STUDY PROTOCOL

Feasibility of measuring sleep-dependent brain activity at home in people with Mild Cognitive Impairment and mild Alzheimer's disease to help delay symptoms

Short title: SleepAD

Address: Bristol Brain Centre
Southmead Hospital
Bristol
BS10 5NB

Protocol Authors: **Prof. Liz Coulthard** (Primary Author)

Dr David Woodstoke
Ms Victoria Gabb
Dr Jonathan Blackman
Dr Hamish Morrison
Dr Nicholas Turner
Ms Immi Biswas

Chief Investigator: Prof. Liz Coulthard

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PRIMARY & CHIEF INVESTIGATOR:

Prof. Liz Coulthard
Associate Professor in Dementia Neurology
ReMemBr Group, University of Bristol
Learning & Research,
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: Elizabeth.coulthard@nbt.nhs.uk
Contact for clinical queries

CO-INVESTIGATORS:

Dr David Woodstoke
Research Associate
ReMemBr Group, Translational Health Sciences
Bristol Medical School
Level 2, Learning & Research,
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: david.woodstoke@bristol.ac.uk

Ms Immi Biswas
PhD Student
University of Bristol
Level 2, Learning & Research,
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: lu20001@bristol.ac.uk

Dr Hamish Morrison
Clinical Research Fellow
North Bristol NHS Trust
Trust Headquarters
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: hamish.morrison@nbt.nhs.uk

Ms Victoria Gabb
Research Associate
ReMemBr Group, Translational Health Sciences
Bristol Medical School
Level 2, Learning & Research,
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: victoria.gabb@bristol.ac.uk

Dr Jonathan Blackman
Clinical Research Fellow
North Bristol NHS Trust
Trust Headquarters
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: jonathan.blackman@nbt.nhs.uk

Dr Alex Gordon
Clinical Research Fellow
North Bristol NHS Trust
Trust Headquarters
Southmead Hospital, BS10 5NB
Tel: 0117 414 5739
Email: alexander.gordon@nbt.nhs.uk

SPONSOR AND MONITOR:

University of Bristol
Department of Research, Enterprise & Innovation
University of Bristol
2nd Floor St Augustine's Courtyard
Orchard Lane
Bristol BS1 5DS
Email: research-governance@bristol.ac.uk

STUDY SITE:

North Bristol NHS Trust
Helen Lewis-White
Deputy Director of Research and Innovation
R&I, Floor 3, Learning and Research Building
Southmead Hospital, Bristol
BS10 5NB
Tel: 0117 4149330
Email: research@nbt.nhs.uk

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1 INTRODUCTION

1.1 Background

Introduction

New approaches to treatment of Alzheimer's disease (AD) are desperately needed. There are 850,000 people living with dementia in the UK and this is set to increase as the population ages. Annual financial costs exceed £36 billion in UK alone and dementia is the most feared condition of old age. Dementia Roadmap, James Lind Alliance and Lancet Commission prioritise effective routes to timely diagnosis and interventions to help people retain independence and quality of life.

AD pathology accrues over 2-3 decades before diagnosis – with amyloid beta (abeta) plaques emerging very early and then tau deposition detected later (but still before clinical symptoms). There are no licensed treatments for AD that can delay progression although one anti-amyloid therapy has recently been approved by the Food and Drug Administration review and is under NICE review after one of two phase III trials suggested modest benefit in early symptomatic AD.

Through targeting therapy early in the course of disease before symptoms interfere with day-to-day life, we could alter the trajectory of cognitive decline and slow progression to AD dementia. Economic modelling suggests that delaying progression between the prodromal phase of AD, Mild Cognitive Impairment (MCI), and AD dementia by 3 years would reduce the number of cases in the UK by 394000 (as dementia often occurs in the last few years of life) with estimated annual cost saving of £12.7billion.

Modifying sleep quality is an untapped opportunity with potential to delay progression of neurodegenerative diseases such as AD [1] while promoting physiological processes that improve cognition, mental health and wellbeing. There is a multidimensional relationship between sleep disturbance and AD progression [2-4]. Poor sleep is associated with increased likelihood of future dementia [2], AD worsens sleep and poor sleep is linked to worse cognition [5]. Deficits in non-REM (slow wave) sleep [6] have been associated with the degree of abeta and tau burden prior to AD onset as well as memory impairments [7, 8]. Treating sleep might therefore help slow AD progression and improve symptoms of memory loss.

The programme of work here will deliver feasibility, acceptability and diagnostic sensitivity data for home high density overnight EEG and blood biomarkers that will be translated directly into clinical trials to delay progression of Alzheimer's and improve independence and quality of life in older people at risk of AD.

<u>Link between sleep macro and microarchitecture and AD</u>

Sleep and circadian rhythm disturbance are well recognised in both AD and MCI with over 60% of memory clinic attendees experiencing at least one recognised sleep disorder such as sleep apnoea or insomnia [9-12]. There are a broad range of sleep abnormalities found in individuals with AD including insomnia, excessive daytime sleepiness and 'sundowning'.

Decreased sleep efficiency, increased duration of stage 1 sleep and an increase in sleep fragmentation compared to age-matched people without dementia is also seen. Circadian rhythm disorders, contributing to sleep disturbance are also generally more marked than in healthy ageing.

While it seems very likely that sleep disturbance results from the pathological cascade underlying AD, more recent data also points to sleep abnormalities themselves causing or exacerbating both cognitive impairment and pathological progression of AD. Toxic breakdown products (including amyloid) are removed via the glymphatic system in mice only during slow wave sleep (SWS). A single night of SWS deprivation has been shown to increase cerebrospinal fluid (CSF) amyloid beta 42 levels in healthy adults[13], and individuals with more severe obstructive sleep apnoea (OSA) have shown increased brain amyloid burden [14]. Furthermore SWS at baseline predicts accumulation of toxic proteins that cause AD in future years [15-17]. Alongside biomarkers, sleep has also been shown to be disrupted long before the onset of symptomatic AD dementia [2, 3]. Therefore, poor sleep might cause or exacerbate pathological changes of AD through failure to remove amyloid and consequent accumulation in turn worsening cognition. Therefore, modifying sleep represents an untapped opportunity with potential to delay progression of neurodegenerative diseases such as AD while promoting physiological processes that improve cognition (particularly long-term memory consolidation), general health and wellbeing. Furthermore, its presence prior to onset of clinical symptoms, may provide an ideal means by which to identify those at highest risk. Early identification is potentially crucial in the future when further therapeutic modalities may be available to alter the pathological disease course.

