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Research Protocol

The Co-Production and Evaluation of the Computerised Cognitive Assessment for Preclinical Alzheimer's Disease (CoCoA-PAD)

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1. Aim

The aim of this study is to test the classification accuracy and neural associations of a series of newly created neuropsychological assessment, which collectively form the computerised cognitive assessment for preclinical Alzheimer's disease (CoCoA-PAD).

2. Background and Rationale

Alzheimer's disease (AD) healthcare is on the verge of significant change. Healthcare providers can now diagnose people with pre-dementia AD (i.e., preclinical and prodromal AD), and new disease modifying medications can slow cognitive decline (see Jack Jr et al., 2024). Health services are now faced with the challenge of implementing these developments into clinical practice. NHS England and the National Dementia Team have developed an initial implementation strategy (Murdoch & Stewart, 2024). It states that diagnostic assessments will be delivered in newly commissioned neurology and neuropsychology clinics, and that the completion of a 'comprehensive cognitive assessment' is required to diagnose the AD clinical syndrome, and stage the disease severity.

While AD biomarker assessments, such as plasma and cerebral spinal fluid assessments, provide information on the presence of AD proteins (Amyloid and Tau), they are not predictive of future dementia, i.e., only 22% of 65-year-olds with preclinical AD biomarkers will develop Alzheimer's dementia in their lifetime (Brookmeyer & Abdalla, 2018). As such, the International Working Group (IWG) provide clear recommendations that the use of AD biomarkers in isolation in cognitive unimpaired older adults is not advisable and in fact may lead to harm (Dubois et al., 2024). In contrast, meta-analytic research has demonstrated that the combination of biomarkers and cognitive assessments improves predictive accuracy for future AD dementia to 73% (Parnetti et al., 2019). The IWG have proposed that a clinical-biological definition of AD is adopted into clinical practice (Dubois et al., 2024), and that the combination of plasma and sensitive cognitive markers of AD represent the most feasible strategy for a meaningful diagnosis of preclinical and prodromal AD (Vonk, 2025).

2.1. The Implementation of Cognitive Assessment Pathways

There are severe barriers to the implementation of comprehensive cognitive assessments for early AD into NHS practice. Most cognitive assessments are grossly insensitive to the early cognitive difficulties associated with AD and therefore not fit for purpose (Curiel Cid & Loewenstein, 2022). Indeed, large scale research including over 5,000 participants, identified that traditional cognitive assessments do not add any predictive accuracy above demographic factors and genetics, to determine the risk of preclinical AD (Liu et al., 2025). There are some notable exceptions (e.g., APICC & PACC, Langbaum et al., 2020; Bransby et al., 2019), but these rely on tests that can only be administered by practitioner psychologists, e.g., Logical Memory from Wechsler Memory Scales (WMS-IV). There is currently a national shortage of practitioner psychologists in the UK (NHS England, 2023). Two recent economic modelling studies demonstrate that the implementation of 'psychologist' delivered cognitive assessment onto early AD pathways would cost the NHS £4.2 billion to deliver (Mattke et al., 2024a), and without this investment, waiting lists would reach over 10 years by 2029 (Mattke et al., 2024b).

Therefore, the delivery of early AD cognitive assessment cannot be achieved by relying on existing cognitive tests or the existing workforce model. There is an urgent need for an implementation strategy for the delivery of large-scale cognitive assessment for early AD into the NHS, but there is no agreed upon strategy to achieve this.

Memory nurses are the largest staffing group in memory services and already have considerable experience administering and scoring brief cognitive *screening* tests, e.g., Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Examination (ACE-III). Additionally, there is an impetus to increase the psychological workforce in the NHS through the delivery of the clinical associate psychologist (CAP) profession. In my opinion, the most realistic option of delivering comprehensive cognitive assessments at a large scale is to develop an assessment that can be reliably and robustly delivered by memory nurses and CAPs. Following consultation with memory nurses and neuropsychologists, there are two identified barriers to achieve this: 1) a lack of a standardised training protocol for non-practitioner psychologists on how to deliver cognitive assessments; and 2) a lack of available cognitive assessments that nurses and CAPs can use. This proposal seeks to co-design a nurse or non-practitioner psychologist administered cognitive assessment for preclinical AD, and co-produce a robust training protocol for nurses and allied health professionals to deliver cognitive assessments. If successful, this will contribute to the widespread delivery of early AD diagnosis and treatment through the NHS.

2.2. CoCoA-PAD Assessment

The long-term aim of the CoCoA-PAD project is to develop a validated assessment app which can be used in clinical practice. The CoCoA-PAD project seeks to collate the best experimental neuropsychological tests in the academic literature, and work with a team of stakeholders to co-produce these tests into a viable clinical assessment. In its current format, the CoCoA-PAD assessment is experimental, and none of the subtests have been validated previously. Therefore, the CoCoA-PAD assessment in its current form is not a medical device and does not require MHRA registration.

CoCoA-PAD is comprised of 16 standalone subtests, which are used to generate seven index scores (premorbid intelligence, memory, language and fluency, spatial processing, perceptual discriminability, cognitive control and performance validity). Figure 1 provides a list of the CoCoA-PAD subtests and the theorised hierarchical structure, and Appendix 1 provides a brief description of the subtest, the theoretical justification, and the reference test it is based on. CoCoA-PAD is designed based on an up-to-date understanding of the cognitive neurology of preclinical and prodromal Alzheimer's disease and the temporal ordering of cognitive difficulties (see Vogel et al., 2021). The assessments have been designed to assess the cognitive sequelae of preclinical AD, and the four preclinical syndromes identified by Vogel and colleagues (2021) (see figure 2).

CoCoA-PAD was designed to achieve two ambitions:

- *Maximise Efficiency.* CoCoA-PAD includes automatic and timed stimuli presentation, and automated scoring and psychometric calculations. This includes embedded machine learning approaches to maximise classification accuracy without the need for labour intensive scoring procedures. These steps ensure accuracy and reduce clinical time.
- *Maximise Clinical Value.* CoCoA-PAD incorporates many features that are designed to maximise clinical value, which do not exist in conventional neuropsychological assessments. This includes embedded measures of premorbid ability and performance validity, structured observational assessments of validity, functional cognitive disorder, and other cognitive difficulties, e.g., language.

2.3. Co-Production of CoCoA-PAD

The CoCoA-PAD assessment battery, and indeed all aspects of this research study, have been developed using a coproduction methodology, as outlined by the NIHR (NIHR Guidance on co-producing a research project). The co-production group consists of five older adults (including two with neurological conditions, one from an ethnic minority background, and one with educational deprivation), five assistant psychologists, two memory nurses, and seven clinical psychologists and neuropsychologists. The older adult coproduction group are involved in ensuring the assessment is well tolerated, the instructions are clear, that the test does not unduly discriminate against people with low computer literacy. The assistant psychologist group are involved in coproducing the usability of the assessment for the examiner. The memory nurses are coproducing the clinical observation checklists. The clinical psychologist and neuropsychology group are involved in coproducing the assessment governance and training requirements. All aspects of the assessment have been or are currently being co-produced.

CoCoA-PAD is delivered using Gorilla Experiment Builder 2.0 (EB2). Approximately half of the subtests (COBALT, MANE, SILT, Verbal Fluency, Connected Speech, Clock Drawing, and ALF) were initially developed and coproduced using a CoCoA-PAD web-based app, but due to costs associated with data storage, these tasks were transferred directly into Gorilla EB2. The remaining subtests were designed and co-produced using Gorilla EB2, an online platform for designing and running behavioural experiments. Gorilla Experiment Builder provides precise stimulus delivery, secure data collection, and easy remote access, making it well-suited for this research.

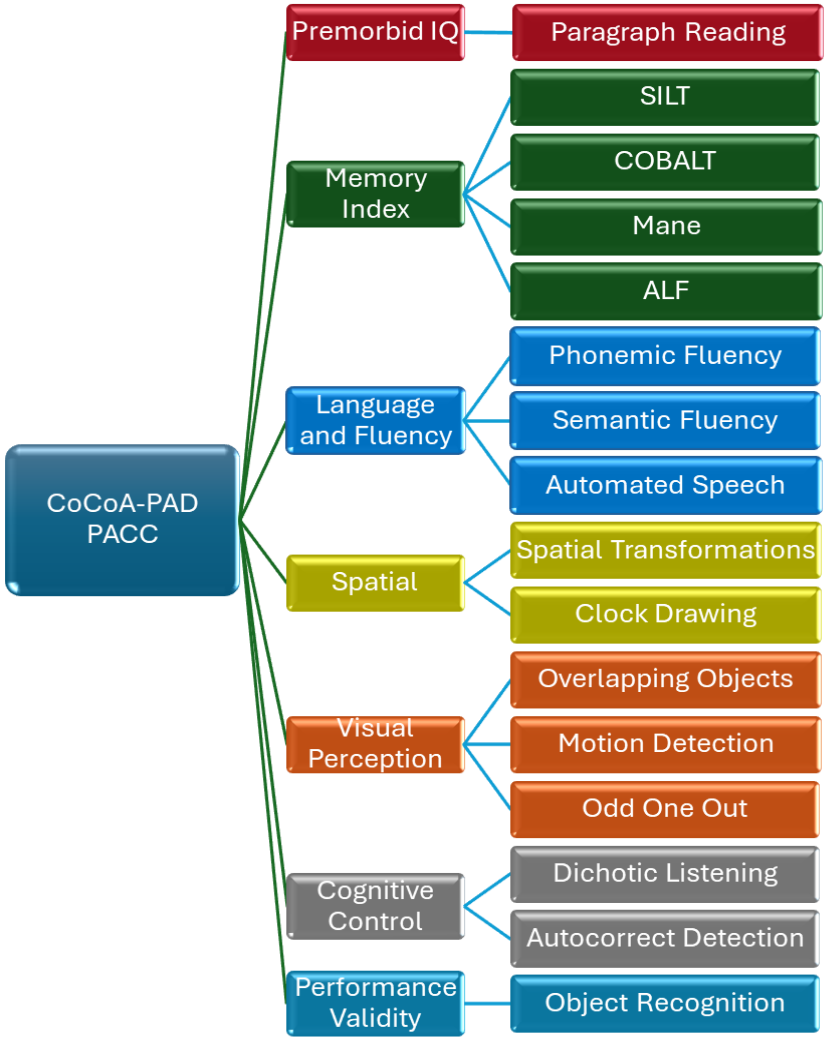

Figure 1. Proposed hierarchical structure of CoCoA-PAD

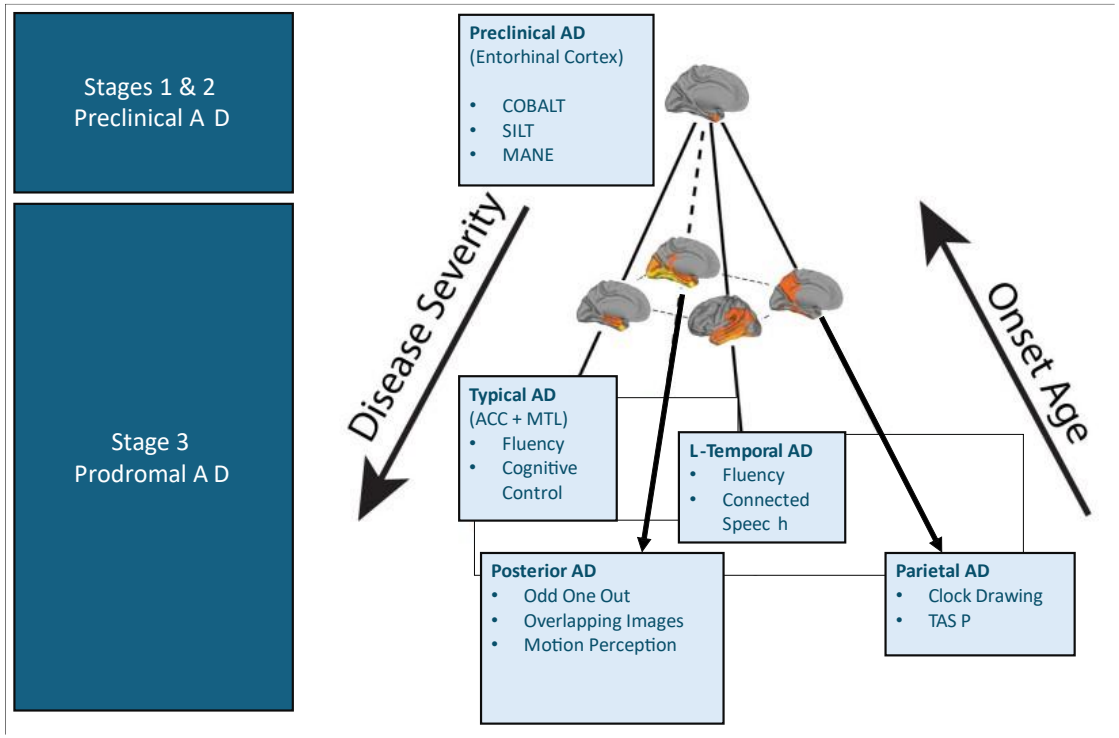

Figure 2. Mapping of CoCoA-PAD subtests onto the preclinical AD syndrome, and the four prodromal AD syndromes.

3. Objectives

3.1. Primary objective:

The long-term aim of this research is to develop a cognitive assessment which can be implemented into memory services and provides clinically meaningful information for healthcare staff. There are four primary research objectives, which stem from this ambition:

i. To establish the diagnostic accuracy of the CoCoA-PAD subtests at distinguishing people with preclinical Alzheimer's disease (stages 1 and 2) from healthy controls.
ii. To establish the diagnostic accuracy of the CoCoA-PAD subtests at distinguishing people with prodromal Alzheimer's disease (stage 3) from healthy controls.
iii. To measure the relationship between CoCoA-PAD subtests and measures of neurodegeneration.
iv. To test whether CoCoA-PAD subtests are sensitive at detecting cognitive deterioration over a one-year period.

3.2. Secondary objectives:

i. To assess the usability of the assessment from both a service user and assessor perspective.
ii. To determine the strength of the relationship between pTau-217 levels and cognitive assessment performance on the CoCoA-PAD subtests
iii. To establish the diagnostic accuracy of the CoCoA-PAD subtests at distinguishing people with prodromal Alzheimer's disease against those with non-AD related Mild Cognitive Impairment (MCI).

4. Study Design and Sampling Method

This research study is comprised of three sub-studies. Although each study includes a cohort of the same participants, each sub-study has its own sampling procedure and research design, which I have outlined below:

4.1. Study 1. Evaluating the Diagnostic Accuracy of CoCoA-PAD subtests

Participants

A total of 120 participants will be recruited: 60 participants with subjective cognitive decline (SCD) and 60 participants with mild cognitive impairment (MCI). Participants will be classified post-recruitment into four distinct diagnostic groups: healthy controls, preclinical AD, prodromal AD, and non-AD related MCI. Figure 3 provides a flow of the estimated frequencies of each diagnostic group within the sample.

Sampling

This study will use a stratified sampling approach with post-hoc diagnostic classification. A prospective quasi-experimental between-group research design will be employed.

A stratified sampling approach will ensure that key demographic information, including years of education and ethnicity, will match national population demographics of the UK. 2021 census data revealed that 6% of 70–74-year-olds in the UK are from non-white ethnic minority backgrounds. However, given that people from minority ethnic backgrounds are significantly more likely to have dementia but less likely to receive a diagnosis (Okeoghene Ighomereho, 2025), for the purpose of this study, the stratified sampling target will be inflated to 10%.

Similarly, 2021 census data has mapped the educational attainment of the UK population. No age-specific education attainment values were published, but regional values have been published, and Plymouth demographics have been selected for this study. This is based on coastal communities having higher rates of dementia, lower rates of diagnosis, and significant social inequalities which often exclude them from research (Alzheimer's Research UK, 2024). This study will replicate educational attainment values, with provision for 5% variation in the recruitment to each education level – see Table 1.

Table 1. Educational Attainment and Stratified Sampling Target

Educational Attainment	Plymouth Demographics	CoCoA-PAD Recruitment Target Range
No Qualification	17%	14-26
Level 1 (O level any grade)	10%	6-18
Level 2 (O levels passes)	14%	11-23
Apprenticeship	6%	1-13
Level 3 (A level equivalent)	17%	14-26
Level 4 (3rd level qualifications)	34%	35-47
Other	2%	0-8

Procedure

Participants will be recruited and classified post-recruitment into diagnostic groups on the basis of AD biomarker results (pTau-217) and performance on the M-ACE, using a cut-off score of 20 for MCI (Potts et al., 2022).

Measures

Performance on the CoCoA-PAD subtests will be compared across diagnostic groups. Scores will be compared across the different diagnostic categories, i.e., non-AD subjective cognitive decline (i.e., healthy controls) versus preclinical AD, versus prodromal AD.

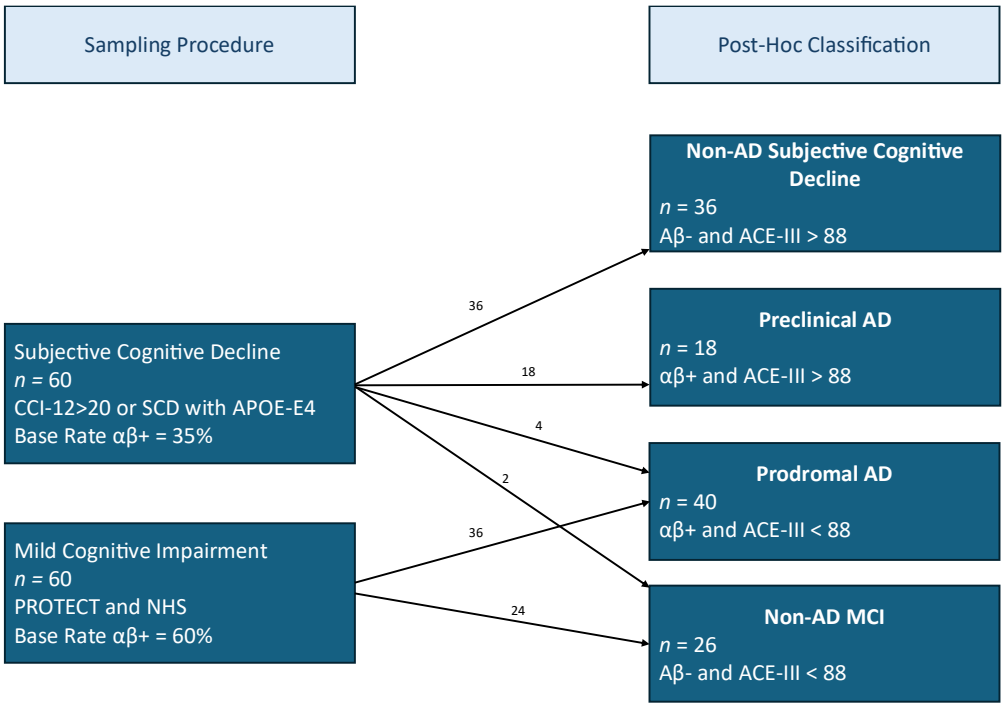

Figure 3. Estimated post-diagnostic participant numbers for Study 1

4.2. Study 2. Relationship Between Brain Health and CoCoA-PAD Performance

Participants

All participants from Study 1 who live within driving distance of Plymouth (n=81) will be invited to undergo a magnetic resonance imaging (MRI) assessment. As such, study 2 will consist of participants who fit into each diagnostic criteria from Study 1.

