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Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy

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3 **Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and**
4 **Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO)**
5 **SubStudy**
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42 43 44 45 46 **Trial Registration**

47
48 The CHARIOT:PRO SubStudy is registered with clinicaltrials.gov (NCT02114372). Notices
49 of Protocol modifications will be made available through this trial registry.

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53
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Chinedu Udeh-Momoh, Josip Car, Robert Pernecky, Geraint Price, Celeste de-Jager Loots, Heather Ward and Miia Kivipelto served as co-principal study investigators at ICL for Janssen Research & Development, LLC and all declare no conflict of interest. Josip Car's and Azeem Majeed's posts at ICL are in part supported by the NIHR NW London Applied Research Collaboration. Catherine Robb, Darina Bassil, Martin Cohn, Parthenia Giannakopoulou, Dimitra Kafetsouli, Yellappa Chowdary-Seemulamoodi, Dinithi Perera, Lisa Curry, Kristina Lakey, Heather McLellan-Young, Jennifer Crispin and Azeem Majeed were study investigators at ICL and declare no conflict of interest. Karen Ritchie served as co-principal study investigator at EDI for Janssen Research & Development, LLC and declares no conflict of interest. Tamlyn Watermeyer and Natalia Reglinska-Matveyev were study investigators at EDI and declare no conflict of interest. David Scott and Luc Bracoud are employees of Bioclinica Inc. and declare no competing interests.

ABSTRACT

Introduction: The CHARIOT:PRO SubStudy (CPSS), sponsored by Janssen Pharmaceutical Research & Development LLC, is an Alzheimer's disease (AD) biomarker enriched observational study. CPSS aims to identify and validate determinants of AD, alongside cognitive, functional and biological changes in older adults with or without detectable evidence of AD pathology at baseline.

Methods and Analysis: CPSS is a dual-site longitudinal cohort (3.5 years) assessed quarterly. Cognitively normal participants (60-85 years) were recruited across Greater London (n=2508) and Edinburgh (n=1695). Participants are classified as high, medium (amnesic or non-amnesic) or low risk for developing mild cognitive impairment–Alzheimer's disease (MCI-AD) based on their Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) performance at screening. Additional AD-related assessments include: a novel cognitive composite, the Global Preclinical Alzheimer's Cognitive Composite (G-PACC), brain magnetic resonance imaging (MRI) and positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis. Lifestyle, other cognitive and functional data, as well as bio-samples (blood, urine, and saliva) are collected. Primarily, study analyses will evaluate longitudinal change in cognitive and functional outcomes. Annual interim analyses for descriptive data occur throughout the course of the study, although inferential statistics are conducted as required.

Ethics and Dissemination: CPSS has received national and local ethics approvals required for each participating site. The study is at the forefront of global AD prevention efforts, with frequent and robust sampling of the well-characterised cohort, allowing for detection of incipient pathophysiological, cognitive and functional changes that could inform therapeutic strategies to prevent and/or delay cognitive impairment and dementia. Dissemination of results will target the scientific community, research participants, volunteer community, public, industry, regulatory authorities and policymakers. Upon study completion, and following a predetermined embargo period, CPSS data is planned to be made accessible for analysis to facilitate further research into the determinants of AD pathology, onset of symptomatology and progression.

Key Words: Epidemiology; Neurology; Psychiatry; Dementia; Preventative Medicine

STRENGTHS AND LIMITATIONS

Strengths

- Prospectively-designed, high-powered longitudinal cohort of cognitively-healthy (at baseline) elders across the Alzheimer's pathological continuum followed up at high-throughput
- Deep and frequent phenotyping of participants with extensive biological, psychosocial, cognitive, behavioural and lifestyle measures will enable robust interrogation of the determinants of Alzheimer's disease (AD) progression and symptom development.
- High frequency (quarterly) follow-up of participants will facilitate determination of assessments most sensitive for identifying the earliest signs and symptoms of AD-dementia
- Study adopts a unique cognition-based classification method for designating risk of MCI-AD development from baseline.
- The conduct of the study at only 2 sites minimized several sources of variability that are independent of aging and incipient Alzheimer's disease (e.g., inter-rater variability and differences in psychometric equivalence among different translations).

Limitations:

- Given the low amyloid positivity rate and the requirement of an equal number of CPSS participants above and below threshold, a high number of participants (78.6%) were excluded from the longitudinal CPSS study. As a mitigating measure, enrichment criteria were introduced, with requirement of first-degree family history in volunteers aged 60-65.
- Following completion of enrolment, but prior to any participants reaching end of study, the outbreak of the COVID-19 epidemic required suspension of in-clinic assessments.
- The conduct of the study at only 2 sites does not fit the model of a typical, multi-site international clinical trial.

INTRODUCTION

Background and Rationale: The last few decades have witnessed unparalleled growth in aged populations. Hence, the global incidence and prevalence of Alzheimer's disease (AD), the most-common form of late-onset dementia, continue to increase exponentially, with numbers expected to exceed 150 million global cases by 2050 [1]. The paucity of any viable therapy for dementia prevention and/or disease modification necessitates a re-think of the conventional approach towards preventative research. Indeed, the AD field will benefit from concerted efforts for preventative strategies combining biomarker discovery studies with detailed validation of clinical characteristics as well as longitudinal explorations of associated pathologies and symptoms.

The asymptomatic stage of AD is characterized by biomarker evidence of amyloid- β ($A\beta$) deposition, as measured by either low cerebrospinal fluid (CSF) $A\beta_{42}$ peptide concentrations or elevated tracer uptake on $A\beta$ positron emission tomography (PET) scans [2]. Multiple studies have now reported that higher $A\beta$ burden in cognitively normal (CN) individuals is associated with measurably poorer performance in neuropsychological tests [3]. The accumulating longitudinal data also strongly suggest that evidence of abnormal levels of $A\beta$ deposition in CN individuals increases the risk for cognitive decline and progression to mild cognitive impairment (MCI) and AD dementia [3]. The current consensus among members of the Alzheimer's scientific community is that these CN individuals with detectable pathogenic $A\beta$ represent an early stage on the AD continuum [2,4,5]. Indeed, a meta-analysis of 55 studies suggested that approximately 20% to 35% of study participants aged over 60 years without dementia symptoms are likely to have above-threshold pathogenic $A\beta$ pathology detected by PET [6], with numbers increasing to 90% by age 85 [7].

Rate of cognitive decline in CN individuals with or without evidence of abnormal $A\beta$ deposition can be measured using sensitive cognitive composite instruments. These measures focus on the cognitive domains affected earliest in AD, namely episodic memory and executive function, with decline noted as early as 7 to 10 years prior to the diagnosis of MCI or AD dementia [8–10]. Yet, gaps remain in our understanding of the exact predictors of AD pathological onset, accumulation and resultant development of clinical symptoms. There is a need to identify individuals at varying levels of risk for AD, prior to development of AD dementia. Such information would be useful to improve our understanding of the natural history of AD progression and identify opportunities for intervention.

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3 The CHARIOT:PRO program seeks to address such gaps via detailed explorations of the
4 determinants of AD-related biological, clinical and cognitive changes. The previously-reported
5 main study of 987 participants at ICL, conducted from 2013 to 2016 (following early
6 termination by the study Sponsor) [11] was further adapted into a large prospective
7 observational trial – The CHARIOT: PRO SubStudy (CPSS) aimed at enhancing the scientific
8 robustness of the main study objectives with the addition of imaging and other AD-related
9 assessment tools.

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11 Here we describe the protocol (from Amendment version 15, dated 15th Aug 2018) of this
12 biomarker enriched CPSS featuring neuropsychological, functional, lifestyle, imaging and
13 other biomarker assessments and the schedule for their collection. We provide an outline of the
14 study design and a summary of the recruitment and screening process leading to the fully
15 enrolled cohort of 519 cognitively unimpaired adults.

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17 **Objectives of the CPSS:** CPSS is a prospective dual-centre, UK cohort study that at its core
18 aims to characterise deeply the clinico-biological attributes of the non-symptomatic AD stage
19 in individuals at differing levels of risk for development of MCI and AD-dementia, based on
20 cognitive test scores at screening. CPSS participants thus could form a readiness cohort to be
21 recruited onto future AD-dementia prevention trials.

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23 Specifically, using data from participants with evidence of detectable A β pathology versus
24 those with below-threshold levels, the study will:

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- Investigate the longitudinal change of the global and composite measures of the newly-developed Global Preclinical Alzheimer's Cognitive Composite (G-PACC) in comparison to the Repeatable Battery for the Assessment of Neuropsychological Status [RBANS, 12] and other study neuropsychological assessments, as well as psychometrically evaluate the test batteries
 - Determine precise baseline predictors of longitudinal AD-related cognitive and functional decline, and clinical progression to improve future screening of participants most likely to develop MCI-AD/ AD dementia

METHODS

Population

The CPSS participants are adults aged 60 to 85 years old (inclusive), residing in Greater London, South West England, Edinburgh and surrounding districts. Those included had documented evidence of A β pathology (A β positives: above-threshold brain A β deposition on PET or below-threshold CSF A β_{42} concentration), or evidence of below-threshold A β pathology (A β negatives: below-threshold brain A β deposition on PET or above-threshold CSF A β_{42} concentration), and a baseline global Clinical Dementia Rating (CDR) score=0. CPSS participants were classified at screening as *high*, *medium-amnesic* or *non-amnesic*, or *low* risk for developing MCI due to AD (MCI-AD), based on cognitive test performance as described previously [11].

Study Design

The CPSS is a UK prospective observational study taking place across two sites (ICL and EDI). The study is planned to follow approximately 250 CN participants who are A β positive and approximately 250 A β negative CN control participants for up to three and a half years. Evidence of A β pathology was assessed via CSF A β_{42} except where lumbar puncture (LP) was medically contraindicated or refused by participants, in which case A β PET was permitted as an alternative method of determination of A β status. CSF samples were tested with the Meso Scale Discovery (MSD) triplex (A $\beta_{38/40/42}$). A binary classification for A β load was applied using a cut-off value for CSF A $\beta_{42} \leq 600$ ng/L. The cut-off for brain A β PET via standardized uptake value ratio (SUVR) was based on three independent F18-radiolabeled amyloid tracers - florbetapir, flutemetamol, and florbetaben. A specific SUVR threshold (i.e. a cut-point) was used for each of the three radiotracers (Amyvid: 1.14 with whole-cerebellum as a reference region, Neuraceq: 1.20 with cerebellar grey matter, Vizamyl: 1.23 with whole cerebellum). Scans were reported as amyloid positive if the composite cortical SUVR value was above the defined tracer-specific threshold, and negative if less than or equal to the threshold value.

All study investigators, sponsor team and participants are blinded as to A β status information, with the exception of an unblinded team member for verification of imaging and CSF A β information. Blinding was put in place to avoid bias for conducting, monitoring and interpreting results from the clinical assessments (except for research analysis purposes). The same double-blind is maintained for apolipoprotein E (*APOE*) genotype, in view of allele-specific positive correlation with A β load [13–15]. A β status and *APOE* genotype results were

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3 not disclosed to participants as the clinical value (i.e., diagnostic or predictive) of such a
4 disclosure in a CN population is still unestablished. If clinical value is established from this or
5 other studies, then amyloid and *APOE* genotype will be disclosed to participants, at the end of
6 the study.
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10 Numbers of A β negative participants who passed screening assessments were deliberately
11 controlled to ensure equivalency with number of eligible A β positive participants. There was
12 no deliberate effort to balance the groups by age or gender.
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16 **Study schedule**

17 *Participant recruitment*

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19 At the ICL site, participants were recruited primarily from the CHARIOT Register, a well-
20 established dementia prevention and prediction register of older adults without dementia who
21 have provided consent to be contacted for relevant ageing research [16,17]. Some participants
22 transitioned directly to CPSS from the Main study, though most of these individuals had
23 previously been recruited also from the CHARIOT Register. Additional methods of
24 recruitment at the site, with very limited numbers of enrolled participants, included self-
25 referrals and response from media advertisements. At the Edinburgh site, participants were
26 recruited via SHARE (<https://www.registerforshare.org>), Join Dementia Research (JDR,
27 <https://www.joindementiaresearch.nihr.ac.uk/>) and the Scottish Primary Care Research
28 Network (SPCRN [http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)
29 [the-network](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)) (See Figure 1 for the participant recruitment pathway).
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41 *Selection of study participants: summary of eligibility criteria*

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43 The major exclusion criteria for CPSS include known familial autosomal dominant AD,
44 diagnosis of AD dementia, MCI, or any other degenerative brain disorder that is associated
45 with dementia at screening. Evidence of brain disease or other conditions leading to dementia,
46 other than AD-related structural pathologies were assessed centrally by blinded neuro-
47 radiologists via magnetic resonance imaging (MRI) during screening. Additionally, use of AD
48 pharmacological therapies, and evidence of psychiatric/cognitive disorders/other abnormalities
49 such as low vitamin B12 (specifically those with abnormal homocysteine and methylmalonic
50 acid), and linked to cognitive deficits are exclusionary. Further, history of first-degree family
51 member with diagnosed clinical AD was required for participants aged 60-65 years. This
52 measure was put in place to enrich the cohort for cerebral A β positivity given typically lower
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3 prevalence in asymptomatic young elders i.e. below 70 years of age [18], thereby effectively
4 minimizing screen failure rates. Following participants' consent, self-reported medical and
5 medication history was confirmed from full history provided by participants' general
6 practitioner (GP). Upon receipt of any medical information, current medical conditions and
7 past medical history was updated on source documents and subsequently on electronic data,
8 including medication, past and planned procedures. Medical summaries from GPs were used
9 to ascertain self-reported histories.

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11 During screening, participants whose cognitive performance on any RBANS Index fell more
12 than 1.5 standard deviations below the (age- and education-adjusted) population mean (based
13 on normative sample from [19])) were referred to an adjudication panel. This panel, comprised
14 of neurologists, psychiatrists and neuropsychologists, considered whether the low performance
15 was likely to be attributable to undiagnosed cognitive impairment and, if so, excluded the
16 participant from the study. These participants were contacted directly by the study team to
17 inform them of their exclusion. At that time, where any concerns were noted regarding their
18 performance, the option to notify their GP with information about the study and their exclusion
19 was offered.

20 21 *Screening schedule*

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23 The screening was usually completed in four separate visits within a 90-day window. On
24 certain occasions, this timeline was extended up to 180 days to allow for treatment of transient
25 conditions, laboratory retesting, and scheduling of other screening assessments. This allowed
26 time for results to be received and evaluated against study eligibility criteria. Any clinically
27 significant findings were passed on for follow-up to the participant's GP, and participants who
28 were determined to have an active unstable illness as defined by the inclusion/exclusion
29 criteria. Screening involved collection of demographic data which included age, ethnicity,
30 education and occupational status. During screening, potential participants completed
31 cognitive tests, the G-PACC and RBANS, and CDR including the study partner interview. A
32 clinical evaluation (pulse, blood pressure, weight, head, waist & hip circumference,
33 temperature (tympanic), physical and neurological examination) and clinical lab assessments
34 were carried out to determine general health status. Participants not excluded at this stage then
35 underwent a brain MRI. If MRI did not reveal exclusionary abnormalities (see Table 1), it was
36 followed by an A β assessment based on CSF analysis or brain PET scan. After the A β
37 determination, baseline assessments were undertaken at two consecutive visits where the
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3 RBANS (form A), G-PACC (form A) as well as the Neuropsychological Assessment Battery
4 (NAB) Memory and Executive Function modules (form 1) and the National Adult Reading
5 Test (NART) were administered alongside self-reported study questionnaires. Bio-samples
6 were further collected for biomarker assessments. (See Figure 3 for schematic depiction of
7 screening and baseline assessments).
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10 11 12 *Post-screening schedule*

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15 Following the baseline assessment, CPSS participants were randomized in a balanced 1:1:1
16 ratio, stratified by A β status and level of performance on the screening RBANS, to one of three
17 supplemental neuropsychological tests namely: CogState Brief Battery [20], Cognitive Drug
18 Research Assessment System, and either Delis-Kaplan Executive Function System [DKEFS,
19 21, ICL only] (ICL only) or COGNITO [22, EDI only]. Participants who enrolled in the
20 Substudy from the Main Study retained their previous Main Study-assigned randomized group.
21 Participants are expected to attend study visits every quarter and will be followed up for a
22 period of up to 3.5 years.
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29 **Study outcomes and assessments**

30 31 *Primary neurocognitive outcomes*

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34 The primary outcomes of the CPSS are performance in two neurocognitive measures, the novel
35 G-PACC and the RBANS.
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38 The G-PACC: is a retrospectively validated measure, weighted towards episodic memory but
39 including a timed executive function test and a global cognitive screening test. For this study,
40 the four PACC components include: the Free and Cued Selective Reminding Test -Immediate
41 Recall [FCSRT-IR, 23,24], the Delayed Paragraph Recall score on a single administration of
42 the Logical Memory story from the WMS – Revised [25], the WAIS-IV Coding subtest [26]
43 and the MMSE [27]. Each component score is transformed into z-scores. These z-scores are
44 summed to form the composite. The battery takes about 25 minutes to administer. Alongside
45 screening and baseline time points, alternating forms of the G-PACC are administered at the
46 following time points: Months 6, 12, 18, 24, 30, 36, 42.
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54 The RBANS: is a 25-minute composite battery with 12 subtests that measure 5 cognitive
55 domain indices: Attention, composed of Digit Span and Coding, Language, with Picture
56 Naming and Semantic Fluency subtests, Visuospatial Construction including Figure Copy and
57 Line Orientation subtests, Immediate Memory comprising List Learning and Story Memory
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3 subtests, and Delayed Memory composed of List Recall, List Recognition, Story Recall, and
4 Figure Recall subtests. The sum of these 5 Index scores is converted to a Total Scale value via
5 a mapping table. The Total Scale is a norm-based t-score based on a distribution with a mean
6 of 100 and standard deviation of 15. The RBANS is administered face-to-face, has 3 alternate
7 forms, is available in over 30 languages, and has been used in multinational clinical trials
8 including AD trials. Alternating forms of the RBANS are also administered at the following
9 timepoints: Months 3, 9, 15, 21, 27, 33, 39. During screening, participants' RBANS scores
10 were used to delineate risk (low, medium, high) for developing MCI-AD, as described in the
11 Main study [11].

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Secondary Cognitive outcomes and Functional outcomes are described in Table 2. More
detailed description of these measures are provided in the CHARIOT PRO Main Study
Protocol [11].

Neuroimaging outcomes

Safety and volumetric scans (3DT1, FLAIR, T2*, PD/T2, T1 and DWI): All potential CPSS
participants underwent brain MRI at screening to assess eligibility, based on a central
radiologist's interpretation of the MRI scan under the supervision of Bioclinica Inc. Borderline
findings were reviewed by the Medical Monitor prior to determining participant eligibility.
Image acquisition was performed at multiple sites based on a standardized MRI protocol.
General Electric Signa HDxt 1.5T and Siemens TrioTim, Verio, Skyra and Prisma 3T scanners
were used to acquire a volumetric 3D T1 weighted series in a sagittal plane, using 1.2 mm thick
slices and a 192x192 acquisition matrix over a square FOV of 240 mm. Contrast parameters
were field-strength and manufacturer dependent (Siemens MP-RAGE and GE IR-Prep Fast
SPGR). The standardized MRI protocol also included 2D axial FLAIR, T2* gradient echo,
dual-echo proton-density and T2-weighted turbo/fast spin echo, T1-weighted turbo/fast spin
echo and diffusion-weighted imaging. Proper implementation of the MRI protocol on each
participating scanner was verified prior to first subject scan by use of American College of
Radiology (ACR) phantom scans.

Exploratory scans (Task-free BOLD functional MRI (tf-fMRI) and high-resolution coronal
T2sequences): At the ICL site, the first 800 subjects who were eligible for MRI underwent a
dual-echo GRE field map and task-free functional MRI time series. For the remainder of the
subjects, a high-resolution 2D coronal T2-weighted sequence was acquired, in order to
visualize hippocampal subfields.

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3 A β PET: At final stage of screening, evidence of A β pathology in potential CPSS participants
4 was assessed by a brain PET scan. All images derived were evaluated centrally at Bioclinica
5 Inc. for A β status assessment. The assessments were performed by neuro-radiologists trained
6 in the assessment of A β PET scans using F18-radiolabeled amyloid tracers (Amyvid, Vizamyl
7 and Neuraceq) for amyloid status according to the reading process developed by radiotracer
8 vendors. The PET scan was evaluated at baseline to determine each patient's A β status as
9 positive or negative and therefore inclusion or exclusion into the trial. PET exams were
10 acquired using a uniform scanning protocol that minimizes and accounts for between-site
11 differences in PET systems, as characterized with a Hoffman phantom exam. All exams were
12 acquired in 3D mode and employed correction for attenuation, scatter and random coincidence.
13 Semi-quantitative SUVR assessment was performed prior to the visual read. SUVR
14 calculations leveraged a FreeSurfer-based native-space MRI segmentation method. The A β
15 status assessment was a hybrid visual and quantitative approach (see Figure 2). A visual review
16 was performed by a single reader, followed by positivity assignment based on SUVR cutpoint.
17 In case of discrepancies between visual and SUVR results, a second reader was asked to
18 participate in a final decision on amyloid status, as part of a consensus review. The second
19 reader was given both the initial visual read and the SUVR measurement and convened with
20 the first reader to arrive at a consensus assessment.

34 ***Fluid Biomarkers***

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37 Blood, saliva and urine samples for clinical assessments and future biomarker discovery
38 studies: At ICL and EDI, blood and urine samples were collected at screening to assess general
39 health status. These included: Haematology and Differential Panel, Lipid Panel, Chemistry
40 Panel, Electrolyte Panel, Coagulation Group, C-Reactive Protein, TSH, Folate, Vitamin B12
41 and Urine Macro Panel (with Urine Microscopy if abnormal Macro Panel).

