will be made available for analysis to help researchers improve their understanding of early Alzheimer's disease stages, and facilitate collaborations.

Study registration number: NCT02804789.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Prospective, multicentre, pan-European longitudinal cohort study with a large sample size recruited mainly from existing Parent Cohorts
- Well-phenotyped "probability-spectrum" population covering the entire continuum of probability for Alzheimer dementia development.
- Disease modelling based on four dimensions including cognitive and other clinical features, biomarkers, risk factors (fixed and modifiable), and trajectories of change in these over time.
- Readiness population for a Bayesian adaptive designed Proof of Concept trial, with high quality run in, pre-randomisation data against which the impact of various interventions will be measured.
- Limitations: alignment of the cohort with the Proof of Concept trial means that this is not a traditional epidemiologically selected real-life population.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia globally.[1] As the population ages, the number of people with dementia will rise, and the economic burden of AD will increase dramatically from an already high baseline (~ €262 billion in 2015).[2] Clinical trials targeting populations with manifest dementia have so far failed.[3] There is now consensus that the genesis of AD predates dementia onset by over 20 years,[4] presenting an opportunity for early disease course modification. The key challenge is to accurately identify individuals with a high probability of subsequent AD dementia development, who are suitable for trial inclusion and willing to participate in secondary prevention studies. Secondary prevention populations can have e.g. evidence of AD pathology through relevant biomarker abnormalities, but without a clinical diagnosis of dementia.[5]

Current proposals for defining an individual's probability for dementia development have focused mainly on the AD stage proximal to dementia onset, and have relied on a very limited number of factors, e.g. cognition and amyloid or tau biomarkers.[6-10] Disease models and their phenotypic expression needed for probability estimation in earlier disease stages are currently less well defined. It is important to firstly develop accurate disease models for dementia onset or AD progression in early, asymptomatic or mildly symptomatic disease stages. These people need to be followed-up longitudinally, after which they could be recruited into trials designed to reduce early disease burden and therein decrease the probability of developing dementia. Moreover, the refined definition of populations at risk of dementia will provide data for the optimal stratification of these populations to match onto tailored disease modifying therapies as the basis for better personalised medicine.[11]

The European Prevention of Alzheimer's Dementia (EPAD) is a project to develop an environment for and then test multiple different interventions targeting the secondary prevention of AD dementia.[5] The EPAD project is ongoing across Europe with 38 partners from academia and the

commercial sector. EPAD is conducting a Longitudinal Cohort Study (EPAD LCS) in alignment with a Bayesian adaptive designed EPAD Proof-of-Concept (PoC) trial (Figure 1). This article presents the EPAD LCS study protocol.

OBJECTIVES OF EPAD LCS

EPAD LCS is a prospective, multicentre, pan-European, cohort study that will 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 potential recruitment into the EPAD PoC trial. EPAD LCS will have a well phenotyped "probability-spectrum" population, i.e. covering the entire continuum of probability for dementia development, from low to high and everywhere in between. EPAD LCS has four main 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. Probability for subsequent dementia will consider four different dimensions: cognitive and other clinical features; biomarkers; risk factors (fixed and modifiable); and trajectories of change in these over time.

3. To use disease models for assessing where and why participants fall in the overall probability continuum, and thereafter inform selection of participants into 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.

EPAD LCS STUDY DESIGN AND METHODS

Recruitment sources for EPAD LCS

EPAD LCS participants will be recruited mainly from existing Parent Cohorts (PCs) across Europe. These can be research cohorts (e.g. observational studies with participants from the general population or other populations; prevention trials; or pre-existing readiness cohorts), or clinical/routine care cohorts (memory clinic or general practitioner/primary care-based). Cohort eligibility criteria are: active cohorts including participants without dementia aged at least 50 years; willingness of the Principal Investigator of the Parent Cohort to provide research participants for EPAD LCS and EPAD PoC trial; and existing consent from participants for re-contact by Parent Cohort team, or possibility to obtain consent to re-contact by Parent Cohort team.

To ensure PCs engagement, 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) and regional initiatives like the Dementias Platform UK (DPUK). Many other cohorts will also be included as needed.

Recruitment from existing PCs will be complemented with participants coming directly from clinical settings without a PC.

The involvement of existing PCs and clinics where some data is already available on potential participants will facilitate fast recruitment. In addition, the variety of recruitment sources (from general populations to memory clinics) will provide a probability-spectrum population covering the entire continuum of probability for AD dementia development.