Sampling

This study will use a convenience sampling procedure based on recruitment to Study 1 and participant location. A cross-sectional design will be employed.

Procedure

Participants will undergo MRI assessment following their participation in Study 1.

Measures

This study will measure the relationship between CoCoA-PAD subtest scores and key indicators of neuronal health. MRI data will be obtained using both single (T1-weighted) and multi-shell imaging approaches.

The specific measures of brain health include:

1. Volumetric measures using T1-weighted imaging of key regions of interest (ROI) associated with early Alzheimer's disease.

2. Diffusion Tensor Imaging (DTI) measures, including Fractional Anisotropy (FA), Radial Diffusivity (RD) and Mean Diffusivity (MD) of defined white matter tracts associated with Alzheimer's disease.

3. Neurite Density Index (NDI), Free Water Fraction (FWF), and Orientation Dispersion Index (ODI) metrics from Neurite Orientation Dispersion and Density Imaging (NODDI) of key grey matter regions of interest.

Figure 3 illustrates the estimated post-diagnostic participant numbers from Study 1.

4.3. Study 3. Measuring the Ability of CoCoA-PAD Subtests at Determining Change Over Time

Participants

A sub-sample of 36 participants from the Study 1 sample will be reassessed on CoCoA-PAD approximately one year after their initial engagement in the CoCoA-PAD study. 18 participants will be selected from both the healthy control and prodromal AD groups.

Sampling

This study will use a criterion based sampling procedure, selecting participants from Study 1 retrospectively based on diagnostic classification.

Procedure

Participants will complete the CoCoA-PAD battery a second time, approximately 11-15 months after their initial assessment.

Measures

The primary outcome measure will be change in scores on CoCoA-PAD subtests (time 2 – time 1 score). This study will therefore use a retrospective (known-group) between-group quasi-experimental research design.

4.4. Study design summary

A summary of the sample size, sampling approach, and research design for the three sub-studies is outlined in Table 2.

Table 2. Summary of sampling size, sampling approach and research design

Study	Total Sample	Sampling Approach	Design	Primary Outcome Measure

1	120	Stratified: 60 MCI and 60 SCD, matched to population demographics	Prospective between group quasi-experimental research design	CoCoA-PAD index and subtest scores.
2	81	Convenience: based on proximity to Plymouth	Cross sectional research design	CoCoA-PAD subtest scores Diffusion tensor imaging measures (FA, RD and MD) of key white matter tracts Neurite Density Index (NDI) of key grey matter regions of interest.
3	36	Stratified: 18 people with prodromal AD and 18 healthy controls.	Retrospective between group quasi-experimental research design	Change scores on CoCoA-PAD subtests (time 2 – time 1 subtest scores).

4.5. Duration of Study

In total, this study will run from February 2026 to September 2028 (two years and seven months). Recruitment will commence in February 2026 and run until March 2028 (2 years and one month). Most participants will complete a single appointment, which will last approximately 2 to 3 hours in duration. A small cohort of participants will be recruited for a follow up cognitive assessment approximately 1 year later. The follow up assessment will occur prior to March 2028.

4.6. Bias Reducing Factors

Several different methods have been used to ensure as many confounding variables as possible are controlled for.

Sampling Procedure

- A stratified research design will be used to ensure the research sample is representative of UK demographics for ethnicity and low educational attainment, both of which are risk factors for Alzheimer's disease and frequently under-represented in research (Chan et al., 2024).
- The All-Party Parliamentary Group on Dementia (2023) report outlined that access to transport is a key barrier that prevents or delays people living in rural and coastal communities for receiving a diagnosis of dementia. To ensure people with poor transport access are not excluded from this study, this study includes the option for all participants to travel to the research sites via taxi, at no cost to the participant.
- All data collected in Study 1 and Study 2 will be collected blind to the participants AD biomarker status. The AD diagnosis will be determined after the entire Study 1 and 2 samples are collected, when the AD biomarkers will be sent to the Dementia Biomarker Factory for analysis.
- Participant diagnostic status will be determined using objective criteria based on AD biomarker status and established cut off scores for MCI on the Mini Addenbrooke's Cognitive Examination (M-ACE) note that English as a first language is an inclusion criterion for this study. This is due to the confounding impact of performing cognitive assessments in a non-native language. Subsequent research will aim to adapt the CoCoA-PAD assessment so that it can be administered and scored automatically in different languages, to minimise this source of bias in the future.

Accessibility

All participant facing documents have been coproduced by members of the PPI group, who have 'signed off' on the research poster, participant information sheet, and debrief document.

Standardisation

- The recruitment screening and assessment battery will be heavily standardised and will use an assessment script (CRF). This will ensure consistency in screening and data collection for all participants.
- The scoring of all CoCoA-PAD tests will be completed using validated automated procedures, which reduces the potential for human error.

Data Analysis

- The full analysis plan will be reviewed by a statistician and approved.
- The full analysis plan will be pre-registered on the Open Science Framework.
- The analysis plan will include corrections for multiple comparisons to reduce the risk of type 1 error using false discovery rate adjustments.
- The associated anonymised research data set will be published with each academic article to provide a full audit trail of analyses.
- The full anonymised research data set will be made available to researchers, subject to receipt of a data access request to University of Plymouth.

5. Recruitment

5.1. Recruitment Sites

This study will run across three research sites: University Hospitals Plymouth NHS Trust, Devon Partnership Trust, and North East London NHS Foundation Trust. Additionally, Cornwall Foundation NHS Trust and Livewell Southwest will be patient identification centres (PICs). Given that this research is funded by the NIHR, it is eligible to be adopted onto the NIHR portfolio, which includes 'service support costs' to recruit through local NHS research teams. Most participants (81) will be recruited through the Plymouth site, and all will be offered an MRI scan. Participants in the other sites will not be offered this scan due to the limited availability of 3 tesla imaging protocols, and the costs associated with delivering MRI scans through the NHS. 19 participants will be recruited through both Devon Partnership NHS Trust and 20 from North East London Foundation NHS Trust. These participants will not be offered an MRI scan. A visual map of the recruitment sites and participant numbers are provided in Figure 4.

5.2. Recruitment Personnel

Recruitment at the Plymouth research site will be the responsibility of the Principal Investigator, who may delegate specific tasks to members of the research team subject to appropriate training and qualification. Delegation of authority in this manner will be recorded on delegation logs. Any persons involved in recruitment and obtaining consent will be trained in GCP. All recruitment undertaken by the undergraduate and honorary assistant psychologists

will be overseen by Dr Murphy and his team. Dr Murphy will provide all training, monitoring of quality standards and take responsibility for all aspects of research governance. Recruitment at the other research sites will be managed by local NHS research teams. Any persons involved in recruitment and obtaining consent will be trained in GCP.

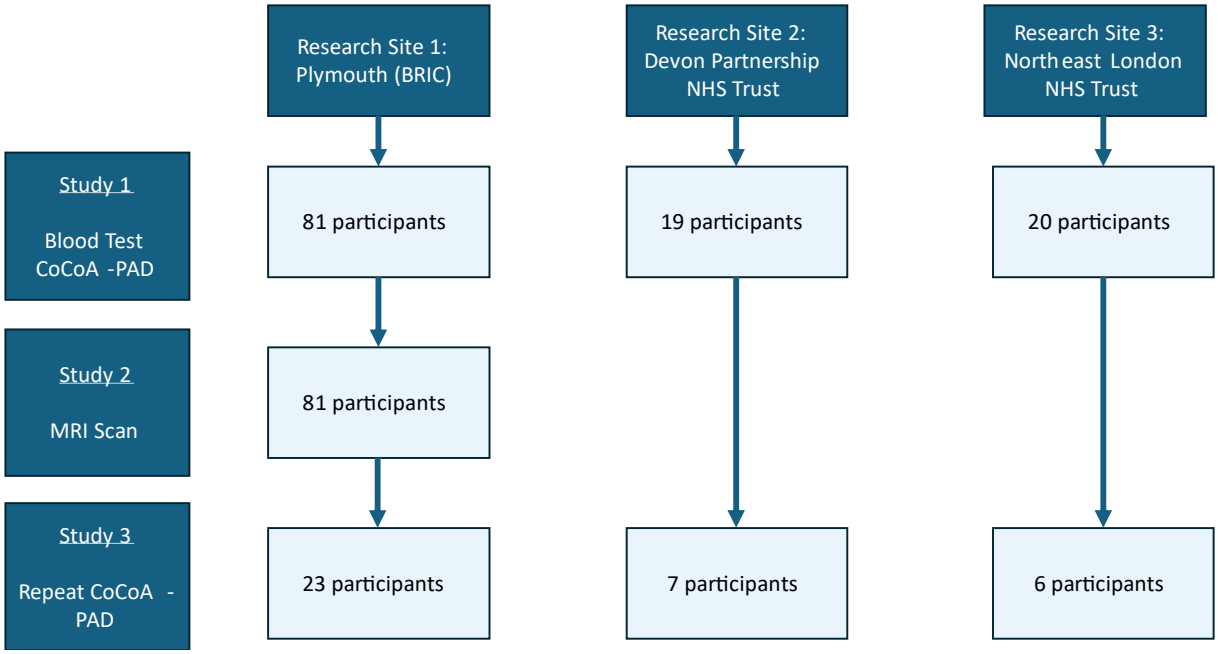

Figure 4. CoCoA-PAD Research Sites and Recruitment Targets

5.3. Primary Recruitment Strategy

This study aims to recruit all participants through the PROTECT research study https://www.protectstudy.org.uk/. However, if this is not possible, a range of alternative recruitment strategies have been outlined in the secondary recruitment strategy. The PROTECT study is run by the University of Exeter and King's College London, in partnership with the NHS. As of 2022, the study had over 22,000 participants (Stewart et al., 2022) and aims to recruit 50,000 participants nationally. The PROTECT study asks participants to complete yearly cognitive assessments and rating scales and has validated procedures for classifying participants as having mild cognitive impairment (Brooker et al., 2020). The PROTECT authors facilitate the recruitment of participants through their database.

5.4. Secondary Recruitment Strategy

In addition to the PROTECT database, potential participants may be approached through online research databases, NHS memory services and community events.

Research Databases

Individuals may also be contacted through a research database. These include the NIHR Join Dementia Research (JDR) and the Be Part of Research databases (BPR), both of which involve

individuals who have provided consent to be contacted about future research. An application will be made for the CoCoA study team to access the JDR and BPR databases to identify individuals who may be interested in participating.

Recruitment from NHS clinics

The relevant physicians and specialist nurses holding regular clinics at Livewell Southwest and University Hospitals Plymouth NHS Trust will be informed about the study. The physician, specialist nurse, or therapist will discuss the study with the patient if appropriate. If the patient expresses an interest, verbal consent will be sought, and recorded in the patient's medical notes, by the clinician for the patient to be contacted by a member of the research team. If verbal consent is provided, the clinician will let the research team know that the participant is interested in the study and confirm verbal consent has been given to contact the patient.

Recruitment from Community Events

The CoCoA-PAD study may be promoted at community events (e.g., University of the 3rd Age) and on social and traditional media (Facebook posts, posters, radio promotion). Potential participants will be provided with information on how to access study information (QR code, email address and/or website link), and will register their interest and consent to be contacted by completing a brief Microsoft Forms, or a similarly secure system recommended by the UHP research team.

5.5. Participant Screening Criteria

Subjective Cognitive Decline

Subjective cognitive decline (SCD) is a research descriptor used to refer to people who believe that their cognitive functioning has deteriorated despite performing in the 'normal' range on objective measures of cognitive functioning. People with SCD are at increased risk of developing dementia (Glodzik-Sobanska et al., 2007), and therefore SCD is considered a potential early clinical manifestation of Alzheimer's disease. Jessen and colleagues (2014) developed a widely used research criteria to define SCD. It includes:

1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
2. Normal age, gender, and education adjusted performance on standardised cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal AD.

Exclusion criteria for SCD include mild cognitive impairment, prodromal AD, or dementia; that difficulties can be explained by a psychiatric or neurologic disease (apart from AD), medical disorder, medication, or substance use.

In addition, the authors also provide guidance on the criteria for SCD *plus*, which increases the likelihood of preclinical AD, and includes:

- Subjective decline in memory, rather than other domains of cognition

- Onset of SCD within the last 5 years
- Age at onset of SCD ≥60
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a descriptor used to refer to people who report experiencing a decline in cognitive functioning *and* demonstrate cognitive impairment on objective testing. It is thought to be a transitional phase between normal aging and dementia. Albert and colleagues (2011) on behalf of the National Institute on Aging - Alzheimer's Association (NIA-AA) developed diagnostic guidelines for research. They include:

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
- Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- Not demented.

With regards to how cognitive impairment is classified, the authors state that 'cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data'.

Table 3 provides a breakdown of the specific inclusion and exclusion criteria used in the CoCoA-PAD study.

Table 3. Recruitment Criteria for Subjective Cognitive Decline and Mild Cognitive Impairment

Subjective Cognitive Decline	
Inclusion Criteria	**Exclusion Criteria**
• >3.38 on IQCODE Self-Report items 1-7 (PROTECT) OR • ≥4 on SCD-Q9 (non-Protect) AND • Age ≥65 years • Onset of SCD within the last 5 years • English as a first language • Normal demographically adjusted performance on standardised cognitive tests • Specific Race and Education (using stratified sampling approach)	• Cognitive impairment, i.e., performance ≥1 SD below demographically adjusted norms (PROTECT) OR • ≤17 on the telephone MoCA (non-PROTECT) AND • Lacks mental capacity to consent to research • Diagnosis of dementia • Sensory impairment that cannot be corrected for with sensory aids, e.g., blindness. • Previous neurological injury (stroke, traumatic brain injury, severe epilepsy, brain tumour)

	• Other neurodegenerative syndrome (e.g., Parkinson's disease, multiple sclerosis, etc) • Diagnosis of learning disability • Severe depression (PHQ-9≥15 OR score ≥1 on PHQ-9 suicide question • Current severe psychiatric disorder (bipolar disorder, schizophrenia, or psychotic disorders) • Current drug or alcohol abuse • Untreated diagnosis of sleep apnoea.
Mild Cognitive Impairment	
Inclusion Criteria	**Exclusion Criteria**
• >3.38 on IQCODE Self-Report items 1-7 (PROTECT) • Cognitive impairment, i.e., performance ≥1 SD below demographically adjusted norms (PROTECT) OR • ≥4 on SCD-Q9 (non-PROTECT) • ≤17 on the telephone MoCA (non-PROTECT) OR • MCI diagnosis according to DSM or ICD-11 criteria through an NHS memory clinic. AND • Age ≥65 years • Onset of SCD within the last 5 years • English as a first language • Specific Race and Education (using stratified sampling approach)	• A score of ≥3 on any item on the Instrumental Activities of Daily Living scale, subject to clinical judgement. • Lacks mental capacity to consent to research • Diagnosis of dementia • Sensory impairment that cannot be corrected for with sensory aids, e.g., blindness. • Previous neurological injury (stroke, traumatic brain injury, severe epilepsy, brain tumour) • Other neurodegenerative syndrome (e.g., Parkinson's disease, multiple sclerosis, etc) • Diagnosis of learning disability • Severe depression (PHQ-9≥15 OR score ≥1 on PHQ-9 suicide question • Current severe psychiatric disorder (bipolar disorder, schizophrenia, or psychotic disorders) • Current drug or alcohol abuse • Untreated diagnosis of sleep apnoea.

The study is restricted to English-speaking participants to ensure validity of the assessment tools. We recognise this limitation and plan future work to adapt and validate the platform in other languages.

6. Study Procedures

6.1. Measures for Screening for Participant Eligibility

Participant's eligibility to participate in the CoCoA-PAD study will be determined based on self-reported screening tests, cognitive screening assessments and/or clinical diagnosis. For participants recruited through the PROTECT study, their eligibility will be determined based on previous scores on PROTECT assessments – Factors of Longitudinal Attention, Memory and Executive Function (FLAME) and Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE). For participants recruited through other research databases and community events, they will be asked to complete stand-alone screening over the phone to determine their eligibility. The screening assessments will include The Subjective Cognitive Decline Questionnaire (SCD-Q9) and Telephone Montreal Cognitive Assessment (MoCA).

All the screening measures are outlined below, even though the FLAME and IQ-CODE will not be administered as part of the CoCoA-PAD study. A visual flow-chart of the measures used in screening, the main research appointment, and the follow up, are outlined in Figure 5.

Factors of Longitudinal Attention, Memory and Executive Function (FLAME)

The FLAME is an online cognitive assessment battery designed for use in the PROTECT study. It consists of measures of speed of attention, accuracy of attention, memory, executive functioning and a global composite score. The FLAME has demographically adjusted norms and has been used to classify patients with stage 2 and stage 3 cognitive difficulties associated with Alzheimer's disease (Brooker et al., 2020).

Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE)

The IQCODE is a screening tool used to assess cognitive decline over time, based on reports from someone who knows the individual well — typically a family member, friend, or caregiver. The measure asks people to rate their cognitive ability compared to how it was 10 years ago, and as such, it is designed to measure perceived cognitive decline. It has been adjusted for self-administration, which is how it is currently used in PROTECT study. Although cut off scores vary across trials, a cut off score of 3.34 on the short version has reasonable accuracy for diagnosing dementia (AUC = 0.85, sensitivity = 0.79, specificity = 0.82) (Jorm, 1994).

The Subjective Cognitive Decline Questionnaire (SCD-Q9)

The SCD-Q9 is a nine item self-report tool designed to assess subjective cognitive complaints, specifically those related to perceived memory and cognitive difficulties. Participants are asked whether they have experienced examples of cognitive decline in the preceding five years, and responses are as Yes = 1, No = 0. This format makes it easy to administer over the phone. The SCD-Q9 has been used in large scale research aiming to investigate preclinical AD, e.g., the European Medical Information Framework for Alzheimer's Disease (Bos et al., 2018). It has adequate internal reliability (Chronbach's alpha = 0.78), and a score of ≥4 is used to classify SCD (Lin et al., 2022).

Telephone Montreal Cognitive Assessment (MoCA)

The telephone version of the MoCA is a brief cognitive screening measure. It includes just the verbal items from the MoCA, which has been widely validate, and can therefore be administered over the phone. It takes approximately 7 to 10 minutes to administer, and scores range from 0-22 (with lower scores being associated with worse cognitive ability). T-MoCA has been validated in a large older adult community population in USA (cut off score ≥17, AUC = 0.71, sensitivity 0.72, specificity = 0.59) (Katz et al., 2021)

6.2. Measures included in the Research Appointment

Demographic Questionnaire

A brief demographic questionnaire will be used to collect information regarding participants date of birth, age, gender, ethnicity, educational history and occupational history. The demographic questionnaire will only be administered in the time 1 assessment.