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46 At ICL, serum, plasma, buffy coat, whole blood, urine and saliva samples are processed and
47 stored at baseline and annually thereafter for future biomarker exploration. Samples for
48 biobanking are collected between 9-11.30am and following an overnight fast; and are stored at
49 the ICL purpose-built -80°C biobank for future analyses. All samples are processed within two
50 hours of collection, as per guidelines on biomarker pre-processing [28]. Planned analyses
51 include untargeted metabolite and proteome profiling, to generate novel targets for future
52 hypothesis-testing and biomarker discovery studies.

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3 CSF biomarkers: For those participants not receiving A β PET, CSF samples were collected
4 during screening and analyses for AD-related markers including beta-amyloid, total tau and
5 phosphorylated tau. The A β data was used for determination of enrolment eligibility, and in
6 addition to the tau data, will be useful for disease modelling and staging of pre-clinical AD per
7 NIA-AA criteria [2]. At ICL, additional aliquots of CSF samples are stored in the -80°C
8 biobank for future analyses.
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14 Genetic outcomes: Whole blood is collected in EDTA tubes for extraction of genomic DNA
15 (gDNA) using standard methods. gDNA were thus isolated via commercially available kit
16 following manufacturer instructions (QIAGEN QIAasympphony DSP DNA Mini Kits or Promega
17 Maxwell RSC Whole Blood DNA Kit). Both kits facilitate automated magnetic bead-based
18 extractions that successfully extract DNA from Human Whole Blood samples with good
19 quantitation and purity assessments. The QPS validated pyrosequencing genotyping assays for
20 *APOE* codon 112T>C and codon 158C>T polymorphic variants were used to genotype
21 participant's gDNA samples and identify *APOE* ϵ 4 Carriers and *APOE* ϵ 4 Non-Carriers status.
22 By interrogating these two polymorphic variants, we identified the three *APOE* alleles: *APOE*
23 ϵ 2(TGC 112, TGC 158), *APOE* ϵ 3 (TGC 112, CGC 158), and *APOE* ϵ 4 (CGC 112, CGC 158).
24 *APOE* genotype status has been determined for the enrolled cohort. A genome-wide-analysis
25 study is under-way and data expected to be available during the study. At ICL, whole blood is
26 also collected in a PAXgene® Blood RNA tube containing reagent for stabilization of
27 intracellular RNA, and stored -80°C. These samples will be used for future genetic analyses.
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39 ***Medical History and Clinical examinations (Physical and neurological examination)***

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41 A thorough medical history was obtained including an evaluation of all body systems (ENT,
42 ophthalmic, musculoskeletal, gastrointestinal, urinary, respiratory, renal, cardiovascular,
43 dermatological) with an emphasis on relevant medical history (e.g. neurological, psychiatric,
44 substance abuse, endocrine and metabolic). Safety and compatibility for neuroimaging were
45 further ensured prior to the procedure.
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51 Clinical examination included General Physical examination and a separate comprehensive
52 Neurological Physical examination. The General Physical examination assessment included:
53 General appearance, Dermatologic (including Mucous Membranes), Ear, nose, throat (ENT),
54 Cardiovascular, Respiratory, Abdomen, Lymph Nodes, Musculoskeletal and any other
55 findings. At Neurological Examination, Mental status, Cranial nerves, Motor (strength), Tone,
56 Involuntary movements, Coordination (Finger-nose, Gait, Postural reflexes and Heel to shin),
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3 Sensation (Proprioception, Cold, Light touch), Deep tendon reflexes, Plantar reflexes and
4 presence of other neurological signs (e.g. tremor) were assessed.
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7 ***Safety reporting***

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9 During the whole course of the study, new medical conditions and changes in medication were
10 assessed at every site visit. All adverse events (serious and non-serious) were documented and
11 reported according to the same protocol procedures applied in the main CHARIOT:PRO Main
12 Study [11].
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16 **Study participant and public involvement**

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18 The ICL (via CHARIOT register) and EDI team have established Research volunteer panels
19 consisting of lay members who met on an ad-hoc basis to support study development during
20 the planning stage. These panels provided feedback on study design, procedures and
21 dissemination for lay audiences. A newsletter is provided to study participants with updates
22 regarding recruitment, study milestones and any important changes to the Protocol.
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28 CPSS participants further provide feedback on the experience of research participation at the
29 different study visits, to ensure that their perspectives are represented in decision-making about
30 the future of the project and to advise on planned study activities, including dissemination
31 plans. Annual participant seminars are conducted for dissemination of study results and
32 discussion of future plans. A newsletter is provided to study participants quarterly for study
33 updates, as well as future plans. Participant input and feedback on volunteer experiences is
34 typically encouraged for inclusion in the newsletter.
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41 **Ethical and regulatory considerations**

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43 To ensure the quality and integrity of research, CPSS is conducted in accordance with GCP
44 Guidelines, GPPs issued by ISPE, applicable national guidelines, and to the Declaration of
45 Helsinki 2013, as modified by the 52nd World Medical Assembly (WMA), Edinburgh,
46 Scotland, 2000, and clarified by the WMA General Assembly, Washington 2002 and Tokyo
47 2004. The study has received approval from the National Research Ethics Service (NRES)
48 Committee London Central (reference 15/LO/0711 [IRAS 140764]), as well as independent
49 ethics review by committees from the local sites.
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56 Informed consent: Formal informed consent is taken using an informed consent form (ICF)
57 from both participant and study partners before participation in the study. Given the possibility
58 that participants might lose mental capacity during the study; it was recommended at the outset
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3 of participation that the participant identified a Legally Authorized Representative (LAR). A
4 LAR may include the spouse, a person specifically appointed to take care of the legal interests
5 of the participant, an individual with guardianship, and a health care proxy, who provides
6 consenting for research studies which is within the legal scope of the proxy's delegated
7 responsibilities (according to local applicable laws). The LAR must have the cognitive and
8 mental capacities (as determined by the site Investigator) enabling him/her to understand the
9 procedures, risks, and benefits involved with the study. The consent was given, and the form
10 signed, at the initial visit or at follow-up visits at the study sites, based on the choice of the
11 participant, and, where necessitated, on the choice of the LAR.
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19 Duty of care: As part of the duty of care during the study, all clinically relevant information is
20 shared with study participants where relevant and, with participant's consent, communicated
21 to the GP for medical follow-up. The clinically relevant findings shared included systemic
22 hypertension and significant changes in cognitive assessments where the investigator felt they
23 were relevant.
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29 Confidentiality: Participant confidentiality is strictly maintained. Each participant is assigned
30 a unique participant identifier upon study enrolment, which is used for all subsequent data
31 analysis and reporting. Participants' National Health Service (NHS) numbers are collected and
32 stored in keeping with industry standards for encryption/data protection, allowing for
33 subsequent data collection from electronic health records in primary or secondary care within
34 NHS. This data collection only occurs following NRES approval. All parties ensure that
35 participant personal data is not included on any study forms, reports, publications, or in any
36 other disclosures, except where required by law. The Investigators in compliance with Federal
37 regulations, other applicable laws and International Conference on Harmonization (ICH) GCP
38 Guidelines keep documents that are not for submission to the Sponsor and/or its designee (e.g,
39 signed ICFs and Participant Information Sheets) in strict confidence. In accordance with
40 regulations in the UK, participants are informed about data handling procedures.
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50 **Data management, analysis, and dissemination plans**

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52 **Data Management:** The SubStudy is conducted in accordance with Good Clinical Practice
53 (GCP) Guidelines as such data is recorded and stored in a way that could be verified and
54 reported in an accurate manner. All essential documents are filed in the Trial Master
55 File/Investigator Site File. Source documents are kept in both paper and electronic formats.
56 The main Electronic Data Capture system used in the current study is Medidata Rave. Both
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3 paper and electronic data are subject to daily and monthly internal audits based on Standard
4 Operating Procedures (SOPs). In addition, the Investigator Site Files, paper source
5 documentation and electronic source data are routinely monitored to maintain data accuracy
6 collection to the highest degree.
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10 **Statistical Analysis:** Assuming the 3.5-year change from baseline in the G-PACC score has a
11 standard deviation of 2.4 for the A β positive participants (Donohue et al., 2014), a sample size
12 of n = 250 with a 3.5-year dropout rate of 31% (i.e., 10%/year) ensures the 95% confidence
13 interval (CI) for the 3.5-year mean change in G-PACC score in A β positive participants to be
14 no wider than 0.72, assuming that the sample mean follows a Gaussian distribution. Analysis
15 of change in G-PACC and RBANS over time will be performed with mixed models for
16 repeated measures (MMRM) which assumes that missing data due to dropout are missing-at-
17 random (MAR). The robustness of the analysis with respect to deviations from the MAR
18 assumption will be evaluated. Analyses of the accruing results may be performed periodically
19 while the study is ongoing. Analyses will generally be descriptive, but inferential analyses
20 might be performed as needed. Potential unblinded interim analyses include:
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30 (i) Analyses for baseline characterization of participants.

31 (ii) Analyses for determining longitudinal change in study endpoints once the last ongoing
32 subject completes the Month 12, Month 24, and Month 36 visits.

33 These analyses will include descriptive statistics (n, mean, standard deviation) and/or
34 proportions for the A β positive and negative groups, but the A β status of individual participants
35 will remain blinded.
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41 **Dissemination plan:** Findings will be disseminated to several target audiences, including the
42 scientific community, research participants, patient community, public, industry, regulatory
43 authorities, and policymakers. Study results will be communicated via scientific publications
44 and conference presentations, guided by the Uniform Requirements for Manuscripts Submitted
45 to Biomedical Journals: Writing and Editing for Biomedical Publication of the International
46 Committee of Medical Journal Editors (ICMJE). Press releases, interviews and other media
47 communications (including social media) will also serve as a medium for disseminating study
48 findings and research plans.
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58 DISCUSSION

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3 With the pre-clinical disease stages being increasingly recognized as the best timing for
4 intervention, it is paramount that trial evaluations are sensitive enough to detect and track
5 cognitive, functional and biological changes emerging in these stages while also
6 possessing sufficient efficacy to detect therapeutic effects for drug trials. Furthermore, there is
7 an urgency to identify robust and sensitive predictors of clinical progression in order to estimate
8 individual risks for clinical AD and develop and apply therapeutic strategies prior to emergence
9 of clinically evident AD dementia.
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17 The CHARIOT:PRO SubStudy (CPSS) contributes towards this global agenda of AD-
18 dementia prevention. The study features detailed and frequent clinical and cognitive
19 assessments in a deeply phenotyped, presymptomatic cohort of older adults. An overall aim of
20 the study is to prospectively compare changes in cognition, and other clinical measures,
21 between individuals with presence of pathological levels of brain A β detected in PET scans or
22 CSF and those without such evidence. CPSS also introduces a novel cognitive composite, the
23 G-PACC, as a possible endpoint for future clinical trials. In this way, CPSS will expand upon
24 prior retrospective investigations of proposed cognitive composites [29], by prospectively
25 investigating the longitudinal change of the components of the G-PACC composite. The
26 performance of the G-PACC to detect effects will be compared against another cognitive
27 composite and its component measures, the RBANS. The addition of the RBANS component
28 measures, alongside other clinical data, will allow for the exploration of novel cognitive risk
29 profiles for the progression of future AD. The baseline data will determine which measures are
30 most sensitive for predicting longitudinal AD-related cognitive decline, informing future
31 screening methods for clinical trials. The study includes both patient and proxy-versions of
32 functional interviews, such as the CFI and ADCS-ADL, to investigate longitudinal changes in
33 everyday functioning in preclinical-AD individuals alongside cognitive decline and clinical
34 characteristics. Dietary patterns and other lifestyle variables will also be assessed to consider
35 the impact of environmental exposures on AD development. Therefore, the CPSS will also
36 allow for the exploration of environmental and lifestyle predictors of cognitive decline and
37 impairment.
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54 The uniqueness of this study lies in its breadth and frequency (every 3 months) of assessments,
55 as well as the planned explorations and comparisons of proposed cognitive composites for AD
56 detection and tracking. The prolonged and detailed follow-up data offers opportunities for
57 precise disease modelling and the evaluation of several methodological controversies within
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3 clinical trial design, such as the influence of practice effects on cognitive performance, in
4 addition to mechanisms of reserve and resilience against cognitive senescence. To date, CPSS
5 has successfully completed its enrolment of 519 participants across two UK research sites, from
6 2,451 screened volunteers. Next steps in CPSS's milestones include the exploration of the
7 baseline data for initial comparative analyses between stratified participant groups. The
8 CHARIOT:PRO SubStudy will continue as a multinational and multidisciplinary collaboration
9 between industry, academia and the NHS to promote greater understanding of the etiology of
10 AD pathological attributes and symptom development, and champion the search for effective
11 preventative therapies. Future plans include study extension to at least 4.5 years, at the ICL
12 site, with addition of Tau-PET and follow-up structural MRI, and extensive state-of-art fluid
13 biomarker discovery explorations at multiple timepoints.
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26
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28 commitment towards the SubStudy. We thank the staff at various sites who assist in the
29 collection of biological, cognitive and other clinical data, and we thank the Sponsor for funding
30 this work. Imperial College London is grateful for support from the NIHR NW London Applied
31 Research Collaboration.
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Author Statement:

Prof Middleton served as the ICL study site principal investigator. Prof Ritchie served as the EDI study site principal investigator. Dr. Udeh-Momoh served as the lead author, with Dr Watermeyer as co-lead. Drs. Udeh-Momoh, Kivipelto, Car, Perneczky, Price, de-Jager Loots and Ward were co-investigators at School of Public Health, Imperial College London. Dr Ritchie was co-investigator at Centre for Dementia Prevention, University of Edinburgh. All principal and co-investigators contributed to the study design, coordination, data acquisition, development and critical review of the manuscript. Dr. Scott and Mr Bracoud were employees at Bioclinica Inc., and developed the imaging protocol for the study, and participated in development and critical review of the manuscript. Prof Majeed co-developed the Chariot Register at School of Public Health, Imperial College London. Drs. Bassil, Robb, Cohn, Giannakopoulou, Kafetsouli, Chowdary and Ms Perera, Mclellan-Young, Lakey, Crispin and Curry were study investigators at School of Public Health, Imperial College London; Drs. Tamlyn Watermeyer and Natalia Reglinska-Matveyev were study investigators at Centre for Dementia Prevention, University of Edinburgh, and all contributed to data acquisition and review of the manuscript. Drs. Novak, Ropacki, Arrighi, Ketter, Raghavan, Saad and Brashear and Mr Fogle contributed to the study conception, protocol design, and development. Drs. Novak, Baker, Kacher, Saad and Mr Fogle contributed to study design and were responsible for data review, interpretation, and development of the manuscript. In addition, Dr. Arrighi was project pharmacoepidemiologist and Drs. Raghavan, Di and Kacher served as project biostatisticians, responsible for aspects of study design, statistical data analysis and statistical input. Dr Saad served as the unblinded statisticaian and imaging lead for the project.

All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors provided direction and comments on the manuscript, made the final decision about where to publish this protocol and approved the final draft and submission to this journal.

Table 1: CHARIOT PRO study exclusionary findings post screening MRI

- edema including amyloid-related imaging abnormalities (ARIA-E)
- hydrocephalus
- >25% age related white matter disease,
- frontal or temporal atrophy not typical of AD)
- history or evidence of a single prior hemorrhage >1 cm³
- multiple lacunar infarcts (2 or more) or
- single prior infarct >1 cm³
- cerebral contusion, encephalomalacia
- aneurysms, vascular malformations
- subdural hematoma
- space occupying lesions (eg, abscess or brain tumors such as meningioma >1cm)
- MRI features atypical of AD dementia.

*Evidence of brain edema (eg, ARIA-E, vasogenic edema, hemosiderin deposits [HD] ≥10 mm in size or HD <10 mm in size but >10 in number) will be reviewed by the Sponsor's Medical Monitor to address plans for clinical evaluation and follow up as well as for potential inclusion/exclusion in the study.

Table 2 CHARIOT PRO study Cognitive and Functional outcomes

Cognitive Outcome	Description	Assessment Schedule
<i>Secondary outcomes</i>		
National Adult Reading Test (NART) [30]	The NART is a word reading and pronunciation task comprising 50 English words with irregular grapheme-phoneme and stress rules. It is used to provide an estimate of premorbid intellectual functioning. Average administration time: 10 minutes.	BL
Neuropsychological Assessment Battery (NAB) Executive Function module (PAR Inc)	The executive function module comprises subtasks that examine planning, impulse control and psychomotor speed (through pen and paper mazes trials of increasing difficulty); judgement and decisional capacity (through questions pertaining to home safety, health and medical issues); concept formation, cognitive flexibility and response set (through a classification and categorization task) and fluency and generativity (through a word fluency task). Average administration time: 30 minutes.	M12, M24, M36

Neuropsychological Assessment Battery (NAB) - Memory module (PAR, Inc)	The memory module comprises explicit learning, free recall, delayed recall and/or delayed recognition subtasks across verbal (list learning; story learning; medication instructions and name and address) and visual (shape learning) information. Average administration time: 45 minutes.	M12, M24, M36
NEUROTRACK (Neurotrack Technologies, Inc)	Neurotrack is a declarative memory test based on digital eye tracking, administered on an IPAD. The task is a recognition memory test, relying on an individual's innate preference for novelty. In a familiarization phase, participants are presented with 2 identical images, side by side on the computer screen. This is followed by a test phase, in which a familiar image presented during the familiarization phase and a novel image are shown together. The ratio of time an individual gazes at the novel stimulus relative to the total viewing time constitutes a novelty preference score, with higher scores indicating superior declarative memory function and lower scores indicating impaired function. Average administration time: 10 minutes.	M3, M9, M15, M21, M27, M33, M39
<i>Randomised tasks</i>		
Cognitive Drug Research Assessment System (CDRAS) (Bracket; United BioSource Corporation)	The CDRAS measures three domains of cognition: Attention (simple and choice reaction time, digit vigilance); Working memory (articulatory and spatial working memory); Episodic secondary memory (word recall, word recognition and picture recognition). Average administration time: 20 minutes.	M3, M9, M15, M21, M27, M33, M39
Cogstate (Cogstate, Inc)	CogState consists of 4 tasks involving the presentation of playing cards. These tasks measure the functions of attention, processing speed, visual learning, and working memory using standard psychometric paradigms (ie, simple and choice reaction time, n-back and pattern separation learning). For the first assessment visit, M3, the task is administered twice within one session to control for task familiarity and practice effects. Average administration time: 15 minutes.	M3, M9, M15, M21, M27, M33, M39

<p>Delis-Kaplan Executive Function System (Pearson)</p> <p>ICL Site Only</p>	<p>The DKEFS is a paper and pencil measure of verbal and nonverbal executive functions and comprises 9 subtests. For this study, the Trail Making Test (visual attention and task switching) and Verbal Fluency (fluency and generativity) subtests are used. Total average administration time to complete these 2 subtests: 15 minutes.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Cognito [22]</p> <p>EDI Site Only</p>	<p>COGNITO is a computerized task which assesses reaction time, primary and working memory (an articulation subtest further permitting identification of problems related to the articulatory loop), visuospatial and verbal secondary memory (with free, cued and multiple choice paradigms), implicit learning (priming), language skills (word and syntax comprehension, naming, verbal fluency), functional and semantic categorization of visual data (visual reasoning and form perception), focused and divided attention (visual and auditory modalities), and crystallized intelligence (vocabulary). Responses are made via a tactile screen which permits the recording of response latency (deducting reaction time provides an estimation of information processing time). Qualitative aspects of performance (perseveration, intrusions, visual field neglect) are also recorded. Administration time varies between 45- to 60-minute, depending on level of impairment.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Functional Outcomes</p>	<p>Description</p>	<p>Assessment Schedule</p>
<p>Clinical Dementia Rating Scale [31]</p>	<p>The CDR is used as a clinical staging instrument and is administered to both participant and study partner, using a semi-structured format. It assesses six domains: memory; orientation; judgment and problem solving; involvement in community affairs; home and hobbies; and personal care. Average administration time: 15-20 minutes with the study partner and 10-15 minutes with the participant, depending on the severity of cognitive impairment.</p>	<p>M12, M24, M36</p>

<p>Cognitive Function Index [32]</p>	<p>The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument (MCFSI, Walsh et al, 2006) a self- and informant-reported subjective outcome measure regarding activities of daily living. It includes 14 questions that assess participants' perceived ability to perform high level tasks in daily-life and their sense of overall cognitive functional ability, indicating whether or not there has been a change in performance (yes/no/maybe) compared to 1 year ago. Study participants and their study partners independently rate the participant's level of ability. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>
<p>Alzheimer's disease Cooperative Study ADL prevention instrument (ADCS-ADL-PI) [33]</p>	<p>The ADCS-ADL-PI includes 15 subjectively rated questions related to activities of daily living and 5 questions related to physical functioning. Error! Reference source not found. Study participants and their study partners independently rate the study participant's level of ability. Partners are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if errors were made performing the task. Physical functioning items are rated as yes or no. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>