EPAD LCS study population

EPAD LCS eligibility and exclusion criteria are listed in Table 1.

Table 1. Criteria for selection of EPAD LCS participants.

Eligibility criteria	• Age at least 50 years • Completing all EPAD LCS screening/baseline assessments • Able to read and write and with minimum 7 years of formal education • Willing in principle to participate in the EPAD PoC trial subject to further informed consent

	• Have a study partner or can identify someone willing in principle to be a study partner*.
Exclusion criteria	• Research participants who fulfill diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLB, NINCDS-AIREN Criteria for Vascular Dementia) • CDR>=1 • Known carriers of a PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD or any other neurodegenerative disease • Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse; or major psychiatric disorders including current major depressive disorder, schizophrenia, schizoaffective or bipolar disorder. • Any cancer or history of cancer in the preceding 5 years (excluding cutaneous basal or squamous cell cancer resolved by excision) • Any current medical conditions that are clinically significant and might make the subject's participation in an investigational trial unsafe, e.g., uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including revascularisation procedures; severe renal or hepatic failure; unstable or poorly controlled diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in men); any clinically relevant abnormalities in blood parameters included in local routine assessments; severe loss of vision, hearing or communicative ability; or any conditions preventing co-operation or completion of the required assessments in the trial, as judged by the investigator • Any contraindications for MRI/PET scan • Any contraindications for Lumbar Puncture • Any evidence of intracranial pathology which, in the opinion of the investigator, may affect cognition including but not limited to brain tumours (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent haemorrhage (parenchymal or subdural), or obstructive hydrocephalus. 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. • Participation in a Clinical Trial of an Investigational Product (CTIMP) in the last 30 days (continued participation in the parent cohort is expected). Participation in a non-CTIMP is not an exclusion criterion • Diminished decision-making capacity/not capable of consenting at the screening or 6-month visit. If at a subsequent annual EPAD LCS visit health professionals suspect diminished consent capacity according to local 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). 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. Capacity will be assessed at each

	study visit using the correct legal framework.

AD: Alzheimer's disease; APP: amyloid precursor protein; DLB: dementia with Lewy bodies; FTD: fronto-temporal dementia; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (now Alzheimer's Association); NINCDS-AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PSEN: presenilin; MRI: magnetic Resonance Imaging; PET: Positron Emission Tomography

* A study partner is e.g. relative or friend who is at least 18 years old, may or may not live together with the participant, and is available either for face to face or telephone contact with the EPAD LCS team. As EPAD LCS participants do not have dementia, have no or only slight impairment (i.e. Clinical Dementia Rating, CDR 0 or 0.5), and are fully capable of providing informed consent (as per Exclusion criteria), the primary role of the study partner in EPAD LCS will be as informant.

EPAD LCS will be maintained over time by continuous refilling from the PCs or clinical settings as participants move into the PoC trial or drop out. Initial duration of EPAD LCS will be from May 2016 (start of recruitment) to December 2019 (end of current Innovative Medicines Initiative-IMI funding), and after that extension of consent will be asked from participants who are still eligible for EPAD LCS. EPAD LCS participants will not be asked to leave their PCs. Participants recruited into the EPAD PoC trial may return to EPAD LCS at least 30 days after trial completion, if they wish to and if they are still eligible for EPAD LCS.

The current status of the LCS can be followed on the EPAD website (http://ep-ad.org/) where updates are continuously posted as new research participants, recruiting sites and countries join the project. There are now about 800 participants from 19 active sites in 6 countries. Recruitment status as of 4th July 2018 is shown in Figure 2. Recruitment rate is expected to increase as recently opened sites reach their full capacity, and new sites/countries also start recruiting.

EPAD LCS participant selection process

Selection from Parent Cohorts (PrePAD)

Potential EPAD LCS research participants will be identified by each PC team based on data in their own PC. Individual-level PC data does not have to be shared with EPAD. To ease the search process, a data discovery software tool is provided to PCs by EPAD. The Participant Register for EPAD (PrePAD) solution has been developed by EPAD study partners working with EMIF and DPUK.[12] PrePAD queries will be run that provide counts of participants, without giving EPAD

LCS access to individual-level data. Only the PC team will be able to identify the selected PC research participants and contact them. Those who express interest in EPAD LCS participation are then referred to the local LCS site.

As of March 2018, 10 different cohorts with a total of 17500 participants aged >50 years and without dementia have been included in PrePAD [12]. New cohorts are continuously added.