Health History

Participants will be asked to identify whether there experience any comorbid health related difficulties, including sleep apnoea, arthritis, motor problems, sensory loss, etc. Additionally, participants will be asked to list their current medications. At the follow up assessment, participants will be asked whether their health history has changed in the past year.

pTau-217

Phosphorylated tau-217 (p-tau217)—tau phosphorylated at threonine-217—is a blood biomarker of Alzheimer's-type tauopathy downstream of amyloid-β pathology. Multiple studies show that plasma p-tau217 identifies biological Alzheimer's disease with diagnostic accuracy comparable to established CSF tests (and sometimes similar or superior in head-to-head evaluations), including for Aβ-PET and tau-PET status (Barthélemy et al., 2024; Martínez-Dubarbie et al., 2025). Levels become abnormal early and increase with disease burden, supporting its potential use for biological staging from at least stage 2 onward and tracking longitudinal change (Mattsson-Carlgren et al., 2020). Research has demonstrated that the combination of SCD+ criteria and a positive plasma pTau-217 biomarker result are effective at classifying stage-2 of the AD spectrum (Mengel et al., 2025).

In the 2024 NIA–AA revised criteria, p-tau217 was classified as a Core-1 biomarkers that can establish the biological diagnosis of AD across the disease continuum; however, while cut-offs exist, routine clinical use is not yet established and implementation remains guidance-led and setting-dependent (Jack et al., 2024; Palmqvist et al., 2025).

For this study, we will use the ALZpath pTau217 Simoa® immunoassay (the platform used by the UK DRI Dementia Biomarker Factory), which has been validated in a large, international JAMA Neurology study and supports a two-cutoff, three-range workflow (Ashton et al., 2024). In this study, which included a large sample (n = 786) spanning memory-clinic populations, ALZpath p-tau217 showed diagnostic accuracy comparable to CSF measures for detecting abnormal Aβ and tau. To reduce false classifications and limit confirmatory testing, the authors recommend two plasma p-tau217 thresholds:

1. < 0.40 pg/mL to rule-out amyloid pathology
2. > 0.63 pg/mL to rule-in amyloid pathology
3. 0.40–0.63 pg/mL "grey zone" – confirmatory testing required.

This approach was reproducible across cohorts and substantially reduced the need for confirmatory testing while maintaining high overall accuracy (Ashton et al., 2024). This approach will be used for the purposes of the current study.

Patient Health Questionnaire (PHQ-2) and Generalised Anxiety Disorder (GAD-2)

The PHQ-2 is a brief screening measure for clinical depression. It consists of only 2 items, both of which related to the core diagnostic criteria for clinical depression outlined in the DSM-V. Meta-analytic research has identified that a cut off score of ≥3 has good diagnostic accuracy for identifying clinical depression (AUC = 0.88) (Aktürk et al., 2025).

The GAD-2 is a brief screening measure for generalised anxiety. It consists of only 2 items, both of which related to the core diagnostic criteria for generalised anxiety outlined in the DSM-V. Meta-analytic research has identified that a cut off score of ≥3 has good diagnostic accuracy for identifying generalised anxiety (AUC = 0.828) (Mitchell et al., 2016).

Insomnia Severity Index **(ISI)**

The ISI is a brief self-report questionnaire that assesses sleep quality and disturbances over the past month. It includes 7 items and takes less than 5 minutes to administer. The ISI has been validated in a large older adult cohort, and achieved adequate reliability and validity (Dragioti et al., 2017). Higher scores on the ISI indicates greater insomnia severity. The total score is divided into four categories: no clinically significant insomnia (ISI = 0–7); sub-threshold insomnia, (ISI = 8–14); moderate clinical insomnia (ISI = 15–21); and severe clinical insomnia (ISI = 22–28).

Numeric Rating Scale (NRS) for pain

The NRS is a unidimensional pain scale, which is made up of a single question. The test involves asking an individual to rate the intensity of their pain on a scale of 0 (no pain) to 10 (worst possible pain). Although the NRS is unidimensional and therefore should not be used in specialist pain clinics, it has been shown to be a valid, albeit crude, measure of pain in older adults (Wood et al., 2010).

Sensory Screening: HearWHO and FrACT

Participants will complete brief sensory screening measures to identify hearing or visual difficulties that may affect performance on the cognitive assessment battery. Hearing screening will be completed using HearWHO, a hearing screening application developed by the World Health Organization. Visual acuity screening will be completed using the Freiburg Visual Acuity and Contrast Test (FrACT), a well validated web-based visual screening platform.

These tools are used only to support interpretation of cognitive assessment performance and to identify whether sensory difficulties may have affected task engagement. No direct participant identifiers will be entered into HearWHO or FrACT. HearWHO requires age and gender to generate the screening result, but no name, date of birth, NHS number, address, or contact details will be entered. FrACT does not require any demographic information. The screening outcome will be recorded directly into REDCap by the assessor during the research appointment, and the results are not stored on either platform.The Subjective Cognitive Decline Questionnaire (SCD-Q9)

A description of the SCD-Q9 has already been provided in the screening measures section. This self-report scale will be administering in the main research appointment also.

Mini Addenbrooke's Cognitive Examination (M-ACE)

The M-ACE is the most widely used cognitive screening test used in dementia services in the UK, and the most sensitive screening measure for identifying mild cognitive impairment (Matias-Guiu et al., 2017). The M-ACE was created by selecting the most sensitive items from the ACE-III and converting it into a briefer screening assessment. It consists of 4 domains, attention, memory, fluency and visuospatial ability and takes 5-10 minutes to administer. The M-ACE has been evaluated, and a cut off score of 20 achieved good diagnostic accuracy for MCI (sensitivity = 0.96, specificity = 0.90) (Miranda et al., 2018).

Computerised Cognitive Assessment in Preclinical Alzheimer's Disease (CoCoA-PAD)

The CoCoA-PAD assessment was developed as part of this research study. The test consists of measures of premorbid ability, memory binding, semantic processing, visuoperceptual functioning, spatial processing, cognitive control, and performance validity (see Appendix 1 for a more detailed description of the subtests). In total, the assessment takes approximately 90 minutes to complete.

Structure-from-Motion Task

Participants will complete a Structure-from-Motion task as part of the CoCoA-PAD spatial assessment component of the study. This task will be administered locally on a secure access controlled laptop using MATLAB. This task is run locally rather than via the browser due to its specific resolution requirements, and the risk that variable internet connection strength could contaminate the stimulus presentation. The task will not include direct participant identifiers. The participant will complete the task, and the relevant task output will be recorded directly into REDCap by the assessor into the participants data file. No demographic information whatsoever will be entered into MATLAB.

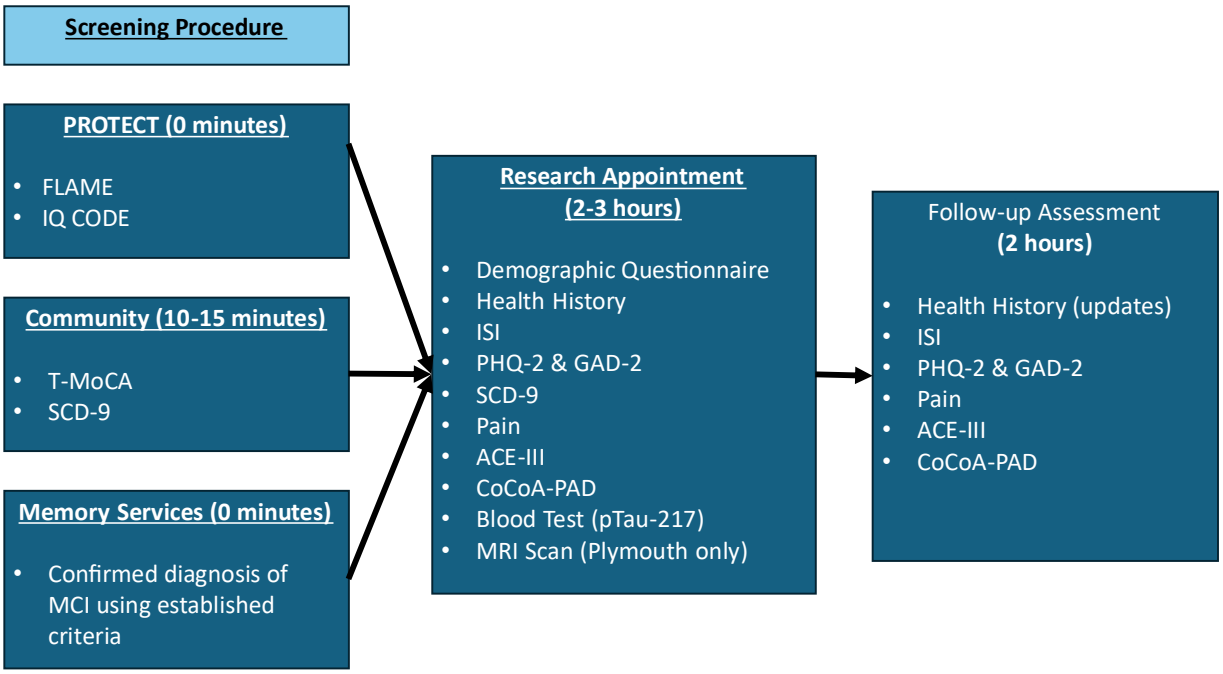

Figure 5. An overview of the measures used in the CoCoA-PAD study at screening, assessment and follow up.

6.3. Initial Recruitment

The primary recruitment strategy involves the use of the PROTECT database. Participants who meet the inclusion criteria of the study will be sent both a patient accessible information sheet and the full information sheet, to consider whether they would like to participate in the CoCoA-study. Potential participants who are interested in participating in the CoCoA-PAD study can consent for their information to be shared with the CoCoA-PAD PI.

Potential participants on the Join Dementia Research and Be Part of Research platforms will be sent both a patient accessible information sheet and the full information sheet to consider if they are interested in participating. Potential participants can then 'opt-in' on the online portal to allow the CoCoA-PAD researcher to contact them.

Potential participants approached through NHS clinics and community settings will be sent both a patient accessible information sheet and the full information sheet, and a QR code where they can register their interest and consent to be contacted.

6.4. Screening

Prior to the data collection session, potential participants will be contacted by a CoCoA-PAD researcher and asked to complete a screening questionnaire to ensure they meet the inclusion and exclusion criteria for the CoCoA-PAD study. The screening will take place over email, phone call, or online using MS Teams. In-person screening sessions will be completed if there are technological or social barriers which prevent other forms of communication. This

questionnaire will gather information establishing the potential participants identity and their eligibility to complete the study. If participants are recruited via JDR, BPR or community events, a short screening questionnaire (the Subjective Cognitive Decline Questionnaire (SCD-Q9)) and brief cognitive screening assessment (Telephone Montreal Cognitive Assessment (T-MoCA) will be administered to determine participants eligibility and diagnostic group.

Potential participants who are eligible to particate in the CoCoA-PAD study will be provided with study related information. For participants with mild cognitive impairment (based on screening data), they will undergo a mental capacity assessment, to ensure they are making a capacitous decision to particate (see Mental Capacity Assessment Protocol). Participants who are eligible to participate and who make a capacitous decision to do so, will be invited to attend an in-person research appointment

6.5. Informed Consent

All research appointments at the Plymouth site will take place at the Brain Research and Imaging Centre (BRIC). Data collection at the Devon and North East London sites will be conducted by local NHS research teams in NHS clinical settings. The environment will be quiet and distraction free. At the beginning of the session the investigator will read through the relevant information sheet with the participant and answer any questions. For participants with a mild cognitive impairment, a mental capacity assessment will be completed again. For participants who demonstrate mental capacity to participate, and who indicate their willingness to do so, they will be asked to review the electronic consent form (see Electronic Consent Form).

Informed consent will be documented using the REDCap secure electronic data capture system, hosted on University of Plymouth servers. The consent form will display version and date control, and the wording is identical to the Electronic Consent Form attachment. Participants will be required to tick each statement. An electronic signature will be collected using a finger or stylus signature and stored securely in the REDCap database. An audit trail will record the date and time and identity of the consenting individual. The process allows participants to ask questions before completing consent, ensuring compliance with the Joint statement on seeking consent by electronic methods (hra-mhra-econsent-statement-sept-18.pdf)

At the point of consent, participants will be asked whether they wish their General Practitioner (GP) to be informed of their participation in this research. This is optional and will not affect eligibility or clinical care. Where a participant provides explicit consent, a brief notification letter will be emailed to their GP at the time of consent, confirming study participation and outlining that the research is observational, does not alter routine care, and that no clinical results will be returned. No notification will be sent without the participant's explicit consent.

6.6. Data Collection

Participation at the Plymouth site includes the completion of demographic and health screening questionnaires (10 minutes), a 2-hour cognitive assessment, which includes a 10-minute break, a blood test by a trained NHS research nurse or phlebotomist (5 minutes), and an MRI scan (30

minutes). In total, the appointment is estimated to last approximately 2 hours 45 minutes. Participation at the Devon and North East London sites will be similar, but without the MRI scan, and therefore it will take approximately 2 hours 15 minutes. The assessment will follow the flow outlined below. However, on occasion when the MRI scan is unavailable immediately after the appointment, or if the participant indicates they are too fatigued, the participant may be asked to return for a separate appointment to complete the MRI imaging.

- Review Information Sheet
- Sign Consent Form
- Collect Demographic Information (age, gender, education etc)
- Collect Health History Information (e.g., comorbidity, sensory difficulties)
- Screening Health Questionnaires: PHQ-2, GAD-2, ISI and NRS
- Disease Severity Screening: SCD-Q9 and M-ACE
- Sensory screening (hearing, visual acuity and visual contrast sensitivity)
- CoCoA-PAD Assessment (Gorilla EB2 and MATLAB)
- Blood Test
- MRI Scan (only for participants at the Plymouth site)
- De-brief

This is a long appointment, and it may pose barriers for some participants' engagement due to fatigue, stress or medical issues. Firstly, all participants will receive breaks after every 40 minutes of research activity. Breaks are scheduled for a minimum of five minutes, with longer breaks supported, if needed. Participants will be informed in the consenting process that they can request additional breaks, also. Given that some participants may minimise discomfort, fatigue or distress, the assessor will routinely ask participants whether they are experiencing signs of fatigue, headache, brain fog, and pain. If the participant discloses this, the assessor will offer an additional break and use their clinical judgement on whether continuing the appointment is appropriate.

For participants who are unable to complete the assessment in a single appointment, they can request that the appointment is delivered over two sessions instead. These appointments would be scheduled approximately 1 week apart.

6.7. Post Assessment Feedback and Disclosure

Following the assessment, participants who consent to receive feedback on their cognitive assessment performance will be provided with an information sheet see 7.7 Disclosure of Research Data, and they will be asked to provide feedback on the assessment experience. All aspects of this appointment will follow a standardised process – see Structured Participant Feedback V1. 06.08.2025 and Cognitive Status Disclosure (MCI) V1. 06.08.2025 documents.

At the feedback session, participants will be asked if they are happy to be contacted by the research team for a follow up assessment, approximately one year later.

6.8. Follow up Assessment

Participants who consented to being contacted for a follow-up session will be contacted approximately one year after their initial assessment. The target window for the follow up assessment is 11 to 15 months following their initial assessment. They will again be sent the accessible participant information sheet and the full patient information sheet. If they agree to participate, participants will be asked to provide their informed consent to participate, i.e., the consenting process will reoccur. The follow-up appointment no longer requires the assessment of disease severity, blood tests or MRI tests. The assessment is estimated to take approximately 2 hours and 10 minutes, and will include the following structure:

- Review Information Sheet
- Sign Consent Form
- Collect Health History Information (ask if there are any updates to their health in the past 12 months)
- Screening Health Questionnaires: PHQ-2, GAD-2, ISI and NRS
- M-ACE Assessment
- CoCoA-PAD Assessment
- De-brief

Given that both the initial and follow up appointments are long, and may be stressful and fatiguing for participants, there is flexibility to deliver the assessment in a person-centred way, i.e., to include longer breaks or to deliver it over multiple appointments within a one-month window. This will be discussed with the participant at the beginning, and the examiner will be responsible to making appropriate adjustments to the research appointment to facilitate participant comfort.

Once the assessment has been completed, the study will be discussed, and the participants will be given a debrief document to keep for their records. The debrief document includes information on the study, contact details for the investigators, as well as information on how they will be informed of the study results.

6.9. Monitoring Recruitment Progress

REDCap is a cloud-based Clinical Research Management System. It supports the management, governance, and monitoring of clinical research studies — including study setup, recruitment, and performance tracking. Recruitment updates from each site, including tracking potential and successful participant recruitment, will be uploaded to REDCap to support CI oversight. For each participant, the participant ID, screening date, recruitment date, and site location will be uploaded to REDCap.

6.10. End of Study

For this study, the end of study is defined as the date on which the last participant completes their final scheduled visit or data collection, whichever is later. At the conclusion, all study activities will be formally closed in accordance with sponsor, NHS R&D governance, and

HRA/REC approval. The Chief Investigator, or designated sponsor representative, will submit the REC end-of-study declaration form (or via IRAS/Combined Review) within 90 days of study closure.

All participants will receive a written summary of the key findings from the research study. Study data will be checked for completeness and accuracy, then locked within REDCap. Once locked, personal identifiable information will be deleted, with that deletion documented in an auditable record. After this point, participants will no longer be able to request removal of their data, but the dataset will be fully anonymised under GDPR. Raw data, including cognitive assessments and MRI scans, will be stored securely for a minimum of 10 years, as outlined in the University of Plymouth's Research Data Management Policy.

Plasma does not contain relevant material under the Human Tissue Act. Nonetheless, plasma will be destroyed at the point of analysis at UCL, and therefore by the completion of the study all plasma samples will have been destroyed.

Upon study closure, the finalised database will be uploaded to the University of Plymouth institutional repository. The database will be made available to external researchers through a formal application process, conditional on host institutions complying with GDPR, data protection standards, and the study's data sharing conditions. The study will also be registered on a recognised public research database at initiation, and the registry record will be updated upon study completion, including posting summary results where applicable, to maintain an audit trail.

Within 12 months of study end, the final report, including a lay summary and key outputs, will be submitted to the REC via the HRA/IRAS mechanism. Any changes to the definition of end of study or associated procedures after REC approval will be submitted as a protocol amendment.

7. Ethical Issues

This study includes numerous ethical issues that require careful planning. These issues are outlined below. The current study will seek ethical approval from the University of Plymouth's Faculty Research Ethics and Integrity (FREIC) and the NHS Research Ethics Committee (REC) and Health Research Authority (HRA).

7.1. Justification of Research Assessment Protocol

It is important to consider whether the research demands being asked of participants are justifiable and proportionate. This study involves invasive and potentially distressing procedures. The assessments included in this study (cognitive screening assessment, blood test, MRI and neuropsychological assessment) and the target population (people who report experiencing cognitive decline) are an exact replication of the assessment pathway proposed in the National Dementia Service and NHS England's commissioning proposal (see Annex B: *Draft diagnostic and treatment pathway*; Murdock and Stewart, 2024). As such, this research study involves asking participants to engage with a comparable assessment process to those outlined

in clinical guidelines. On this basis, the stresses that participants are subjected to are proportionate.

7.2. Informed Consent

The process of obtaining informed consent in this study is designed to uphold the ethical principles of autonomy, comprehension, and voluntariness, particularly in a population that may experience mild cognitive difficulties. Prior to participation, all individuals will be provided with both a comprehensive and accessible version of the participant information sheet. This includes details of the study's purpose, procedures (including cognitive testing, MRI scanning, and blood sampling), anticipated time commitments, potential risks and benefits, and the ways in which their data and biological samples will be stored, used, and protected. The information also makes clear that participation is entirely voluntary, the right to withdraw, that transport costs will be refunded, and that they will be remunerated for their time in vouchers.