Note: BL – Baseline

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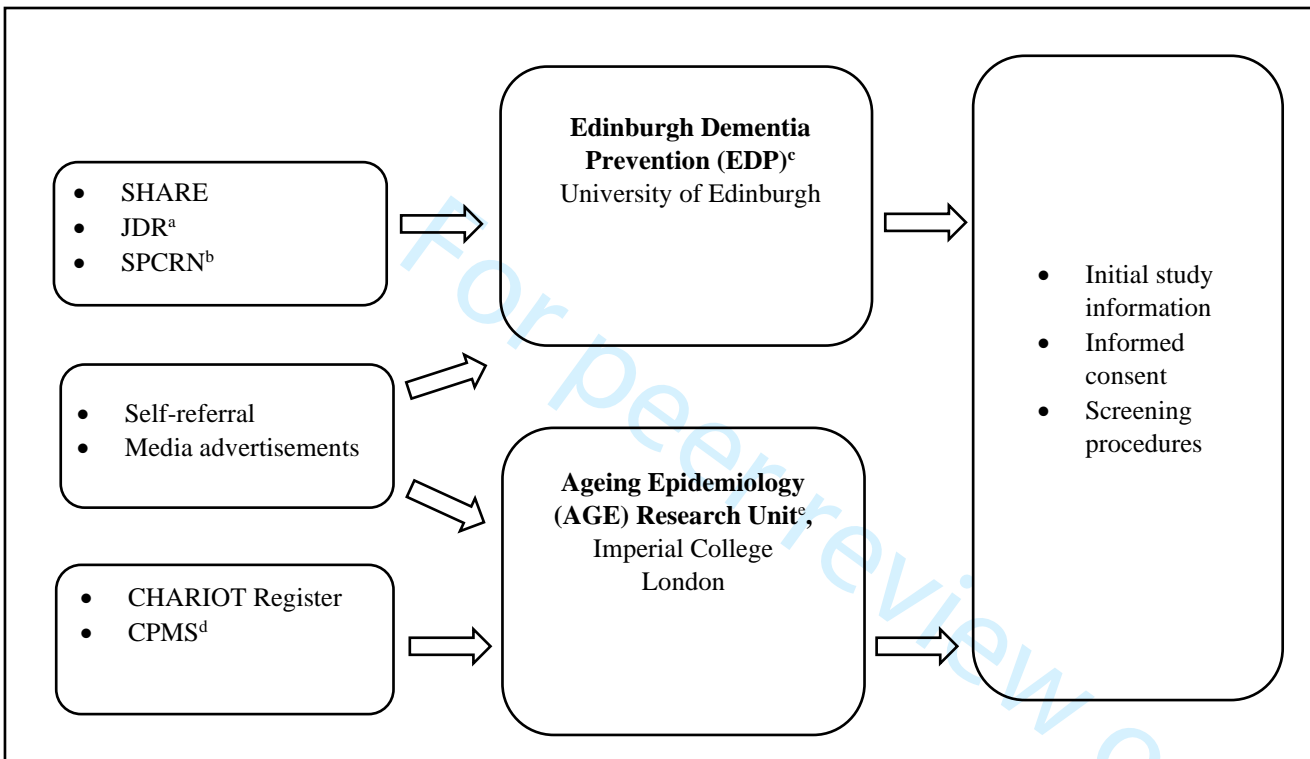


Figure 1 The CHARIOT: PRO Substudy Recruitment pathway

a. Join Dementia Research; b. Scottish Primary Care Research Network; c. formerly Centre for Dementia Prevention
 d. CHARIOT:PRO Main Study, e. formerly Neuroepidemiology and Ageing (NEA) Research Unit

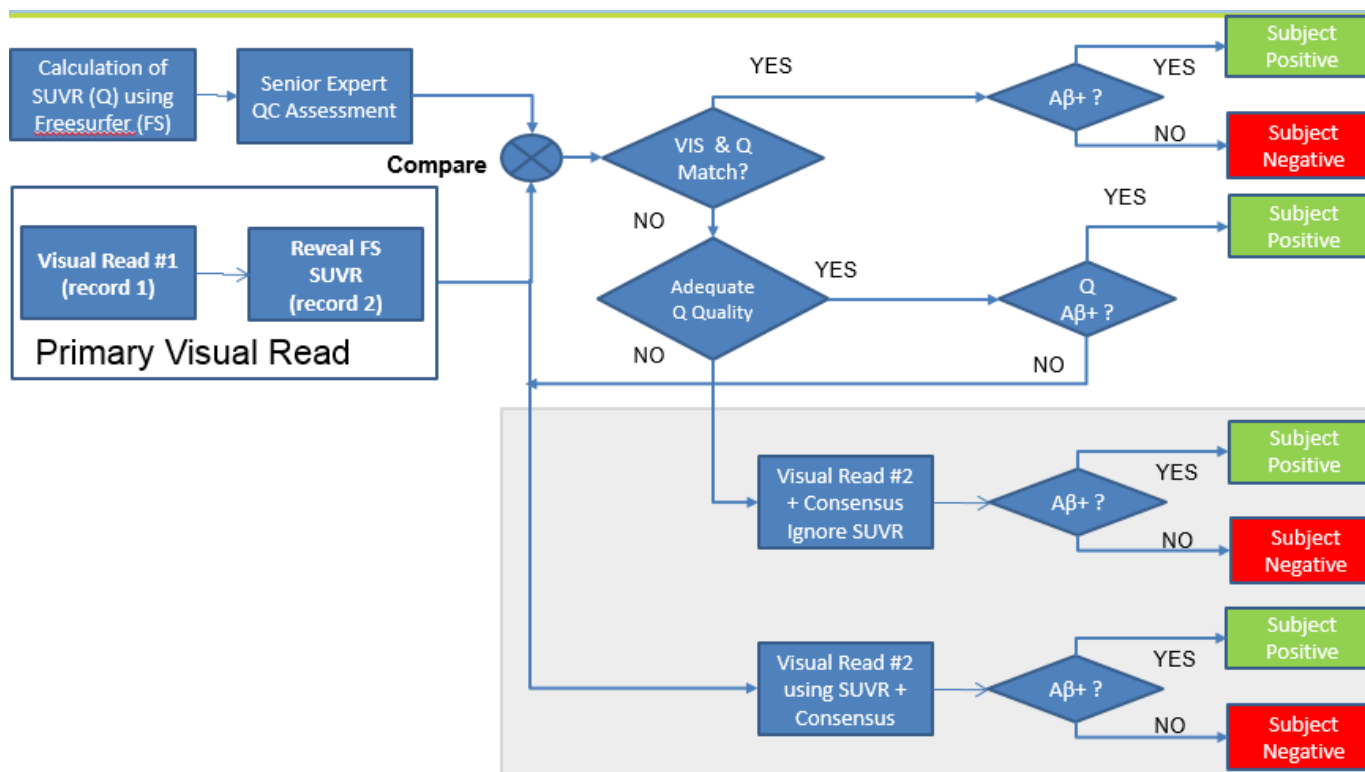


Figure 2: PET Aβ Status Reading Workflow

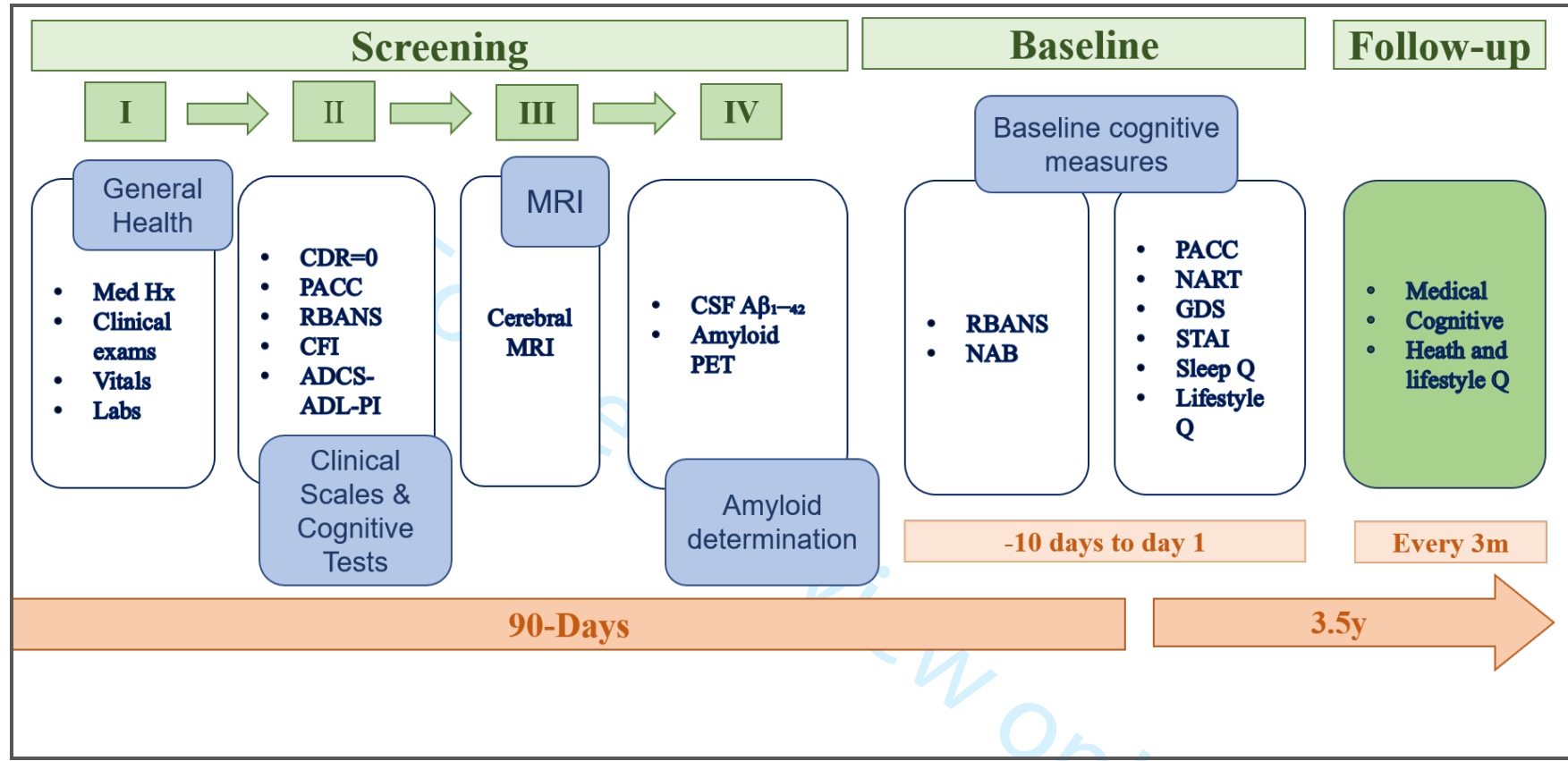


Figure 3 Screening and baseline assessment schedule

CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; PACC=Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; CFI=Cognitive Function Index; ADCS-ADL-PI=ADCS-Activities of Daily Living - Prevention Instrument; NAB=Neuropsychological Assessment Battery; NART-National Adult Reading Test; GDS=Geriatric Depression Scale; STAI –State Trait Anxiety Inventory

BMJ Open

Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy

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3 **Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and**
4 **Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO)**
5 **SubStudy**
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42 43 44 45 46 **Trial Registration**

47
48 The CHARIOT:PRO SubStudy is registered with clinicaltrials.gov (NCT02114372). Notices
49 of Protocol modifications will be made available through this trial registry.

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54
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Competing Interests Statement:

The study is funded by Janssen Research & Development, LLC. Michael T. Ropacki was formerly employee of Janssen and is an industry consultant. Gerald Novak, Susan Baker, H. Michael Arrighi, Michael Fogle, Keith Karcher, Ziad Saad and Nandini Raghavan are employees of Janssen Research & Development, LLC and own stock/stock options in the company. Nzeera Ketter and H. Robert Brashear are former employees of Janssen Research & Development, LLC and both own stock/stock options in the company. Jianing Di is an employee of Janssen China Research and Development Center and owns stock/stock options in the company. Lefkos Middleton served as principal study investigator at Imperial College of London (ICL) and has held consultancy agreements, in the last five years, with Eli Lilly, Astra Zeneca and Takeda and is National Coordinator for the TOMMORROW, Amaranth and Generation Clinical Studies; and does not hold any agreement with any of the funders in relation to patents, products in development relevant to this study or marketed products. Craig Ritchie served as principal study investigator at Edinburgh University (EDI), and has served as a consultant in the last five years for: Actinogen, Biogen, Roche Pharmaceuticals and Roche Diagnostics, Eisai, Abbott Pharmaceuticals, Eli Lilly, Kyowa Kirin, Signant Health, Merck and Nutricia. He is also the Chief Investigator and Co-coordinator of IMI-EPAD which is a public-private partnership of 39 partners www.ep-ad.org.

Chinedu Udeh-Momoh, Josip Car, Robert Pernecky, Geraint Price, Celeste de-Jager Loots, Heather Ward and Miia Kivipelto served as co-principal study investigators at ICL for Janssen Research & Development, LLC and all declare no conflict of interest. Josip Car's and Azeem Majeed's posts at ICL are in part supported by the NIHR NW London Applied Research Collaboration. Catherine Robb, Darina Bassil, Martin Cohn, Parthenia Giannakopoulou, Dimitra Kafetsouli, Yellappa Chowdary-Seemulamoodi, Dinithi Perera, Lisa Curry, Kristina Lakey, Heather McLellan-Young, Jennifer Crispin and Azeem Majeed were study investigators at ICL and declare no conflict of interest. Karen Ritchie served as co-principal study investigator at EDI for Janssen Research & Development, LLC and declares no conflict of interest. Tamlyn Watermeyer and Natalia Reglinska-Matveyev were study investigators at EDI and declare no conflict of interest. David Scott and Luc Bracoud are employees of Bioclinica Inc. and declare no competing interests.

ABSTRACT

Introduction: The CHARIOT:PRO SubStudy (CPSS), sponsored by Janssen Pharmaceutical Research & Development LLC, is an Alzheimer's disease (AD) biomarker enriched observational study that began 3rd July 2015 CPSS aims to identify and validate determinants of AD, alongside cognitive, functional and biological changes in older adults with or without detectable evidence of AD pathology at baseline.

Methods and Analysis: CPSS is a dual-site longitudinal cohort (3.5 years) assessed quarterly. Cognitively normal participants (60-85 years) were recruited across Greater London (n=2508) and Edinburgh (n=1695). Participants are classified as high, medium (amnesic or non-amnesic) or low risk for developing mild cognitive impairment–Alzheimer's disease (MCI-AD) based on their Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) performance at screening. Additional AD-related assessments include: a novel cognitive composite, the Global Preclinical Alzheimer's Cognitive Composite (G-PACC), brain magnetic resonance imaging (MRI) and positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis. Lifestyle, other cognitive and functional data, as well as bio-samples (blood, urine, and saliva) are collected. Primarily, study analyses will evaluate longitudinal change in cognitive and functional outcomes. Annual interim analyses for descriptive data occur throughout the course of the study, although inferential statistics are conducted as required.

Ethics and Dissemination: CPSS received ethical approvals from the London - Central Research Ethics Committee (15/LO/0711) and the Administration of Radioactive Substances Advisory Committee (RPC 630/3764/33110) The study is at the forefront of global AD prevention efforts, with frequent and robust sampling of the well-characterised cohort, allowing for detection of incipient pathophysiological, cognitive and functional changes that could inform therapeutic strategies to prevent and/or delay cognitive impairment and dementia. Dissemination of results will target the scientific community, research participants, volunteer community, public, industry, regulatory authorities and policymakers. Upon study completion, and following a predetermined embargo period, CPSS data is planned to be made accessible for analysis to facilitate further research into the determinants of AD pathology, onset of symptomatology and progression.

Key Words: Epidemiology; Neurology; Psychiatry; Dementia; Preventative Medicine

STRENGTHS AND LIMITATIONS

Strengths

- Prospectively-designed, high-powered longitudinal cohort of cognitively-healthy (at baseline) elders across the Alzheimer's pathological continuum followed up at high-throughput using biological, psycho-social, cognitive, behavioural and lifestyle measures
- Study adopts a unique cognition-based classification method for designating risk of MCI-AD development from baseline.

Limitations:

- Given the low amyloid positivity rate and the requirement of an equal number of CPSS participants above and below threshold, a high number of participants (78.6%) were excluded from the longitudinal CPSS study.
- The conduct of the study at only 2 sites does not fit the model of a typical, multi-site international clinical trial.

INTRODUCTION

Background and Rationale: The last few decades have witnessed unparalleled growth in aged populations. Hence, the global incidence and prevalence of Alzheimer's disease (AD), the most-common form of late-onset dementia, continue to increase exponentially, with numbers expected to exceed 150 million global cases by 2050 [1]. The paucity of any viable therapy for dementia prevention and/or disease modification necessitates a re-think of the conventional approach towards preventative research. Indeed, the AD field will benefit from concerted efforts for preventative strategies combining biomarker discovery studies with detailed validation of clinical characteristics as well as longitudinal explorations of associated pathologies and symptoms.

The asymptomatic stage of AD is characterized by biomarker evidence of amyloid- β ($A\beta$) deposition, as measured by either low cerebrospinal fluid (CSF) $A\beta_{42}$ peptide concentrations or elevated tracer uptake on $A\beta$ positron emission tomography (PET) scans [2]. Multiple studies have now reported that higher $A\beta$ burden in cognitively normal (CN) individuals is associated with measurably poorer performance in neuropsychological tests [3]. The

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3 accumulating longitudinal data also strongly suggest that evidence of abnormal levels of A β
4 deposition in CN individuals increases the risk for cognitive decline and progression to mild
5 cognitive impairment (MCI) and AD dementia [3]. The current consensus among members of
6 the Alzheimer's scientific community is that these CN individuals with detectable pathogenic
7 A β represent an early stage on the AD continuum [2, 4, 5]. Indeed, a meta-analysis of 55 studies
8 suggested that approximately 20% to 35% of study participants aged over 60 years without
9 dementia symptoms are likely to have above-threshold pathogenic A β pathology detected by
10 PET [6], with numbers increasing to 90% by age 85 [7].

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18 Rate of cognitive decline in CN individuals with or without evidence of abnormal A β
19 deposition can be measured using sensitive cognitive composite instruments. These measures
20 focus on the cognitive domains affected earliest in AD, namely episodic memory and executive
21 function, with decline noted as early as 7 to 10 years prior to the diagnosis of MCI or AD
22 dementia [8-10]. Yet, gaps remain in our understanding of the exact predictors of AD
23 pathological onset, accumulation and resultant development of clinical symptoms. There is a
24 need to identify individuals at varying levels of risk for AD, prior to development of AD
25 dementia. Such information would be useful to improve our understanding of the natural
26 history of AD progression and identify opportunities for intervention.

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34 The CHARIOT:PRO program seeks to address such gaps via detailed explorations of the
35 determinants of AD-related biological, clinical and cognitive changes. The previously-reported
36 main study of 987 participants at ICL, conducted from 2013 to 2016 (following early
37 termination by the study Sponsor) [11] was further adapted into a large prospective
38 observational trial – The CHARIOT: PRO SubStudy (CPSS) aimed at enhancing the scientific
39 robustness of the main study objectives with the addition of imaging and other AD-related
40 assessment tools.

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46 Here we describe the protocol (from Amendment version 15, dated 15th Aug 2018) of this
47 biomarker enriched CPSS featuring neuropsychological, functional, lifestyle, imaging and
48 other biomarker assessments and the schedule for their collection. We provide an outline of the
49 study design and a summary of the recruitment and screening process leading to the fully
50 enrolled cohort of 519 cognitively unimpaired adults.