Microarchitectural features of sleep including the slow oscillations in SWS are causally linked to AD. There are potential treatments to augment SWS. As an example, we have recently shown that a cheap, safe and widely available medication, levodopa, prolongs slow wave sleep (deep, non-REM sleep). Physiological processes during non-REM sleep help to remove pathological proteins that are associated with AD – abeta42 and phosphorylated tau. Therefore prolonging non-REM sleep offers the potential to delay progression of Alzheimer's. There are other emerging interventions to modify sleep being developed by other research groups such as auditory stimulation during non-REM and medications such as zolpidem. For any of these to be rolled out into clinical trials, we need to be able to treat patients for AD when symptoms are mild, and test patients' sleep in their homes.

But, we cannot detect these without EEG measurement (data under review), and there is no standardised way to measure sleep in MCI and AD [18]. EEG has not been implemented at scale in dementia trials and the best system to capture EEG in clinical trials is not established. Therefore we test here home EEG using a set-up as close as possible to in-lab polysomnography but reducing the need for participant travel and overnight stays. We will test the feasibility of this approach alongside memory test testing that would typically be required as part of a clinical trial. In addition, as we know the prevalence of OSA can be high in this population and that this impacts on sleep, we will also monitor for OSA.

<u>Why measure blood biomarkers</u>

Alzheimer's Disease (AD) is currently not diagnosed sufficiently early for effective treatment. Earlier intervention in AD is crucial, to avert accumulation of AD pathology that begins 20

years before clinical dementia diagnosis, and to prevent distress from delayed diagnosis. Novel AD blood biomarkers identify early AD in research settings [19]

People with Mild Cognitive Impairment (MCI) or early AD dementia could benefit from lifestyle interventions and/or the trial pipeline of disease-modifying drugs [20] but most people (c. 567k people in UK currently) with AD are not diagnosed until they have overt dementia. Moreover, early robust reassurance, using molecular diagnostics, for people with cognitive symptoms but without neurodegenerative disease or dementia could avoid extensive unnecessary testing and reduce distress from diagnostic uncertainty.

Blood levels of phospho-tau (P-tau, marker of tau leakage due to abeta42 oligomeric toxicity) and neurofilament light chain (NFL, marker of all-cause neurodegeneration) are recently validated measures of AD pathology and neurodegeneration respectively that are ready for real-world testing [21]. SIMOA (Single Molecular Array) technology is just now available in UCL employing validated assays of NFL, P-tau-181 and P-tau-217.

Blood biomarkers will support accurate classification at the initial presentation, reduce unnecessary tests and evaluation, enable treatment for conditions which can masquerade as dementia, such as depression, facilitate post-diagnostic support, and therefore support maintaining independence. Potential therapies target specific stages of Alzheimer's disease, with many designed for and tested in early AD dementia and/or MCI due to AD. Dementia services will need to stratify patients according to molecular pathology of AD and disease stage to deliver treatments, but this is not available across the UK in an equitable or affordable way, and in many countries is not accessible at all. If as accurate as expected, acceptable and cost-effective, blood biomarkers can be widely used clinically.

There is less known about blood biomarkers in Lewy body diseases. However, post mortem studies predict that around 50% of people with Lewy Body Dementia will have evidence of Alzhiemer's pathology too [22]. People with dual AD and Lewy body pathology decline faster. Therefore, idenitifying AD pathology in Lewy body diseases is likely to be of prognostic significance.

Accuracy

For people with Mild AD dementia or MCI due to AD reference ranges are available from research cohorts and P-tau 181 alone has an Area Under Receiver Operating Characteristic curve (AUROC) of 0.80 compared to amyloid PET [23] and the combination of NFL and P-tau 181 has an AUROC of 0.88 compared to delayed verification of AD (sensitivity 83-88%, specificity 82-83%) to identify people who have progressive AD pathology as a cause of their MCI at baseline. Simple cognitive tests carried out in clinic such as the Montreal Cognitive Assessment have 90% and 100% sensitivity for MCI and mild AD dementia respectively, with specificity varying according to the cohort (up to 87% when comparing to healthy control in a research cohort) [24]. For people without AD – cerebrospinal fluid (CSF) biomarkers have a very high negative predictive value (94% on a real-world sample after median 4.7 years follow-up). Modelling suggests that combining blood biomarkers with simple cognitive tests will be more sensitive and specific than either test alone.

As blood biomarkers make large scale interventional studies possible in AD at vastly reduced expense (as we can avoid CSF testing or PET scanning), new therapeutic targets for intervention can be tested more rapidly.

The value of blood biomarkers is ultimately determined by the accuracy with which they can predict future AD, and therefore collecting longitudinal data is essential, with progression from MCI to AD as the key outcome of interest. To this end, our pre-clinical/MCI cohort will be followed up at 2 and 5 years after their involvement in the study, to check whether their diagnosis has converted to AD or another dementia. Diagnostic accuracies of all included biomarkers will be assessed, and we will use modelling to examine how specific biomarkers improve dementia risk prediction when combined with baseline demographic and clinical information.

Molecular classification of AD is important alongside exploration of sleep as several studies have suggested distinct interaction between different underlying AD pathology (amyloid, tau or other) and different sleep metrics e.g. [17, 25]. Only by deep characterisation of sleep phenotype as in SleepAD, can we develop clinical trials that target the right sleep treatment to the right patient.