Participants who have read the information sheet and express a willingness to participate in the research study will be contacted by a member of the research team for an information and screening phone call. This will provide potential participants with an opportunity to ask any questions, and for the full eligibility screening assessment to take place. Provided that potential participants are eligible and express an interest in participating in this study, they will be invited to attend a research appointment.

The informed consent conversation will be conducted by a trained member of the research team at the beginning of the research appointment. This will take place in a quiet, private setting that facilitates attention and comfort. Given that some participants will experience mild cognitive difficulties, steps will be taken to maximise understanding and support decision-making. Information will be presented in plain language, avoiding technical jargon, and delivered in small sections to avoid cognitive overload. To assess comprehension, participants will be invited to ask questions. The researchers will use a "teach-back" approach, encouraging participants to explain the study in their own words. This allows any misunderstandings to be addressed in real time. If the participant is unable to recount information about the study back to the researcher, the researcher will again explain and revise this information with the potential participant. If the participant is again unable to demonstrate an ability to recount information about the study, the researcher will either revisit this information again or make a clinical judgement that the participant does not have the mental capacity to make a decision about their participation (in accordance with the Mental Capacity Act, 2005), and they will subsequently be excluded from further participation. The process for assessing mental capacity, is outlined in the document: *CoCoA-PAD Mental Capacity Assessment. V1. 06.08.2025*.

Participants will be asked to provide their informed consent. This will involve asking them to read a series of statements about the research and indicate their consent to each statement by checking a box. They will be asked to sign and date their consent. The researcher will also sign the consent form. This process complies with HRA guidance on gaining electronic consent. Informed consent will be completed using REDCap, and participants will receive a copy of their

signed consent form via email. Participant initials will not be collected per statement because of the limitations of REDCap.

Throughout the study, ongoing consent will be respected, and participants will be reminded of their right to withdraw. If there are any indications of uncertainty, confusion, or distress at the time of consent or during the study, researchers will be trained to pause participation and re-assess mental capacity or understanding as appropriate. These measures are intended to ensure that all participants are adequately informed and confident in their decision to take part in the research.

7.3. Participant Remuneration and Reimbursement

Participants will be remunerated for their time and participation in this research study. The National Institute for Health and Care Research (NIHR) guidance on participant payment outlines that "*it is good practice to offer payment or recognition for involvement. This should be made clear to members of the public at the earliest opportunity, and arrangements for payment or recognition must be clearly agreed and documented before involvement starts*".

Remuneration for Research Activity

For the purposes of participant remuneration in this study, research activity for participants includes the informed consenting process outlined in section 7.2, answering questionnaires, completing neuropsychological assessments, blood tests and MRI scans. Research activities are outlined in Figure 5. Remunerated research activity does *not* include participant screening, travel time, the time it takes for potential participants to read the participant information sheets, or the feedback and disclosure session.

Participants will be provided a £40 One for All vouchers for their participation (both primary research assessment and the follow up assessment one year later). This rate is based on NIHR guidance and local institutional policy. The researcher will issue a physical voucher and thank you card at the end of the appointment. In the event of unforeseen circumstances where physical vouchers are not available, the researchers will contact the Primary Care Research Team, University of Plymouth at the end of the research appointment, notifying them of the participant involvement. Vouchers are typically issued within 24 hours, but based on staffing availability, may take up to a maximum of 5 working days to be issued.

Participant vouchers provided to research participants in recognition of their time and contribution are generally not considered taxable income and do not affect employment status. However, participants in receipt of means-tested welfare benefits should be aware that such vouchers may be treated as income by the Department for Work and Pensions (DWP), which could have implications for benefit entitlement. Although the use of vouchers is intended to reduce barriers to participation and does not constitute formal payment or salary, individuals in receipt of means tested welfare payments are advised to consult with the NIHR Benefits Advice Service, who can support participants to understand the potential impact of research payments on their welfare payments. Participants will be given the option to decline or reduce the value of the voucher offered, or delay acceptance while further information is sought.

Participant remuneration can create a conflict for participants who may wish to withdraw from the study, or who wish to withdraw their data, but may be concerned about receiving or returning participation vouchers and travel costs. Potential participants will be informed that remuneration is for their time, and even if they withdraw their data, or are unable to complete the research appointment, they will still be compensated for their time and travel costs.

Travel Costs

Participant travel costs will be reimbursed. This includes travel milage (45p per mile) and parking costs, public transport costs, or taxi fares, depending on participant preference.

Given that access to transport is a recognised barrier for older adults to receive a diagnosis of dementia in rural and coastal communities, this study will offer people the option of travelling to the appointment via pre-booked taxi, which will be arranged entirely through the University of Plymouth. That way, there are no 'out of pocket' expenses which could discriminate against people with financial considerations. Additionally, prebooked train fares can also be provided to participants.

Reimbursement for travel miles, parking and bus fares cannot be prepaid. Participants will be advised to keep receipts of travel costs and will be reimbursed after the appointment.

The reimbursement of travel costs will be managed by Molly Webb, Primary Care Research Team, University of Plymouth. Participants will receive reimbursed travel costs within 30 days of receipt of travel expenses.

Remuneration and Reimbursement Oversight

Dr Murphy, the study's CI, is the budget holder for the project, and will be responsible for ensuring that participants are remunerated and reimbursed for their time and travel (unless the participant opts out of either payment). The project finances, including reimbursement and remuneration will be reviewed every 6 months at the project steering group meeting, and a full audit trail of payments will be developed.

7.4. Risk of Physical Harm or Injury

Blood Tests

The inclusion of blood tests in this study involves some minor physical risks commonly associated with venepuncture. Participants may experience discomfort or pain at the site of the needle insertion, as well as temporary bruising or swelling. In some cases, individuals may develop a hematoma (a small collection of blood under the skin) or experience light-headedness, dizziness, or fainting, particularly if they have a history of needle-related anxiety or vasovagal responses. There is also a very small risk of infection if the area is not properly sterilised, although this is minimised using sterile, single-use equipment and standard NHS infection control protocols. Rarely, participants may have allergic reactions to antiseptics or

adhesive dressings. These risks are considered minimal and comparable to those encountered during routine clinical blood draws.

To minimise these risks, all blood draws will be conducted by trained NHS healthcare professionals, such as nurses or phlebotomists, who are experienced at completing blood tests with older adults. Strict aseptic techniques will be always followed, using sterile, single-use needles and other disposable equipment. Participants will receive a clear explanation of the procedure in accessible language and will have the opportunity to ask questions beforehand. They will be closely monitored during and after the procedure for any signs of discomfort, distress, or adverse effects. First aid supplies will be readily available on site.

Magnetic Resonance Imaging

MRI is considered a safe, non-invasive imaging technique, but it is not entirely without physical risks. The most significant safety concern involves the presence of metallic implants or foreign bodies, which may be affected by the strong magnetic field and pose a hazard if undetected. Participants may also experience discomfort from lying still in the scanner for an extended period, which can cause stiffness or mild pain, especially in older adults. Additionally, the noise produced by the scanner can reach high decibel levels and, if not properly mitigated, may contribute to temporary hearing discomfort.

To prevent physical risks, all participants will undergo a standardised MRI safety screening led by trained NHS radiographers before scanning. This includes detailed checks for implants, surgical history, or metallic objects, with exclusion of any participant for whom MRI would be contraindicated. During the scan, participants will be positioned comfortably with the aid of cushions or supports and instructed to inform staff of any discomfort. Noise-cancelling headphones will be provided to reduce scanner noise, along with the option to listen to the radio to improve comfort. The scan will be conducted under the supervision of qualified NHS radiographers, with continuous two-way communication and a panic button available throughout to ensure participant safety and immediate response to any issues.

7.5. Participant Distress

Cognitive Screening and Neuropsychological Assessment

Cognitive assessments can sometimes cause emotional or psychological distress, particularly among individuals concerned about memory or cognitive difficulties. Participants may feel anxious about their performance or fear that poor results indicate the presence of a neurological condition such as Alzheimer's disease. Tasks that are perceived as challenging or unfamiliar may lead to frustration, embarrassment, or reduced self-esteem. This emotional response may persist beyond the session, especially if the experience reinforces existing worries about cognitive decline.

To minimise distress, all assessments have been designed using a co-production approach to ensure that the assessment battery is well-tolerated by older adults. As part of the informed consenting process, the experience of having difficulty on the cognitive assessment will be

normalised by informing participants that the tests have been designed to be difficult for everyone, and that nobody will get all the questions correct. The goal of this is to minimise participants experiencing heightened distress in response to having a perceived difficulty on the assessments. The assessment will be delivered by trained clinical researchers (clinical neuropsychologist or research nurse), who can make decisions to adapt the assessment procedures in response to participant distress, fatigue or anxiety. This includes discontinuing tests that trigger untoward distress, facilitating additional breaks, and administering the neuropsychological assessment over two appointments to minimise distress, if required. Additionally, even with these adaptations, it may be that the participant experiences untoward distress. If this is the case, the examiner can decide to end the assessment prematurely to minimise participant distress.

Assessment Instructions will be delivered in a clear, supportive, and non-judgmental manner. The testing environment will be quiet and comfortable, and breaks will be offered as needed. Participants will be continuously monitored for signs of fatigue, frustration, or anxiety, and assessments will be paused or stopped if significant distress is observed. They will be reassured that they may withdraw at any time without giving a reason. All participants will be debriefed following the session.

MRI Scan

MRI scans involve the use of powerful magnets to measure brain tissue. While in well-controlled environments, this is a very low risk procedure, there are numerous potential hazards which required active management. Hazards include the movement of metal through the static field, radio-frequency fields leading to heating or burns, and loud acoustic noise. These risks are outlined in the BRIC Local Rules document, and their management strategy is outlined in the BRIC Safety and Risk Operational Policy (21.09.21). Steps to manage and reduce risk include the delivery of MRI scanning by an NHS radiographer, who is experienced in running MRI scans with older adults with cognitive difficulties, and the use of the BRIC MRI Safety Questionnaire, to identify participants who may be at risk of serious adverse outcomes. All BRIC documents referred to have been submitted alongside the protocol.

While properly managed MR imaging is a low-risk procedure, it can occasionally cause discomfort or distress, particularly among participants who are unfamiliar with the scanning environment. Common issues include anxiety related to the confined space of the MRI scanner (claustrophobia), sensitivity to loud scanner noises, and discomfort from remaining still for an extended period. Participants with subjective cognitive concerns or mild cognitive impairment may be more sensitive to unfamiliar procedures or experience heightened anxiety about the purpose of the scan. Although rare, some individuals may find the experience emotionally taxing, especially if they associate MRI with potential disease detection or diagnosis.

To reduce the risk of distress, all participants will attend a pre-scan session with an experienced NHS radiographer. This session will help familiarise them with the MRI procedure, address any concerns, and prepare them for common experiences such as the confined space, the need to remain still, and the loud scanner noises. The radiographer will offer clear, accessible

explanations and practical guidance to help manage any anxiety or claustrophobic feelings. During the actual scan, participants will be provided with noise-cancelling headphones and will have the option to listen to the radio to reduce discomfort. They will also have access to a panic button and two-way communication with the radiographer throughout the scan, ensuring they feel safe and always supported.

Blood Test

Although blood tests are common medical procedures, they can cause psychological distress for some participants. Common reactions include anxiety, nervousness, or anticipatory stress, particularly among individuals with needle phobia (trypanophobia) or a history of negative medical experiences. Some participants may feel faint, dizzy, or panicked before or during the procedure.

To minimise psychological distress, all blood tests will be conducted by trained clinical research staff, such as NHS phlebotomists or nurses, who are experienced in working with older adults. Participants will receive clear, simple explanations of the procedure in advance, including reassurance that the test is safe and quick, and optional. They will have the opportunity to ask questions. During the blood draw, participants will be encouraged to sit or lie in a comfortable position, and will be monitored for signs of distress, dizziness, or fainting. If needed, breaks and recovery time will be provided. Researchers will take a calm and supportive approach throughout and ensure that the environment is as relaxed and non-threatening as possible.

7.6. Recording Adverse Effects

"An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment." (ICH-GCP E6(R2), Section 1.2).

This study will include close monitoring of adverse effects. A brief adverse event checklist will be administered following each of the research procedures (neuropsychological assessment, MRI scan and blood test), see CoCoA-PAD Adverse Event Checklist.

Adverse effects will be classified as mild, moderate, severe and serious. The classification framework for AEs is outlined in Table 4. Mild AEs, such as transient discomfort or low-level anxiety, will be recorded in the adverse event log and monitored locally, with appropriate reassurance or breaks offered to the participant. Moderate AEs, which may cause temporary interference with study participation or require minimal intervention (e.g. dizziness, distress), will be recorded in the adverse event log and followed up to resolution. Severe or serious adverse events (SAEs) including those requiring medical attention or resulting in withdrawal from the study, will be reported to the sponsor within 24 hours and reviewed for potential onward reporting to the Research Ethics Committee (REC) within 15 days, in line with governance requirements. All AEs will be reviewed during the monthly Trial Management Group and the bi-yearly Project Steering Group meetings. Where feasible, the research protocol will be amended to reduce the likelihood or moderate or severe future adverse events, and participant safety will remain the primary consideration in all procedural decisions.

Table 4. Classification of Adverse Events

Severity Level	Definition	Example Events
Mild	An event that is easily tolerated, causes minimal discomfort, and does not interfere with daily activities. No treatment or intervention is required.	Temporary low-level anxiety, minor bruising from blood draw, brief fatigue or headache
Moderate	An event that causes some interference with daily functioning or study activities and may require minimal intervention or advice.	Dizziness after blood draw, discomfort in MRI, need to stop a cognitive task due to distress
Severe	An event that causes marked limitation of activity, requires medical attention, or prevents continued participation. May result in study withdrawal.	Panic attack in MRI scanner, syncope, allergic reaction, serious psychological distress
Serious Adverse Event (SAE)	Any AE that results in death, is life-threatening, requires hospitalisation or prolongs existing hospital stay, causes disability/incapacity, or is a congenital anomaly.	Hospitalisation due to fall, life-threatening reaction, suicidal ideation requiring intervention

7.7. Disclosure of Research Data

Best practice guidelines on the disclosure of research findings to participants emphasise the importance of balancing ethical obligations to inform participants of their results, with the potential psychological, legal, and clinical consequences of disclosing uncertain or non-clinically validated information. The Wellcome Trust and Medical Research Council (MRC) Framework on the Feedback of Health-Related Findings in Research (2014) outlines clear ethical conditions under which individual research results should be disclosed to participants. Feedback should only be provided when three key criteria are met: analytical validity, clinical significance, and actionability. This means that any findings must be generated using reliable, validated methods; must have clear and serious implications for the participant's health; and must point to a condition for which effective treatments or preventive actions are available. The framework strongly advises against disclosing results that are uncertain, not clinically validated, or non-actionable—particularly when they are generated in a research-only context (such as in a non-

clinically accredited laboratory). It also emphasises that participants should be informed during the consent process about what types of results may or may not be disclosed. Feedback, when given, should be delivered by appropriately trained professionals and should include a clear pathway for follow-up care if needed. This approach ensures that participants are protected from unnecessary anxiety or harm while upholding ethical transparency.

The appropriateness of disclosure of data from the CoCoA-PAD study has been considered carefully.

MRI Data Disclosure

Some participants in the study will undergo structural MRI scans; however, no individual feedback will be provided from these scans. This is because the MRI data will not be reviewed or interpreted by a qualified medical professional such as a neurologist or neuroradiologist, and therefore any feedback would be speculative and ethically inappropriate. Nevertheless, there is a safety protocol in place: if the radiographer operating the scanner, who is an NHS professional radiographer registered with the Health and Care Professionals Council and employed by University Hospitals Plymouth NHS Trust observes any incidental findings of potential clinical concern during acquisition (e.g., possible tumours or significant abnormalities), they will follow the local NHS policy for flagging these findings to the participant's GP. Participants have the option to opt-in to finding out if their GP has been notified. If they opt in, the participant will be informed whether any information has been shared with their GP at the feedback meeting. This disclosure will be scripted and will follow the process outlined in the MRI Disclosure document. Given that this information will not be medically verified by a professional trained in interpreting MRI scans, participants will not be provided with any clinical details regarding the unexpected finding on their scan. This process is outlined on the participant information sheet.

Biomarker Data Disclosure

The disclosure of biomarker results, such as plasma pTau-217 levels, must be approached with care, particularly in light of evolving ethical guidance. Current best practice (see Largent et al., 2023) supports offering disclosure protocols to individuals with cognitive difficulties, where appropriate, as disclosure can help people better understand their condition, make informed decisions about future care, and implement lifestyle changes that may support cognitive health. This position is also supported by the Patient and Public Involvement (PPI) group involved in this study, who advocate for responsible and transparent communication of biomarker findings in individuals experiencing cognitive symptoms. Biomarker disclosure is not recommended for cognitively healthy individuals. For this group, the risks include increased anxiety, potential psychological distress, insurance and employment discrimination, and the lack of clinical certainty regarding prognosis, particularly given the low conversion rate from biomarker positivity to dementia in cognitively intact populations.

In the CoCoA-PAD study, we have weighed the potential advantages against the risks to develop a biomarker disclosure procedure. Although pTau-217 using the ALZpath Simoa immunoassay, processed on Quanterix's Simoa HD-X platform, has demonstrated research validity, it is not

currently licenced or approved for clinical use in the UK, and the UKRI Biomarker Factory at UCL is not a licenced laboratory for clinical work. Following consultation with the UKRI Biomarker Factory team, they explicitly stated that the biomarker results must not be disclosed under any circumstances, as a condition of their use.

Based on the Wellcome Trust and MRC criteria for disclosure (2014), the pTau-217 biomarker used in this study does not meet the criterion for '*analytical validity*' or '*clinical significance*'. As such, the CoCoA-PAD team have concluded that the risk of iatrogenic harm caused by disclosing biomarker results outweighs the potential benefits, and therefore, biomarker results will not be disclosed to CoCoA-PAD participants.

It is important to note that the validity of pTau-217 is a rapidly developing topic. The biomarker analysis for this study is not expected to take place until May 2027. If, during this time, the pTau217 assay being used is approved for clinical use, and the UKRI Biomarker Factory becomes a clinically approved laboratory, a substantial amendment to the CoCoA-PAD protocol will be submitted to the research ethics committee, outlining a revised biomarker disclosure procedure with significant PPI input.

Cognitive Staging Disclosure

As part of the study protocol, all participants will undergo cognitive screening using the Addenbrooke's Cognitive Examination – Third Edition (ACE-III). This is a widely validated cognitive screening tool that provides a detailed assessment of five cognitive domains: attention, memory, verbal fluency, language, and visuospatial function. The ACE-III is extensively used across UK memory services, particularly within specialist settings where a more detailed cognitive profile is clinically useful. It is the primary cognitive screening instrument used within NHS memory clinics in the local region, including Devon Partnership NHS Trust, Cornwall Partnership NHS Foundation Trust, Livewell Southwest, and University Hospitals Plymouth NHS Trust.