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56 **Objectives of the CPSS:** CPSS is a prospective dual-centre, UK cohort study that at its core
57 aims to characterise deeply the clinico-biological attributes of the non-symptomatic AD stage
58 in individuals at differing levels of risk for development of MCI and AD-dementia, based on
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3 cognitive test scores at screening. CPSS participants thus could form a readiness cohort to be
4 recruited onto future AD-dementia prevention trials.
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7 Specifically, using data from participants with evidence of detectable A β pathology versus
8 those with below-threshold levels, the study will:
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11 - Investigate the longitudinal change of the global and composite measures of the newly-
12 developed Global Preclinical Alzheimer's Cognitive Composite (G-PACC) in
13 comparison to the Repeatable Battery for the Assessment of Neuropsychological Status
14 [RBANS, 12] and other study neuropsychological assessments, as well as
15 psychometrically evaluate the test batteries
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17 - Determine precise baseline predictors of longitudinal AD-related cognitive and
18 functional decline, and clinical progression to improve future screening of participants
19 most likely to develop MCI-AD/ AD dementia
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30 **METHODS**

31 **Population**

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33 The CPSS participants are adults aged 60 to 85 years old (inclusive), residing in Greater
34 London, South West England, Edinburgh and surrounding districts. Those included had
35 documented evidence of A β pathology (A β positives: above-threshold brain A β deposition on
36 PET or below-threshold CSF A β_{42} concentration), or evidence of below-threshold A β
37 pathology (A β negatives: below-threshold brain A β deposition on PET or above-threshold CSF
38 A β_{42} concentration), and a baseline global Clinical Dementia Rating (CDR) score=0. CPSS
39 participants were classified at screening as *high*, *medium-amnestic or non-amnestic*, or *low risk*
40 for developing MCI due to AD (MCI-AD), based on cognitive test performance as described
41 previously [11].
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50 **Study Design**

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52 The CPSS is a UK prospective observational study taking place across two sites (ICL and EDI).
53 The study is planned to follow approximately 250 CN participants who are A β positive and
54 approximately 250 A β negative CN control participants for up to three and a half years.
55 Evidence of A β pathology was assessed via CSF A β_{42} except where lumbar puncture (LP) was
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3 medically contraindicated or refused by participants, in which case A β PET was permitted as
4 an alternative method of determination of A β status. CSF samples were tested with the Meso
5 Scale Discovery (MSD) triplex (A $\beta_{38/40/42}$). A binary classification for A β load was applied
6 using a cut-off value for CSF A $\beta_{42} \leq 600$ ng/L. The cut-off for brain A β PET via standardized
7 uptake value ratio (SUVR) was based on three independent F18-radiolabeled amyloid tracers
8 - florbetapir, flutemetamol, and florbetaben. A specific SUVR threshold (i.e. a cut-point) was
9 used for each of the three radiotracers (Amyvid: 1.14 with whole-cerebellum as a reference
10 region, Neuraceq: 1.20 with cerebellar grey matter, Vizamyli: 1.23 with whole cerebellum).
11 Scans were reported as amyloid positive if the composite cortical SUVR value was above the
12 defined tracer-specific threshold, and negative if less than or equal to the threshold value.
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21 All study investigators, sponsor team and participants are blinded as to A β status information,
22 with the exception of an unblinded team member for verification of imaging and CSF A β
23 information. Blinding was put in place to avoid bias for conducting, monitoring and
24 interpreting results from the clinical assessments (except for research analysis purposes). The
25 same double-blind is maintained for apolipoprotein E (*APOE*) genotype, in view of allele-
26 specific positive correlation with A β load [13-15]. A β status and *APOE* genotype results were
27 not disclosed to participants as the clinical value (i.e., diagnostic or predictive) of such a
28 disclosure in a CN population is still unestablished. If clinical value is established from this or
29 other studies, then amyloid and *APOE* genotype will be disclosed to participants, at the end of
30 the study.
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39 Numbers of A β negative participants who passed screening assessments were deliberately
40 controlled to ensure equivalency with number of eligible A β positive participants. There was
41 no deliberate effort to balance the groups by age or gender.
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45 **Study schedule**

46 *Participant recruitment*

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49 At the ICL site, participants were recruited primarily from the CHARIOT Register, a well-
50 established dementia prevention and prediction register of older adults without dementia who
51 have provided consent to be contacted for relevant ageing research [16, 17]. Some participants
52 transitioned directly to CPSS from the Main study, though most of these individuals had
53 previously been recruited also from the CHARIOT Register. Additional methods of
54 recruitment at the site, with very limited numbers of enrolled participants, included self-
55 referrals and response from media advertisements. At the Edinburgh site, participants were
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3 recruited via SHARE (<https://www.registerforshare.org>), Join Dementia Research (JDR,
4 <https://www.joindementiaresearch.nihr.ac.uk/>) and the Scottish Primary Care Research
5 Network (SPCRN [http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)
6 [the-network](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)) (See Figure 1 for the participant recruitment pathway).
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10 *Selection of study participants: summary of eligibility criteria*

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13 The major exclusion criteria for CPSS include known familial autosomal dominant AD,
14 diagnosis of AD dementia, MCI, or any other degenerative brain disorder that is associated
15 with dementia at screening. Evidence of brain disease or other conditions leading to dementia,
16 other than AD-related structural pathologies were assessed centrally by blinded neuro-
17 radiologists via magnetic resonance imaging (MRI) during screening. Additionally, use of AD
18 pharmacological therapies, and evidence of psychiatric/cognitive disorders/other abnormalities
19 such as low vitamin B12 (specifically those with abnormal homocysteine and methylmalonic
20 acid), and linked to cognitive deficits are exclusionary. Further, history of first-degree family
21 member with diagnosed clinical AD was required for participants aged 60-65 years. This
22 measure was put in place to enrich the cohort for cerebral A β positivity given typically lower
23 prevalence in asymptomatic young elders i.e. below 70 years of age [18], thereby effectively
24 minimizing screen failure rates. Following participants' consent, self-reported medical and
25 medication history was confirmed from full history provided by participants' general
26 practitioner (GP). Upon receipt of any medical information, current medical conditions and
27 past medical history was updated on source documents and subsequently on electronic data,
28 including medication, past and planned procedures. Medical summaries from GPs were used
29 to ascertain self-reported histories.
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43 During screening, participants whose cognitive performance on any RBANS Index fell more
44 than 1.5 standard deviations below the (age- and education-adjusted) population mean (based
45 on normative sample from [19]) were referred to an adjudication panel. This panel, comprised
46 of neurologists, psychiatrists and neuropsychologists, considered whether the low performance
47 was likely to be attributable to undiagnosed cognitive impairment and, if so, excluded the
48 participant from the study. These participants were contacted directly by the study team to
49 inform them of their exclusion. At that time, where any concerns were noted regarding their
50 performance, the option to notify their GP with information about the study and their exclusion
51 was offered.
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59 *Screening schedule*

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3 The screening was usually completed in four separate visits within a 90-day window. On
4 certain occasions, this timeline was extended up to 180 days to allow for treatment of transient
5 conditions, laboratory retesting, and scheduling of other screening assessments. This allowed
6 time for results to be received and evaluated against study eligibility criteria. Any clinically
7 significant findings were passed on for follow-up to the participant's GP. Participants who were
8 determined to have an active unstable illness, as defined by the inclusion/exclusion criteria,
9 were excluded. Screening involved collection of demographic data which included age,
10 ethnicity, education and occupational status. During screening, potential participants
11 completed cognitive tests, the G-PACC and RBANS, and CDR including the study partner
12 interview. A clinical evaluation (pulse, blood pressure, weight, head, waist & hip
13 circumference, temperature (tympanic), physical and neurological examination) and clinical
14 lab assessments were carried out to determine general health status. Participants not excluded
15 at this stage then underwent a brain MRI. If MRI did not reveal exclusionary abnormalities
16 (see Table 1), it was followed by an A β assessment based on CSF analysis or brain PET scan.
17 After the A β determination, baseline assessments were undertaken at two consecutive visits
18 where the RBANS (form A), G-PACC (form A) as well as the Neuropsychological Assessment
19 Battery (NAB) Memory and Executive Function modules (form 1) and the National Adult
20 Reading Test (NART) were administered alongside self-reported study questionnaires. Bio-
21 samples were further collected for biomarker assessments. (See Figure 2 for schematic
22 depiction of screening and baseline assessments).

38 *Post-screening schedule*

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40 Following the baseline assessment, CPSS participants were randomized in a balanced 1:1:1
41 ratio, stratified by A β status and level of performance on the screening RBANS, to one of three
42 supplemental neuropsychological tests namely: CogState Brief Battery [20], Cognitive Drug
43 Research Assessment System, and either Delis-Kaplan Executive Function System [DKEFS,
44 21, ICL only] or COGNITO [22, EDI only]. Participants who enrolled in the Substudy from
45 the Main Study retained their previous Main Study-assigned randomized group. Participants
46 are expected to attend study visits every quarter and will be followed up for a period of up to
47 3.5 years. Due to the COVID-19 restrictions that were implemented in March 2020 in the UK,
48 the CPSS was transitioned to virtual visits to allow continued longitudinal assessments. For
49 further details on our strategy for operationalising this activity, please see [23]. As part of the
50 general visits, we collect detailed information on all medical, especially Covid-related incidents
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3 including more recently information on Covid-19 vaccinations. These data are designated
4 Covid-related within our database for easy identification of such cases.
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7 **Study outcomes and assessments**

8 *Primary neurocognitive outcomes*

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11 The primary outcomes of the CPSS are performance in two neurocognitive measures, the novel
12 G-PACC and the RBANS.
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16 The G-PACC: is a retrospectively and theoretically derived and validated measure, weighted
17 towards episodic memory but including a timed executive function test and a global cognitive
18 screening test [24]. For this study, the four PACC components include: the Free and Cued
19 Selective Reminding Test -Immediate Recall [FCSRT-IR, 25], the Delayed Paragraph Recall
20 score on a single administration of the Logical Memory story from the WMS – Revised [26],
21 the WAIS-IV Coding subtest [27] and the MMSE [28]. Each component score is transformed
22 into z-scores. These z-scores are summed to form the composite. The battery takes about 25
23 minutes to administer. Alongside screening and baseline time points, alternating forms of the
24 G-PACC are administered at the following time points: Months 6, 12, 18, 24, 30, 36, 42.
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33 The RBANS: is a 25-minute composite battery with 12 subtests that measure 5 cognitive
34 domain indices: Attention, composed of Digit Span and Coding, Language, with Picture
35 Naming and Semantic Fluency subtests, Visuospatial Construction including Figure Copy and
36 Line Orientation subtests, Immediate Memory comprising List Learning and Story Memory
37 subtests, and Delayed Memory composed of List Recall, List Recognition, Story Recall, and
38 Figure Recall subtests. The sum of these 5 Index scores is converted to a Total Scale value via
39 a mapping table. The Total Scale is a norm-based t-score based on a distribution with a mean
40 of 100 and standard deviation of 15. The RBANS is administered face-to-face, has 3 alternate
41 forms, is available in over 30 languages, and has been used in multinational clinical trials
42 including AD trials. Alternating forms of the RBANS are also administered at the following
43 timepoints: Months 3, 9, 15, 21, 27, 33, 39. During screening, participants' RBANS scores
44 were used to delineate risk (low, medium, high) for developing MCI-AD, as described in the
45 Main study [11].
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56 Secondary Cognitive outcomes and Functional outcomes are described in Table 2. More
57 detailed description of these measures are provided in the CHARIOT PRO Main Study
58 Protocol [11].
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Neuroimaging outcomes

Safety and volumetric scans (3DT1, FLAIR, T2*, PD/T2, T1 and DWI): All potential CPSS participants underwent brain MRI at screening to assess eligibility, based on a central radiologist's interpretation of the MRI scan under the supervision of Bioclinica Inc. Borderline findings were reviewed by the Medical Monitor prior to determining participant eligibility. Image acquisition was performed at multiple sites based on a standardized MRI protocol. General Electric Signa HDxt 1.5T and Siemens TrioTim, Verio, Skyra and Prisma 3T scanners were used to acquire a volumetric 3D T1 weighted series in a sagittal plane, using 1.2 mm thick slices and a 192x192 acquisition matrix over a square FOV of 240 mm. Contrast parameters were field-strength and manufacturer dependent (Siemens MP-RAGE and GE IR-Prep Fast SPGR). The standardized MRI protocol also included 2D axial FLAIR, T2* gradient echo, dual-echo proton-density and T2-weighted turbo/fast spin echo, T1-weighted turbo/fast spin echo and diffusion-weighted imaging. Proper implementation of the MRI protocol on each participating scanner was verified prior to first subject scan by use of American College of Radiology (ACR) phantom scans.

Exploratory scans (Task-free BOLD functional MRI (tf-fMRI) and high-resolution coronal T2sequences): At the ICL site, the first 800 subjects who were eligible for MRI underwent a dual-echo GRE field map and task-free functional MRI time series. For the remainder of the subjects, a high-resolution 2D coronal T2-weighted sequence was acquired, in order to visualize hippocampal subfields.

A β PET: At final stage of screening, evidence of A β pathology in potential CPSS participants was assessed by a brain PET scan. All images derived were evaluated centrally at Bioclinica Inc. for A β status assessment. The assessments were performed by neuro-radiologists trained in the assessment of A β PET scans using F18-radiolabeled amyloid tracers (Amyvid, Vizamyl and Neuraceq) for amyloid status according to the reading process developed by radiotracer vendors. The PET scan was evaluated at baseline to determine each patient's A β status as positive or negative and therefore inclusion or exclusion into the trial. PET exams were acquired using a uniform scanning protocol that minimizes and accounts for between-site differences in PET systems, as characterized with a Hoffman phantom exam. All exams were acquired in 3D mode and employed correction for attenuation, scatter and random coincidence. Semi-quantitative SUVR assessment was performed prior to the visual read. SUVR calculations leveraged a FreeSurfer-based native-space MRI segmentation method. The A β

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3 status assessment was a hybrid visual and quantitative approach (see Figure 3). A visual review
4 was performed by a single reader, followed by positivity assignment based on SUVR cutpoint.
5 In case of discrepancies between visual and SUVR results, a second reader was asked to
6 participate in a final decision on amyloid status, as part of a consensus review. The second
7 reader was given both the initial visual read and the SUVR measurement and convened with
8 the first reader to arrive at a consensus assessment.
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14 *Fluid Biomarkers*

16 Blood, saliva and urine samples for clinical assessments and future biomarker discovery
17 studies: At ICL and EDI, blood and urine samples were collected at screening to assess general
18 health status. These included: Haematology and Differential Panel, Lipid Panel, Chemistry
19 Panel, Electrolyte Panel, Coagulation Group, C-Reactive Protein, TSH, Folate, Vitamin B12
20 and Urine Macro Panel (with Urine Microscopy if abnormal Macro Panel).
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22 At ICL, serum, plasma, buffy coat, whole blood, urine and saliva samples are processed and
23 stored at baseline and annually thereafter for future biomarker exploration. Samples for
24 biobanking are collected between 9-11.30am and following an overnight fast; and are stored at
25 the ICL purpose-built -80°C biobank for future analyses. All samples are processed within two
26 hours of collection, as per guidelines on biomarker pre-processing [29]. Planned analyses
27 include untargeted metabolite and proteome profiling, to generate novel targets for future
28 hypothesis-testing and biomarker discovery studies.
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30 CSF biomarkers: For those participants not receiving A β PET, CSF samples were collected
31 during screening and analyses for AD-related markers including beta-amyloid, total tau and
32 phosphorylated tau. The A β data was used for determination of enrolment eligibility, and in
33 addition to the tau data, will be useful for disease modelling and staging of pre-clinical AD per
34 NIA-AA criteria [2]. At ICL, additional aliquots of CSF samples are stored in the -80°C
35 biobank for future analyses, which may include the exploration of putative biomarkers of AD
36 pathophysiology as they arise in the literature.
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38 Genetic outcomes: Whole blood is collected in EDTA tubes for extraction of genomic DNA
39 (gDNA) using standard methods. gDNA were thus isolated via commercially available kit
40 following manufacturer instructions (QIAGEN QIASymphony DSP DNA Mini Kits or Promega
41 Maxwell RSC Whole Blood DNA Kit). Both kits facilitate automated magnetic bead-based
42 extractions that successfully extract DNA from Human Whole Blood samples with good
43 quantitation and purity assessments. The QPS validated pyrosequencing genotyping assays for
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3 *APOE* codon 112T>C and codon 158C>T polymorphic variants were used to genotype
4 participant's gDNA samples and identify *APOE* ε4 Carriers and *APOE* ε4 Non-Carriers status.
5 By interrogating these two polymorphic variants, we identified the three *APOE* alleles: *APOE*
6 ε2(TGC 112, TGC 158), *APOE* ε3 (TGC 112, CGC 158), and *APOE* ε4 (CGC 112, CGC 158).
7 *APOE* genotype status has been determined for the enrolled cohort. A genome-wide-analysis
8 study is under-way and data expected to be available during the study. At ICL, whole blood is
9 also collected in a PAXgene® Blood RNA tube containing reagent for stabilization of
10 intracellular RNA, and stored -80°C. These samples will be used for future genetic analyses.
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17 ***Medical History and Clinical examinations (Physical and neurological examination)***

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20 A thorough medical history was obtained including an evaluation of all body systems (ENT,
21 ophthalmic, musculoskeletal, gastrointestinal, urinary, respiratory, renal, cardiovascular,
22 dermatological) with an emphasis on relevant medical history (e.g. neurological, psychiatric,
23 substance abuse, endocrine and metabolic). Safety and compatibility for neuroimaging were
24 further ensured prior to the procedure.
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31 Clinical examination included General Physical examination and a separate comprehensive
32 Neurological Physical examination. The General Physical examination assessment included:
33 General appearance, Dermatologic (including Mucous Membranes), Ear, nose, throat (ENT),
34 Cardiovascular, Respiratory, Abdomen, Lymph Nodes, Musculoskeletal and any other
35 findings. At Neurological Examination, Mental status, Cranial nerves, Motor (strength), Tone,
36 Involuntary movements, Coordination (Finger-nose, Gait, Postural reflexes and Heel to shin),
37 Sensation (Proprioception, Cold, Light touch), Deep tendon reflexes, Plantar reflexes and
38 presence of other neurological signs (e.g. tremor) were assessed.
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43 ***Safety reporting***

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46 During the whole course of the study, new medical conditions and changes in medication were
47 assessed at every site visit. All adverse events (serious and non-serious) were documented and
48 reported according to the same protocol procedures applied in the main CHARIOT:PRO Main
49 Study [11]. Briefly, serious and non-serious events that occur from inception of participation
50 all through to completion of last study-related procedure are captured and recorded for all
51 participants. Events are judged as serious if fatal, immediately life-threatening; require
52 hospitalization or prolonging of existing hospitalization; permanently (or significantly)
53 disabling; a congenital anomaly or birth defect (in an offspring); or medically significant.
54 Further data recorded for each suspected adverse event included the description (signs and
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3 symptoms or diagnosis), seriousness criteria, severity rating, duration (onset and resolution
4 date), actions taken and outcome.
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10 **Study participant and public involvement**

11 The ICL (via CHARIOT register) and EDI team have established Research volunteer panels
12 consisting of lay members who met on an ad-hoc basis to support study development during
13 the planning stage. These panels provided feedback on study design, procedures and
14 dissemination for lay audiences. A newsletter is provided to study participants with updates
15 regarding recruitment, study milestones and any important changes to the Protocol.
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21 CPSS participants further provide feedback on the experience of research participation at the
22 different study visits, to ensure that their perspectives are represented in decision-making about
23 the future of the project and to advise on planned study activities, including dissemination
24 plans. Annual participant seminars are conducted for dissemination of study results and
25 discussion of future plans. A newsletter is provided to study participants quarterly for study
26 updates, as well as future plans. Participant input and feedback on volunteer experiences is
27 typically encouraged for inclusion in the newsletter.
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34 **Ethical and regulatory considerations**

35 To ensure the quality and integrity of research, CPSS is conducted in accordance with GCP
36 Guidelines, GPPs issued by ISPE, applicable national guidelines, and to the Declaration of
37 Helsinki 2013, as modified by the 52nd World Medical Assembly (WMA), Edinburgh,
38 Scotland, 2000, and clarified by the WMA General Assembly, Washington 2002 and Tokyo
39 2004. The study has received approval from the National Research Ethics Service (NRES)
40 Committee London Central (reference 15/LO/0711 [IRAS 140764]), as well as independent
41 ethics review by committees from the local sites.
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49 Informed consent: Formal informed consent is taken using an informed consent form (ICF)
50 from both participant and study partners before participation in the study. Given the possibility
51 that participants might lose mental capacity during the study; it was recommended at the outset
52 of participation that the participant identified a Legally Authorized Representative (LAR). A
53 LAR may include the spouse, a person specifically appointed to take care of the legal interests
54 of the participant, an individual with guardianship, and a health care proxy, who provides
55 consenting for research studies which is within the legal scope of the proxy's delegated
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responsibilities (according to local applicable laws). The LAR must have the cognitive and mental capacities (as determined by the site Investigator) enabling him/her to understand the procedures, risks, and benefits involved with the study. The consent was given, and the form signed, at the initial visit or at follow-up visits at the study sites, based on the choice of the participant, and, where necessitated, on the choice of the LAR.

Duty of care: As part of the duty of care during the study, all clinically relevant information is shared with study participants where relevant and, with participant's consent, communicated to the GP for medical follow-up. The clinically relevant findings shared included systemic hypertension and significant changes in cognitive assessments where the investigator felt they were relevant.

Confidentiality: Participant confidentiality is strictly maintained. Each participant is assigned a unique participant identifier upon study enrolment, which is used for all subsequent data analysis and reporting. Participants' National Health Service (NHS) numbers are collected and stored in keeping with industry standards for encryption/data protection, allowing for subsequent data collection from electronic health records in primary or secondary care within NHS. This data collection only occurs following NRES approval. All parties ensure that participant personal data is not included on any study forms, reports, publications, or in any other disclosures, except where required by law. The Investigators in compliance with Federal regulations, other applicable laws and International Conference on Harmonization (ICH) GCP Guidelines keep documents that are not for submission to the Sponsor and/or its designee (e.g, signed ICFs and Participant Information Sheets) in strict confidence. In accordance with regulations in the UK, participants are informed about data handling procedures.

Data management, analysis, and dissemination plans

Data Management: The CPSS is conducted in accordance with Good Clinical Practice (GCP) Guidelines as such data is recorded and stored in a way that could be verified and reported in an accurate manner. All essential documents are filed in the Trial Master File/Investigator Site File. Source documents are kept in both paper and electronic formats. The main Electronic Data Capture system used in the current study is Medidata Rave. Both paper and electronic data are subject to daily and monthly internal audits based on Standard Operating Procedures (SOPs). In addition, the Investigator Site Files, paper source documentation and electronic source data are routinely monitored to maintain data accuracy collection to the highest degree.

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3 **Statistical Analysis:** Assuming the 3.5-year change from baseline in the G-PACC score has a
4 standard deviation of 2.4 for the A β positive participants [30], a sample size of n = 250 with a
5 3.5-year dropout rate of 31% (i.e., 10%/year) ensures the 95% confidence interval (CI) for the
6 3.5-year mean change in G-PACC score in A β positive participants to be no wider than 0.72,
7 assuming that the sample mean follows a Gaussian distribution. Analysis of change in G-PACC
8 and RBANS over time will be performed with mixed models for repeated measures (MMRM)
9 which assumes that missing data due to dropout are missing-at-random (MAR). The robustness
10 of the analysis with respect to deviations from the MAR assumption will be evaluated.
11 Analyses of the accruing results may be performed periodically while the study is ongoing.
12 Analyses will generally be descriptive, but inferential analyses might be performed as needed.
13 Potential unblinded interim analyses include:
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22 (i) Analyses for baseline characterization of participants.