Selection from clinical settings (PrePAD Velocity)

The participant or referring clinician will contact the local EPAD LCS site directly. The referring clinician will verify eligibility using a checklist based on assessments available in each referring clinical setting.

Novel flexible approach to selection

EPAD LCS will provide a probability-spectrum population, i.e. where the entire continuum from low to high probability of subsequent dementia is represented at any time during the study. Probability of developing dementia is determined by multiple dimensions, e.g. cognition, biomarkers, traditional risk factors (genetic and environmental). However, no disease model covering all these dimensions is currently available to determine where an individual is located on the probability continuum. In addition, an individual may move across the continuum over time due to changes in these dimensions.

EPAD LCS needs to ensure that at any time (i) the entire probability continuum is represented, and (ii) there are enough participants potentially eligible for an adaptive designed trial, where multiple active experimental drugs may be assessed concurrently with a shared placebo arm, and interim analyses may affect participant accrual or stopping/continuing trial arms. For this purpose, a flexible approach to selection will be used (Table 2). This will allow for adjustments over time as

data accumulate, disease models improve, and the needs of the EPAD PoC trial's intervention pipeline change.

To guarantee a well-organized selection process, EPAD LCS has a Balancing Committee (biostatisticians, data managers and LCS senior investigators) responsible for data monitoring and algorithm adaptations, and an Algorithm Running Committee responsible for algorithm documenting, and sending outputs to PCs or clinics in PrePAD Velocity.[13]

This centralized selection process was also set up because investigators will be blinded to results of new data collected in the EPAD LCS, namely CSF biomarkers of tau and amyloid, imaging results and apolipoprotein E (APOE) ε4 allele carrier status, to limit biases in clinical assessments that may affect disease modelling work in EPAD LCS. This blinding is only compromised if a research participant enters LCS via PrePAD Velocity with known and disclosed biomarker status or if the research participant enters an arm of the EPAD PoC which requires only biomarker-positive individuals.

Table 2. Novel flexible approach to participant selection

Flexible algorithm for identification of potential participants from Parent Cohorts
• For example, probability of subsequent dementia (and the selection algorithm) may be initially based on age, absence of dementia diagnosis, and family history of AD in a PC with less extensive assessments; or age, cognitive performance, and APOE genotype in another PC with more detailed assessments; or age, cognitive performance, MRI and CSF biomarkers in a PC where such data are available • The PrePAD queries of PCs will be conducted potentially every month and may be adjusted depending on several factors: types of available data in the PC; the structure of the probability spectrum at any given time point in EPAD LCS; the EPAD PoC trial's intervention pipeline; and the capacity at each EPAD LCS site to baseline and manage new participants • The flexible algorithm will be agreed upon and applied by the EPAD LCS Balancing Committee, and the output will be provided to each Parent Cohort by the Algorithm Running Committee
Oversampling or under-sampling from different types of Parent Cohorts
• For example, if some PCs are more likely to provide participants with a profile suitable for a certain PoC trial arm, oversampling from such cohorts and under-sampling from others may occur before and during the trial recruitment period.
Flexible algorithm and over/under-sampling for PrePAD Velocity
• For similar reasons, a central element of PrePAD Velocity will be that the AD biomarker status of referred patients should be known from their regular clinical assessments. • The selection algorithm will be agreed upon by the Balancing Committee based on information

about assessments available in each referring clinical setting. The Algorithm Running Committee will provide a checklist to the referring clinician for verifying eligibility before contacting the local EPAD LCS site.
Flexible algorithm for refilling EPAD LCS over time
• The aforementioned procedures will be applied for both establishing and refilling the EPAD LCS. • The structure of the probability spectrum in LCS may change over time because participants (i) move into the PoC trial; (ii) drop out; or (iii) their characteristics (e.g. cognition, biomarkers, risk factors) change. • Depending on the structure of the probability spectrum at any given time point in LCS, participants coming in may or may not need to match participants moving out.

EPAD LCS outcomes and other assessments

EPAD LCS outcomes, other assessments and the data collection schedule are detailed in Table 3 and Table 4. The assessments are based on recommendations developed by the five EPAD Scientific Advisory Groups (SAGs) (Clinical and Cognitive Outcomes, Epidemiology, Fluid Biomarkers, Genetics, and Imaging). SAGs recommendations were based on reviewing the current literature, following widely accepted practices, and minimizing participant burden.

Table 3. EPAD LCS outcomes and other assessments.