Participants will be provided with the option of receiving feedback on their M-ACE assessment results. This will be reviewed with on the PIS on both the day of data collection. Participants who consent to receive feedback, will receive individualised feedback on the results of their ACE-III assessment. This feedback will include a clear and supportive explanation of whether their results suggest:

- A cognitive profile within expected limits for age and education
- A profile consistent with Mild Cognitive Impairment (MCI)

Although MCI is a label that it often used in practice, it is a descriptive label to refer to people with cognitive difficulties, and it does not specify a cause or underlying pathology. It is important to note that participants will not be given a diagnostic label or interpretation regarding the cause of any difficulties. Participants who receive feedback indicating possible MCI will be provided with a lay summary information sheet, explaining what MCI is, how it differs from normal ageing and dementia, and evidence-based brain health and lifestyle

strategies to support cognitive wellbeing. All feedback will be delivered in a sensitive, person-centred manner, and with a written feedback summary. Participants will be provided with information about the referral route for a memory assessment, should they wish to undergo a clinically assessment with a memory service.

This feedback will be primarily provided by the Chief Investigator, a qualified clinical neuropsychologist with substantial experience in cognitive assessment and communicating results to patients and their families. For sites outside of the primary research centre, feedback will either be delivered directly by the Chief Investigator or by a local research nurses trained and supervised by the Chief Investigator.

This approach reflects ethical guidance that supports sharing clinically meaningful information with participants when it is generated using validated tools, has clear interpretive value, and can support health literacy and informed decision-making.

CoCoA-PAD Disclosure

The study also includes novel digital cognitive assessments developed under the CoCoA-PAD protocol. These assessments are research tools under development and currently lack an any normative data or diagnostic benchmarks to interpret results in individual participants. Without reference values or validated clinical thresholds, it is not possible to determine what constitutes 'normal' or 'impaired' performance in the older adult population. Therefore, results from these digital cognitive tasks will not be disclosed to participants, as doing so would be speculative.

7.8. Development of a Medical Device

The long-term ambition of CoCoA-PAD is to validate the cognitive assessments and then work towards achieving NICE registration as a tier 3 digital health technology to ‘inform clinical management’. Subsequent research will therefore require MHRA approval.

Having reviewed the UKMDR2002 flowchart for MHRA approval (flowchart_CIs_-_Studies_under_UKMDR2002_v1_A4.pdf), this study does not require MHRA approval for the following reasons:

- All the CoCoA-PAD cognitive tests are novel and have not been previously validated. Therefore, the CoCoA-PAD assessment battery is currently experimental.
- Depending on the results of this study, the CoCoA-PAD assessment will be altered, i.e., insensitive tests will be removed from the assessment to reduce time. Therefore, the assessment battery is not yet finalised.
- The CoCoA-PAD tests are not being used for a medical purpose in this study. Participants’ results will not be used for classification purposes, and participants will not receive any feedback on the CoCoA-PAD performance, because this data is currently uninterpretable.
- The data from the CoCoA-PAD tests are not being used to develop another medical device.

7.9. Commercialisation Strategy and Conflict of Interest

The long-term aim of the CoCoA-PAD project is to progress from a research-only tool to a validated, regulated digital health technology that can be implemented in NHS memory services. Intellectual property (IP) for the CoCoA-PAD assessment and associated training materials is owned by the University of Plymouth. Intellectual property (IP) for the speech biomarkers and associated training materials is owned by the University of Birmingham.

On the proviso that the CoCoA-PAD achieves diagnostic accuracy to reliably detect early AD related cognitive difficulties, the CoCoA-PAD team and University of Plymouth will pursue a non-profit commercialisation strategy to implement this tool into NHS clinical practice. This will involve seeking funding to recode the assessments into an app, so that they are compliant with Digital Technology Assessment Criteria (DTAC), applying for MHRA medical device registration, and completing subsequent large scale research validation (which will include groups excluded from this study, i.e., individuals with drug or alcohol dependency or English as a second language).

As the IP owner, the University of Plymouth may receive a proportion of any revenue generated from future licensing or deployment of CoCoA-PAD. The exact terms and percentage of this revenue share will be negotiated after the research phase, in accordance with the University's intellectual property policy and sector-standard commercialisation processes. At present, CoCoA-PAD is an experimental research tool, not a CE/UKCA-marked medical device, and there is no commercial sale or licensing during the study. The data collected will be used solely for research and development purposes, and participants will not receive any clinical diagnosis or treatment recommendations from the tool.

All members of the research team are either University or NHS employees with no personal financial stake in the commercialisation of CoCoA-PAD. Should any member of the research team acquire a personal interest in future commercial activity, this will be declared to the Sponsor, documented in the site file, and managed in accordance with University of Plymouth and NHS conflict-of-interest policies.

8. Study Management

8.1. Chief Investigator and Oversight

The Chief Investigator (CI) for the CoCoA-PAD study is Dr Donnchadh Murphy, Doctoral Clinical and Practitioner Academic Fellow and Neuropsychology lab lead at the Brain Research and Imaging Centre at the University of Plymouth and Honorary Principal Clinical Neuropsychologist at University Hospitals Plymouth NHS Trust and Livewell Southwest. Dr. Murphy holds a Doctorate in Clinical Psychology and postdoctoral training in Neuropsychology. He has eight years of experience in clinical neuropsychology and is listed on the British Psychological Society's Specialist Register of Clinical Neuropsychologists, representing the gold standard for professional competence in the field. Dr Murphy has overall responsibility for all aspects of the study, including adherence to the study protocol, participant safety, data integrity, and the

reporting of adverse events. He is funded by the National Institute for Health Research (NIHR) from June 2025 to September 2028 to deliver this project.

8.2. Research Team

The research team includes:

- **Dr. Nicolas Farina**, Co-Investigator, Associate Professor in Dementia Research, University of Plymouth
- **Professor Stephen Hall**, Collaborator, Professor in Human Neuroimaging, University of Plymouth
- **Dr. Alastair Smith**, Collaborator, Associate Professor in Psychology, University of Plymouth
- **Dr. Matt Roser**, Collaborator, Lecturer in Psychology, University of Plymouth
- **Dr Lizzy Atkins**, Consultant Neuropsychologist, Livewell Southwest
- **Dr. Rupert Noad**, Collaborator, Consultant Neuropsychologist, University Hospitals Plymouth NHS Trust
- **Dr. Jon Scott**, Collaborator, Clinical Psychologist in Neuropsychology, Livewell Southwest
- **Ore Ogundipe**, Collaborator NEUROFUSION Research Inc.
- **Dr. Melanie Jouaiti**, Collaborator, Assistant Professor in Computer Science, University of Birmingham
- **Dr. Abdel-Karim Al-Tamimi**, Collaborator, Senior Lecturer in Computer Science and Software Engineering, Sheffield Hallam University
- **Ben Walton**, Lead Radiographer, Brain Research and Imaging Centre, University Hospitals Plymouth NHS Trust
- **Dr. Jamie Roberts,** MR Physicist, Brain Research and Imaging Centre, University Hospitals Plymouth NHS Trust
- **Ms Izzy Mountain**, Trainee Clinical Psychologist, University of Exeter
- **Ms Jade Chynoweth**, Research Fellow in Medical Statistics. Peninsula Medical School, University of Plymouth
- **Dr Mahesh Joshi**, Lecturer in Optometry, School of Health Professions, University of Plymouth

- **Dr Gunnar Schmidtmann**, Associate Professor of Optometry and Vision Science School of Health Professions, University of Plymouth
- **Miss Hanna Abraham**, Database Manager, Peninsula Medical School, University of Plymouth
- **Muchineripi Kanengoni**, Research Governance Manager at University Hospitals Plymouth.

8.3. Trial Management Group (TMG)

The Trial Management Group will meet monthly. This meeting will be attended by:

- Dr Murphy, Chief Investigator
- Members of the research team at University Hospitals Plymouth NHS Trust (UHP)
- Site representatives from North East London NHS Foundation Trust (NELFT) and Devon Partnership NHS Trust (DPT) sites
- A representative from the research sponsor, University of Plymouth

These meetings will provide structured opportunities to review recruitment progress, adverse events, protocol deviations, and upcoming amendments to the study design or documentation. The minutes of the monthly TMG meeting will be distributed to the research team and stored on the site file. This will facilitate an audit trail of decision making and research governance.

8.4. Project Steering Group / Advisory Group

A Project Steering Group will meet twice a year and will provide additional oversight. The group will include members from the project team, including:

- A PPI representative from the project coproduction group.
- Sponsor representative from University of Plymouth
- Dr. Nicolas Farina, Co-Investigator, Associate Professor in Dementia Research, University of Plymouth
- Professor Stephen Hall, Collaborator, Professor in Human Neuroimaging, University of Plymouth
- Dr. Alastair Smith, Collaborator, Associate Professor in Psychology, University of Plymouth
- Dr. Rupert Noad, Collaborator, Consultant Neuropsychologist, University Hospitals Plymouth NHS Trust

This group will review overall study performance against project targets, oversee any serious incidents or emerging risks, and serve as a forum for maintaining the ethical and scientific integrity of the study.

8.5. Sponsor and R&D Oversight

The study sponsor is University of Plymouth (UoP). Governance oversight will be supported by the Trial Management Team. The sponsor will ensure that the Site File is maintained to GCP standards and that monitoring and auditing activities are conducted across research sites. The sponsor will ensure the study complies with ethical standards.

8.6. Training and Protocol Compliance

All study personnel will be trained in Good Clinical Practice (GCP) and safeguarding protocols. The training requirements differ for different aspects of this study, so will be reported separately.

Blood Tests

All blood tests will be completed by NHS clinical research teams, as outlined in the Schedule of Events Cost Attribution Tool (SoECAT). Responsibility for training and oversight therefore sits with the local clinical research team, and their NHS trust. Only suitably qualified NHS Clinical Research Nurses and phlebotomists, who have experience working with older adults, will collect this data. Any deviations to the protocol or AEs will be recorded by the clinical professional.

MRI Scans

The MRI scans will be completed by an experienced radiographer at the Brain Research and Imaging Centre (BRIC), University of Plymouth. BRIC radiographers are employed by University Hospitals Plymouth NHS Trust and are therefore subject to NHS clinical training and governance standards. Their role involves providing clinical radiography services on 3 days per week, and research radiography services 2 days a week. As such, they have significant experience performing MRI imaging for older adults and people with significant cognitive difficulties. Ben Walton, lead radiographer, will oversee all MRI imaging activities.

Any staff involved in MRI activity, including being present at the time of the scan, are required to complete training on MRI safety (https://brichandbook.readthedocs.io/en/latest/mri.html#safety).

Neuropsychological Assessment

Dr Murphy will administer the neuropsychological assessments to all Plymouth based participants and will provide full training to clinical research professionals at the two additional research sites: Devon Partnership NHS Trust and North East London NHS Foundation Trust. Professionals from both sites will receive training and ‘sign off’ before they are deemed eligible to deliver the assessment. Training and ‘sign off’ will be captured on the delegation log in the site file.

8.7. Training and Delegation Log

Training Procedures

All members of the CoCoA-PAD research team will receive study specific training before undertaking any delegated tasks. This will include:

- An overview of the study design, objectives, and procedures.
- Detailed instruction in participant recruitment, consent, capacity assessment, cognitive testing, MRI scanning, blood sampling, and data entry.
- Review of Good Clinical Practice (GCP) principles, the Mental Capacity Act (2005), data protection, and safeguarding.
- Familiarisation with the study's standard operating procedures (SOPs) and REDCap data management system.

Training will be delivered by the Chief Investigator (CI) or delegated senior research staff. Completion of training will be documented in REDCap, with an electronic signature and date for each staff member. This record will be available for monitoring and audit.

Delegation Log

A delegation log will be maintained electronically in REDCap for each research site. This will record:

- Staff member's name, job title, and site affiliation.
- GCP training completion date.
- Date of study specific training.
- Specific delegated tasks (e.g., obtaining consent, capacity assessments, administering cognitive tests, collecting blood samples, MRI scanning, data entry, adverse event reporting).
- PI signature and date confirming delegation.
- Staff signature and date confirming acceptance of delegated tasks.

Only staff listed and signed off on the delegation log will be permitted to carry out the tasks assigned to them.

PI and CI Responsibilities

The Principal Investigator (PI) at each site will:

- Ensure only qualified staff are delegated study duties.

- Verify that staff have current GCP certification and have completed study-specific training.
- Sign the delegation log to confirm delegation of tasks.
- Review and update the delegation log promptly if staff roles change.

The Chief Investigator (CI) will:

- Oversee delegation log maintenance across all sites.
- Ensure that training is consistent across sites.
- Monitor compliance with training and delegation requirements.

Data Security

The REDCap system will be hosted on secure University of Plymouth servers, meeting GDPR standards. Access to the training and delegation log will be access controlled, restricted to authorised study team members.

- All activity in REDCap is audit-trailed.
- Logs will be stored for the duration of the study and archived in line with sponsor policy.
- No delegation or training records will be shared outside the research team except for sponsor monitoring, audit, or regulatory inspection

8.8. Monitoring and Reporting

Internal monitoring will occur at least once per year. Additional audits will be triggered in response to serious adverse events, breaches of protocol, or concerns regarding data management. Dr. Murphy will conduct routine audits in parallel with sponsor-led oversight.

Serious adverse events (SAEs) will be reported in accordance with established Good Clinical Practice (GCP) standards and UK research governance frameworks. All SAEs will be reported to the study sponsor, University of Plymouth, within 24 hours of the research team becoming aware of the event. This immediate notification will include a detailed description of the event, an initial assessment of seriousness, expectedness, and relatedness to the study procedures, and any actions taken in response. The sponsor will be responsible for assessing whether the SAE meets the criteria for onward reporting. In accordance with Health Research Authority (HRA) guidance, only SAEs that are both related to study procedures and unexpected—classified as Related and Unexpected Serious Adverse Events (RUSAEs) in non-CTIMP studies—will be reported to the Research Ethics Committee (REC). These events will be reported without delay and within a maximum of 15 calendar days from when the sponsor is made aware. All SAEs will be documented in the study's adverse event log and reviewed at regular Trial

Management Group meetings, with findings used to inform any necessary amendments to study procedures or participant-facing materials.

8.9. Insurance and Liability

This research is sponsored by the University of Plymouth, which has appropriate insurance in place (including public liability and professional indemnity) to provide cover for negligent harm arising from the management and design of the study. Where the research is conducted within the NHS, NHS indemnity will apply for clinical treatment and care provided to participants by NHS staff in the course of their normal duties. There are no arrangements for non-negligent harm indemnity in this study.

8.10. Timeline and Milestones

The CoCoA-PAD project timelines and milestones are outlined in Table 5. The progress of this research study will be reviewed against these targets are each project steering group to ensure the project delivery is on track to be completed on time.

Table 5. CoCoA-PAD Project Timeline

Milestone	Start	Finish
Submit to research ethics	June 2025	September 2025
CoCoA-PAD co-production	April 2025	November 2025
CoCoA-PAD reliability assessment	October 2025	November 2025
Finalise MRI sequence and pipeline	October 2025	November 2025
Finalise Statistical Plan	October 2025	November 2025
CoCoA-PAD pilot	November 2025	December 2025
Finalise REDCap Database	October 2025	December 2025
Publish protocol and analysis plan	November 2025	January 2026
Train staff at research sites	December 2025	February 2026
Data Collection (Study 1 & 2)	February 2026	May 2027
Send plasma to UCL Biomarker Factory	May 2027	May 2027
Launch Study 3 data collection	June 2027	December 2027
Finalise database for Study 1 & 2	June 2027	August 2027
Data analysis for Study 1 & 2	August 2027	January 2028
Review Study 1 & 2 with statistician	January 2028	February 2028
Finalise database for Study 3	January 2028	March 2028
Coproduce dissemination strategy	January 2028	March 2028
Data analysis for Study 3	March 2028	May 2028
Review Study 3 results with statistician	May 2028	June 2028
Send participants accessible infographic	June 2028	August 2028
Project write up	February 2028	September 2028
Finalise database for publication	March 2028	September 2028
End of Project	September 2028	September 2028

9. Data Management

The CoCoA-PAD data management plan has been developed in compliance with the Data Protection Act 2018 and GDPR. All aspects of the data management plan are developed in compliance with University of Plymouth's Research Data Management Plan. A summary of the CoCoA-PAD data management plan is outlined in Figure 6, and a separate data management plan has been submitted alongside the protocol, which provides additional information.

9.1. CoCoA-PAD Site File

All data will be stored securely using platforms that comply with GDPR, NHS digital governance standards and the Data Protection Act 2018. Other than personal identifiable information, all other research data will be stored on the site file. The site file will be stored using an institutional version of MS SharePoint, with multi-factor authentication log-in procedures, access control, encryption (e.g., password protecting .xlsx files), and a clear audit trail of activity (including tracking file activity and version control history). The site file will include real-time cloud backup and scheduled monthly full project exports into an access-controlled University of Plymouth network drive.

The CoCoA-PAD site file and the CoCoA-PAD database will be created and maintained in compliance with the data quality standards set in the University of Plymouth's Data Quality Policy (Research Data Policy). The CoCoA-PAD team will ensure that the data is created and maintained following the data quality standards set in. Consideration has been given to the use of open or widely available file-formats and metadata standards that will facilitate the discovery, interpretation and reusability of the data

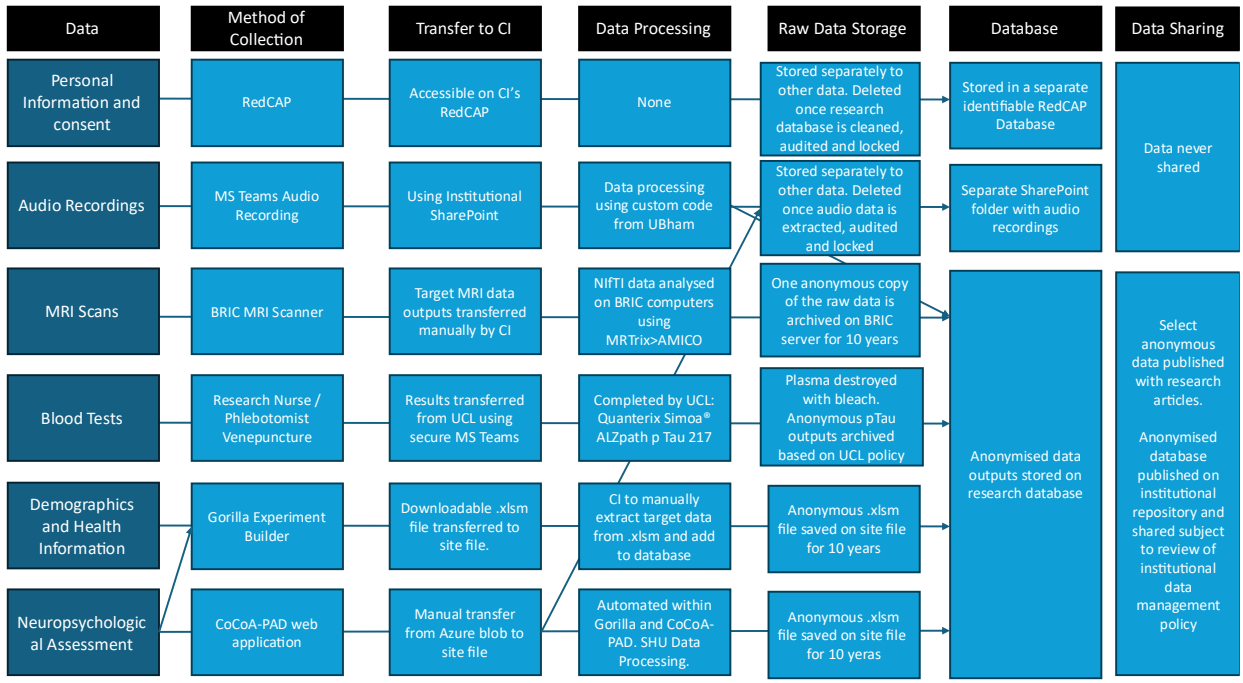

Figure 6. Summary of CoCoA Data Management Plan

9.2. Data Pseudonymisation and Anonymisation

All participants will be assigned a unique, continuous alphanumeric identifier, hereon referred to as the participant ID. Personal information will be stored in a secure database, stored separately to the research database, and only accessible to the CI (Dr Donnchadh Murphy), Dr Nicolas Farina, Professor Stephen Hall, Dr Alastair Smith, and Dr Rupert Noad. The primary research database will not contain any personal or identifiable information and will therefore be fully anonymised. The participant ID will serve as a re-identification key, which links participant's data in the research database to their personal information. The ability to link the participant with their data could be required, for example if a participant requests that their data is withdrawn from the study.