23 (ii) Analyses for determining longitudinal change in study endpoints once the last ongoing
24 subject completes the Month 12, Month 24, and Month 36 visits. These analyses will include
25 descriptive statistics (n, mean, standard deviation) and/or proportions for the A β positive and
26 negative groups, but the A β status of individual participants will remain blinded.
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33 DISCUSSION

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36 With the pre-clinical disease stages being increasingly recognized as the best timing for
37 intervention, it is paramount that trial evaluations are sensitive enough to detect and track
38 cognitive, functional and biological changes emerging in these stages while also
39 possessing sufficient efficacy to detect therapeutic effects for drug trials. Furthermore, there is
40 an urgency to identify robust and sensitive predictors of clinical progression in order to estimate
41 individual risks for clinical AD and develop and apply therapeutic strategies prior to emergence
42 of clinically evident AD dementia. Although an ambitious project, some limitations of this
43 work are worth mentioning. The amyloid positivity rate is low and due to a need for an equal
44 number of participants in each group (amyloid positive; amyloid negative), a high number of
45 participants (78.6%) were excluded from the longitudinal follow-up phase. As a mitigating
46 measure, enrichment criteria were introduced, with requirement of first-degree family history
47 in volunteers aged 60-65 years old. The conduct of the study at only two sites is not typical of
48 multi-site international trials; on the other hand, this minimizes several sources of variability
49 that are independent of aging and incipient Alzheimer's disease (e.g., inter-rater variability and
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3 differences in psychometric equivalence among different translations). It could be argued that
4 the cognitive battery set may not be sensitive in predicting AD in healthy older adults, since
5 these mostly tax modalities associated with AD dementia diagnostic criteria. Nonetheless, the
6 high frequency (quarterly) follow-up of participants will facilitate determination of those
7 assessments most sensitive for identifying the earliest signs and symptoms of AD-dementia
8 and offers an opportunity to assess other performance parameters (e.g. qualitative errors, lack
9 of practice effect; speed-accuracy trade-offs) that may indicate changes in cognitive and/or
10 cerebral integrity in the lead up to AD dementia [31]. Similarly, other assessments of physical
11 health pertinent to AD risk, such as gait, hearing, or dental health are not included in our study.
12 However, we do collect extensive medical history information at baseline and follow-ups that
13 includes clinical abnormalities (e.g. mobility issues; hearing impairment) that may be useful in
14 our analyses.
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26 The CPSS contributes towards this global agenda of AD-dementia prevention. The study
27 features detailed and frequent clinical and cognitive assessments in a deeply phenotyped,
28 presymptomatic cohort of older adults. An overall aim of the study is to prospectively compare
29 changes in cognition, and other clinical measures, between individuals with presence of
30 pathological levels of brain A β detected in PET scans or CSF and those without such evidence.
31 CPSS also introduces a novel cognitive composite, the G-PACC, as a possible endpoint for
32 future clinical trials. In this way, CPSS will expand upon prior retrospective investigations of
33 proposed cognitive composites [30], by prospectively investigating the longitudinal change of
34 the components of the G-PACC composite. The performance of the G-PACC to detect effects
35 will be compared against another cognitive composite and its subtests, the RBANS. The
36 addition of the RBANS subtests, alongside other clinical data, will allow for the exploration of
37 novel cognitive risk profiles for the progression of future AD. The baseline data will determine
38 which measures are most sensitive for predicting longitudinal AD-related cognitive decline,
39 informing future screening methods for clinical trials. The study includes both patient and
40 proxy-versions of functional interviews, such as the CFI and ADCS-ADL, to investigate
41 longitudinal changes in everyday functioning in preclinical-AD individuals alongside cognitive
42 decline and clinical characteristics. Dietary patterns and other lifestyle variables will also be
43 assessed to consider the impact of environmental exposures on AD development. Therefore,
44 the CPSS will also allow for the exploration of environmental and lifestyle predictors of
45 cognitive decline and impairment.
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3 The uniqueness of this study lies in its breadth and frequency (every 3 months) of assessments,
4 as well as the planned explorations and comparisons of proposed cognitive composites for AD
5 detection and tracking. The prolonged and detailed follow-up data offers opportunities for
6 precise disease modelling and the evaluation of several methodological controversies within
7 clinical trial design, such as the influence of practice effects on cognitive performance, in
8 addition to mechanisms of reserve and resilience against cognitive senescence.
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14 To date, CPSS has successfully completed its enrolment of 519 participants across two UK
15 research sites, from 2,451 screened volunteers. Next steps in CPSS's milestones include the
16 exploration of the baseline data for initial comparative analyses between stratified participant
17 groups. The CPSS will continue as a multinational and multidisciplinary collaboration between
18 industry, academia and the NHS to promote greater understanding of the etiology of AD
19 pathological attributes and symptom development, and champion the search for effective
20 preventative therapies. Future plans include study extension to at least 4.5 years, at the ICL
21 site, with addition of Tau-PET and follow-up structural MRI, and extensive state-of-art fluid
22 biomarker discovery explorations at multiple timepoints.
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15 **Author Statement:**

16
17 Prof Middleton served as the ICL study site principal investigator. Prof Ritchie served as the
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22 principal and co-investigators contributed to the study design, coordination, data acquisition,
23 development and critical review of the manuscript. Dr. Scott and Mr Bracoud were employees
24 at Bioclinica Inc., and developed the imaging protocol for the study, and participated in
25 development and critical review of the manuscript. Prof Majeed co-developed the Chariot
26 Register at School of Public Health, Imperial College London. Drs. Bassil, Robb, Cohn,
27 Giannakopoulou, Kafetsouli, Chowdary and Ms Perera, Mclellan-Young, Lakey, Crispin and
28 Curry were study investigators at School of Public Health, Imperial College London; Drs.
29 Tamlyn Watermeyer and Natalia Reglinska-Matveyev were study investigators at Centre for
30 Dementia Prevention, University of Edinburgh, and all contributed to data acquisition and
31 review of the manuscript. Drs. Novak, Ropacki, Arrighi, Ketter, Raghavan, Saad and Brashear
32 and Mr Fogle contributed to the study conception, protocol design, and development. Drs.
33 Novak, Baker, Kacher, Saad and Mr Fogle contributed to study design and were responsible
34 for data review, interpretation, and development of the manuscript. In addition, Dr. Arrighi was
35 project pharmacoepidemiologist and Drs. Raghavan, Di and Kacher served as project
36 biostatisticians, responsible for aspects of study design, statistical data analysis and statistical
37 input. Dr Saad served as the unblinded statisticaian and imaging lead for the project.
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54 All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors.
55 All authors provided direction and comments on the manuscript, made the final decision about
56 where to publish this protocol and approved the final draft and submission to this journal.
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Table 1: CHARIOT PRO study exclusionary findings post screening MRI

- edema including amyloid-related imaging abnormalities (ARIA-E)
- hydrocephalus
- >25% age related white matter disease,
- frontal or temporal atrophy not typical of AD)
- history or evidence of a single prior hemorrhage >1 cm³
- multiple lacunar infarcts (2 or more) or
- single prior infarct >1 cm³
- cerebral contusion, encephalomalacia
- aneurysms, vascular malformations
- subdural hematoma
- space occupying lesions (eg, abscess or brain tumors such as meningioma >1cm)
- MRI features atypical of AD dementia.

*Evidence of brain edema (eg, ARIA-E, vasogenic edema, hemosiderin deposits [HD] ≥10 mm in size or HD <10 mm in size but >10 in number) will be reviewed by the Sponsor's Medical Monitor to address plans for clinical evaluation and follow up as well as for potential inclusion/exclusion in the study.

Table 2 CHARIOT PRO study Cognitive and Functional outcomes

Cognitive Outcome	Description	Assessment Schedule
<i>Secondary outcomes</i>		
National Adult Reading Test (NART) [32]	The NART is a word reading and pronunciation task comprising 50 English words with irregular grapheme-phoneme and stress rules. It is used to provide an estimate of premorbid intellectual functioning. Average administration time: 10 minutes.	BL
Neuropsychological Assessment Battery (NAB) Executive Function module (PAR Inc)	The executive function module comprises subtasks that examine planning, impulse control and psychomotor speed (through pen and paper mazes trials of increasing difficulty); judgement and decisional capacity (through questions pertaining to home safety, health and medical issues); concept formation, cognitive flexibility and response set (through a classification and categorization task) and fluency and generativity (through a word fluency task). Average administration time: 30 minutes.	M12, M24, M36

Neuropsychological Assessment Battery (NAB) - Memory module (PAR, Inc)	The memory module comprises explicit learning, free recall, delayed recall and/or delayed recognition subtasks across verbal (list learning; story learning; medication instructions and name and address) and visual (shape learning) information. Average administration time: 45 minutes.	M12, M24, M36
NEUROTRACK (<i>Neurotrack Technologies, Inc</i>)	Neurotrack is a declarative memory test based on digital eye tracking, administered on an IPAD. The task is a recognition memory test, relying on an individual's innate preference for novelty. In a familiarization phase, participants are presented with 2 identical images, side by side on the computer screen. This is followed by a test phase, in which a familiar image presented during the familiarization phase and a novel image are shown together. The ratio of time an individual gazes at the novel stimulus relative to the total viewing time constitutes a novelty preference score, with higher scores indicating superior declarative memory function and lower scores indicating impaired function. Average administration time: 10 minutes.	M3, M9, M15, M21, M27, M33, M39
<i>Randomised tasks</i>		
Cognitive Drug Research Assessment System (CDRAS) (Bracket; United BioSource Corporation)	The CDRAS measures three domains of cognition: Attention (simple and choice reaction time, digit vigilance); Working memory (articulatory and spatial working memory); Episodic secondary memory (word recall, word recognition and picture recognition). Average administration time: 20 minutes.	M3, M9, M15, M21, M27, M33, M39
Cogstate (Cogstate, Inc) [20]	CogState consists of 4 tasks involving the presentation of playing cards. These tasks measure the functions of attention, processing speed, visual learning, and working memory using standard psychometric paradigms (ie, simple and choice reaction time, n-back and pattern separation learning). For the first assessment visit, M3, the task is administered twice within one session to control for task familiarity and practice effects. Average administration time: 15 minutes.	M3, M9, M15, M21, M27, M33, M39

<p>Delis-Kaplan Executive Function System (Pearson) [21]</p> <p>ICL Site Only</p>	<p>The DKEFS is a paper and pencil measure of verbal and nonverbal executive functions and comprises 9 subtests. For this study, the Trail Making Test (visual attention and task switching) and Verbal Fluency (fluency and generativity) subtests are used. Total average administration time to complete these 2 subtests: 15 minutes.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Cognito [22]</p> <p>EDI Site Only</p>	<p>COGNITO is a computerized task which assesses reaction time, primary and working memory (an articulation subtest further permitting identification of problems related to the articulatory loop), visuospatial and verbal secondary memory (with free, cued and multiple choice paradigms), implicit learning (priming), language skills (word and syntax comprehension, naming, verbal fluency), functional and semantic categorization of visual data (visual reasoning and form perception), focused and divided attention (visual and auditory modalities), and crystallized intelligence (vocabulary). Responses are made via a tactile screen which permits the recording of response latency (deducting reaction time provides an estimation of information processing time). Qualitative aspects of performance (perseveration, intrusions, visual field neglect) are also recorded. Administration time varies between 45- to 60-minute, depending on level of impairment.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Functional Outcomes</p>	<p>Description</p>	<p>Assessment Schedule</p>
<p>Clinical Dementia Rating Scale [33]</p>	<p>The CDR is used as a clinical staging instrument and is administered to both participant and study partner, using a semi-structured format. It assesses six domains: memory; orientation; judgment and problem solving; involvement in community affairs; home and hobbies; and personal care. Average administration time: 15-20 minutes with the study partner and 10-15 minutes with the participant, depending on the severity of cognitive impairment.</p>	<p>M12, M24, M36</p>

<p>Cognitive Function Index [34]</p>	<p>The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument (MCFSI, Walsh et al, 2006) a self- and informant-reported subjective outcome measure regarding activities of daily living. It includes 14 questions that assess participants' perceived ability to perform high level tasks in daily-life and their sense of overall cognitive functional ability, indicating whether or not there has been a change in performance (yes/no/maybe) compared to 1 year ago. Study participants and their study partners independently rate the participant's level of ability. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>
<p>Alzheimer's disease Cooperative Study ADL prevention instrument (ADCS-ADL-PI) [35]</p>	<p>The ADCS-ADL-PI includes 15 subjectively rated questions related to activities of daily living and 5 questions related to physical functioning. Error! Reference source not found. Study participants and their study partners independently rate the study participant's level of ability. Partners are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if errors were made performing the task. Physical functioning items are rated as yes or no. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>

Note: BL – Baseline

Figure 1 The CHARIOT:PRO Substudy Recruitment Pathway

a. Join Dementia Research; b. Scottish Primary Care Research Network; c. formerly Centre for Dementia Prevention; d. CHARIOT:PRO Main Study, e. formerly Neuroepidemiology and Ageing (NEA) Research Unit

Figure 2 Screening and baseline assessment schedule

CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; PACC=Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; CFI=Cognitive Function Index; ADCS-ADL-PI=ADCS-Activities of Daily Living - Prevention Instrument; NAB=Neuropsychological Assessment Battery; NART-National Adult Reading Test; GDS=Geriatric Depression Scale; STAI –State Trait Anxiety Inventory

Figure 3: PET A β Status Reading Workflow

SUVR = Standardized Uptake Value Ratio; Q = quantification of SUVR; FS = parcellation of cerebral structures based on Freesurfer imaging pipeline; QC = quality control assessment; VIS = result of visual assessment of amyloid PET; A β + = assessed as A β positive based on visual and/or quantitative (SUVR) analysis of amyloid PET

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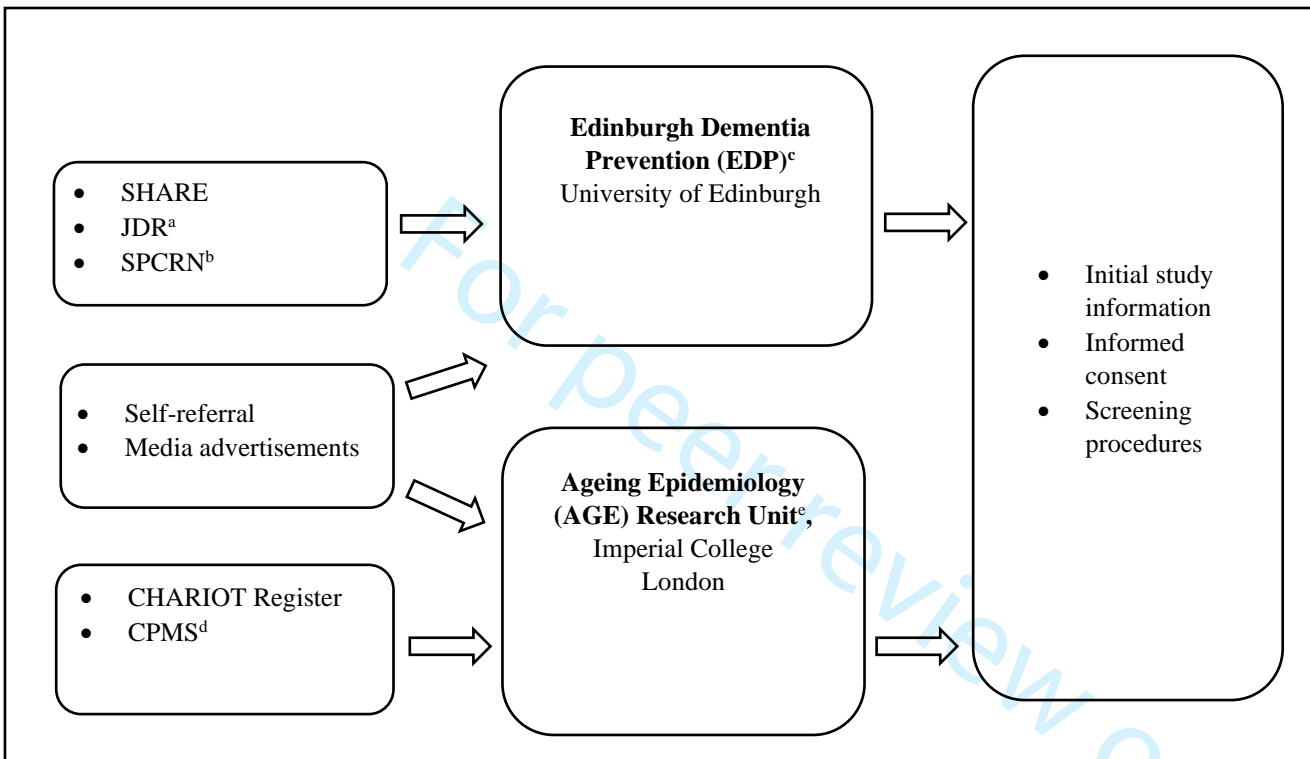


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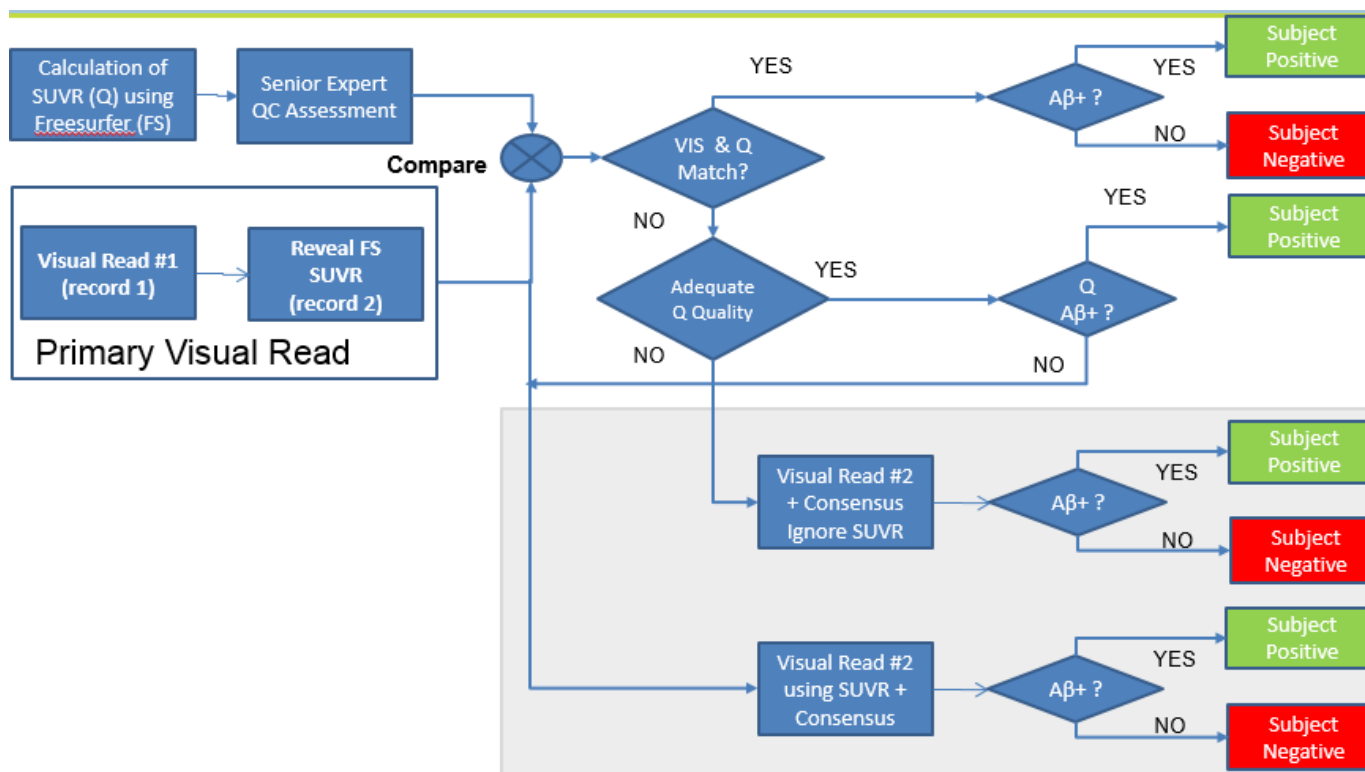