<u>*APOE* genotyping</u>

Apolipoprotein E (*APOE*) is a susceptibility gene for late onset AD. The *APOE* Ɛ2 allele is protective and the Ɛ3 allele is neutral, but the Ɛ4 allele increases the carrier's lifetime risk of developing AD. Increasing allele dose is positively associated with AD risk, in a Caucasian sample *APOE* Ɛ4 heterozygosity conferred an odds ratio of approximately 3, and Ɛ4 homozygosity an odds ratio of approximately 14 [26]. *APOE* Ɛ4 is known to have a number of neurophysiological effects decades prior to clinical signs emerge. For Ɛ4 carriers these include disrupted resting state brain activity, changes in brain structure, and impact on brain function [27]. Furthermore, *APOE* Ɛ4 has been linked with sleep disturbance in healthy older adults, and increased risks of insomnia and obstructive sleep apnoea [28, 29]. Total time spent in SWS was found to be significantly altered in older male Ɛ4 homozygotic *APOE* carriers [30]. *APOE* Ɛ4 may act as a mediator of the relationship between cognitive decline and sleep, independent of AD pathological change [31]. Of note, sleep has also been shown to modify the relationship between *APOE* Ɛ4 and AD, which indicated that sleep consolidation may provide some protection [32]. It would clearly be of great interest to further examine the associations between *APOE* Ɛ4, sleep and cognitive decline.

APOE Ɛ4 carrier status is also an important factor when evaluating AD risk. In a large prospective longitudinal study (BALTAZAR), baseline plasma p-tau 181 combined with *APOE* Ɛ4 carrier status (plus age, sex and cognitive screening test score) was found to improve the model's predictive performance for conversion from MCI to AD [33]. In a recent prognostic study of preclinical AD cohorts, the combination of *APOE*4 status and plasma P-tau 217 biomarkers was optimal for predicting longitudinal cognitive decline [34]. In another prognostic study of preclinical AD cohorts using progression to AD as the outcome, plasma P-tau in combination with brief cognitive tests and *APOE* genotyping significantly improved prediction accuracy [35]. In sum, combining blood biomarkers with *APOE*4 carrier status and simple cognitive tests, will likely be more sensitive and specific than a single test alone.

We therefore include *APOE* genotyping within the SleepAD study. Determining *APOE* Ɛ4 carrier status will further enhance deep characterisation of our sample, and enable us to examine links between Ɛ4 carrier status, sleep phenotype, and the presence of positive biomarkers within a real world clinical population.

Orexin as a biomarker

Orexins are neuropeptides produced in the hypothalamus that play a critical role in maintaining wakefulness [36]. Discovered in 1997, orexin A and orexin B bind to two G-protein-coupled receptors [37]. Their dysfunction is implicated in conditions such as narcolepsy, where deficient orexin production leads to excessive daytime sleepiness and cataplexy [38].

Emerging evidence suggests that orexins are also involved in the pathophysiology of AD, particularly in relation to sleep disturbances and cognitive decline. Abnormal CSF orexin levels have been observed in both transgenic mouse models of AD [39], and in humans with AD pathology [40], where these levels are associated with disruptions in sleep architecture and alterations in biomarkers of Alzheimer's disease.

In cognitively healthy individuals, sleep deprivation has been linked to increased levels of amyloid-beta and phosphorylated tau in the brain and CSF [41, 42], reflecting changes seen in AD [43]. Additionally, orexin levels have been correlated with p-tau in patients with AD [44], suggesting a potential role in the phosphorylation of tau proteins and the progression of AD pathology.

Adding further weight to a role for orexins in AD pathology, dual orexin receptor antagonists (DORAs) have shown promise in improving sleep parameters in this population, particularly in individuals with a mini mental state exam concordant with a diagnosis of MCI [45].

The efficacy of DORAs appears to be circadian-dependent, with administration timed to circadian cycles being crucial for optimal cognitive outcomes [46-48]. Mice with transgenic predisposition to AD pathology administered orexin antagonists at the start of a dark cycle had aggravated pathology [47], in comparison to mice administered orexin antagonists at the end who had ameliorated cognition [48]. This suggests that monitoring orexin levels and accounting for the point in the circadian cycle they were taken could be vital in understanding and optimizing the therapeutic effects of DORAs.

The effect on cognition of DORAs appears to be related to their effect on the quantity of pathogenic proteins in CSF. A small randomized controlled trial (RCT) demonstrated that suvorexant, a DORA, significantly reduced the ratio of phospho-tau 181 to total tau in cognitively unimpaired individuals [46]. Similar effects were observed on CSF amyloid-beta levels in this study, indicating that orexin may directly influence tau phosphorylation and amyloid aggregation, key processes contributing to neuronal and synapse loss in AD.

While CSF orexin appears to have a significant relationship with cognition, this does not appear to be the case with plasma orexin (which does not undergo circadian variability, although this has always been assumed to be insignificant) [49]. Indeed, the only current literature in MCI relates to a methodologically flawed study that found a positive association between constipation and orexin in MCI [50]. Regardless, it may be a helpful comparator because it may provide a baseline value by which to compare CSF level.

Measuring orexin levels in plasma and CSF could therefore provide valuable insights into the degree of sleep-wake cycle and circadian rhythm impairments in patients across the AD pathology spectrum. This approach could serve as a less cumbersome alternative to polysomnography for assessing these disturbances and offer a target for evaluating the effects of orexin antagonists.

Notably, no study to date has examined the relative levels of plasma and CSF orexin, or their relationship to plasma biomarkers of Alzheimer's disease. This is what we propose to do in this protocol amendment. This may provide additional diagnostic clarity about stage of AD, and a potential way to monitor response to DORAs in future clinical trials. Furthermore, it will enable us to better understand the links between sleep characteristics and the presence of positive AD biomarkers within a real-world clinical population.

1.2 Rationale For Study Programme

Enhancing sleep holds great promise to improve brain health in later life. Our overarching goal is to improve identification and treatment of disease-related sleep and memory impairment in MCI and AD.