9.3. Data Collection and Processing

The CoCoA-PAD study will involve the collection and processing of a broad range of participant data.

Identifiable personal data

Identifiable personal information will include participants' full names, dates of birth, addresses, general practitioner (GP), and contact details. These identifiers are required for correspondence, safeguarding, and follow-up purposes. This data will be collected at the screening assessment and will be added to a REDCap database that is stored securely and separately from the primary research database. Researchers at the Devon and North East

London sites will have data entry and export permissions on REDCap to upload their participant information data.

Audio Recordings

Although our audio recordings will exclude direct identifiers (e.g. full name, date of birth, NHS number, address), a participant's voice is personal data under the UK GDPR/DPA 2018 because it could indirectly identify an individual. We will not process voices for the purpose of uniquely identifying participants (no voice-print recognition), so the audio is not treated as special-category biometric data under UK GDPR Article 9.

Audio recordings are required to develop speech-based biomarkers for Alzheimer's disease. The research appointment will be recorded, and therefore each participant will provide up to two hours of audio to enable reliable natural language processing and acoustic feature extraction, which in turn supports accurate digital biomarker development. Although a large sample is required, data minimisation is applied: only research-relevant material is recorded, inadvertent identifiers will be redacted during transcription, and access is strictly role-based. Audio is captured on institutionally managed devices via institutional Microsoft Teams accounts (with MFA and SharePoint sync), encrypted at rest and in transit. The University of Birmingham acts as a Data Processor under a formal Article 28 agreement, and analysis is conducted by Dr Jouaiti as an employee of that organisation.

Specific audio data collection procedures are in place for each research site:

- North East London NHS Foundation Trust (NELFT) research team will record sessions on NHS-managed laptops using the Trust's institutional Microsoft Teams accounts (MFA enabled), with automatic syncing to SharePoint.
- Devon Partnership NHS Trust research team will record sessions on NHS-managed laptops using the Trust's institutional Microsoft Teams accounts (MFA enabled), with automatic syncing to SharePoint.
- University of Plymouth / University Hospitals Plymouth NHS Trust site will record sessions on a university-managed laptop using the University's institutional Microsoft Teams account (MFA enabled), with automatic syncing to SharePoint.

All recordings will use the institution's professional Microsoft 365 environment with multi-factor authentication, automatic SharePoint sync and encryption. No consumer devices or personal accounts will be used. These controls ensure audio—treated as potentially identifiable personal data due to the recognisable nature of voice—is captured and stored securely, with access restricted to authorised study personnel only.

Data will be shared with the CI using the SharePoint share function with access control (i.e., only the CI can access it), and an expiration date of 4 weeks. The CI will download the audio file and save it in a separate and secure encrypted folder on SharePoint. The sharing of audio data

will be recorded on REDCap, so that there is a clear audit trail. For data collected at the Plymouth site, this will be recorded directly onto a University of Plymouth MS Teams account and manually transferred to the separate and secure audio recordings folder in the site file.

The MS SharePoint audio data folder will have access-controlled sharing. This data will only be available to the CI, Dr Jouaiti, Dr Nicolas Farina, Professor Stephen Hall, Dr Alastair Smith, and Dr Rupert Noad. The audio data will be accessed by Dr Jouaiti, at the University of Birmingham, who are listed as a Data Processor. Given the need complexity of this analysis and the need for multiple analysis pipelines, proportional data minimisation processes will be completed, as outlined previously, and Dr Jouaiti will have access to the raw audio recording files. Audio data will be uploaded to a locally downloaded and run version of Whisper, OpenAI, transcription service. When run locally on a computer, Whisper AI does not upload any data onto a server, and it is GDPR compliant. A transcript of the research session will be produced. Similarly, the audio file will be analysed using code that has been fully developed by Dr Jouaiti. Different types of acoustic and linguistic features will be extracted using Python code that is run locally - the data will not be uploaded to any third-party server at any point. Using those extracted features, a neural network classifier will be trained. The outcome of this classifier will be manually added to the REDCap database.

Demographic and Health Information

Participant demographic and health information will be collected using the Questionnaire feature of Gorilla Experiment Builder. The research sites will be provided with a survey link, with which they can administer the questionnaires and demographic survey to participants. Demographic variables collected will include participants' years of education, socioeconomic status, and relevant health history. Clinical self-report data will be gathered using standardised screening instruments for mood, sleep, and pain.

Gorilla Experiment Builder stores raw data on secure servers, which are only accessible to the primary researcher using their unique multi-factor log-in details. Therefore, only the CI will have access to this data, irrespective of where it was collected. No direct identifiers are stored in Gorilla, and therefore the data are pseudonymised. Raw data will be downloaded onto a Microsoft Excel spreadsheet and manually extracted and transferred into the primary research database on REDCap.

Neuropsychological Assessment Data

Cognitive data will include both quantitative performance-based scores and qualitative observational data derived from neuropsychological tasks. These assessments will be administered digitally using Gorilla Experiment Builder 2.0. All data collection will be conducted electronically; no paper-based data collection methods will be used.

Neuropsychological assessment data collected using Gorilla Experiment Builder will follow an identical process as that outlined in the Demographic and Health Data section. The CoCoA-PAD assessment battery is delivered using Gorilla Experiment Builder, an online behavioural research platform operated by Cauldron Science Ltd. Gorilla is hosted on Microsoft Azure, with

web hosting and data storage located in the EU, specifically the Republic of Ireland. Gorilla is used to present the computerised cognitive tasks and questionnaires, and to collect, store, and export pseudonymised assessment data on behalf of the Data Controllers. Cauldron Science Ltd acts as Data Processor for participant research data collected through Gorilla. UoP acts as the Data Controller. University Hospitals Plymouth NHS Trust, North East London NHS Foundation Trust and Devon Partnership Trust are data processors.

Sensory Screening Data

Sensory screening will be completed using HearWHO and FrACT. These tools will not be used to store direct participant identifiers. HearWHO requires age and gender to generate the screening result, but no other directly identifiable information will be entered. FrACT will be used to generate the relevant visual screening result. Screening outcomes will be entered directly into REDCap by the assessor during the assessment appointment.

MATLAB Structure-from-Motion Task Data

The Structure-from-Motion task will be administered locally on a study laptop using MATLAB. Other than the participants research ID code, no direct participant identifiers will be entered into MATLAB. The task will generate behavioural output, which will be recorded directly into REDCap by the assessor. Where temporary local output files are generated by MATLAB, these will use the participant's pseudonymised study ID only and will be transferred to the approved study storage location or deleted once the relevant REDCap entry has been checked.

CoCoA-PAD Data Processing

In the CoCoA-PAD study, most raw assessment data is automatically within the secure Microsoft Azure environment using embedded analysis pipelines. Outputs from these automated processes are scored within Azure and can be extracted directly through Gorilla's data access platform. Some assessments, however, are not automatically scored and are therefore exported in their raw format. This includes audio recordings, clock drawings, and verbal fluency tasks. These raw files are placed into separate, access-controlled folders in the University of Plymouth SharePoint site file. Authorised researchers at the University of Birmingham (for audio analysis) and Sheffield Hallam University (for clock drawing and verbal fluency analysis) are granted access to these folders. They conduct their analyses, generate derived scores, and return these results to update the research database. Following completion of analysis, both institutions confirm in writing that all working copies of raw data have been deleted at or before study close. Full details of these processes are set out in the Data Management Plan.

- **University of Birmingham (UBham)** will act as a Data Processor for secondary analysis of exported audio recordings and related transcripts and anonymised MRI scans. UBham receives only pseudonymised audio and associated technical metadata (for example, timestamps, task identifiers) via the UoP SharePoint environment. UBham processes these data strictly on the documented instructions of the Controllers, co-ordinated by UoP as lead Controller, and returns only derived speech features to the Controllers. UBham does not receive linkage files or direct participant identifiers.

- **Sheffield Hallam University (SHU)** will act as a Data Processor for secondary analysis of anonymised clock drawings and verbal fluency data. SHU receives only exported clock drawings in raw image format and verbal fluency outputs in raw score format, all pseudonymised and containing no direct identifiers. SHU applies machine-learning and feature extraction methods to generate derived measures, which are returned to the Controllers. SHU processes data strictly on the documented instructions of the Controllers, co-ordinated by UoP as lead Controller, and does not receive linkage files or direct identifiers.

Both institutions act strictly under formal Controller–Processor agreements in accordance with Article 28 of the UK GDPR.

Data Transfers and Access Control. All secondary analyses are supported via a University of Plymouth SharePoint environment with UK data residency. Access is limited to named institutional accounts for authorised staff at UBham and SHU, with mandatory multi-factor authentication. No data are transferred outside the UK. UBham and SHU hold separate, access-controlled copies of data for their analyses within their own secure research environments.

Retention and Deletion. Secondary analysis working copies at UBham and SHU are retained only for the duration required to complete analysis and quality checks. Both institutions will confirm in writing the deletion of their working copies at or before study close in September 2028. The University of Plymouth will retain the raw research dataset in SharePoint for 10 years post-study (until September 2038) in line with sponsor policy.

Compliance and Oversight. Article 28 UK GDPR Controller–Processor agreements are in place with the University of Birmingham and Sheffield Hallam University. Both institutions are contractually bound to maintain confidentiality, apply equivalent security standards to the primary Processor, and notify the Controllers of any personal data breach within 24 hours of

The raw unprocessed CoCoA-PAD data will be stored securely on the site file. In contrast, processed CoCoA-PAD data will be stored anonymously and linked only to the participant identification ID. This data will be available through Gorilla EB2 in .xlsx format and will be transferred to a secure access-controlled folder in the CoCoA-PAD site file. The target data will be manually extracted and transferred into the primary research database on REDCap.

MRI Imaging Data

MRI data are acquired using a Siemens 3T Prisma scanner with a Syngo workstation located at BRIC. After data-acquisition, the MR images are available on the console (directly on the scanner) in DICOM-format. Research data will include whole-head and partial-head MR volumes, T1-weighted hi-resolution volumes, and multi-shell diffusion-weighted images. The MR scanner is operated by a trained Radiographer or Physicist from UHP.

Participant data will be entered manually on the scanner at the start of each participant session. All research acquisitions will use sequences pre-approved by the MR lab heads and

developed in collaboration with the UHP Physicists. All identifying DICOM tags will be filled with non-identifying information. The patient's name with a code. Dob will not be used, only the age of the participant is entered in the system. MR data are, therefore, 'pseudonymised'.

Data are exported using the DICOM protocol to a DICOM server (AET: ORTHANC-Lin2) located on the University of Plymouth's premises and connected to the University network. This server acts as the receptacle for MR data which can then be disseminated across the BRIC Analysis System (AS). This system is delivered, secured, and part managed by Microsoft Azure. The BRIC System Administrator and Lab heads will also have some administrator privileges. MR data will be transferred using the Export function of the scanner Syngo workstation by a trained Radiographer or Physicist. Data transfer will occur at the conclusion of scanning at the end of each day of research.

Data transfer will proceed from the Syngo workstation through the BRIC firewall and via a VPN connection to the Azure environment hosting the DICOM server. The VPN is dedicated only to the transfer of data from the BRIC Syngo workstation to PU and for the transfer of data from PU to Azure and is distinct from the wider PU VPN. Only PU Technology and Information Services (TIS) and BRIC MR lab heads will have access to this VPN, ensuring data cannot be viewed across the PU network.

Data will be subject to filtering (https://book.orthanc-server.com/users/lua.html#filtering-incoming-dicom-instances) at transfer to eliminate the possibility of clinical MR data being sent to the PU BRIC Analysis System. A subset of DICOM tags that are present in all clinical scans, but not present in any research scans, will be identified as exclusions for data-transfer acceptance.

At the end of data transfer the Radiographer/Physicist who initiated the transfer, and a MR-lab head or BRIC Systems Administrator, will check the record of transfer on the scanner workstation and on the BRIC Analysis System repository. If clinical data have been found to have been accidentally transferred they will be immediately deleted on the BRIC AS by the MR-lab head or BRIC Systems Administrator and the details will be logged for reporting to the UHPT Clinical Radiography team, UHPT Physics, and Imaging IT [named individuals: David Reed, Kelly Sargent, Katie Corin, Christian Allen, Jason Hubbard, Tim Relf, Rowenna Tamblyn, Sally Cabo, Jamie Roberts, Abdelmalek Benattayallah, Catherine McDonough, Matthew Harvey]

Data will remain on the scanner until the researcher has confirmed receipt (see below) or one month has elapsed since acquisition.

The DICOM server will be accessed only by the MR lab heads and the BRIC System Administrator. The DICOM server is only accessible via a VNP. Once received by the PU system the DICOM data are converted into the BIDS-format for dissemination to individual researchers. In the course of this conversion, the metadata (DICOM header) relevant to identification of the individual will be separated from the data file and stored separately. The dataset will contain a header and will be accompanied by a json descriptor file and a README file. The BIDS standards provide a simple way of organizing behavioural and neuroimaging data. The increasing

adoption of this format in the community of neuroscientists and psychologists makes data sharing easier.

The BIDS data are made available to named researchers in Neuroimaging Informatics Technology Initiative (NIfTI) format. In order to meet all data protection criteria, all image information of the facial area is removed from structural imaging data prior to its dissemination to researchers.

One copy of the raw data is archived in original DICOM format. Data converted to NIfTI is made available to researchers and students within a managed cloud-based BRIC analysis and storage system. Data are backed up regularly and tiered storage is used to balance cost and accessibility.

The imaging data will be subjected to the following capture and processing pipeline:

Data Acquisition:

- T1 MPRAGE sequence from Alzheimer's Disease Neuroimaging Initiative (ADNI)
- High Resolution T2 (HRT2) of medial temporal lobe sequence from ADNI
- Multishell diffusion sequence from ADNI
- FLAIR sequence from ADNI

Analysis Pipeline

- FSL ANAT for volumetric based analysis of subcortical ROIs
- Freesurfer for regional cortical thickness
- Automatic Segmentation of Hippocampal Subfields (ASHS-PMC) for medial temporal lobe subfield volumetric analysis
- FSL TOPUP, eddy correction and FSL BET
- FSL Probabilistic tractography and Tract-Bases Spatial Statistics (DTI)
- FSL CUDA Diffusion Modelling Toolbox (cuDIMOT) for NODDI
- FSL Brain Intensity AbNormality Classification Algorithm (BIANCA)

The data will be extracted for each participant and added to the CoCoA-PAD research database on REDCap.

Plasma Samples

Biomarker data will be collected from blood samples. Blood samples will be collected by a research nurse or phlebotomist using a venepuncture technique.

1. Pre-Collection Materials

- Tubes (Collection): 9ml EDTA vacutainers (x1 per participant = 9ml total whole blood), although a second EDTA vacutainer can be used if required.
- Aliquots / Cryovials: 2ml polypropylene cryovials with screw caps and barcodes

- Labels: Participant ID, date/time of draw, sample type (EDTA plasma), aliquot number, volume

2. Venipuncture

- Draw 1 × 9ml EDTA tubes (total 9ml whole blood)
- Gently invert tubes 8–10 times to mix anticoagulant
- Avoid vigorous shaking to prevent hemolysis
- Keep tubes upright until processing

3. Time to Processing

- Aim to process within 2 hours of collection
- Absolute maximum time before centrifugation: 4 hours

4. Primary Centrifugation

- Centrifuge at 2000g for 10 minutes
- Temperature: Room temperature

5. Aliquoting

- If possible, use DAPI staining, to indicate the presence of cellular material.
- Carefully extract the plasma (top layer) using a pipette, avoiding the buffy coat and cellular layers. Each EDTA tube will provide plasma for a single cryovial, ensuring that extraction remains well clear of any cellular material.
- Dispense plasma into two 2ml cryovials

6. Freezing & Storage

- If samples remain at room temperature: transfer to freezer as soon as possible
- If stored at 4 °C (refrigerated): transfer to freezer within 24 hours
- Store cryovials in a labelled cryo box
- Label box and vials with:
    - Participant ID
    - Date and time of collection
    - Aliquot number

7. Shipping to UCL (Biomarker Laboratory)

- Notify the receiving laboratory prior to shipment
- Ship samples on dry ice (< –78 °C)
- Use a private courier organised by the Chief Investigator (CI)
- Include sample manifest with participant IDs and aliquot details

8. Plasma Analysis and Sharing

- The samples will be received by the UCL Biomarker Factory, who will complete the biomarker analysis using Quanterix Simoa® ALZpath pTau 217.
- A research database with pTau217 levels and the participant ID will be created and shared with the CI via the share function on MS SharePoint, which will include multi-factor log-in procedures, access control and an expiration.

9.4. Data Storage, Retention and Archiving

All aspects of the CoCoA-PAD data storage, retention and archiving strategy are compliant with the University of Plymouth's Data Retention and Erasure Policy.

Personal Identifiable Information

Personal identifiable information will be stored in a REDCap database, which will be stored securely and separately to the site file. This data will only be accessible to the CI, Dr Nicolas Farina, Professor Stephen Hall, Dr Alastair Smith, and Dr Rupert Noad. Personal identifiable information will be stored until the REDCap research database has been cleaned, audited and finalised, after which, the personal identifiable information database will be permanently deleted.

REDCap Research Database

As outlined in section 9.3: Data Collection and Processing, participant's demographic and health data, neuropsychological assessment data, MRI data, plasma biomarker data, and post-processed speech data, will be transferred to the anonymous research database. This

The CoCoA-PAD database, developed in REDCap, has been designed to fully align with the principles outlined in the Good Clinical Data Management Practices (GCDMP) standards. The database structure is underpinned by a version-controlled data dictionary that defines all variables, field types, validation rules and export classifications. Data integrity will be supported through field-level validation (i.e., to ensure the data is entered in the correct format and within specified parameters), automated logic checks, audit trails, and restricted, role-based access controls. All modifications to the database and records will be logged, providing a complete audit trail in compliance with regulatory expectations. The database is hosted on a secure, university-managed REDCap instance, with encryption at rest and in transit, daily backups, and alignment with institutional information governance policies.