Figure 2: PET Aβ Status Reading Workflow

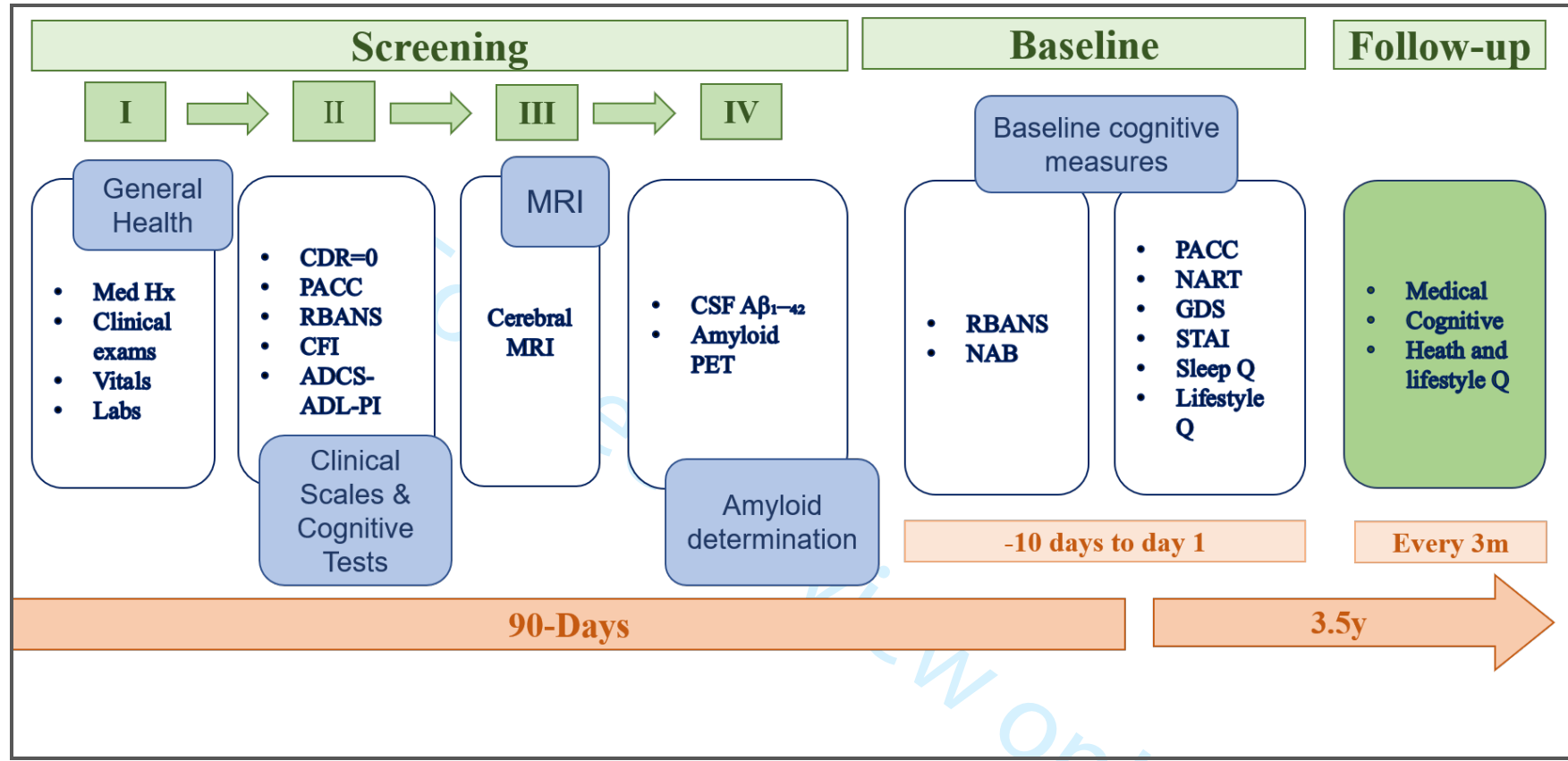


Figure 3 Screening and baseline assessment schedule

CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; PACC=Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; CFI=Cognitive Function Index; ADCS-ADL-PI=ADCS-Activities of Daily Living - Prevention Instrument; NAB=Neuropsychological Assessment Battery; NART-National Adult Reading Test; GDS=Geriatric Depression Scale; STAI –State Trait Anxiety Inventory

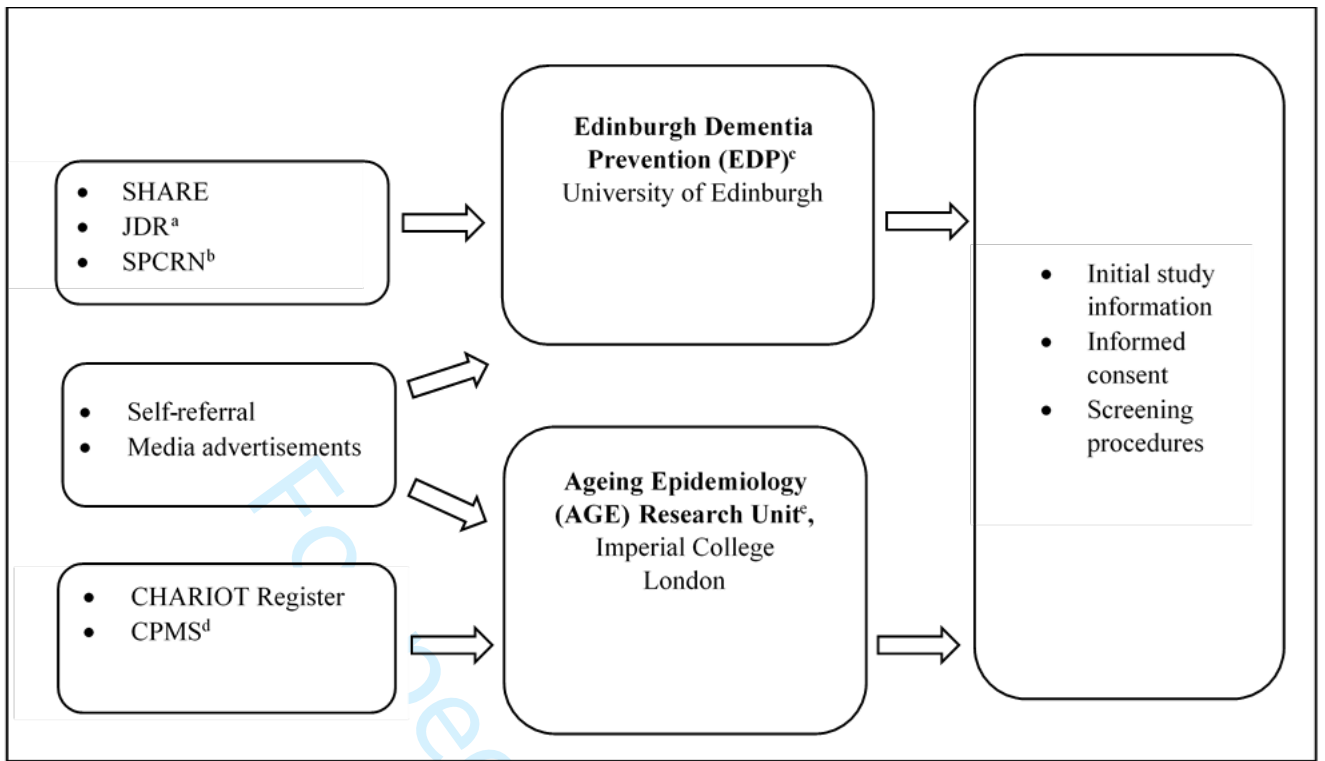


Figure 1. The CHARIOT:PRO Recruitment Pathway

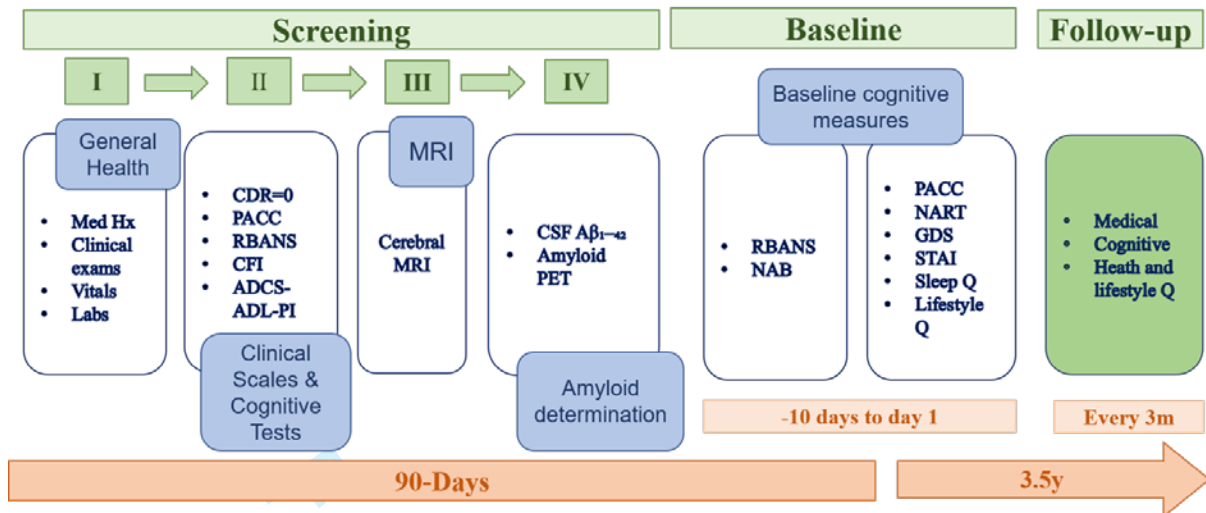


Figure 2 Screening and baseline assessment schedule

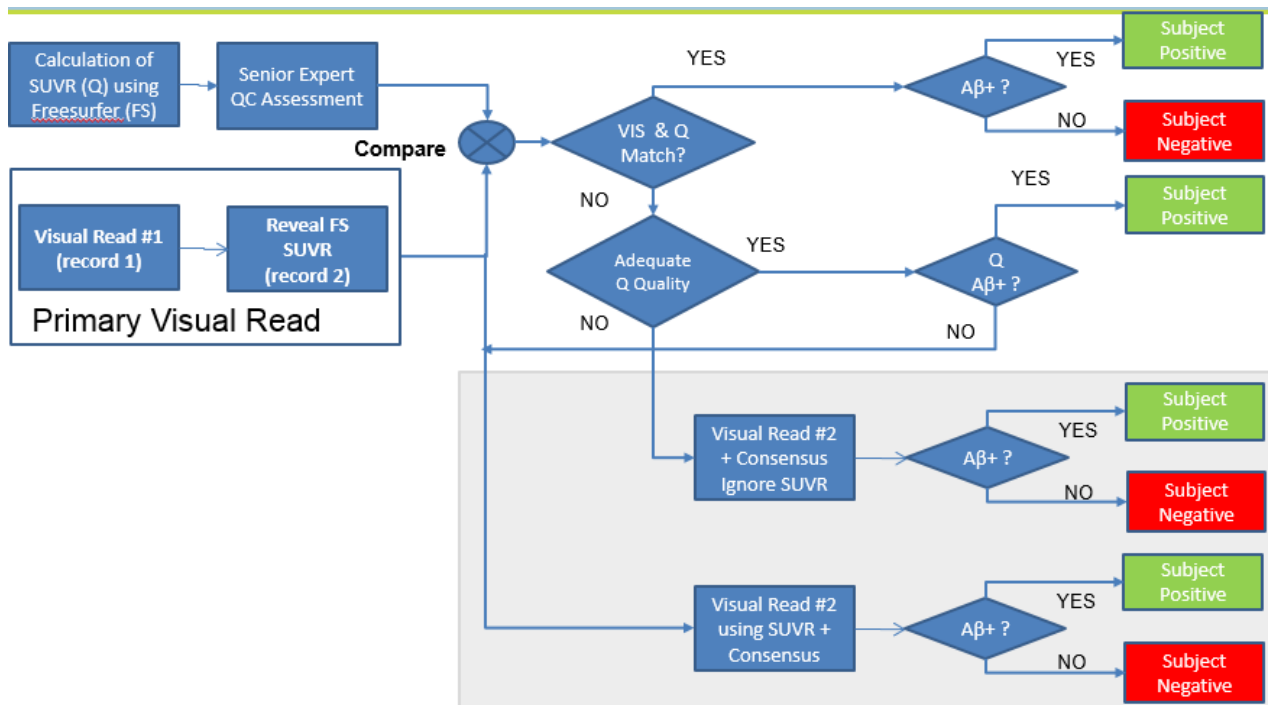


Figure 3: PET Aβ Status Reading Workflow

BMJ Open

Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO) SubStudy

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Date Submitted by the Author:	24-May-2021
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3 **Protocol of The Cognitive Health in Ageing Register: Investigational, Observational and**
4 **Trial Studies in Dementia Research (CHARIOT): Prospective Readiness cOhort (PRO)**
5 **SubStudy**
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42 43 44 45 46 **Trial Registration**

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48 The CHARIOT:PRO SubStudy is registered with clinicaltrials.gov (NCT02114372). Notices
49 of Protocol modifications will be made available through this trial registry.

50 51 52 **Funding statement**

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ABSTRACT

Introduction: The CHARIOT:PRO SubStudy (CPSS), sponsored by Janssen Pharmaceutical Research & Development LLC, is an Alzheimer's disease (AD) biomarker enriched observational study that began 3rd July 2015 CPSS aims to identify and validate determinants of AD, alongside cognitive, functional and biological changes in older adults with or without detectable evidence of AD pathology at baseline.

Methods and Analysis: CPSS is a dual-site longitudinal cohort (3.5 years) assessed quarterly. Cognitively normal participants (60-85 years) were recruited across Greater London and Edinburgh. Participants are classified as high, medium (amnesic or non-amnesic) or low risk for developing mild cognitive impairment–Alzheimer's disease (MCI-AD) based on their Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) performance at screening. Additional AD-related assessments include: a novel cognitive composite, the Global Preclinical Alzheimer's Cognitive Composite (G-PACC), brain magnetic resonance imaging (MRI) and positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis. Lifestyle, other cognitive and functional data, as well as bio-samples (blood, urine, and saliva) are collected. Primarily, study analyses will evaluate longitudinal change in cognitive and functional outcomes. Annual interim analyses for descriptive data occur throughout the course of the study, although inferential statistics are conducted as required.

Ethics and Dissemination: CPSS received ethical approvals from the London - Central Research Ethics Committee (15/LO/0711) and the Administration of Radioactive Substances Advisory Committee (RPC 630/3764/33110) The study is at the forefront of global AD prevention efforts, with frequent and robust sampling of the well-characterised cohort, allowing for detection of incipient pathophysiological, cognitive and functional changes that could inform therapeutic strategies to prevent and/or delay cognitive impairment and dementia. Dissemination of results will target the scientific community, research participants, volunteer community, public, industry, regulatory authorities and policymakers. Upon study completion, and following a predetermined embargo period, CPSS data is planned to be made accessible for analysis to facilitate further research into the determinants of AD pathology, onset of symptomatology and progression.

Key Words: Epidemiology; Neurology; Psychiatry; Dementia; Preventative Medicine

STRENGTHS AND LIMITATIONS

Strengths

- Prospectively-designed, high-powered longitudinal cohort of cognitively-healthy (at baseline) elders across the Alzheimer's pathological continuum followed up at high-throughput using biological, psycho-social, cognitive, behavioural and lifestyle measures
- Study adopts a unique cognition-based classification method for designating risk of MCI-AD development from baseline.

Limitations:

- Given the low amyloid positivity rate and the requirement of an equal number of CPSS participants above and below threshold, a high number of participants (78.6%) were excluded from the longitudinal CPSS study.
- The conduct of the study at only 2 sites does not fit the model of a typical, multi-site international clinical trial.

INTRODUCTION

Background and Rationale: The last few decades have witnessed unparalleled growth in aged populations. Hence, the global incidence and prevalence of Alzheimer's disease (AD), the most-common form of late-onset dementia, continue to increase exponentially, with numbers expected to exceed 150 million global cases by 2050 [1]. The paucity of any viable therapy for dementia prevention and/or disease modification necessitates a re-think of the conventional approach towards preventative research. Indeed, the AD field will benefit from concerted efforts for preventative strategies combining biomarker discovery studies with detailed validation of clinical characteristics as well as longitudinal explorations of associated pathologies and symptoms.

The asymptomatic stage of AD is characterized by biomarker evidence of amyloid- β ($A\beta$) deposition, as measured by either low cerebrospinal fluid (CSF) $A\beta_{42}$ peptide concentrations or elevated tracer uptake on $A\beta$ positron emission tomography (PET) scans [2]. Multiple studies have now reported that higher $A\beta$ burden in cognitively normal (CN) individuals is associated with measurably poorer performance in neuropsychological tests [3]. The

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3 accumulating longitudinal data also strongly suggest that evidence of abnormal levels of A β
4 deposition in CN individuals increases the risk for cognitive decline and progression to mild
5 cognitive impairment (MCI) and AD dementia [3]. The current consensus among members of
6 the Alzheimer's scientific community is that these CN individuals with detectable pathogenic
7 A β represent an early stage on the AD continuum [2, 4, 5]. Indeed, a meta-analysis of 55 studies
8 suggested that approximately 20% to 35% of study participants aged over 60 years without
9 dementia symptoms are likely to have above-threshold pathogenic A β pathology detected by
10 PET [6], with numbers increasing to 90% by age 85 [7].

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18 Rate of cognitive decline in CN individuals with or without evidence of abnormal A β
19 deposition can be measured using sensitive cognitive composite instruments. These measures
20 focus on the cognitive domains affected earliest in AD, namely episodic memory and executive
21 function, with decline noted as early as 7 to 10 years prior to the diagnosis of MCI or AD
22 dementia [8-10]. Yet, gaps remain in our understanding of the exact predictors of AD
23 pathological onset, accumulation and resultant development of clinical symptoms. There is a
24 need to identify individuals at varying levels of risk for AD, prior to development of AD
25 dementia. Such information would be useful to improve our understanding of the natural
26 history of AD progression and identify opportunities for intervention.

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34 The CHARIOT:PRO program seeks to address such gaps via detailed explorations of the
35 determinants of AD-related biological, clinical and cognitive changes. The previously-reported
36 main study of 987 participants at ICL, conducted from 2013 to 2016 (following early
37 termination by the study Sponsor) [11] was further adapted into a large prospective
38 observational trial – The CHARIOT: PRO SubStudy (CPSS) aimed at enhancing the scientific
39 robustness of the main study objectives with the addition of imaging and other AD-related
40 assessment tools.

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46 Here we describe the protocol (from Amendment version 15, dated 15th Aug 2018) of this
47 biomarker enriched CPSS featuring neuropsychological, functional, lifestyle, imaging and
48 other biomarker assessments and the schedule for their collection. We provide an outline of the
49 study design and a summary of the recruitment and screening process leading to the fully
50 enrolled cohort of 519 cognitively unimpaired adults.

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56 **Objectives of the CPSS:** CPSS is a prospective dual-centre, UK cohort study that at its core
57 aims to characterise deeply the clinico-biological attributes of the non-symptomatic AD stage
58 in individuals at differing levels of risk for development of MCI and AD-dementia, based on
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3 cognitive test scores at screening. CPSS participants thus could form a readiness cohort to be
4 recruited onto future AD-dementia prevention trials.
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7 Specifically, using data from participants with evidence of detectable A β pathology versus
8 those with below-threshold levels, the study will:
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11 - Investigate the longitudinal change of the global and composite measures of the newly-
12 developed Global Preclinical Alzheimer's Cognitive Composite (G-PACC) in
13 comparison to the Repeatable Battery for the Assessment of Neuropsychological Status
14 [RBANS, 12] and other study neuropsychological assessments, as well as
15 psychometrically evaluate the test batteries
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17 - Determine precise baseline predictors of longitudinal AD-related cognitive and
18 functional decline, and clinical progression to improve future screening of participants
19 most likely to develop MCI-AD/ AD dementia
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30 **METHODS**

31 **Population**

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33 The CPSS participants are adults aged 60 to 85 years old (inclusive), residing in Greater
34 London, South West England, Edinburgh and surrounding districts. Those included had
35 documented evidence of A β pathology (A β positives: above-threshold brain A β deposition on
36 PET or below-threshold CSF A β_{42} concentration), or evidence of below-threshold A β
37 pathology (A β negatives: below-threshold brain A β deposition on PET or above-threshold CSF
38 A β_{42} concentration), and a baseline global Clinical Dementia Rating (CDR) score=0. CPSS
39 participants were classified at screening as *high*, *medium-amnestic or non-amnestic*, or *low risk*
40 for developing MCI due to AD (MCI-AD), based on cognitive test performance as described
41 previously [11].
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51 **Study Design**

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53 The CPSS is a UK prospective observational study taking place across two sites (ICL and EDI).
54 The study is planned to follow approximately 250 CN participants who are A β positive and
55 approximately 250 A β negative CN control participants for up to three and a half years.
56 Evidence of A β pathology was assessed via CSF A β_{42} except where lumbar puncture (LP) was
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3 medically contraindicated or refused by participants, in which case A β PET was permitted as
4 an alternative method of determination of A β status. CSF samples were tested with the Meso
5 Scale Discovery (MSD) triplex (A $\beta_{38/40/42}$). A binary classification for A β load was applied
6 using a cut-off value for CSF A $\beta_{42} \leq 600$ ng/L. The cut-off for brain A β PET via standardized
7 uptake value ratio (SUVR) was based on three independent F18-radiolabeled amyloid tracers
8 - florbetapir, flutemetamol, and florbetaben. A specific SUVR threshold (i.e. a cut-point) was
9 used for each of the three radiotracers (Amyvid: 1.14 with whole-cerebellum as a reference
10 region, Neuraceq: 1.20 with cerebellar grey matter, Vizamyl: 1.23 with whole cerebellum).
11 Scans were reported as amyloid positive if the composite cortical SUVR value was above the
12 defined tracer-specific threshold, and negative if less than or equal to the threshold value.
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21 All study investigators, sponsor team and participants are blinded as to A β status information,
22 with the exception of an unblinded team member for verification of imaging and CSF A β
23 information. Blinding was put in place to avoid bias for conducting, monitoring and
24 interpreting results from the clinical assessments (except for research analysis purposes). The
25 same double-blind is maintained for apolipoprotein E (*APOE*) genotype, in view of allele-
26 specific positive correlation with A β load [13-15]. A β status and *APOE* genotype results were
27 not disclosed to participants as the clinical value (i.e., diagnostic or predictive) of such a
28 disclosure in a CN population is still unestablished. If clinical value is established from this or
29 other studies, then amyloid and *APOE* genotype will be disclosed to participants, at the end of
30 the study.
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39 Numbers of A β negative participants who passed screening assessments were deliberately
40 controlled to ensure equivalency with number of eligible A β positive participants. There was
41 no deliberate effort to balance the groups by age or gender.
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45 **Study schedule**

46 *Participant recruitment*

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49 At the ICL site, participants were recruited primarily from the CHARIOT Register, a well-
50 established dementia prevention and prediction register of older adults without dementia who
51 have provided consent to be contacted for relevant ageing research [16, 17]. Some participants
52 transitioned directly to CPSS from the Main study, though most of these individuals had
53 previously been recruited also from the CHARIOT Register. Additional methods of
54 recruitment at the site, with very limited numbers of enrolled participants, included self-
55 referrals and response from media advertisements. At the Edinburgh site, participants were
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3 recruited via SHARE (<https://www.registerforshare.org>), Join Dementia Research (JDR,
4 <https://www.joindementiaresearch.nihr.ac.uk/>) and the Scottish Primary Care Research
5 Network (SPCRN [http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)
6 [the-network](http://www.nhsresearchscotland.org.uk/research-areas/primary-care/about-the-network)) (See Figure 1 for the participant recruitment pathway). Recruitment efforts
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8 resulted in 1,914 individuals screened at ICL to enrol 409 participants, and 537 screened at
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10 Edinburgh to enrol 110. Screened participants were not selected based on race/ethnicity or
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12 gender, resulting in a predominance of participants of European ancestry (> 95%) and a slight
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14 majority of women.
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17 *Selection of study participants: summary of eligibility criteria*

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20 The major exclusion criteria for CPSS include known familial autosomal dominant AD,
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22 diagnosis of AD dementia, MCI, or any other degenerative brain disorder that is associated
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24 with dementia at screening. Evidence of brain disease or other conditions leading to dementia,
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26 other than AD-related structural pathologies were assessed centrally by blinded neuro-
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28 radiologists via magnetic resonance imaging (MRI) during screening. Additionally, use of AD
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30 pharmacological therapies, and evidence of psychiatric/cognitive disorders/other abnormalities
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32 such as low vitamin B12 (specifically those with abnormal homocysteine and methylmalonic
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34 acid), and linked to cognitive deficits are exclusionary. Further, history of first-degree family
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36 member with diagnosed clinical AD was required for participants aged 60-65 years. This
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38 measure was put in place to enrich the cohort for cerebral A β positivity given typically lower
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40 prevalence in asymptomatic young elders i.e. below 70 years of age [18], thereby effectively
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42 minimizing screen failure rates. Following participants' consent, self-reported medical and
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44 medication history was confirmed from full history provided by participants' general
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46 practitioner (GP). Upon receipt of any medical information, current medical conditions and
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48 past medical history was updated on source documents and subsequently on electronic data,
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50 including medication, past and planned procedures. Medical summaries from GPs were used
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52 to ascertain self-reported histories.