This study programme has two simple major themes, united by the need for sleep and molecular diagnostic data collection in people with early AD. The work is funded by Rosetrees charity to develop feasibility data to enable future large scale roll out of sleep intervention trials in people with early accurate molecular diagnosis of AD.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Summary Of Themes

The two themes are as follows:

1) To determine whether home EEG characterisation of sleep is sufficient for clinical trials of patients with early AD through testing
2) To determine potential utility of blood biomarkers in sleep and dementia research

2.1.2 Primary Objectives

<u>Theme 1</u>
2.1.2.1 Feasibility of home high-density EEG (primary objective);
2.1.2.2 Acceptability of home EEG;

<u>Theme 2</u>
2.1.2.3 Feasibility of blood biomarkers for AD;

2.1.3 Secondary Objectives

<u>Theme 1</u>

2.1.3.1 Sensitivity of home high-density EEG to detect behaviourally relevant sleep neurophysiology
2.1.3.2 Feasibility of using concurrent overnight pulse oximetry to screen for obstructive sleep apnoea (OSA)

Theme 2
2.1.3.3 Accuracy of blood biomarkers for AD compared to CSF testing;
2.1.3.4 Explore the relationship between blood biomarkers, *APOE* carrier status and sleep metrics in subgroup who have had both.
2.1.3.5 Diagnostic sensitivity of blood biomarkers for predicting progression to AD.
2.1.3.6 Characterisation of the relationship between CSF orexin and blood biomarkers in predicting sleep-wake disturbance and disease status

2.2 Hypotheses

2.2.1 Primary Hypotheses:

Theme 1
- Home high-density EEG are feasible and acceptable in people with MCI and AD

Theme 2
- Blood biomarkers are feasible and acceptable in people with MCI and AD.

2.2.2 Secondary Hypotheses:

Theme 1
- Home high-density EEG will capture behaviourally relevant sleep metrics
- Concurrent pulse oximetry testing will capture accurate data to enable screening for OSA

Theme 2
- Blood biomarkers are accurate compared to CSF biomarkers for AD
- Blood biomarkers will show acceptable diagnostic sensitivity, which is further improved when combined with other clinical and demographic information.
- Blood biomarkers of AD pathology will correlate with sleep abnormalities in the pattern suggested by CSF.
- *APOE* carrier status will correlate with both sleep abnormalities and blood biomarkers of AD pathology
- Distinct sleep characteristics will be detectable in those with blood biomarkers of AD pathology and *APOE* carrier status.
- CSF orexin levels will have a statistically significant positive correlation with blood biomarker levels of amyloid beta and p-tau.

3 PROGRAMME DESIGN

The SleepAD programme is comprised of two sub-studies which will run in parallel utilising distinct but potentially overlapping participants.

Sub-Study 1

Design: Single centre, prospective observational feasibility study with longitudinal follow up.

Setting: Southmead Hospital cognitive disorders clinic and participants' homes.

Sub-Study 2

Design: Single centre, prospective observational feasibility and diagnostic accuracy study with longitudinal follow up.
Setting: Southmead Hospital cognitive disorders clinic.

4 STUDY POPULATION

4.1 Method Of Recruitment

Sub-Study 1

Target population and inclusion/exclusion criteria: The primary method of recruitment will be to approach participants who fulfil the criteria of Mild Cognitive Impairment (MCI) or early dementia due to Alzheimer's Disease (AD) [51] in the ARUK funded DOPAMIND 2 trial (set to begin recruitment November 2022) and the Above and Beyond Funded RESTED study (recruiting from November 2021). Both studies are run by our research group and participants have consented to being approached about other research opportunities.

If we do not meet the sample size from these two studies, participants will be identified by the research team through one of six sources:

1. The North Bristol NHS Trust Cognitive Disorders Clinic (led by EC) which receives approximately 20-25 referrals on a weekly basis.
2. The North Bristol NHS Trust Mild Cognitive Impairment Clinic / Brain Health Clinic which currently holds a caseload of approximately 80.
3. Memory Clinic Database
   A confidential and secure database maintained by the ReMemBr group in North Bristol NHS Trust for the purposes of undertaking medical research and statistical analysis currently holding approximately 1600 records. This contains contact details for current and previous CDC or MCI clinic attendees, a proportion of whom have previously expressed an interest in future research participation.
4. In addition we will recruit through the Join Dementia Research (JDR) national research register for local people interested in taking part. If clinical research network portfolio status is granted, we will recruit with support of local clinical research network staff where appropriate.
5. Participants in other research studies (beyond those already stated above) run at the Bristol Brain Centre, who meet eligibility criteria.
6. Members of the public who have approached the Brain Centre expressing interest in research participation.

We plan to recruit through primary care and from public spaces using posters and leaflets where we may reach potential participants e.g. hospital and GP waiting rooms. We will advertise this study on our website at www.remembrgroup.com and possibly on other websites.

We will also be using 'Join dementia research' (JDR) as a recruitment tool. This is an online self-registration service that enables volunteers with memory problems or dementia, carers of those with memory problems or dementia and healthy volunteers to register their interest in

taking part in research. The purpose of JDR is to allow such volunteers to be identified by researchers as potentially eligible for their studies. Researchers can then contact volunteers, in line with the volunteers' preferred method of contact, to further discuss potential inclusion. JDR is funded by Department of Health working in partnership with the charities Alzheimer Scotland, Alzheimer's Research UK and Alzheimer's Society and is Health Research Authority (HRA) endorsed. The online service and all associated documentation, methods of contacting volunteers and handling of data, were reviewed by a specially convened HRA committee which included experts in research ethics, data protection and information governance. Formal endorsement was issued by the HRA in a letter dated 20 May 2014.

Sub-Study 2

Target population and inclusion/exclusion criteria: we will approach every person in whom we are performing LP for Alzheimer's biomarkers. We use CSF testing in patients with early disease or in whom the diagnosis is not clear and where Alzheimer's disease is a possibility and many of these patients will also take part in objective 1.