To ensure the data can be reused by external researchers, the CoCoA-PAD database includes a comprehensive metadata structure at both the variable and project levels. Each variable is clearly defined in REDCap's data dictionary. In addition, project-level metadata will be provided alongside the dataset, including a README file explaining study aims, variable naming conventions, missing data codes, and scoring instructions, and a metadata guide mapping variable to clinical constructs and study timepoints. This approach ensures that de-identified data shared with external teams will be accompanied by all the necessary contextual information for independent analysis, promoting transparency, reproducibility, and alignment with Findable, Accessible, Interoperable, and Reusable (FAIR) data principles.

At the conclusion of data collection for the CoCoA-PAD study, the database will undergo a formal closure process to ensure data integrity, regulatory compliance, and readiness for analysis. The datasets will be reviewed by a database specialist with the Peninsula Clinical Trials Unit (PenCTU) at University of Plymouth, who will review it against best practice guidance and the procedure outlined above. Any issues identified by the database specialist will be addressed. Prior to locking the database, a structured internal audit will be conducted by the study team to verify the accuracy, completeness, and consistency of the dataset. This will involve resolving all outstanding data queries, reviewing audit trails, checking for missing or anomalous values, and confirming that data entry aligns with the study protocol and consent

requirements. Once all discrepancies have been addressed and all fields are verified, the REDCap database will be transitioned to read-only status, locking all data fields to prevent further modification. The final dataset, along with a complete version-controlled data dictionary, codebook, and audit documentation, will be exported and securely archived on the University of Plymouth's institutional repository – (Plymouth Electronic Archive and Research Library (PEARL)).

Raw Audio Data

Raw audio files in mp4 format will be stored in a separate access-controlled and secure SharePoint folder on the site file, with access restricted only to the CI, Drs Jouaiti, Farina, Smith and Noad and Professor Stephen Hall. All audio files will be stored with AES-256-bit encryption, due to the identifiable nature of audio recordings. Each audio file is estimated to range from 60 to 100 megabytes, and therefore in total, this folder will be approximately 7.2 to 12GB in size.

Raw audio will be stored securely for 10 years after data collection, in compliance with the University of Plymouth's Data Retention and Erasure Policy (version 3.0).

Raw Demographic and Health Information

Raw demographic and health data will be downloaded from the Gorilla Experiment Builder website in .xlsx format (Microsoft Excel spreadsheet). The raw data file will be encrypted with a strong password (three random words, as recommended by the National Cyber Security Centre, https://www.ncsc.gov.uk/collection/top-tips-for-staying-secure-online/three-random-words).

Target data will be extracted from the .xlsx file into the research database on REDCap. The raw demographic and health .xlsx files will be stored in an access-controlled folder on the site file and retained for a period of 10 years. After this period, the raw data will be permanently deleted.

Raw Neuropsychological Assessment Data

Neuropsychological assessment data will be collected using the Gorilla Experiment Builder 2.0. The storage and retention of the data from both platforms follow an identical procedure. Raw cognitive assessment data will be downloaded from the Gorilla Experiment Builder website in .xlsx format (Microsoft Excel spreadsheet) and transferred to a secure and access-controlled folder on the CoCoA-PAD site file. The raw data file will be encrypted with a strong password (three random words, as recommended by the National Cyber Security Centre, https://www.ncsc.gov.uk/collection/top-tips-for-staying-secure-online/three-random-words). Target data will be extracted from the .xlsx file into the research database on REDCap. The raw Neuropsychological Assessment Data .xlsx files will be stored in an access-controlled folder on the site file and retained for a period of 10 years. After this period, the raw data will be permanently deleted.

Raw MRI Imaging Data

Raw anonymised MRI data is archived in original DICOM format on the DICOM server (AET: ORTHANC-Lin2) located on the University premises and connected to the University network. The MRI raw data is stored securely for at least 10 years. The BRIC Data Management Policy v1 (26/03/2021) provides a more detailed description of the BRIC procedures for data storage, retention and archiving).

Raw Blood Samples

Plasma samples will be sent to UCL's Biomarker Factory for analysis. The Biomarker Factory will analyse the plasma samples, and produce an anonymised dataset, which will include the participants' ID codes and pTau217 results. The plasma samples will not be used for any additional research and will be destroyed using bleach once the analysis has been completed and verified.

The UCL Biomarker Factory retain an encrypted version of the anonymous database on a locked Biomarker Factory channel on MS Teams for a period of at least ten years. This database will be transferred securely using MS Teams to the CoCoA-PAD CI, who will transfer the results into the REDCap database, and store this database in an access-controlled folder on the CoCoA-PAD site file for a period of at least 10 years.

9.5. Access and Data Sharing

Access to identifiable data, audio recordings or raw data will be limited to named members of the study team. This data will not be shared with any external partners, nor any members on the project team, unless explicitly stated in sections 9.3 and 9.4.

The CoCoA-PAD dataset will be shared in accordance with principles from the Open Science movement, supporting transparency, reproducibility, and wider scientific collaboration. The full research database will be deposited in a trusted institutional or subject-specific data repository, such as PEARL. Requests for access to the full anonymised database will be reviewed on a case-by-case basis. Access will be granted to qualified researchers who provide evidence of an appropriate data management plan, including commitments to ethical use, secure storage, and compliance with relevant data protection regulations. Requests for access will be reviewed by the sponsor and CI to ensure appropriate controls are in place. A data availability statement, which outlines this plan, will be included in all research publications.

Most of the sample will be recruited through the PROTECT study database. As a condition of recruiting through this database, the PROTECT team have requested that they are provided with access to research data from the CoCoA-PAD study for participants recruited through PROTECT. We agreed that participants will be provided with information about sharing their data with the PROTECT team and asked to provide their informed consent for this during the consenting process (see PIS and electronic consent form (using REDCap)). If participants agree, their PROTECT participant ID will be added to the research database. This allows for targeted sharing of data, while maintaining the anonymity and confidentiality of the research database.

9.6. Data Protection and Legal Compliance

The study complies fully with UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. University of Plymouth is the Data Controller for research data. Univresity Hospitals Plymouth, NHS Trust, Devon Partnership NHS Trust and NELFT act as Processors for local data collection. The University of Birmingham is a Processor for analysing speech data.

A Data Protection Impact Assessment (DPIA) has been completed. The legal basis for processing data is public interest in scientific research. All data handling procedures reflect NHS data protection standards and University of Plymouth research governance requirements. Although the project includes international collaborators, no personal data will be transferred outside the UK/EEA. Only anonymised datasets may be shared with international collaborators. Therefore, neither an International Data Transfer Agreement (UK) nor a Standard Contractual Clauses (EU) are required.

9.7. Data Breach and Incident Response

In the event of a data breach, the University of Plymouth's Data Protection Officer (DPO) and the study sponsor will be notified immediately. Incidents are triaged by the Sponsor and DPO(s); notifiable personal-data breaches are reported to the Information Commissioner's Office ICO within 72 hours, in line with NHS digital governance protocols. The Research Ethics Committee (REC) will be informed of material confidentiality breaches affecting participant welfare. To mitigate risk, all data access is access controlled and encrypted. Regular back-ups are conducted, and audit trails are maintained for all database activities.

The University of Birmingham and Sheffield Hallam University follow the same breach notification requirements as the platform Processor and will notify the Controllers, via the University of Plymouth, within 24 hours of becoming aware of a personal data breach.

9.8. Use of Digital Tools and Software

Digital platforms used in this research include REDCap, Gorilla Experiment Builder, HearWHO, FrACT, MATLAB, Microsoft Teams, Microsoft SharePoint, and MRI processing software used by BRIC. REDCap will be used for consent, case report forms, study database management, and direct entry of screening and assessment outcomes. Gorilla Experiment Builder will be used to deliver the computerised CoCoA-PAD assessment battery and export pseudonymised task data. HearWHO and FrACT will be used for sensory screening only and will not store direct participant identifiers. One Structure-from-Motion task will be administered locally using MATLAB on a study laptop, with no direct identifiers entered into MATLAB. Audio recordings will be captured via Microsoft Teams. MRI data will be processed through imaging pipelines provided by BRIC. Data analysis will be conducted using SPSS, Jamovi, RStudio, and relevant specialist analysis software.

10. Regulatory Compliance

10.1. Declaration of Helsinki

The CI will ensure that this study is conducted taking into account the principles of the Declaration of Helsinki.

10.2. ICH Guidelines for Good Clinical Practice

This study will be conducted in accordance with the principles of Good Clinical Practice as outlined in ICH E6(R2) and will incorporate evolving best practices consistent with the forthcoming ICH E6(R3) update.

10.3. Human Tissue Act 2004.

The Human Tissue Act 2004 regulates the removal, storage, and use of human tissue for research in the UK. Plasma samples are not classed as 'relevant material' under the Human Tissue Act 2004 because they do not contain intact cells. However, if any cellular material were inadvertently present, the samples would fall under the HTA and be treated accordingly. The following steps will be implemented to reduce this risk:

- Where possible, DAPI staining will be used to clearly identify cellular material and confirm that no cellular material is transferred into the cryovials. Please note, this is not available in all research sites.
- As outlined section 9.3 (blood taking and processing section), the EDTA tube (9ml) will produce approximately 5ml of plasma, which is sufficient for the extraction of 4ml of plasma to be extracted transferred into a two cryovials. This ensures that research nurses and phlebotomists can stay well clear of the buffy layers or cellular material when extracting plasma with the pipette, which reduces the risk of contamination.

The CoCoA-PAD study ensures full compliance by obtaining informed consent from participants for the collection, analysis, and secure storage of plasma samples. Samples will be pseudonymised, tracked, and stored in access-controlled freezers at approved facilities, with appropriate material transfer agreements in place for external analysis. The study operates under NHS Research Ethics Committee approval, which provides the legal basis for temporary storage of samples for research purposes in accordance with The Human Tissue Act 2004 guidelines.

10.4. Data Protection Act and GDPR

All aspects of the CoCoA-PAD study will be conducted in full compliance with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. Processing of personal data (voice recordings and cognitive performance) and special-category data (health) is undertaken under UK GDPR Article 6(1)(e) (public task) for NHS sites, and Article 6(1)(f) (legitimate interests) for University of Plymouth, together with Article 9(2)(j) and Data Protection Act 2018 Schedule 1, Part 1(4) for scientific research, with safeguards in line with Article 89(1).

Participants will provide informed consent for the collection, storage, and use of their data. Personal identifiers will be stored separately from research data using pseudonymisation, with access strictly limited to authorised members of the research team. All electronic data will be stored on secure, access-controlled university servers or platforms (e.g. REDCap or SharePoint) with appropriate encryption and audit trails. Data will be retained only for the period specified in the protocol and in line with sponsor and university retention policies. All data processing activities will be overseen by the institution's Data Protection Officer and the study's Chief Investigator.

10.5. Mental Capacity Act 2005

The Mental Capacity Act 2005 (MCA) provides a legal framework for supporting individuals to make decisions and for acting in their best interests if they lack capacity. It applies to adults aged 16 and over in England and Wales. In this study, the MCA is not directly applicable, as having capacity to provide informed consent is an inclusion criterion for participation. Similarly, our recruitment is targeting people with, at worst, *mild* cognitive difficulties with intact functional independence. Therefore, it is very unlikely that their cognitive difficulties would compromise their mental capacity (or indeed whether there would be a legitimate basis to question mental capacity in the absence of a recognised '*impairment or disturbance in the mind or brain*', as specified in the Act. Individuals who lack the mental capacity, as defined by the Mental Capacity Act 2005, will be excluded from participating in this study.

However, to ensure participants have capacity and are making an informed decision, the research team will implement a brief capacity check during the consent process. This will involve asking potential participants to explain in their own words key aspects of the study as outlined in the Participant Information Sheet (PIS), including:

- What the study involves
- Any potential risks or benefits
- Their right to withdraw at any time

This approach ensures the participant has understood the information and can weigh it to make a voluntary and informed decision. If any concerns about capacity arise, and with reasonable adjustments, the potential participant is unable to demonstrate an ability to understand, retain, weigh-up and communicate their decision to participate, they will not be included in the study.

11. Statistical Considerations

11.1. Missing Data

Missing data will be carefully monitored throughout the study. If any data are missing, the research team will first look at how often this happens and whether there is a pattern. If the amount of missing data is small, we may continue with the analysis as planned. If more data are missing, we will use appropriate methods, such regression-based approaches to correct for this. All decisions about how we handle missing data will be agreed with the statistician, and the full

analysis plan, including the procedure for managing missing data, will be pre-registered on the Open Science Framework.

11.2. Discontinue and withdrawal from the study:

Participants are free to discontinue from the study at any time and this will be emphasised during the consent process. If a participant chooses to discontinue during the assessment the session will end immediately. The participant will be asked to provide a reason for their withdrawal, but they do not have to provide a reason. Participants who discontinue with the study will be asked whether they would like the data collected up until that point to be included in the study, or whether they would like to withdraw their data. Data collected on participants prior to discontinuation will be retained for analysis unless the participant requests otherwise.

Participants can withdraw their data from the study at any time without giving a reason. If they choose to withdraw their data, their data will be deleted from the site file and research database. However, once the study database is finalised and the separate personal information file is securely destroyed, which will occur when the database has been finalised, it will no longer be possible to identify individual participants. At that point, their data will be fully anonymised and cannot be withdrawn, in line with ethical and data protection guidelines. This process will be clearly explained in the participant information sheet.

11.3. Sample Size

Given that there are three independent studies, a justification of the proposed sample is outlined for each study.

Study 1: Diagnostic Accuracy of CoCoA-PAD Subtests

The aim of this study is to test whether CoCoA-PAD subtests can distinguish between healthy controls (i.e., people with subjective memory problems without any evidence of AD biomarkers or cognitive decline) and people with preclinical and prodromal Alzheimer's disease. This study uses a prospective research design, and therefore exact participant numbers in each diagnostic criteria cannot be determined until after data collection. Figure 3 provides an estimate of the final sample composition, which includes of 36 healthy controls, 18 people with preclinical AD, and 40 people with prodromal AD. A power calculation using a fixed one-way ANOVA (estimated effect size $f = 0.33$ (moderate effect), $k = 3$) required a minimum sample of 90 to achieve the required power ($\alpha = 0.05$, $1\text{-}\beta = 0.8$). Based on current projections (36 controls, 18 preclinical AD, and 40 with prodromal AD), this would be achieved.

Study 2: The relationship between CoCoA-PAD subtests and the health of key brain regions

This study aimed to measure the strength of the association between key brain regions and performance on CoCoA-PAD subtests. It includes a subgroup of study 1 participants. A power calculation using a linear multiple regression (fixed model, single regression coefficient, effect size f^2 (0.1, small) required a minimum sample of 64 participants to achieve the required power ($\alpha = 0.05$, $1\text{-}\beta = 0.8$).

Study 3: Testing whether CoCoA-PAD is sensitive to pathological cognitive decline in AD

This study aimed to compare 1 year change score (time 2 score – time 1 score) on CoCoA-PAD subtest scores in people with early Alzheimer's disease and healthy controls. It includes a subgroup of study 1 participants. A power calculation using a matched pairs *t* test (Cohen's *d* = 0.5 (moderate)) required a sample of 27 to achieve the required power ($\alpha = 0.05$, $1-\beta = 0.8$).

11.4. Provisional Data Analysis

The CI will work with a medical statistician, Ms Jade Chynoweth, to finalise the data analysis plan, and will publish this on Open Science Framework, prior to the start of data collection. This will ensure both rigour and transparency. A provisional data analysis plan is outlined for each sub-study below. Furthermore, Appendix 2 provides a specific breakdown of the hypotheses and analysis plan for each CoCoA-PAD subtest. This should be considered provisional and may be subject to change prior to the start of the study.

Study 1: Diagnostic Accuracy of CoCoA-PAD Subtests

The aim of this study is to test whether each CoCoA-PAD subtest can distinguish between healthy controls and people with preclinical and prodromal Alzheimer's disease. This study will use a Welch's ANOVA to accommodate unequal variances and sample sizes (k=3, healthy controls, preclinical AD, and prodromal AD) and Games–Howell post hoc test. A series of receiver operator curves, area under the curves, and optimised sensitivity and specificity values based on Youden index, will be calculated to measure the diagnostic accuracy of each subtest also.

Study 2: The relationship between CoCoA-PAD subtests and the health of key brain regions

Associations between CoCoA-PAD subtest scores and regional brain volume, density and connectivity will first be explored using Spearman correlations, adjusted for false discovery rate using the Benjamini-Hochberg Procedure. Multiple linear regression models will then be used to assess the predictive value of MRI-derived volumetric measures on CoCoA-PAD performance, adjusting for potential confounders including age, sex, education, and intracranial volume. Model fit and assumptions will be evaluated to ensure robustness.

Study 3: Testing whether CoCoA-PAD is sensitive to pathological cognitive decline in AD

Change scores on CoCoA-PAD subtests will be calculated by subtracting time 1 score from time 2 score. As such, negative change scores will denote a decline in performance. A series of *t* tests will be used to test whether the prodromal AD group exhibit higher levels of cognitive decline over a one-year interval. To control for the false discovery rate (FDR) across multiple t-tests, the Benjamini–Hochberg procedure was applied with a threshold of $q = 0.05$. This method adjusts p-values to reduce the risk of Type I error when conducting multiple comparisons.

Data Analysis Software

Data analysis will be conducted using SPSS, Jamovi, and RStudio.

12. Dissemination of Results

The study findings will be disseminated through a range of tailored strategies to ensure accessibility and impact across key audiences. Results will be shared with research participants via a co-produced, accessible information infogram, developed in collaboration with the study's PPI group to ensure clarity and relevance. A second, professionally targeted infogram will also be co-developed with the project's professional co-production team to communicate the findings to memory service professionals and researchers. Both infograms will be made available on the CoCoA-PAD website, which is hosted by University of Plymouth.

Academic dissemination will include submission of research articles to peer-reviewed journals, as well as practitioner-facing journals and professional magazines. Study findings will also be presented at academic and clinical conferences, including a planned co-presentation with a representative of the PPI group. This presentation will highlight the co-production process and the evaluation of the cognitive assessment tool. In addition, the anonymised dataset and study protocol will be made available via open science repositories to support research transparency and secondary analysis. These dissemination activities will ensure that results reach service users, professionals, and the broader research community in meaningful and accessible formats.

13. Patient and Public Involvement and Coproduction

Patient and Public Involvement (PPI) has been embedded throughout the CoCoA-PAD study design and development. The PPI group comprises five older adults, including two individuals with neurological conditions, one with a background of educational deprivation, and one from an ethnic minority background. The remaining participants have personal experience of dementia, i.e., spouse, siblings or parents. Their perspectives have helped shape a more inclusive and equitable research process. Over the course of the study, seven structured PPI meetings are scheduled. Each meeting is recorded and documented, with formal minutes produced to ensure a transparent audit trail of decisions and input. This record will be used to demonstrate how PPI contributions have been incorporated into the study, and a GRIPP2 checklist will be published alongside all resulting research outputs.