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54 During screening, participants whose cognitive performance on any RBANS Index fell more
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56 than 1.5 standard deviations below the (age- and education-adjusted) population mean (based
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58 on normative sample from [19]) were referred to an adjudication panel. This panel, comprised
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60 of neurologists, psychiatrists and neuropsychologists, considered whether the low performance
was likely to be attributable to undiagnosed cognitive impairment and, if so, excluded the
participant from the study. These participants were contacted directly by the study team to

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3 inform them of their exclusion. At that time, where any concerns were noted regarding their
4 performance, the option to notify their GP with information about the study and their exclusion
5 was offered.
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8 9 *Screening schedule*

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11 The screening was usually completed in four separate visits within a 90-day window. On
12 certain occasions, this timeline was extended up to 180 days to allow for treatment of transient
13 conditions, laboratory retesting, and scheduling of other screening assessments. This allowed
14 time for results to be received and evaluated against study eligibility criteria. Any clinically
15 significant findings were passed on for follow-up to the participant's GP. Participants who
16 were determined to have an active unstable illness, as defined by the inclusion/exclusion
17 criteria, were excluded. Screening involved collection of demographic data which included
18 age, ethnicity, education and occupational status. During screening, potential participants
19 completed cognitive tests, the G-PACC and RBANS, and CDR including the study partner
20 interview. A clinical evaluation (pulse, blood pressure, weight, head, waist & hip
21 circumference, temperature (tympanic), physical and neurological examination) and clinical
22 lab assessments were carried out to determine general health status. Participants not excluded
23 at this stage then underwent a brain MRI. If MRI did not reveal exclusionary abnormalities
24 (see Table 1), it was followed by an A β assessment based on CSF analysis or brain PET scan.
25 After the A β determination, baseline assessments were undertaken at two consecutive visits
26 where the RBANS (form A), G-PACC (form A) as well as the Neuropsychological Assessment
27 Battery (NAB) Memory and Executive Function modules (form 1) and the National Adult
28 Reading Test (NART) were administered alongside self-reported study questionnaires. Bio-
29 samples were further collected for biomarker assessments. (See Figure 2 for schematic
30 depiction of screening and baseline assessments).
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46 47 *Post-screening schedule*

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49 Following the baseline assessment, CPSS participants were randomized in a balanced 1:1:1
50 ratio, stratified by A β status and level of performance on the screening RBANS, to one of three
51 supplemental neuropsychological tests namely: CogState Brief Battery [20], Cognitive Drug
52 Research Assessment System, and either Delis-Kaplan Executive Function System [DKEFS,
53 21, ICL only] or COGNITO [22, EDI only]. Participants who enrolled in the Substudy from
54 the Main Study retained their previous Main Study-assigned randomized group. Participants
55 are expected to attend study visits every quarter and will be followed up for a period of up to
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3 3.5 years. Due to the COVID-19 restrictions that were implemented in March 2020 in the UK,
4 the CPSS was transitioned to virtual visits to allow continued longitudinal assessments. For
5 further details on our strategy for operationalising this activity, please see [23]. As part of the
6 general visits, we collect detailed information on all medical, especially Covid-related incidents
7 including more recently information on Covid-19 vaccinations. These data are designated
8 Covid-related within our database for easy identification of such cases.
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14 **Study outcomes and assessments**

15 *Primary neurocognitive outcomes*

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19 The primary outcomes of the CPSS are performance in two neurocognitive measures, the novel
20 G-PACC and the RBANS.
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23 The G-PACC: is a retrospectively and theoretically derived and validated measure, weighted
24 towards episodic memory but including a timed executive function test and a global cognitive
25 screening test [24]. For this study, the four PACC components include: the Free and Cued
26 Selective Reminding Test -Immediate Recall [FCSRT-IR, 25], the Delayed Paragraph Recall
27 score on a single administration of the Logical Memory story from the WMS – Revised [26],
28 the WAIS-IV Coding subtest [26] and the MMSE [27]. Each component score is transformed
29 into z-scores. These z-scores are summed to form the composite. The battery takes about 25
30 minutes to administer. Alongside screening and baseline time points, alternating forms of the
31 G-PACC are administered at the following time points: Months 6, 12, 18, 24, 30, 36, 42.
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39 The RBANS: is a 25-minute composite battery with 12 subtests that measure 5 cognitive
40 domain indices: Attention, composed of Digit Span and Coding, Language, with Picture
41 Naming and Semantic Fluency subtests, Visuospatial Construction including Figure Copy and
42 Line Orientation subtests, Immediate Memory comprising List Learning and Story Memory
43 subtests, and Delayed Memory composed of List Recall, List Recognition, Story Recall, and
44 Figure Recall subtests. The sum of these 5 Index scores is converted to a Total Scale value via
45 a mapping table. The Total Scale is a norm-based t-score based on a distribution with a mean
46 of 100 and standard deviation of 15. The RBANS is administered face-to-face, has 3 alternate
47 forms, is available in over 30 languages, and has been used in multinational clinical trials
48 including AD trials. Alternating forms of the RBANS are also administered at the following
49 timepoints: Months 3, 9, 15, 21, 27, 33, 39. During screening, participants' RBANS scores
50 were used to delineate risk (low, medium, high) for developing MCI-AD, as described in the
51 Main study [11].
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3 Secondary Cognitive outcomes and Functional outcomes are described in Table 2. More
4 detailed description of these measures are provided in the CHARIOT PRO Main Study
5 Protocol [11].
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8 *Neuroimaging outcomes*

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10 Safety and volumetric scans (3DT1, FLAIR, T2*, PD/T2, T1 and DWI): All potential CPSS
11 participants underwent brain MRI at screening to assess eligibility, based on a central
12 radiologist's interpretation of the MRI scan under the supervision of Bioclinica Inc. Borderline
13 findings were reviewed by the Medical Monitor prior to determining participant eligibility.
14 Image acquisition was performed at multiple sites based on a standardized MRI protocol.
15 General Electric Signa HDxt 1.5T and Siemens TrioTim, Verio, Skyra and Prisma 3T scanners
16 were used to acquire a volumetric 3D T1 weighted series in a sagittal plane, using 1.2 mm thick
17 slices and a 192x192 acquisition matrix over a square FOV of 240 mm. Contrast parameters
18 were field-strength and manufacturer dependent (Siemens MP-RAGE and GE IR-Prep Fast
19 SPGR). The standardized MRI protocol also included 2D axial FLAIR, T2* gradient echo,
20 dual-echo proton-density and T2-weighted turbo/fast spin echo, T1-weighted turbo/fast spin
21 echo and diffusion-weighted imaging. Proper implementation of the MRI protocol on each
22 participating scanner was verified prior to first subject scan by use of American College of
23 Radiology (ACR) phantom scans.
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36 Exploratory scans (Task-free BOLD functional MRI (tf-fMRI) and high-resolution coronal
37 T2sequences): At the ICL site, the first 800 subjects who were eligible for MRI underwent a
38 dual-echo GRE field map and task-free functional MRI time series. For the remainder of the
39 subjects, a high-resolution 2D coronal T2-weighted sequence was acquired, in order to
40 visualize hippocampal subfields.
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45 A β PET: At final stage of screening, evidence of A β pathology in potential CPSS participants
46 was assessed by a brain PET scan. All images derived were evaluated centrally at Bioclinica
47 Inc. for A β status assessment. The assessments were performed by neuro-radiologists trained
48 in the assessment of A β PET scans using F18-radiolabeled amyloid tracers (Amyvid, Vizamyl
49 and Neuraceq) for amyloid status according to the reading process developed by radiotracer
50 vendors. The PET scan was evaluated at baseline to determine each patient's A β status as
51 positive or negative and therefore inclusion or exclusion into the trial. PET exams were
52 acquired using a uniform scanning protocol that minimizes and accounts for between-site
53 differences in PET systems, as characterized with a Hoffman phantom exam. All exams were
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3 acquired in 3D mode and employed correction for attenuation, scatter and random coincidence.
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5 Semi-quantitative SUVR assessment was performed prior to the visual read. SUVR
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7 calculations leveraged a FreeSurfer-based native-space MRI segmentation method. The A β
8
9 status assessment was a hybrid visual and quantitative approach (see Figure 3). A visual review
10
11 was performed by a single reader, followed by positivity assignment based on SUVR cutpoint.
12
13 In case of discrepancies between visual and SUVR results, a second reader was asked to
14
15 participate in a final decision on amyloid status, as part of a consensus review. The second
16
17 reader was given both the initial visual read and the SUVR measurement and convened with
18
19 the first reader to arrive at a consensus assessment.

20 *Fluid Biomarkers*

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22 Blood, saliva and urine samples for clinical assessments and future biomarker discovery
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24 studies: At ICL and EDI, blood and urine samples were collected at screening to assess general
25
26 health status. These included: Haematology and Differential Panel, Lipid Panel, Chemistry
27
28 Panel, Electrolyte Panel, Coagulation Group, C-Reactive Protein, TSH, Folate, Vitamin B12
29
30 and Urine Macro Panel (with Urine Microscopy if abnormal Macro Panel).

31
32 At ICL, serum, plasma, buffy coat, whole blood, urine and saliva samples are processed and
33
34 stored at baseline and annually thereafter for future biomarker exploration. Samples for
35
36 biobanking are collected between 9-11.30am and following an overnight fast; and are stored at
37
38 the ICL purpose-built -80°C biobank for future analyses. All samples are processed within two
39
40 hours of collection, as per guidelines on biomarker pre-processing [28]. Planned analyses
41
42 include untargeted metabolite and proteome profiling, to generate novel targets for future
43
44 hypothesis-testing and biomarker discovery studies.

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46 CSF biomarkers: For those participants not receiving A β PET, CSF samples were collected
47
48 during screening and analyses for AD-related markers including beta-amyloid, total tau and
49
50 phosphorylated tau. The A β data was used for determination of enrolment eligibility, and in
51
52 addition to the tau data, will be useful for disease modelling and staging of pre-clinical AD per
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54 NIA-AA criteria [2]. At ICL, additional aliquots of CSF samples are stored in the -80°C
55
56 biobank for future analyses, which may include the exploration of putative biomarkers of AD
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58 pathophysiology as they arise in the literature.

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60 Genetic outcomes: Whole blood is collected in EDTA tubes for extraction of genomic DNA
(gDNA) using standard methods. gDNA were thus isolated via commercially available kit
following manufacturer instructions (QIAGEN QIASymphony DSP DNA Mini Kits or Promega

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3 Maxwell RSC Whole Blood DNA Kit). Both kits facilitate automated magnetic bead-based
4 extractions that successfully extract DNA from Human Whole Blood samples with good
5 quantitation and purity assessments. The QPS validated pyrosequencing genotyping assays for
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7 *APOE* codon 112T>C and codon 158C>T polymorphic variants were used to genotype
8
9 participant's gDNA samples and identify *APOE* ε4 Carriers and *APOE* ε4 Non-Carriers status.
10
11 By interrogating these two polymorphic variants, we identified the three *APOE* alleles: *APOE*
12 ε2(TGC 112, TGC 158), *APOE* ε3 (TGC 112, CGC 158), and *APOE* ε4 (CGC 112, CGC 158).
13
14 *APOE* genotype status has been determined for the enrolled cohort. A genome-wide-analysis
15
16 study is under-way and data expected to be available during the study. At ICL, whole blood is
17
18 also collected in a PAXgene® Blood RNA tube containing reagent for stabilization of
19
20 intracellular RNA, and stored -80°C. These samples will be used for future genetic analyses.
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23 ***Medical History and Clinical examinations (Physical and neurological examination)***

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25 A thorough medical history was obtained including an evaluation of all body systems (ENT,
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27 ophthalmic, musculoskeletal, gastrointestinal, urinary, respiratory, renal, cardiovascular,
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29 dermatological) with an emphasis on relevant medical history (e.g. neurological, psychiatric,
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31 substance abuse, endocrine and metabolic). Safety and compatibility for neuroimaging were
32
33 further ensured prior to the procedure.

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35 Clinical examination included General Physical examination and a separate comprehensive
36
37 Neurological Physical examination. The General Physical examination assessment included:
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39 General appearance, Dermatologic (including Mucous Membranes), Ear, nose, throat (ENT),
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41 Cardiovascular, Respiratory, Abdomen, Lymph Nodes, Musculoskeletal and any other
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43 findings. At Neurological Examination, Mental status, Cranial nerves, Motor (strength), Tone,
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45 Involuntary movements, Coordination (Finger-nose, Gait, Postural reflexes and Heel to shin),
46
47 Sensation (Proprioception, Cold, Light touch), Deep tendon reflexes, Plantar reflexes and
48
49 presence of other neurological signs (e.g. tremor) were assessed.

50 ***Safety reporting***

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52 During the whole course of the study, new medical conditions and changes in medication were
53
54 assessed at every site visit. All adverse events (serious and non-serious) were documented and
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56 reported according to the same protocol procedures applied in the main CHARIOT:PRO Main
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58 Study [11]. Briefly, serious and non-serious events that occur from inception of participation
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60 all through to completion of last study-related procedure are captured and recorded for all
participants. Events are judged as serious if fatal, immediately life-threatening; require

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3 hospitalization or prolonging of existing hospitalization; permanently (or significantly)
4 disabling; a congenital anomaly or birth defect (in an offspring); or medically significant.
5 Further data recorded for each suspected adverse event included the description (signs and
6 symptoms or diagnosis), seriousness criteria, severity rating, duration (onset and resolution
7 date), actions taken and outcome.
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15 **Study participant and public involvement**

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17 The ICL (via CHARIOT register) and EDI team have established Research volunteer panels
18 consisting of lay members who met on an ad-hoc basis to support study development during
19 the planning stage. These panels provided feedback on study design, procedures and
20 dissemination for lay audiences. A newsletter is provided to study participants with updates
21 regarding recruitment, study milestones and any important changes to the Protocol. Participants
22 were not directly involved in recruitment activities for the study.
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28 CPSS participants further provide feedback on the experience of research participation at the
29 different study visits, to ensure that their perspectives are represented in decision-making about
30 the future of the project and to advise on planned study activities, including dissemination
31 plans. Annual participant seminars are conducted for dissemination of study results and
32 discussion of future plans. A newsletter is provided to study participants quarterly for study
33 updates, as well as future plans. Participant input and feedback on volunteer experiences is
34 typically encouraged for inclusion in the newsletter.
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41 **Ethical and regulatory considerations**

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43 To ensure the quality and integrity of research, CPSS is conducted in accordance with GCP
44 Guidelines, GPPs issued by ISPE, applicable national guidelines, and to the Declaration of
45 Helsinki 2013, as modified by the 52nd World Medical Assembly (WMA), Edinburgh,
46 Scotland, 2000, and clarified by the WMA General Assembly, Washington 2002 and Tokyo
47 2004. The study has received approval from the National Research Ethics Service (NRES)
48 Committee London Central (reference 15/LO/0711 [IRAS 140764]), as well as independent
49 ethics review by committees from the local sites.
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56 Informed consent: Formal informed consent is taken using an informed consent form (ICF)
57 from both participant and study partners before participation in the study. Given the possibility
58 that participants might lose mental capacity during the study; it was recommended at the outset
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3 of participation that the participant identified a Legally Authorized Representative (LAR). A
4 LAR may include the spouse, a person specifically appointed to take care of the legal interests
5 of the participant, an individual with guardianship, and a health care proxy, who provides
6 consenting for research studies which is within the legal scope of the proxy's delegated
7 responsibilities (according to local applicable laws). The LAR must have the cognitive and
8 mental capacities (as determined by the site Investigator) enabling him/her to understand the
9 procedures, risks, and benefits involved with the study. The consent was given, and the form
10 signed, at the initial visit or at follow-up visits at the study sites, based on the choice of the
11 participant, and, where necessitated, on the choice of the LAR.
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19 Duty of care: As part of the duty of care during the study, all clinically relevant information is
20 shared with study participants where relevant and, with participant's consent, communicated
21 to the GP for medical follow-up. The clinically relevant findings shared included systemic
22 hypertension and significant changes in cognitive assessments where the investigator felt they
23 were relevant.
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29 Confidentiality: Participant confidentiality is strictly maintained. Each participant is assigned
30 a unique participant identifier upon study enrolment, which is used for all subsequent data
31 analysis and reporting. Participants' National Health Service (NHS) numbers are collected and
32 stored in keeping with industry standards for encryption/data protection, allowing for
33 subsequent data collection from electronic health records in primary or secondary care within
34 NHS. This data collection only occurs following NRES approval. All parties ensure that
35 participant personal data is not included on any study forms, reports, publications, or in any
36 other disclosures, except where required by law. The Investigators in compliance with Federal
37 regulations, other applicable laws and International Conference on Harmonization (ICH) GCP
38 Guidelines keep documents that are not for submission to the Sponsor and/or its designee (e.g,
39 signed ICFs and Participant Information Sheets) in strict confidence. In accordance with
40 regulations in the UK, participants are informed about data handling procedures.
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50 **Data management, analysis, and dissemination plans**

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52 **Data Management:** The CPSS is conducted in accordance with Good Clinical Practice (GCP)
53 Guidelines as such data is recorded and stored in a way that could be verified and reported in
54 an accurate manner. All essential documents are filed in the Trial Master File/Investigator Site
55 File. Source documents are kept in both paper and electronic formats. The main Electronic
56 Data Capture system used in the current study is Medidata Rave. Both paper and electronic
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3 data are subject to daily and monthly internal audits based on Standard Operating Procedures
4 (SOPs). In addition, the Investigator Site Files, paper source documentation and electronic
5 source data are routinely monitored to maintain data accuracy collection to the highest degree.
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9 **Statistical Analysis:** Assuming the 3.5-year change from baseline in the G-PACC score has a
10 standard deviation of 2.4 for the A β positive participants [29], a sample size of n = 250 with a
11 3.5-year dropout rate of 31% (i.e., 10%/year) ensures the 95% confidence interval (CI) for the
12 3.5-year mean change in G-PACC score in A β positive participants to be no wider than 0.72,
13 assuming that the sample mean follows a Gaussian distribution. Analysis of change in G-PACC
14 and RBANS over time will be performed with mixed models for repeated measures (MMRM)
15 which assumes that missing data due to dropout are missing-at-random (MAR). The robustness
16 of the analysis with respect to deviations from the MAR assumption will be evaluated.
17 Analyses of the accruing results may be performed periodically while the study is ongoing.
18 Analyses will generally be descriptive, but inferential analyses might be performed as needed.
19 Potential unblinded interim analyses include:
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28 (i) Analyses for baseline characterization of participants.