4.2 Inclusion Criteria

For Sub-Study 1

1. Age > 50
2. All participants must express that they are willing to take part in this study and adhere to the study procedures
3. Full capacity to consent to involvement
4. Clinical diagnosis of MCI due to AD[52] or mild AD[51] according to standardised criteria
   (NB people with a mixed AD/Vascular dementia diagnosis are eligible for inclusion)

For Sub-Study 2

1. All participants undergoing CSF testing clinically including CSF biomarkers of AD.
2. All participants must express that they are willing to take part in this study and adhere to the study procedures.
3. Full capacity to consent to involvement

4.3 Exclusion Criteria

For Sub-Study 1

1. Severe medical or psychiatric co-morbidity, which, in the opinion of the investigator, may substantially impact on sleep.
2. Clinically significant sleep disorder as defined by ICD-10 or equivalent pre-dating and / or not related to AD pathology.
3. Diagnosis of dementia other than AD.
4. Montreal Cognitive Assessment (MoCA) < 11/30, except where the MoCA is not considered to be an accurate reflection of clinical presentation (e.g., in the case of prominent speech disorder) in the opinion of the investigator.

For Sub-Study 2

1. Severe medical or psychiatric co-morbidity, which, in the opinion of the investigator, may substantially impact on the ability to tolerate withdrawal of an extra 10ml of blood.

4.4 Participant Numbers

For Sub-Study 1

Sample Size: of 50 allows key feasibility parameters to be estimated with a suitable level of precision

For Sub-Study 2

Sample Size: of 100 will allow key feasibility and diagnostic accuracy parameters to be estimated with a suitable level of precision e.g. a marginal error of 0.08 assuming an AUROC of 0.9 and 50% prevalence in binary classification of AD | not AD.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 Pre-screening potential participants

For Sub-Study 1

All prospective participants will first be contacted by telephone (or face to face if consultation planned) by a member of the clinical team to establish whether they are potentially interested in participating, and if so, details will be passed to a member of the research team.

A member of the research team will then make contact by phone to provide an outline of the study and will ask about their general health. This is in order to rule out participants who have medical diagnoses or problems that may prevent them from taking part in this study, such as a severe medical co-morbidity interfering with sleep. Another goal of the pre-screening phone call is to schedule the first screening consultation. We will give the potential participant as much time as they need to decide whether they wish to undergo the first screening consultation.

If the prospective participant does not already possess a copy of the Patient Information Sheet (PIS), this will be sent by post or electronically. Prospective participants with a carer are invited to bring this person along with them for the screening consultation.

For Sub-Study 2

Clinicians will consider eligibility for the study at the point of booking patients in for a routine lumbar puncture in the Brain Centre clinic, and if the prospective participant is interested they will be signposted to the research team. A member of the research team will then make contact by phone to discuss the study, and if appropriate to gain verbal consent to participate.

For participants with speech or communication difficulties, a face-to-face appointment will be offered instead of a phone call.

During the subsequent lumbar puncture appointment, consent will be confirmed in writing by a GCP trained member of the team.

5.2 Screening Consultation

For Sub-Study 1

Screening consultations can be conducted in-person or remotely.

Each potential participant will be reviewed by an International Conference on Harmonisation Good Clinical Practice (ICH GCP) trained member of the study team. Participants will first be given a detailed explanation of the study, orally as well as another copy of the PIS if they wish. The research team will check understanding of the PIS and an opportunity to ask questions will be provided. If they agree to take part in the study each participant will sign an Informed Consent Form (ICF). Participants scheduled for remote consultation will have received a copy of the PIS and ICF via post and will be asked to return a signed copy to the research team. Capacity to consent is assessed as explained in Section 5.3.

Each prospective participant will subsequently be reviewed against inclusion / exclusion criteria before final eligibility is determined.

The participant will subsequently undergo medical screening (see Section 6.1) before undergoing baseline assessments (see Section 6.2) if eligible.

Any participant unsure or requiring more time to make a decision as regards to consent will be offered this opportunity and given as much time as they need, providing recruitment is ongoing.

Substudy 2 – no screening visit

5.3 Consenting Participants

Anyone taking part will be informed of the study aims and protocol. It will be made clear to participants that if they wish to, they may withdraw their consent at any time without the need to provide an explanation and that this will not affect future medical care.

The investigator taking consent will be trained in taking consent and will act in accordance with GCP. Capacity to consent is assessed by the researcher as they discuss the information sheet with the patient. The researchers will ensure the volunteer has understood and retained information for long enough to allow risks and benefits to be considered and that a decision can be relayed clearly.

Substudy 1 only Once the volunteer has given consent, they will perform the Montreal Cognitive Assessment (MoCA). This is a widely used assessment for measuring cognitive ability within clinical and research settings. If a participant scores below 11/30 they will be withdrawn from this study as this is highly likely to be associated with a reduced capability to

provide informed consent and adhere to study procedures. However, if the MoCA is not considered to be an accurate reflection of clinical presentation (e.g., in the case of prominent speech disorder) in the opinion of the investigator, then inclusion would still be considered on a case-by-case basis.

5.4 Carer Involvement

We will encourage all prospective patients with MCI/AD to be accompanied with a carer for the screening consultation if they wish.

5.5 Withdrawal of Participation

Participants are free to withdraw from the study and to opt-out at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the participant will have the option as to whether they wish to allow previously collected data to be utilised for ongoing research. The reason for withdrawal will be documented in the participant's case report form (CRF) although a reason would not have to be provided.

6 STUDY ASSESSMENTS

6.1 Screening Assessments

<u>For Substudy 1</u>

The following information will be gathered during the initial screening assessment:-

- Medical History and Current Diagnoses
  Specifically to determine the presence of severe medical comorbidities likely to impact on sleep or the presence of a primary sleep disorder unrelated to a neurodegenerative cause
- Previous Investigation Results
  Including neuroimaging data, CSF biomarker results and neuropsychometry data; information historically collected as part of routine clinical care.
- Medication History
- Physical Observations*
  Blood pressure measurement only

* If undergoing face-to-face consultation

6.2 Baseline Assessments

<u>For Substudy 1</u>

The following assessments will occur following informed consent during the initial consultation. These are validated questionnaires and post hoc analysis will allow us to probe whether any of these questionnaires can help stratify in which patients home EEG will be feasible for future trials.