The PPI group has been actively involved in co-producing the full suite of cognitive tasks used in the study. Their input included reviewing early drafts, simplifying instructions, recommending length adjustments to reduce participant fatigue, and advising on how to make the technology interface more accessible for older adults. In addition to shaping the assessments themselves, the group reviewed and approved all participant-facing documents, including the standard and accessible versions of the Participant Information Sheet, Electronic Consent Form, Debrief Form, and Disclosure Materials. Their guidance ensured that all materials were sensitive, clear, and suitable for a diverse ageing population.

The PPI group will also contribute to dissemination by co-producing summary infographics to communicate findings to both participants and professionals. Their ongoing involvement is

central to the ethos of the study, ensuring that it remains grounded in the needs, experiences, and preferences of older adults.

14. List of documents

- 344617 CoCoA-PAD Study Poster. V1. 06.08.2025
- 344617 Participant information sheet. V1. 06.08.2025
- 344617 Accessible participant information sheet. V1. 06.08.2025
- 344617 Electronic Consent form. V1. 06.08.2025
- 344617 CoCoA-PAD Mental Capacity Assessment. V1. 06.08.2025
- BRIC MRI safety adults questionnaire - research participants
- 344617 Study Debrief. V1. 06.08.2025
- 344617 Adverse Event Checklist. V1. 06.08.2025
- 344617 Cognitive Status Disclosure (MCI) V1. 06.08.2025
- 344617 Cognitive Status Disclosure (normal limits) V2. 06.08.2025
- 344617 MRI Disclosure. V1. 06.08.2025
- BRIC_MRI_Local_Rules-12.09.21
- BRIC_Safety_and_Risk_Operational_Policy-12.09.21
- Donnchadh Murphy Short Academic CV 06.08.2025
- Donnchadh Murphy GCP Refresher 25.03.2024
- OID
- SoECAT

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16. Appendices

16.1. Appendix 1. CoCoA-PAD Subtest Descriptions

CoCoA-PAD Subtest	Minutes	Description	Reference Test and Diagnostic Accuracy	Localisation
Premorbid Cognitive Ability				
The paragraph reading test	4	Participants are provided with a paragraph of text (250 words) and college level difficulty and asked to read it as quickly and accurately as possible. The test measures accuracy and speed.	Paragraph reading is a proxy of cognition, better predictor of scores than years of education, and which can be generalised across cultures (Fernandez & Arriondo, 2021).	n/a
Memory	45			
SILT (Semantic Interference during Learning Test)	15	People are asked to learn 2 separate lists of words which belong to the same three semantic categories. Semantic interference is the increased difficulty people experience learning the second list of words.	The Loewenstein-Acevedo Scales for Semantic Interference and Learning. AUC in βA+ and βA- cognitively unimpaired older adults=0.89 (Curiel Cid et al., 2019)	Entorhinal volume (Matias-Guiu et al., 2018)
The MANE (Matching Animal and Name Examination)	15	People are presented with 12 animal faces and their names e.g., 'Eve'. They are asked to remember the name and face pairing. They are then asked to match the name and face pairs.	Face Name Associative Memory Exam distinguished 122 βA+ and βA- people on the AD spectrum: AUC = 0.73 – 0.77 (Rentz, 2023).	Hippocampus, entorhinal, thalamus, fusiform and dorsolateral prefrontal (Sperling, 2001)
COBALT (Colour and object binding and localising test)	15	This test measures difficulty with memory binding, and tests whether people can pair an object with the correct colour and location.	Visual short term memory binding test. AUC in βA+ and βA- cognitively unimpaired older adults =0.97 (Parra et al., 2024)	Entorhinal Tau (Norton et al., 2020),
Spatial Processing	7			
Test of Allocentric Spatial Processing (TASP)	5	Participants are shown an avatar and an object and asked to encode the allocentric spatial relationship between both, i.e., where is the object relative to the avatar.	Four Mountains Test. AUC between βA+ and βA- in MCI=0.93 (Chan et al., 2016).	Entorhinal cortex (Coughlan et al., 2023).
Clock Drawing Test	2	Asked to draw a clock onto a tablet using a stylus. Key metrics include drawing accuracy and spatial features of the clock.	Digital Clock Drawing Test. AUC between βA+ and βA- cognitive normal adults=0.71 (Rentz et al., 2021).	Medial parietal/precuneus (Rentz, 2021).
Perceptual Discriminability	17			

Motion Perception Test	10	Participants are shown a screen with blue and orange dots. Some dots are moving in a target direction (either left or right - target) and some are moving randomly (noise). The colour of the dots is either random or paired. Participants are asked to detect whether most dots are moving left or right.	Sensory integration test found that people with AD had reduced ability to benefit from colour cueing and higher detection thresholds (Festa, 2005)	Hypothesised as entorhinal (binding), occipital (colour) and parietal (motion).
Odd One Out Test	4	Participants are presented with 6 pictures, one of which differs based on a spatial feature. They are instructed to identify the odd one out as quickly as possible.	Oddity Detection Task used Kanji style symbols in different fonts. AUC in early AD = 0.8. (Frei et al., 2022)	Structural MRI: perirhinal and entorhinal cortices (Frei et al., 2022)
Overlapping Objects Test	3	Participants are presented with 30 overlapping and partially obscured pictures of objects. They are asked to identify as many as possible in 1 minute.	15 Objects Test. AUC between MCI and control=0.85 (Alegret et al., 2009). Not tested using biomarkers.	Hypothesised as occipital-temporal pathway.
Semantic Processing	11			
Verbal Fluency	6	The verbal fluency task asks people to name words belonging to categories (animals and supermarket items), beginning with a letter (F &P), and verbs.	Animal Fluency. AUC in βA+ and βA- older adults with MCI=0.89 (García-Herranz et al., 2019).	Entorhinal cortex (Wright et al., 2023).
Connected Speech	5	This task records 'conversational speech', when asking the participant to describe short biography, current day, and current news.	Lexical-Semantic Speech. AUC between βA+ and βA- adults=0.77 (Hajjar et al., 2022).	Hippocampal volume (Hajjar et al., 2022).
Cognitive Control	10			
Central Auditory Processing	5	Participants are presented with 30 overlapping and partially obscured pictures of objects. They are asked to identify as many as possible in 1 minute.	Dichotic digit test. AUC between βA+ and βA- cognitive normal adults=0.81 (Byun et al., 2023).	Cingulate cortex (Thomsen et al., 2004).
Anti saccade task	5	Participants are presented with a blank tablet screen, and instructed to look in the opposite direction of the stimuli (left or right).	Systematic review demonstrating sensitivity to preclinical AD using standard anti-saccade paradigm (Opwonya et al., 2022).	Hypothesised to involve ACC.
Performance Validity	4			
CoCoA-PAD PVT	4	Participants are presented with forced choice options from the SILT and NAME tests and asked to identify which ones they saw previously.	Standard paradigm in PVT research, e.g., CVLT-III forced-choice (verbal) or TOMM (visual) stimuli.	n/a

16.2. Appendix 2. Analysis Plan for CoCoA-PAD Project

Cognitive Neurology of Alzheimer's Disease and CoCoA-PAD

Domain	Theoretical basis in Alzheimer's disease	Relevance to CoCoA-PAD
Memory	Early AD disrupts binding processes (associative and conjunctive), semantic interference (hippocampal/entorhinal dysfunction), and Accelerated Long-Term Forgetting (ALF), where short-delay recall is intact but rapid attrition over days emerges.	SILT tests semantic interference; MANE assesses associative binding; COBALT tests conjunctive binding. Together these are sensitive to both preclinical and prodromal AD.
Spatial Processing	AD affects hippocampus, entorhinal cortex, posterior parietal lobe, and precuneus, leading to allocentric spatial deficits and visuospatial construction problems.	TASP assesses allocentric navigation; Clock Drawing probes parieto-frontal visuospatial/executive control; COBALT also loads on spatial prediction, requiring localisation of features.
Perceptual Discriminability	The perirhinal cortex supports discrimination of visually/semantically similar items and conjunctive perception; it is an early site of AD pathology. Posterior integration with occipital and fusiform regions is also impaired.	Odd-One-Out and Overlapping Objects depend on perirhinal integrity; Motion Perception is a visuospatial binding task (MT/V5 + parietal). COBALT also taps perceptual discriminability.
Semantic Processing	Semantic networks (anterior temporal cortex, fusiform, left inferior frontal gyrus) degrade in AD, with semantic interference and lexical retrieval difficulty.	SILT is both memory and semantic; MANE also involves semantic binding; Verbal Fluency and Connected Speech probe language and semantic network function.
Cognitive Control	Early dysfunction of anterior cingulate cortex and dorsolateral prefrontal cortex reduces inhibitory control, error	Central Auditory Processing depends on callosal transfer and ACC/DLPFC; Antisaccade taps

Domain	Theoretical basis in Alzheimer's disease	Relevance to CoCoA-PAD
	monitoring, and attentional switching. Interhemispheric transfer via the corpus callosum is also compromised.	inhibitory control and eye-movement regulation, predicted to distinguish prodromal from healthy.

NEUROIMAGING TARGETS

DTI tractography

Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), Axial Diffusivity (AD) in a priori tracts (fornix, parahippocampal cingulum, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, arcuate fasciculus, superior longitudinal fasciculus, vertical occipital fasciculus, corpus callosum, optic radiations, frontostriatal pathways)

NODDI

Neurite Density Index (NDI), Orientation Dispersion Index (ODI), Free Water Fraction (FWF) in cortical ROIs: entorhinal cortex, hippocampus, perirhinal cortex, fusiform gyrus, posterior parietal cortex, precuneus, occipital cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, primary auditory cortex, frontal and parietal eye fields.

T1-weighted volumetry/thickness

Grey matter volume, cortical thickness in medial temporal lobe (hippocampus, entorhinal cortex), fusiform gyrus, posterior parietal lobe, precuneus, occipital cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, anterior temporal lobe

SUBTEST-LEVEL ANALYSIS PLAN

PREMORBID COGNITIVE ABILITY

Paragraph Reading Test

- Cognitive Theory: Index of premorbid verbal ability; not sensitive to AD pathology.
- Diagnostic Hypothesis: No diagnostic role.
- Neuroimaging Hypotheses: None (excluded from MRI analysis).

MEMORY

SILT (Semantic Interference during Learning Test)

- Cognitive Theory: Tests susceptibility to semantic interference; hippocampal–entorhinal associative binding.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy, and prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: fornix; parahippocampal cingulum; uncinate fasciculus; superior longitudinal fasciculus.
    - NODDI regions: entorhinal cortex; hippocampus (CA1, subiculum); dorsolateral prefrontal cortex; anterior cingulate cortex.
    - T1 (secondary): hippocampal & entorhinal thickness.

MANE (Matching Animals and Name Examination)

- Cognitive Theory: Tests associative binding of names to animal images; anterior temporal & fusiform integration.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy, and prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: inferior longitudinal fasciculus; inferior fronto-occipital fasciculus; uncinate fasciculus; arcuate fasciculus.
    - NODDI regions: entorhinal cortex; fusiform gyri; anterior temporal cortex; perirhinal cortex.
    - T1 (secondary): anterior temporal volume; fusiform thickness.

COBALT (Colour and Object Binding and Localising Test)

- Cognitive Theory: Tests conjunctive binding (colour, form, spatial localisation); requires parietal–temporal–entorhinal integration.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy, and prodromal vs healthy.

- Neuroimaging Hypotheses:
    - DTI tracts: superior longitudinal fasciculus; vertical occipital fasciculus; inferior longitudinal fasciculus; uncinate fasciculus (for EC).
    - NODDI regions: entorhinal cortex; posterior parietal cortex (intraparietal sulcus, angular gyrus); precuneus; perirhinal cortex; occipital cortex.
    - T1 (secondary): parietal & occipital cortical thickness.

ALF (Accelerated Long-Term Forgetting)

- Cognitive Theory: Tests delayed memory attrition; hippocampal-dependent consolidation.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy (less sensitive in preclinical).
- Neuroimaging Hypotheses:
    - DTI tracts: fornix; parahippocampal cingulum; uncinate fasciculus.
    - NODDI regions: entorhinal cortex; hippocampus; anterior temporal cortex.
    - T1 (secondary): hippocampal subfield volume.

SPATIAL PROCESSING

TASP (Test of Allocentric Spatial Processing)

- Cognitive Theory: Tests allocentric navigation; hippocampal–parietal–precuneus integration.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy, and prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: fornix; parahippocampal/posterior cingulum; superior longitudinal fasciculus.
    - NODDI regions: entorhinal cortex; hippocampus; precuneus; retrosplenial cortex; posterior parietal cortex.
    - T1 (secondary): hippocampal & precuneus volume.

Clock Drawing Test

- Cognitive Theory: Tests visuoconstruction and executive control; parieto-frontal integration.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: superior longitudinal fasciculus; inferior fronto-occipital fasciculus.
    - NODDI regions: entorhinal cortex; posterior parietal cortex; dorsolateral prefrontal cortex.
    - T1 (secondary): parietal cortical thickness.

PERCEPTUAL DISCRIMINABILITY

Motion Perception Test

- Cognitive Theory: Tests dorsal-stream integration of motion and form; occipital–parietal–entorhinal.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: optic radiations; vertical occipital fasciculus; superior longitudinal fasciculus.
    - NODDI regions: entorhinal cortex; MT/V5 complex; posterior parietal cortex; precuneus.
    - T1 (secondary): occipital cortical thickness.

Odd-One-Out Test

- Cognitive Theory: Tests perceptual discrimination of complex objects; perirhinal & fusiform binding.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy.
- Neuroimaging Hypotheses:

- DTI tracts: inferior longitudinal fasciculus; uncinate fasciculus; inferior fronto-occipital fasciculus.
- NODDI regions: entorhinal cortex; perirhinal cortex; fusiform gyrus; occipital cortex.
- T1 (secondary): perirhinal/fusiform thickness.

Overlapping Objects Test

- Cognitive Theory: Tests conjunctive perceptual binding under ambiguity; perirhinal-dependent.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy.
- Neuroimaging Hypotheses:
  - DTI tracts: inferior longitudinal fasciculus; uncinate fasciculus; inferior fronto-occipital fasciculus.
  - NODDI regions: entorhinal cortex; perirhinal cortex; fusiform gyrus.
  - T1 (secondary): anterior temporal cortical thickness.

SEMANTIC PROCESSING

Verbal Fluency

- Cognitive Theory: Tests lexical retrieval, semantic network integrity, and executive control.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy.
- Neuroimaging Hypotheses:
  - DTI tracts: arcuate fasciculus; uncinate fasciculus; inferior fronto-occipital fasciculus; frontal aslant tract.
  - NODDI regions: entorhinal cortex; anterior temporal lobe; left inferior frontal gyrus; anterior cingulate cortex.
  - T1 (secondary): anterior temporal thickness.

Connected Speech

- Cognitive Theory: Tests discourse and semantic integration; exploratory in AD.
- Diagnostic Hypothesis: Exploratory (not primary).
- Neuroimaging Hypotheses:
    - DTI tracts: arcuate fasciculus; inferior fronto-occipital fasciculus; uncinate fasciculus.
    - NODDI regions: entorhinal cortex; anterior temporal lobe; perisylvian regions.
    - T1 (secondary): temporal lobe cortical thickness.

COGNITIVE CONTROL

Central Auditory Processing

- Cognitive Theory: Tests binaural integration and interhemispheric transfer.
- Diagnostic Hypothesis: Distinguishes preclinical vs healthy, and prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: acoustic radiations; corpus callosum (splenium); arcuate fasciculus.
    - NODDI regions: entorhinal cortex; primary auditory cortex; anterior cingulate cortex; dorsolateral prefrontal cortex.
    - T1 (secondary): auditory cortical thickness.

Antisaccade

- Cognitive Theory: Tests inhibitory control, attentional regulation, and eye-movement control.
- Diagnostic Hypothesis: Distinguishes prodromal vs healthy.
- Neuroimaging Hypotheses:
    - DTI tracts: superior longitudinal fasciculus; frontostriatal tracts; cingulum bundle.

- NODDI regions: entorhinal cortex; dorsolateral prefrontal cortex; anterior cingulate cortex; frontal eye fields; parietal eye fields.
- T1 (secondary): frontal cortical thickness.

PERFORMANCE VALIDITY

CoCoA-PAD PVT

- **Cognitive Theory**: Ensures task engagement and response validity.
- **Diagnostic Hypothesis**: Not diagnostic.
- **Neuroimaging Hypotheses**: None.

	Cognitive theory (summary)	Diagnostic hypothesis	Key DTI tracts (primary)	Key NODDI regions (primary)
Paragraph Reading (premorbid)	Premorbid ability	No diagnostic role	–	–
SILT	Semantic interference; associative binding	Preclinical vs HC; Prodromal vs HC	Fornix; Parahippocampal cingulum; Uncinate; SLF	Entorhinal; Hippocampus; DLPFC; ACC
MANE	Associative binding (names ↔ animals)	Preclinical vs HC; Prodromal vs HC	ILF; IFOF; Uncinate; Arcuate	Entorhinal; Fusiform; Perirhinal; Anterior temporal
COBALT	Conjunctive binding of colour/object/location; spatial prediction	Preclinical vs HC; Prodromal vs HC	SLF; VOF; ILF; Uncinate	Entorhinal; Posterior parietal; Precuneus; Perirhinal; Occipital
ALF	Accelerated forgetting (consolidation deficit)	Prodromal vs HC	Fornix; Parahippocampal cingulum; Uncinate	Entorhinal; Hippocampus; Anterior temporal
TASP	Allocentric spatial representation	Preclinical vs HC; Prodromal vs HC	Fornix; Posterior cingulum; SLF	Entorhinal; Hippocampus; Precuneus; Retrosplenial; Parietal
Clock Drawing	Visuoconstruction & executive control	Prodromal vs HC	SLF; IFOF	Entorhinal; Posterior parietal; DLPFC
Motion Perception	Dorsal-stream visuospatial binding	Preclinical vs HC	Optic radiations; VOF; SLF	Entorhinal; MT/V5; Parietal; Precuneus
Odd-One-Out	Object discrimination (perirhinal)	Prodromal vs HC	ILF; Uncinate; IFOF	Entorhinal; Perirhinal; Fusiform; Occipital
Overlapping Objects	Conjunctive perceptual binding	Prodromal vs HC	ILF; Uncinate; IFOF	Entorhinal; Perirhinal; Fusiform
Verbal Fluency	Semantic retrieval & executive	Prodromal vs HC	Arcuate; UF; IFOF; FAT	Entorhinal; Anterior temporal; LIFG; ACC
Connected Speech	Discourse/semantic integration	Exploratory	Arcuate; IFOF; UF	Entorhinal; Anterior temporal; Perisylvian
Central Auditory Processing	Binaural integration & callosal transfer	Preclinical vs HC; Prodromal vs HC	Acoustic radiations; Corpus callosum (splenium); Arcuate	Entorhinal; Primary auditory cortex; ACC; DLPFC
Antisaccade	Inhibitory control, eye-movement regulation	Prodromal vs HC	SLF; Frontostriatal; Cingulum	Entorhinal; DLPFC; ACC; Frontal eye fields; Parietal eye fields
PVT (validity)	Effort/engagement	Not diagnostic	–	–