Primary cognitive outcome	The *RBANS Total Scale Index Score* based on: • 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
Secondary outcomes	*Cognitive outcomes* • Working memory: Dot counting (NIH EXAMINER,[14, 15]) • Choice reaction time and set shifting: Flanker (NIH EXAMINER) • Paired associate learning: Favourites (University of California, San Francisco,[16]) *CSF biomarkers* • Beta-amyloid, total tau, phosphorylated tau *Neuroimaging outcomes (MRI)* • Hippocampal and whole brain volume
Exploratory outcomes	*Cognitive outcomes* • Allocentric Space: Four Mountains Task (Cambridge University, [17]) • Navigation in Egocentric Space: Virtual Reality Supermarket Trolley (University College London, [18])

	Other clinical outcomes • Amsterdam Instrumental Activities of Daily Living Questionnaire [19, 20] *Neuroimaging outcomes* • Multi-region structural MRI analysis • Functional regional and network measures
Other assessments	**Clinical:** • *Dementia* diagnosed by the participant's physician, including type and date of diagnosis • *MMSE*, Mini-Mental Status Exam [21] • *CDR*, Clinical Dementia Rating Scale [22] • *GDS*, 30-item Geriatric Depression Scale [23, 24] • *STAI,* State-Trait Anxiety Inventory [25] • *Pittsburgh Sleep Quality Index* [26] • *Physical examination*, including e.g. neurological examination, blood pressure, pulse, weight, height, and hip-waist circumference measurements • *Medical history* (yes/no): family history of AD (first degree relatives), stroke, diabetes mellitus (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 (Brain Injury Screening Questionnaire (BISQ, [27]), Mild Cognitive Impairment, other conditions • *Current medication*: name of drugs; treatment duration (<1year / 1-5years / >5years) **Biomarkers:** • *Collection of CSF and blood, urine & saliva samples* for future biomarker assessments (emerging AD biomarkers) • *APOE* genotype, Polygenic Scores **Other:** • *Sociodemographics*: date of birth, sex, ethnicity, years of formal education, marital status • *Lifestyle factors*: - Smoking (never / past / current) - Alcohol consumption (units/week) - Drug abuse/misuse (never / past / current) - Diet (questionnaire, Healthy Ageing through Internet Counselling in the Elderly, HATICE [28]) - Physical activity: leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating. Frequency 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 [29, 30] - Life events (brief questionnaire based on the Swedish National study on Aging and Care, SNAC [31]) - Self-rated health and self-rated fitness (Likert-type questions with response options very good / good / satisfactory / relatively poor / very poor [30]) • *Handedness*

Table 4. Data collection schedule.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual visits
Procedure	**Screening / Baseline**	**Month 6** ± 21 days[a]	**Month 12** ± 21 days[a]	**Month 24** ± 21 days[a]	**Month 36** ± 21 days[a]	**Year 4 onwards** ± 21 days[a]
Eligibility criteria	X	X	X	X	X	X
Research participant consent[b]	X					
Cognitive outcomes (ENE battery)						
RBANS	X	X	X	X	X	X
Dot Counting (NIH EXAMINER)	X	X	X	X	X	X
Flanker (NIH EXAMINER)	X	X	X	X	X	X
Favourites (University of California, San Francisco)	X	X	X	X	X	X
Four Mountains Task (Cambridge University)	X	X	X	X	X	X
Virtual Reality Supermarket Trolley (University College London)	X	X	X	X	X	X
Clinical outcomes						
Amsterdam Instrumental Activities of Daily Living Questionnaire	X		X	X	X	X
Biomarkers						
*Core MRI sequences	X		X	X	X	X
Advanced MRI sequences	X (subset)		X (subset)	X (subset)	X (subset)	X (subset)
**CSF sampling	X		X	X	X	X
Blood, urine & saliva sampling	X		X	X	X	X
Other assessments						
Socio-demographics (date of birth, sex, ethnicity, education, marital status)	X					
Family history of AD	X					
Medical history	X		X	X	X	X
Current medication	X	X	X	X	X	X
GDS	X		X	X	X	X
STAI	X		X	X	X	X
Pittsburgh Sleep Quality Index	X		X	X	X	X
Lifestyle factors	X		X	X	X	X
Dementia diagnosed by physician	X	X	X	X	X	X
CDR	X	X	X	X	X	X
MMSE	X		X	X	X	X
Physical exam	X		X	X	X	X
Height	X					
Weight, hip-waist circumference	X		X	X	X	X
Blood pressure	X		X	X	X	X
Ongoing research participant safety assessment						
Adverse events[c]	X	X	X	X	X	X

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

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

[c] All adverse events deemed by clinical judgement to be at least possibly related to EPAD LCS study procedures are to be recorded in the CRF. Adverse event collection should start with the first EPAD LCS procedure and will apply to all adverse events that occur within 30 days after a research participant's last study visit/procedure.