<u>Cognitive Assessments</u>

- Montreal Cognitive Assessment (MoCA) [24]

Sleep Assessments

- Pittsburgh Sleep Quality Index (PSQI)[53]
- Epworth Sleepiness Scale (ESS) [54]
- STOP-BANG (OSA Screening Questionnaire)[55]
- Ultra-Short Munich Chronotype Questionnaire (μ-MCTQ)[56]
- REM Sleep Behavioural Disorder Single Screening Question[57]

Blood biomarkers - Venepuncture of 5-10 ml blood biomarkers taken for analysis of biomarkers (P-tau & NFL, GFAP and abeta42/40, and possibly others in future)

Other Assessments

- Restless Leg Syndrome Single Screening Questionnaire [58]
- Generalised Anxiety Disorder – 7 Questionnaire (GAD-7)[59]
- Geriatric Depression Scale Short Form (GDS-15) [60]
- Apathy Evaluation Scale Self-Rated (AES-S) [61]
- SleepAD sleep questionnaire (see appendix)

The study team will also record basic demographic information (e.g. age, sex, ethnic group, occupation, employment status).

6.3 Main Study Assessments

For Substudy 1

i) Venepuncture of 5-10 ml blood biomarkers taken for analysis of biomarkers (P-tau & NFL, GFAP and abeta42/40, and possibly others in future). The blood sample will either be arranged to be taken during a routine clinical appointment venepuncture at the Brain Centre (i.e. not an extra venepuncture), or during a separate appointment (which would require a new venepuncture).

ii) Sleep recording - participants will undergo EEG recording at home for 3 nights and will also complete a Consensus Sleep Diary questionnaire [62] each night. The sleep monitoring will be performed using high-density at-home EEG equipment which will be set up by the researcher in the participant's home. This will involve participants undergoing full polysomnography (PSG), where electrophysiological data from electrodes placed on the scalp, face and body will be recorded. The home setup is designed to closely replicate the setup used in sleep laboratories. Participants will wear a 32-channel sleep cap including scalp and auxiliary channel location using a wireless LiveAmp 32-channel active electrode system (Brain Products UK). EEG recordings are acquired on an internal memory system and will subsequently be downloaded to a secure University of Bristol server. Although we do not currently have experience of sleep recordings in Alzheimer's disease, we have experience from recording sleep in patient populations of similar age, living with chronic pain. In our experience, these patients tolerate sleep recordings

well. Numerous EEG studies in Alzheimer's disease are reported in the literature, as reviewed elsewhere [63].

iii) Pulse oximetry – participants will be asked to undergo two nights of overnight pulse oximetry (concurrent with EEG recording) during the 3 night window of sleep recordings. A pulse oximeter is a device routinely used in NHS practice to collect pulse oximetry data, and will be used in line with NHS protocols to monitor pulse and oxygen saturation levels and screen for obstructive sleep apnoea (OSA). Overnight pulse oximetry is an accepted and widely used screening tool for moderate to severe OSA [64]. Those with abnormal results will be offered referral to the Non-invasive Ventilation Clinic and their GP will be informed with the participant's consent.

iv) Sleep dependent memory testing - a long-term memory word test delivered by the researcher on either the second or third evening of testing (order counterbalanced)

v) Acceptability - participants will be asked to complete a brief questionnaire within 1 week of their final testing session to feedback on their experience (See appendix 2).

For Substudy 2

Venepuncture of 5-10 ml blood biomarkers taken for analysis of biomarkers (P-tau & NFL, GFAP and abeta42/40, and possibly others in future). In all participants undergoing LP, this will be at the time when bloods are taken alongside LP in any case (i.e. there will be not an extra venepuncture, just more blood drawn). In very rare situations, for example, participants who have another form of biomarker testing (e.g. PET scanning), a new venepuncture will be needed.

As an optional addition, the collected blood sample will also be analysed for *APOE* genotype. The venepuncture already being arranged for blood biomarker analysis will provide a sufficient sample for the additional *APOE* analysis. The *APOE* analysis therefore does not require an additional blood sample/procedure.

As an optional addition, an extra < 5 ml of CSF will be taken during the routine LP for analysis and storage, as long as this does not prolong the procedure by more than 1 minute.

All patients will have had a MoCA cognitive test as part of routine care within 3 months of CSF collection. In the very rare case that this has not happened as part of routine clinical care, we will also carry out a MoCA as close as possible in time to their lumbar puncture (taking into account they might be nervous on the day of the procedure, we may do this at a different hospital visit). As an alternative, we will offer the opportunity to complete the MoCA test remotely via video call and save the need for an additional hospital visit. Several studies have demonstrated that administering the MoCA remotely via video call is a valid and reliable alternative to a face-to-face assessment.

6.4 Participant Guidance for Assessments

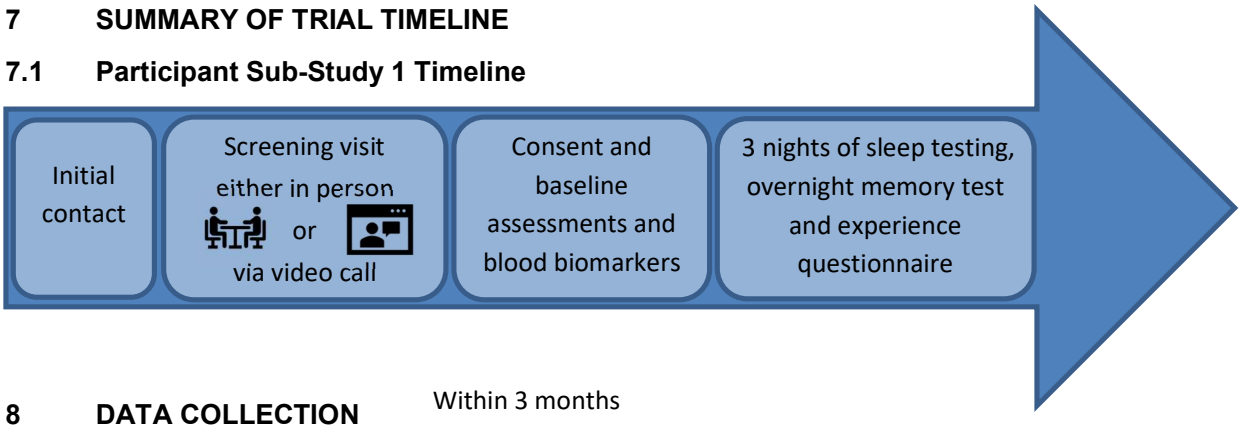
6.4.1 Reminders and support for assessments

A researcher will visit the participants house to place the EEG on each night of the study. This will involve applying the cap, fixing the electrodes and doing an initial check of data quality.