29 (ii) Analyses for determining longitudinal change in study endpoints once the last ongoing
30 subject completes the Month 12, Month 24, and Month 36 visits. These analyses will include
31 descriptive statistics (n, mean, standard deviation) and/or proportions for the A β positive and
32 negative groups, but the A β status of individual participants will remain blinded.
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39 DISCUSSION

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42 With the pre-clinical disease stages being increasingly recognized as the best timing for
43 intervention, it is paramount that trial evaluations are sensitive enough to detect and track
44 cognitive, functional and biological changes emerging in these stages while also
45 possessing sufficient efficacy to detect therapeutic effects for drug trials. Furthermore, there is
46 an urgency to identify robust and sensitive predictors of clinical progression in order to estimate
47 individual risks for clinical AD and develop and apply therapeutic strategies prior to emergence
48 of clinically evident AD dementia. Although an ambitious project, some limitations of this
49 work are worth mentioning. The amyloid positivity rate is low and due to a need for an equal
50 number of participants in each group (amyloid positive; amyloid negative), a high number of
51 participants (78.6%) were excluded from the longitudinal follow-up phase. As a mitigating
52 measure, enrichment criteria were introduced, with requirement of first-degree family history
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3 in volunteers aged 60-65 years old. The conduct of the study at only two sites is not typical of
4 multi-site international trials; on the other hand, this minimizes several sources of variability
5 that are independent of aging and incipient Alzheimer's disease (e.g., inter-rater variability and
6 differences in psychometric equivalence among different translations). It could be argued that
7 the cognitive battery set may not be sensitive in predicting AD in healthy older adults, since
8 these mostly tax modalities associated with AD dementia diagnostic criteria. Nonetheless, the
9 high frequency (quarterly) follow-up of participants will facilitate determination of those
10 assessments most sensitive for identifying the earliest signs and symptoms of AD-dementia
11 and offers an opportunity to assess other performance parameters (e.g. qualitative errors, lack
12 of practice effect; speed-accuracy trade-offs) that may indicate changes in cognitive and/or
13 cerebral integrity in the lead up to AD dementia [30]. Similarly, other assessments of physical
14 health pertinent to AD risk, such as gait, hearing, or dental health are not included in our study.
15 However, we do collect extensive medical history information at baseline and follow-ups that
16 includes clinical abnormalities (e.g. mobility issues; hearing impairment) that may be useful in
17 our analyses.
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31 The CPSS contributes towards this global agenda of AD-dementia prevention. The study
32 features detailed and frequent clinical and cognitive assessments in a deeply phenotyped,
33 presymptomatic cohort of older adults. An overall aim of the study is to prospectively compare
34 changes in cognition, and other clinical measures, between individuals with presence of
35 pathological levels of brain A β detected in PET scans or CSF and those without such evidence.
36 CPSS also introduces a novel cognitive composite, the G-PACC, as a possible endpoint for
37 future clinical trials. In this way, CPSS will expand upon prior retrospective investigations of
38 proposed cognitive composites [29], by prospectively investigating the longitudinal change of
39 the components of the G-PACC composite. The performance of the G-PACC to detect effects
40 will be compared against another cognitive composite and its subtests, the RBANS. The
41 addition of the RBANS subtests, alongside other clinical data, will allow for the exploration of
42 novel cognitive risk profiles for the progression of future AD. The baseline data will determine
43 which measures are most sensitive for predicting longitudinal AD-related cognitive decline,
44 informing future screening methods for clinical trials. The study includes both patient and
45 proxy-versions of functional interviews, such as the CFI and ADCS-ADL, to investigate
46 longitudinal changes in everyday functioning in preclinical-AD individuals alongside cognitive
47 decline and clinical characteristics. Dietary patterns and other lifestyle variables will also be
48 assessed to consider the impact of environmental exposures on AD development. Therefore,
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3 the CPSS will also allow for the exploration of environmental and lifestyle predictors of
4 cognitive decline and impairment.
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8 The uniqueness of this study lies in its breadth and frequency (every 3 months) of assessments,
9 as well as the planned explorations and comparisons of proposed cognitive composites for AD
10 detection and tracking. The prolonged and detailed follow-up data offers opportunities for
11 precise disease modelling and the evaluation of several methodological controversies within
12 clinical trial design, such as the influence of practice effects on cognitive performance, in
13 addition to mechanisms of reserve and resilience against cognitive senescence.
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19 To date, CPSS has successfully completed its enrolment of 519 participants across two UK
20 research sites, from 2,451 screened volunteers. Next steps in CPSS's milestones include the
21 exploration of the baseline data for initial comparative analyses between stratified participant
22 groups. The CPSS will continue as a multinational and multidisciplinary collaboration between
23 industry, academia and the NHS to promote greater understanding of the etiology of AD
24 pathological attributes and symptom development, and champion the search for effective
25 preventative therapies. Future plans include study extension to at least 4.5 years, at the ICL
26 site, with addition of Tau-PET and follow-up structural MRI, and extensive state-of-art fluid
27 biomarker discovery explorations at multiple timepoints.
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39
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41 commitment towards the CPSS. We thank the staff at various sites who assist in the collection
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10 **Author Statement:**

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13 Prof Middleton served as the ICL study site principal investigator. Prof Ritchie served as the
14 EDI study site principal investigator. Dr. Udeh-Momoh served as the lead author, with Dr
15 Watermeyer as co-lead. Drs. Udeh-Momoh, Kivipelto, Car, Pernecky, Price, de-Jager Loots
16 and Ward were co-investigators at School of Public Health, Imperial College London. Dr
17 Ritchie was co-investigator at Centre for Dementia Prevention, University of Edinburgh. All
18 principal and co-investigators contributed to the study design, coordination, data acquisition,
19 development and critical review of the manuscript. Dr. Scott and Mr Bracoud were employees
20 at Bioclinica Inc., and developed the imaging protocol for the study, and participated in
21 development and critical review of the manuscript. Prof Majeed co-developed the Chariot
22 Register at School of Public Health, Imperial College London. Drs. Bassil, Robb, Cohn,
23 Giannakopoulou, Kafetsouli, Chowdary and Ms Perera, Mclellan-Young, Lakey, Crispin and
24 Curry were study investigators at School of Public Health, Imperial College London; Drs.
25 Tamlyn Watermeyer and Natalia Reglinska-Matveyev were study investigators at Centre for
26 Dementia Prevention, University of Edinburgh, and all contributed to data acquisition and
27 review of the manuscript. Drs. Novak, Ropacki, Arrighi, Ketter, Raghavan, Saad and Brashear
28 and Mr Fogle contributed to the study conception, protocol design, and development. Drs.
29 Novak, Baker, Kacher, Saad and Mr Fogle contributed to study design and were responsible
30 for data review, interpretation, and development of the manuscript. In addition, Dr. Arrighi was
31 project pharmacoepidemiologist and Drs. Raghavan, Di and Kacher served as project
32 biostatisticians, responsible for aspects of study design, statistical data analysis and statistical
33 input. Dr Saad served as the unblinded statistician and imaging lead for the project.
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50 All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors.
51 All authors provided direction and comments on the manuscript, made the final decision about
52 where to publish this protocol and approved the final draft and submission to this journal.
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Table 1: CHARIOT PRO study exclusionary findings post screening MRI

- edema including amyloid-related imaging abnormalities (ARIA-E)
- hydrocephalus
- >25% age related white matter disease,
- frontal or temporal atrophy not typical of AD)
- history or evidence of a single prior hemorrhage >1 cm³
- multiple lacunar infarcts (2 or more) or
- single prior infarct >1 cm³
- cerebral contusion, encephalomalacia
- aneurysms, vascular malformations
- subdural hematoma
- space occupying lesions (eg, abscess or brain tumors such as meningioma >1cm)
- MRI features atypical of AD dementia.

*Evidence of brain edema (eg, ARIA-E, vasogenic edema, hemosiderin deposits [HD] ≥10 mm in size or HD <10 mm in size but >10 in number) will be reviewed by the Sponsor's Medical Monitor to address plans for clinical evaluation and follow up as well as for potential inclusion/exclusion in the study.

Table 2 CHARIOT PRO study Cognitive and Functional outcomes

Cognitive Outcome	Description	Assessment Schedule
<i>Secondary outcomes</i>		
National Adult Reading Test (NART) [31]	The NART is a word reading and pronunciation task comprising 50 English words with irregular grapheme-phoneme and stress rules. It is used to provide an estimate of premorbid intellectual functioning. Average administration time: 10 minutes.	BL
Neuropsychological Assessment Battery (NAB) Executive Function module (PAR Inc) [32]	The executive function module comprises subtasks that examine planning, impulse control and psychomotor speed (through pen and paper mazes trials of increasing difficulty); judgement and decisional capacity (through questions pertaining to home safety, health and medical issues); concept formation, cognitive flexibility and response set (through a classification and categorization task) and fluency and generativity (through a word fluency task). Average administration time: 30 minutes.	M12, M24, M36

Neuropsychological Assessment Battery (NAB) - Memory module (PAR, Inc)	The memory module comprises explicit learning, free recall, delayed recall and/or delayed recognition subtasks across verbal (list learning; story learning; medication instructions and name and address) and visual (shape learning) information. Average administration time: 45 minutes.	M12, M24, M36
NEUROTRACK (<i>Neurotrack Technologies, Inc</i>) [33]	Neurotrack is a declarative memory test based on digital eye tracking, administered on an IPAD. The task is a recognition memory test, relying on an individual's innate preference for novelty. In a familiarization phase, participants are presented with 2 identical images, side by side on the computer screen. This is followed by a test phase, in which a familiar image presented during the familiarization phase and a novel image are shown together. The ratio of time an individual gazes at the novel stimulus relative to the total viewing time constitutes a novelty preference score, with higher scores indicating superior declarative memory function and lower scores indicating impaired function. Average administration time: 10 minutes.	M3, M9, M15, M21, M27, M33, M39
<i>Randomised tasks</i>		
Cognitive Drug Research Assessment System (CDRAS) (Bracket; United BioSource Corporation) [34]	The CDRAS measures three domains of cognition: Attention (simple and choice reaction time, digit vigilance); Working memory (articulatory and spatial working memory); Episodic secondary memory (word recall, word recognition and picture recognition). Average administration time: 20 minutes.	M3, M9, M15, M21, M27, M33, M39
Cogstate (Cogstate, Inc) [20]	CogState consists of 4 tasks involving the presentation of playing cards. These tasks measure the functions of attention, processing speed, visual learning, and working memory using standard psychometric paradigms (ie, simple and choice reaction time, n-back and pattern separation learning). For the first assessment visit, M3, the task is administered twice within one session to control for task familiarity and practice effects. Average administration time: 15 minutes.	M3, M9, M15, M21, M27, M33, M39

<p>Delis-Kaplan Executive Function System (Pearson) [21]</p> <p>ICL Site Only</p>	<p>The DKEFS is a paper and pencil measure of verbal and nonverbal executive functions and comprises 9 subtests. For this study, the Trail Making Test (visual attention and task switching) and Verbal Fluency (fluency and generativity) subtests are used. Total average administration time to complete these 2 subtests: 15 minutes.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Cognito [22]</p> <p>EDI Site Only</p>	<p>COGNITO is a computerized task which assesses reaction time, primary and working memory (an articulation subtest further permitting identification of problems related to the articulatory loop), visuospatial and verbal secondary memory (with free, cued and multiple choice paradigms), implicit learning (priming), language skills (word and syntax comprehension, naming, verbal fluency), functional and semantic categorization of visual data (visual reasoning and form perception), focused and divided attention (visual and auditory modalities), and crystallized intelligence (vocabulary). Responses are made via a tactile screen which permits the recording of response latency (deducting reaction time provides an estimation of information processing time). Qualitative aspects of performance (perseveration, intrusions, visual field neglect) are also recorded. Administration time varies between 45- to 60-minute, depending on level of impairment.</p>	<p>M3, M9, M15, M21, M27, M33, M39</p>
<p>Functional Outcomes</p>	<p>Description</p>	<p>Assessment Schedule</p>
<p>Clinical Dementia Rating Scale [35]</p>	<p>The CDR is used as a clinical staging instrument and is administered to both participant and study partner, using a semi-structured format. It assesses six domains: memory; orientation; judgment and problem solving; involvement in community affairs; home and hobbies; and personal care. Average administration time: 15-20 minutes with the study partner and 10-15 minutes with the participant, depending on the severity of cognitive impairment.</p>	<p>M12, M24, M36</p>

<p>Cognitive Function Index [36]</p>	<p>The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument (MCFSI, Walsh et al, 2006) a self- and informant-reported subjective outcome measure regarding activities of daily living. It includes 14 questions that assess participants' perceived ability to perform high level tasks in daily-life and their sense of overall cognitive functional ability, indicating whether or not there has been a change in performance (yes/no/maybe) compared to 1 year ago. Study participants and their study partners independently rate the participant's level of ability. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>
<p>Alzheimer's disease Cooperative Study ADL prevention instrument (ADCS-ADL-PI) [37]</p>	<p>The ADCS-ADL-PI includes 15 subjectively rated questions related to activities of daily living and 5 questions related to physical functioning. Error! Reference source not found. Study participants and their study partners independently rate the study participant's level of ability. Partners are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if errors were made performing the task. Physical functioning items are rated as yes or no. Average administration time: 10 minutes.</p>	<p>M12, M24, M36</p>

Note: BL – Baseline

Figure 1 The CHARIOT:PRO Substudy Recruitment Pathway

a. Join Dementia Research; b. Scottish Primary Care Research Network; c. formerly Centre for Dementia Prevention; d. CHARIOT:PRO Main Study, e. formerly Neuroepidemiology and Ageing (NEA) Research Unit

Figure 2 Screening and baseline assessment schedule

CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; PACC=Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; CFI=Cognitive Function Index; ADCS-ADL-PI=ADCS-Activities of Daily Living - Prevention Instrument; NAB=Neuropsychological Assessment Battery; NART-National Adult Reading Test; GDS=Geriatric Depression Scale; STAI –State Trait Anxiety Inventory

Figure 3: PET A β Status Reading Workflow

SUVR = Standardized Uptake Value Ratio; Q = quantification of SUVR; FS = parcellation of cerebral structures based on Freesurfer imaging pipeline; QC = quality control assessment; VIS = result of visual assessment of amyloid PET; A β + = assessed as A β positive based on visual and/or quantitative (SUVR) analysis of amyloid PET

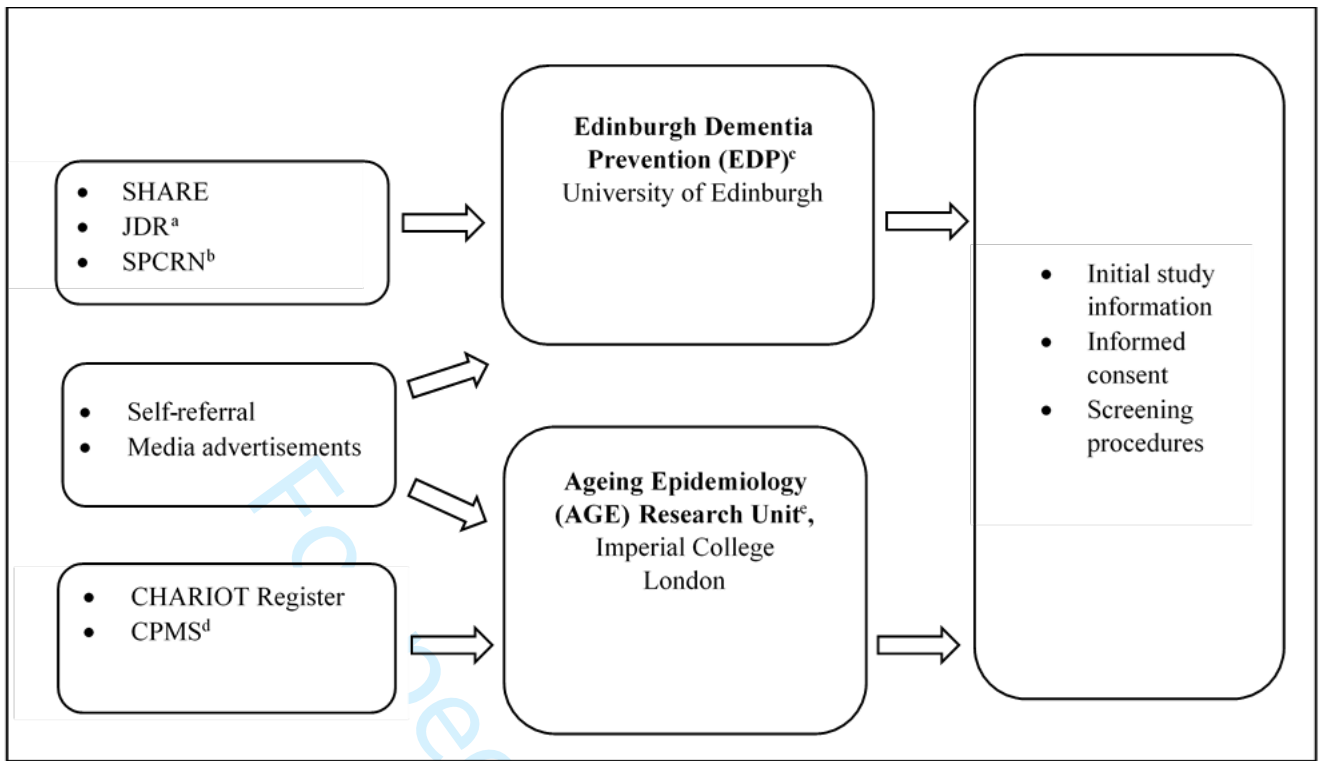


Figure 1. The CHARIOT:PRO Recruitment Pathway

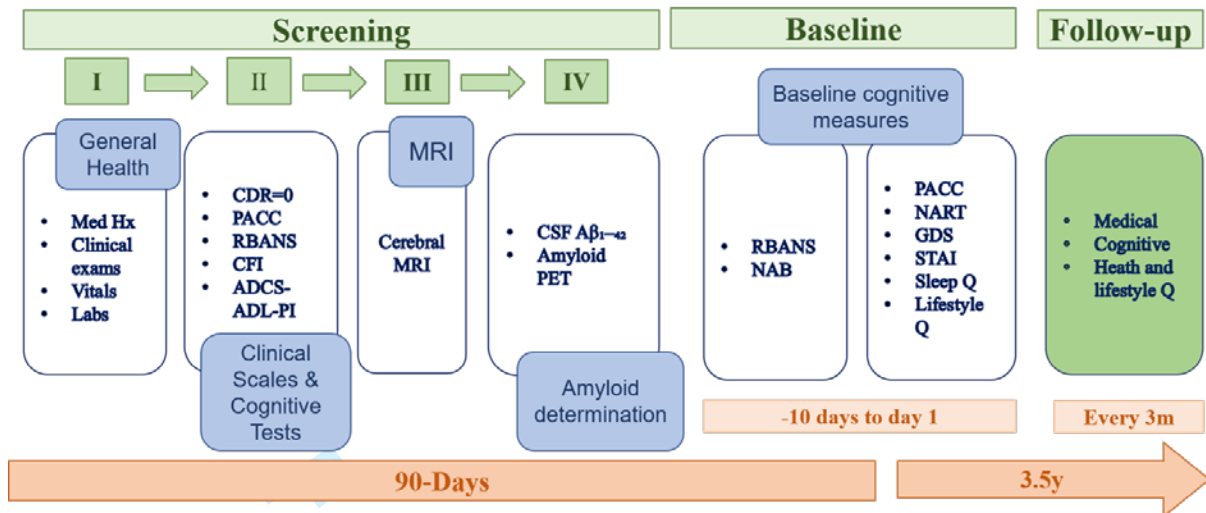


Figure 2 Screening and baseline assessment schedule

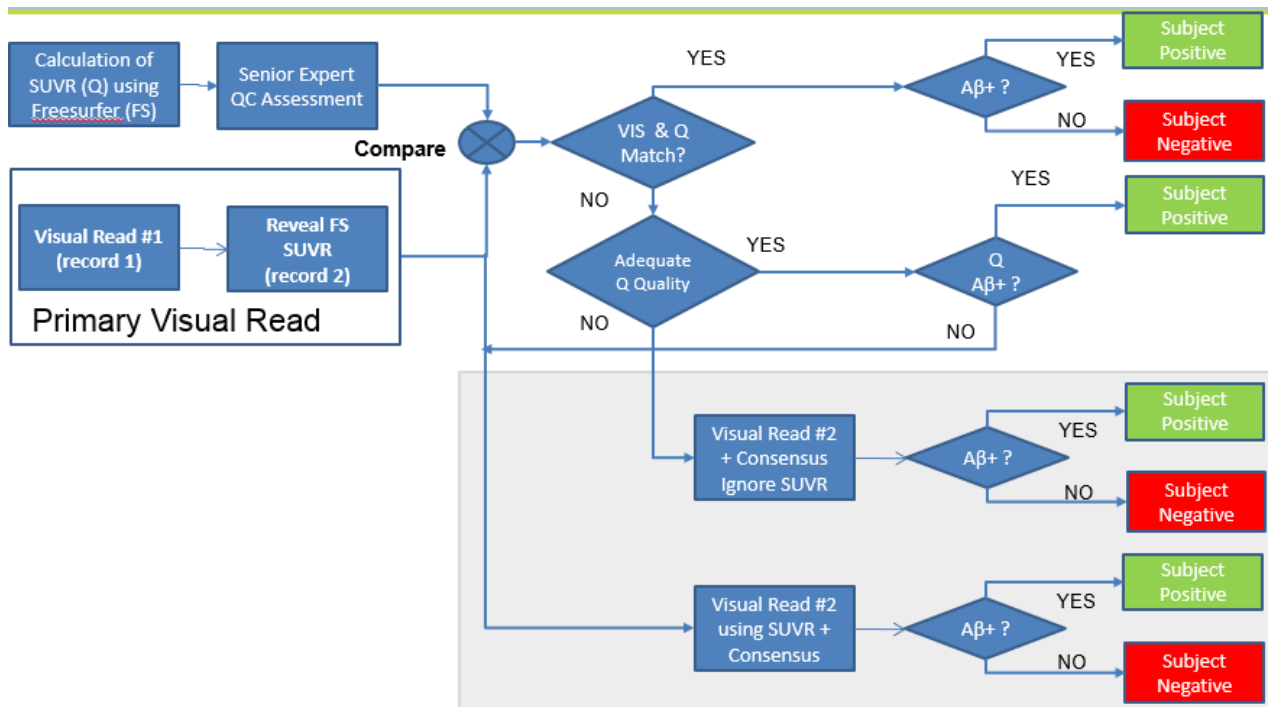


Figure 3: PET Aβ Status Reading Workflow