When an enrolled participant completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s).
* If an individual participant has had an MRI to the specifications in the Core EPAD Scanning protocol within 12 months of the Visit 1 first assessment of the EPAD LCS then this scan can be provided for analysis for the Visit 1 baseline data.
** If an individual participant refuses a lumbar puncture at Visit 3 or a subsequent annual visit this will be defined as missing data. If the participant refuses a lumbar puncture at two sequential visits, then they will be withdrawn from the EPAD LCS as a non-compliant participant.
If an individual participant has had a lumbar puncture and CSF sample collected and stored according to the CSF sampling manual procedure within 12 months of the Visit 1 first assessment of the EPAD LCS then this sample can be provided for analysis for the Visit 1 baseline data.

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; CDR - Clinical Dementia Rating; MMSE - Mini Mental State Exam.

Cognitive Outcomes

The selection process for EPAD LCS cognitive outcome measures has been described previously.[32] The EPAD Neuropsychological Examination (ENE) battery (Table 4) was chosen to cover all relevant cognitive domains, with greatest possible sensitivity to early-stage changes. The ENE 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, component tasks will have four alternative forms for retesting.

For LCS purposes, primary outcomes include anchor or criterion measure(s) accepted by regulatory authorities in previous registration trials. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will serve as the criterion measure for this study.[32] For statistical purposes, the RBANS Total Scale Index Score (Table 4) will serve as the primary outcome. LCS will also help validate the secondary and exploratory cognitive outcome measures against a known and accepted criterion measure. Although the EPAD LCS is conducted in compliance with Good Clinical Practice (GCP), including the primary outcome, the computerized secondary and exploratory cognitive measures are undergoing additional validation in EPAD LCS and, thus, do not yet fully meet GCP (Title 21 CFR Part 11/European Union Annex 11).

CSF biomarker outcomes

Measurements will include AD-related markers (beta-amyloid, total tau and phosphorylated tau), and this data will be used for disease modelling and for staging of disease pathology. CSF sampling follows a harmonised preclinical protocol and analyses take place using the fully automatized Roche Elecsys System in a single laboratory (University of Gothenburg). Additional CSF is stored in the EPAD BioBank at the Roslin Research Institute, University of Edinburgh with all other fluid samples.

Neuroimaging outcomes

The selection process for the neuroimaging measures included in the LCS protocol was based on evidence from available studies with an emphasis on secondary prevention of AD. Other considerations were usefulness of imaging data for the EPAD PoC trial, participant burden, implementation and costs, and avoiding redundancies between imaging and non-imaging measures.

The Magnetic Resonance Imaging (MRI) acquisition is divided into:

[1] Core image acquisition, conducted in all LCS participants to assess study eligibility, for baseline assessment that can be used for subsequent safety monitoring in the EPAD PoC trial, and for quantitative analysis of brain structure and vascular lesions. ADNI-like protocols and quality control will be used to ascertain precision in measuring change.

[2] Advanced image acquisition, which only a sub-set of sites with suitable equipment and experience will acquire. This may include one or more of the following types of acquisition: 3D-Susceptibility Weighted Imaging or 3D-T2*, Diffusion Tensor Imaging, Arterial Spin Labelling, and resting state functional MRI.

Genetic Assessments

The primary genetic assessment will include APOE genotype. The samples may also be sequenced when additional resources become available. Genetic variants with strong effect (e.g. 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 individuals with early onset AD and are therefore unlikely to be included in the EPAD LCS.

Other assessments

A broad range of sociodemographic, medical and lifestyle-related data will be collected (Tables 3 and 4). Mini-Mental Status Exam (MMSE) [21] and Clinical Dementia Rating scale (CDR) [22] will be used given their utility principally as clinical descriptors. Biological samples will include blood, urine and saliva (e.g. for cortisol measurements) stored under optimal conditions in the central EPAD Biobank.