The researcher will deliver the cognitive tasks and be available by telephone for the entire study duration in case there are queries.

7 SUMMARY OF TRIAL TIMELINE

7.1 Participant Sub-Study 1 Timeline



8 DATA COLLECTION

8.1 Methods Of Data Collection

8.1.1 Paper based records

Data will be collected on paper during the initial eligibility check, throughout the first stage of the initial consultation and for the acceptability questionnaire.

8.1.2 Electronic records

Where possible, questionnaire data will be entered directly into an electronic data capture system (REDCap) during the consultation. Data collected on paper records will be entered into the same system following the consultation where appropriate.

8.1.3 Measurement Devices

Raw data from measurement EEG will be downloaded electronically.

8.2 Frequency of Data Collection

<u>For substudy 1</u>

Data will be collected during a one-off eligibility telephone conversation, an initial visit, over 3 nights of sleep EEG and then with acceptability questionnaire within 1 week of overnight testing.

Baseline data collected during the eligibility telephone conversation and initial visit will be entered by researchers into paper case report forms and then into REDCAP (electronic data capture system) or directly into REDCap. Data collected during the Study Assessment Period will comprise raw electronic data from measurement devices which will be downloaded onto secure computers at the end of the assessment period and memory test results that will be uploaded onto REDCap after testing.

<u>For Substudy 2</u>

Demographic and clinical data will be extracted from electronic medical records. Venepuncture will occur only once at the same time as clinical LP.

Follow-up checks of medical records

Medical records from participants in both substudies will be checked again at 2 years and at 5 years after involvement in the study. This will only include available records from those participants in the pre-clinical/MCI phase at time of participation in the study. In both substudies, the date will be measured from the date of the last participant's venepuncture. This follow-up data will be extracted to identify whether the pre-clinical / MCI diagnosis has changed to a dementia diagnosis.

8.3 Source Data Documentation

For the purposes of this section, 'secure computers' describes computers accessible only to study investigators which are password protected and hosted on either the University of Bristol or North Bristol NHS Trust IT infrastructure. All source data stored electronically will be stored securely and will be accessible by investigators involved in collecting or analysing the data and third party organisations involved in maintaining the infrastructure for its collection (e.g. Brain Products UK). Source data refers to any raw, unprocessed data.

8.3 Case Report Forms

Source documents will be entered into a secure database comprising electronic Case Report Forms for all participants within 7 days of the source record being created.

9 DATA MANAGEMENT

9.1 Personal Data

The following personal data will be collected as part of the research:

- Name
- Address
- Telephone Number
- Email Address
- Date of Birth
- NHS Number

Personal data will be stored by the research team at the study site in a locked cabinet in the Bristol Brain Centre, North Bristol NHS Trust. This data will only be available to delegated members of the research team at site. The data will also be made available for monitoring or audit by the sponsor team if required. Personal data will be archived and stored securely in a locked filing cabinet on site for 3 years after the completion of the study, and then securely destroyed.

9.2 Storage

All source data stored electronically will be stored securely and this will be accessible by investigators involved in collecting or analysing the data. Participants will be informed that anonymised data may be shared with other approved reputable researchers utilising data management policies of the University of Bristol and the bris.ac.uk repository. This would

require an appropriate Data Access Agreement and a Data Request Form. We will signpost to the opportunity for data sharing on our professional webpages.

9.2.1 Behavioural and participant data

Behavioural data stored on University of Bristol computers and servers will be pseudo-anonymised. Safety copies will be kept on encrypted hard-drives. The participants will be explicitly consented for the storage of their pseudo-anonymised data on University of Bristol computers in the consent form. Each participant's identity will be linked to their subject ID only on paper forms and in a log file, which will include participants' names, addresses and ID numbers. All identifiable paper records will be stored in secure locked cabinets. No identifiable information about the participant will leave the Bristol Brain Centre in any form. Any identifiable electronic information will be stored on NHS servers.

9.2.2 Sleep recordings

All raw study data relating to sleep recordings will be stored for a period of 20 years after publication as this is a quickly advancing field with the potential for new insights to afford new opportunities for analysis. To support future ethically-approved research, data may be shared anonymously with other bona fide researchers to support their work, and may be uploaded to the Dementia Platforms UK Data Portal (funded by the Medical Research Council).

9.2.3 Samples

Blood samples collected will be centrifuged and the plasma layer divided into 4 separate polypropylene tubes. They will initially be stored in the Bristol Brain Centre -70 freezer. One sample from each participant will be sent by courier to UCL laboratories for the main analysis. The remaining samples will be stored in Bristol Dementia Research Group freezers for future use within our group or by other bonafide researchers with appropriate research ethics and sample transfer agreements. A small sample from the remaining erthyrocyte layer will be transferred to a blood stain card and stored securely in the Bristol Dementia Research Group laboratory. In batches, DNA will be extracted from the blood stain cards and genotying will be performed using Taqman Assays (Applied Biosystems Assay-On-Demand part numbers C__3084793_20 and C__904973_10).

Where CSF is also being collected as part of routine clinical care, we will also send an extra sample (<5ml) to UCL, with the remainder stored in Bristol as above. CSF and blood will only be handled by clinical facilities and laboratories (Bristol Brain Centre, South West Dementia Brain Brank, and UCL) experienced in employing universal precautions to avoid contamination or spills.

9.3 Confidentiality

Participant confidentiality will be respected at all times. Identifiable information may be shared with the participant's GP in line with patient consent.

9.4 Public Release

Any information that could identify individual participants will not be released into the public domain. Participants will be informed that anonymised data may be shared with other approved reputable researchers utilising data management policies of the University of Bristol and the bris.ac.uk repository. This would require an appropriate Data Access Agreement and a Data Request Form. We will signpost to the opportunity for data sharing on our professional webpages.