EPAD LCS-MINI protocol for participants who maintain a low likelihood of trial inclusion

During EPAD LCS it may become clear that some participants maintain a low likelihood of being invited to the PoC trial. This may happen for several reasons, e.g. developing health conditions that preclude trial participation, or showing no impairment/decline in cognition and AD biomarkers. Starting from their third visit (one year after baseline), such participants may have the possibility to continue with a lower-burden protocol, i.e. without the yearly MRI and CSF sampling.

Data Sources, collection and monitoring

The only data source for this study will be data collected as part of the EPAD LCS. Electronic data capture will be used as appropriate, e.g. for cognitive and imaging data. Central laboratories will be used for all CSF (University of Gothenburg) and genetic (University of Edinburgh) assessments, and central reading of all neuroimaging will be undertaken (University of Edinburgh, VU

University Medical Center Amsterdam). A common pre-analytical procedures schedule for sample collection, storage and shipment will be used at all EPAD LCS sites. The study will be monitored in accordance with the ICH GCP (ICH Topic E6, 1996).

STATISTICAL ANALYSIS

Sample Size

To achieve our objective of running a platform trial, we anticipate needing a readiness cohort of several thousand people, i.e. the number will be determined by the EPAD PoC trial needs. The EPAD LCS sample size will be maintained through continuous recruitment from PCs and via PrePAD Velocity. Strategies for motivation and engagement, as well as improving the research experience for participants will be developed, including e.g. newsletters, websites and telephone contact from the study sites.

Disease modelling

AD is a complex condition, and an individual's probability of developing dementia is most likely the result of multiple contributing factors.[1, 3] In EPAD LCS, participants may fall on a continuum of overall probability for subsequent dementia driven by several underlying dimensions: cognition; AD-related biomarkers; traditional risk factors (genetic and environmental); and their longitudinal changes. These dimensions may be continuous in nature. Treating them as such rather than dichotomizing or categorizing them 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. This is especially important as participants with similar overall probability may have different contributions from the various dimensions. Interrogating the underlying dimensions in addition to the overall predicted probability will also facilitate decisions on participant stratification considering the drivers and needs related to compounds to be tested in the EPAD PoC trial.

Longitudinal modelling of cognitive outcomes, biomarkers and risk factors will be used to characterise these dimensions dynamically and relate their trajectories to the probability of AD dementia development or other meaningful intermediate disease states. Modelling will identify and rank strata of sub-populations of different probability. Each sub-population will have a cognitive, biomarker and risk factors profile, and this stratification will be used to identify potential interventions, the size of a potential intervention effect, and to guide the flow of participants from EPAD LCS into subsequent arms of the PoC trial.

The starting point of the modelling will be mixed-effects models for the cognitive outcomes, biomarkers and risk factors, especially as dementia events are expected to be rare in the first few years of follow-up of participants. Complexity of investigated models will subsequently increase and focus on (multivariate) latent trajectory/class mixed models for the longitudinal outcomes and biomarkers; survival and more general event history models for progression to AD dementia and joint models linking these longitudinal outcomes and biomarkers to AD dementia. The longitudinal models will initially be developed for each cognitive outcome and biomarker separately and then combined to ultimately maximise the prediction of probability for subsequent dementia.

Analyses of cognitive outcomes will be carried out at both the individual cognitive domain and composite score (RBANS Total Scale Index) levels. Robustness of models developed will be evaluated using cross-validation.

As data accrues in the EPAD LCS, soft data locks and releases will occur after 500, 1000, 2000 participants (and by intervals of 1,000 thereafter) and by stage of follow up e.g. baseline, 1 year, 2 year etc. to inform selection algorithms for EPAD LCS; provide updated information for improving selection into the EPAD PoC trial; and provide updated disease models.

ETHICAL ASPECTS

The 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. EPAD LCS has received ethical approval from numerous institutional review boards (IRBs) across Europe.

EPAD has an Ethics Workgroup examining the complex ethical considerations involved in the project, and providing appropriate recommendations.[33, 34]

Informed consent

As the EPAD project is multi-staged, staged consent will be used as decision making model.[17] Staged consent feeds relevant information – bit by bit, extended over time - to participants and study partners, and asks informed consent at every step when they need to make important decisions. Although informed consent is given for a specific stage of EPAD (e.g. consent for LCS does not imply consent for the PoC trial), information about the 'totality of EPAD' will always and explicitly be made available.

Potential Disclosure of Risk Information

Overall estimated probability for developing AD dementia will not be disclosed to research participants due to insufficient accuracy/robustness of current disease models. However, findings with established clinical relevance and requiring further monitoring and treatment will be disclosed to participants, and appropriate measures will be taken. AD-related CSF biomarkers may be disclosed if progression to AD dementia is suspected during EPAD LCS, or where it is considered

relevant to an individual's ongoing clinical management, or if a participant is later invited to the PoC trial.

Privacy of Personal Data

EPAD LCS will ensure that data on participants are appropriately managed, and participant and study information are treated as confidential. All participant study records are identified by the participant identification number to maintain participants' confidentiality.

RESEARCH PARTICIPANT INVOLVEMENT

EPAD has established a Research Participants Panel to provide feedback of the experience of research participation, to ensure that participant perspectives are represented in decision making about the future of the project and to advise local and central EPAD LCS teams. The local panel will consist of 6-10 EPAD LCS participants at each site and will meet at least twice annually. All EPAD LCS participants at a site 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. 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.

DISSEMINATION PLAN

Findings will be disseminated to several target audiences, including the scientific community, research participants, patient community, general public, industry, regulatory authorities and policy makers. Types of communication will include scientific publications, conference presentations, press releases, interviews and other media communications (including social media), meetings etc. Information and regular updates are posted on the EPAD project website (www.ep-ad.org).
Data collected from EPAD LCS will be made available for analysis to help researchers everywhere improve their understanding of the early stages of AD and facilitate collaborations.

DISCUSSION

The EPAD project has been established to overcome the major hurdles hampering drug development for the secondary prevention of AD dementia, by conducting the EPAD LCS in alignment with the Bayesian adaptive designed EPAD PoC trial. This set-up addresses the dual need for (i) developing accurate longitudinal models for AD covering the entire disease course, and (ii) developing an adequate infrastructure for facilitating identification of participants and clinical trial recruitment. While several dementia prediction models have already been developed, very few have been validated, and none has been tested in a drug trial. The alignment of a longitudinal cohort study with an adaptive trial design within the same project [5] is a novel approach that closes the previous gap between dementia prediction and prevention. This design aspect differentiates EPAD LCS from other international networks of observational studies, e.g. the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) [35], the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA/Maelstrom) [36], or Stroke and Cognition consortium (STROKOG) [37]. Other novel solutions for facilitating trial recruitment include e.g. online Brain Health Registers [38, 39], but they require older populations with significant internet literacy, and outcome measures cannot yet be aligned between the online observational cohorts and clinical trials.

EPAD LCS recruitment relies on existing cohorts across Europe. The variety of recruitment sources, i.e. from general populations to memory clinics, will ensure that the EPAD LCS probability-spectrum population can cover the entire continuum of probability for AD dementia development. The yearly EPAD LCS follow-up with comprehensive cognitive, clinical and biomarker assessments will provide a well-phenotyped 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 novel flexible

approach to participant selection is designed to balance the disease modelling and adaptive trial design needs.Both EPAD LCS and EPAD PoC trial will be run in an exclusive network of highly selected, expert sites (Trial Delivery Centres) selected on the basis of strictly applied criteria to ensure the highest possible data quality, successful recruitment and adherence to the EPAD principles.

The EPAD project does not operate alone. Together with IMI's EMIF-AD, Amyloid imaging to prevent Alzheimer's disease (AMYPAD), Real world outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP), and Organising Knowledge about Neurodegenerative Disease Mechanisms for the Improvement of Drug Development and Therapy (AETIONOMY) projects, it forms a key and major part of the IMI-AD platform. It is also working closely with other, similar initiatives worldwide, including the US-based Global Alzheimer's Platform. The multi-national approach and academia-industry collaborations are essential for advancing knowledge on the entire spectrum of AD, and for finding effective therapies to prevent the onset of dementia.

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Figure 1. Flow of participants to EPAD LCS and into the EPAD Proof of Concept (PoC) trial

Figure 2. EPAD LCS recruitment status (04 July 2018). Sites: UEDIN-University of Edinburgh (UK); BBRC- BarcelonaBeta Brain Research Center (Spain); CHUT- Centre Hospitalier Universitaire de Toulouse (France); VUMC- VU University Medical Center Amsterdam (Netherlands); KI-Karolinska Institutet (Sweden); CITA- Centre for Research and Advanced Therapies for Alzheimer's disease Foundation (Spain); Nantes- Centre Hospitalier Universitaire de Nantes (France); Montpellier- Centre Hospitalier Universitaire de Montpellier, Gui de Chauliac (France); UNIGE- Geneva University Hospitals (Switzerland); Lille-Centre Hospitalier Régional Universitaire de Lille, Hôpital Roger Salengro (France); UOXF-University of Oxford (UK); Tayside- NHS Tayside, Dundee (UK); Grampian- NHS Grampian, Aberdeen (UK); Paris LSP-Hôpital Universitaire de la Pitié Salpêtrière (France); Paris Nord- Groupe Hospitalier Saint Louis - Lariboisière - Fernand Widal (France); WLMHT- West London Mental Health NHS Trust (UK); Glasgow- Glasgow Clinical Research Facility, NHS Greater Glasgow and Clyde (UK); Manchester- Greater Manchester Clinical Research Network (UK); Bristol- North Bristol NHS Trust (UK).

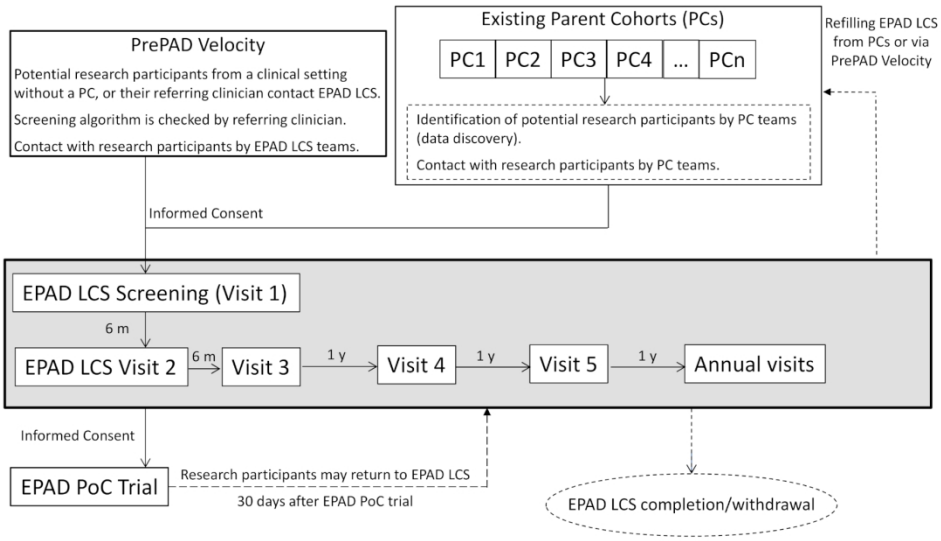

Figure 1. Flow of participants to EPAD LCS and into the EPAD Proof of Concept (PoC) trial

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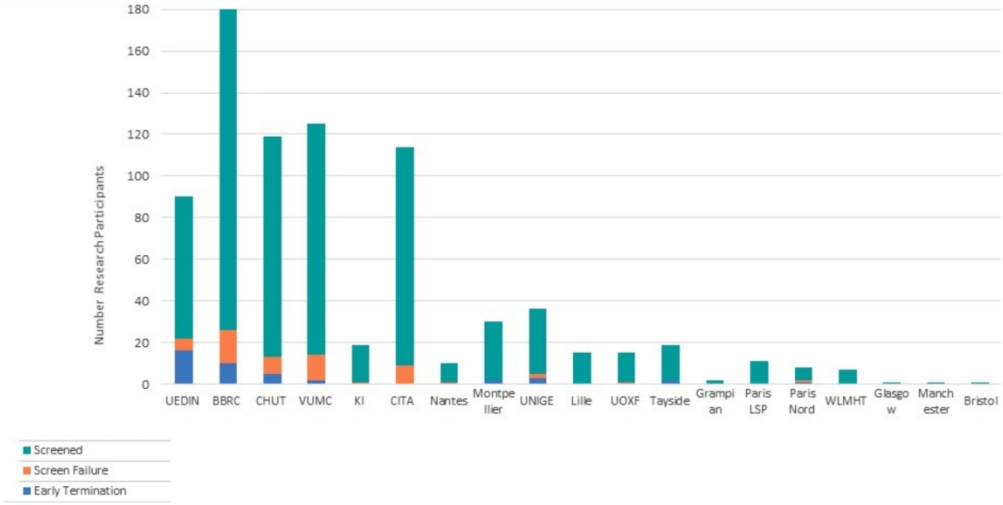

Figure 2. EPAD LCS recruitment status (04 July 2018)

167x118mm (300 x 300 DPI)