9.5 Data Loss

The technology used in the study will be set up for each participant according to a rigorous protocol agreed by the research team, and participants are provided with written and verbal information on study activities to ensure adherence to protocol. However due to the remote and technology-focused nature of the study, it is possible for data to be lost or not collected due to technological issues (e.g., battery failures).

If a significant portion of data is missing on a given task, participants may be asked if they are willing to repeat an EEG night or blood test if appropriate within the 3 month study period. The participant can decline repeating any measures without this affecting their participation in the study. Similarly, if appropriate in the opinion of the Chief Investigator, participants may be asked to complete study activities outside of their main study period if study protocol has changed (and participants will be reconsented as appropriate).

10 STATISTICS AND DATA ANALYSIS

10.1 Sample Size Calculation

For substudy 1
Sample Size: of 50-100 allows key feasibility parameters to be estimated with a suitable level of precision
For substudy 2
Sample Size: of 100 will allow key feasibility and diagnostic accuracy parameters to be estimated with a suitable level of precision e.g. a marginal error of 0.08 assuming an AUROC of 0.9 and 50% prevalence in binary classification of AD | not AD from biomarkers.

10.2 Proposed Analyses

For Substudy 1

Data analysis will:

a) Quantify the proportion of missing data for sleep nights with high density EEG. Post hoc analysis will also explore whether any baseline questionnaire outcomes associate with poor data quality (larger levels of missing data)
b) Calculate acceptability ratings for home EEG
c) We will analyse non-REM duration from high density EEG and assess whether or not we can replicate the observed association between sleep metrics and memory observed from laboratory polysomnography, e.g. in the DOPAMIND study, when using home high density EEG.
d) Quantify the proportion of datasets for sleep nights with pulse oximetry which are sufficiently complete to enable clinical screening for Obstructive Sleep Apnoea.

For Substudy 2
Analysis of samples: will be on using the SIMOA platform for research use.

Data analysis will:

a) Quantify the proportion of lost/degraded blood samples, and data completeness for memory tests
b) Calculate diagnostic accuracy of the separate index tests (NFL, p-tau) for AD, at pre-published thresholds, compared to reference standard (CSF), via AUROC curves[65]
    - and explore heterogeneity in diagnostic accuracy of index tests AD by pre-specified factors listed using cut offs for AD | no AD extrapolated from UCL clinical laboratories.
c) Quantify the relationship between p-tau, NFL and sleep metrics in patients who have had both blood biomarkers and high-density EEG
d) As a post hoc analysis, we will explore the diagnostic accuracy of Montreal Cognitive Assessment (MoCA) as a standard clinical test and visually compare accuracy of NFL and tau to that of MoCA.
e) Where CSF is available, we will run biomarker analyses on the UCL research SIMOA machine to internally validate samples also tested as part of routine clinical care on the UCL clinical laboratory SIMOA machine.
f) Once longitudinal data has been collected from our pre-clinical/MCI cohort, we will calculate the diagnostic accuracy of the separate index tests for AD via AUROC curves. The relationship between conversion to AD and the index tests will be assessed using regression models with age, sex, baseline MoCA score, plasma: CSF orexin ratio, and baseline *APOE* carrier status as covariables.

11 SUMMARY OF SAFETY AND ETHICAL CONSIDERATIONS

11.1 Risks associated with self-report questionnaires and cognitive testing

There are no serious risks involved in completing the experimental tasks and questionnaires. Similar cognitive testing is undertaken regularly by researchers in this group, and almost all patients tolerate it and many enjoy it. Occasionally patients are bored or frustrated by testing and, in that case, we offer them the opportunity to have a break and continue later. The participants also know they are allowed to withdraw their participation at any time.

11.2 Sleep recording

The sleep recordings carry no risks above those encountered in life outside research participation. There is the possibility of a localised skin reaction as a result of wearing the electrodes. If participants report pre-existing irritable skin, the researcher will remain with the patient for up to 2 hours while wearing the device for the first time to ensure irritation is not an issue. EEG recordings are safe and are a non-invasive procedure. To our knowledge, no complications other than skin irritability have been reported previously.

11.3 GP involvement

We will send each participant's GP a letter explaining that the volunteer is taking part in this study. The GP will not be routinely contacted about our findings. However, if the researchers discover a suspected illness (such as undiagnosed Parkinson's disease, sleep apnoea), the Principal Investigator will be informed and subsequent steps may include a direct referral for appropriate specialist follow-up or communication with the participants' GP to facilitate this. This procedure will be explained to the participants in the PIS and participants can agree to GP involvement in case of incidental findings by signing the consent form. In the event results

suggest an unexpected significant clinical finding, participants who do not agree to this on the consent form will be contacted to discuss this further.

11.4 Discontinuation Criteria

11.4.1 For individual participant/consultation

The participant will be withdrawn from the study if the clinician asked to evaluate the screening information does not think it is safe for them to participate.

In addition, if for any reason at all a participant wishes to withdraw their participation from the study, they may do so at any point.

If the participant is happy for us to do so, and if the reason for withdrawal is not one that is likely to affect the data gathered, we will keep data already collected for analyses. If not, all information relating to that participant will be safely disposed of, providing the data has not been analysed. If there has been an adverse effect, this will be recorded accordingly.

If a participant withdraws or is withdrawn from the study, another participant will be recruited to replace them.

11.4.2 Loss of capacity

As the maximum time during which a participant will be enrolled in this study is 1 month, it is unlikely they will lose capacity because of dementia. For this reason we will not routinely assess for this. However, if someone loses capacity and we become aware of this, we will respect their consent and include the data we have already collected from them in our analyses. However, we will exclude them from any further testing as we have defined capability to consent as an inclusion criteria for this study.

11.5 Participant Burden

Overall, this study has a relatively low burden on participants, with the focus being obtaining data (sleep patterns and memory tests) that reflects everyday life for the participants. The technology planned to measure these patterns is specifically designed to be non-invasive, with the exception of a one-off blood test for some participants.

Screening and baseline consultations will be conducted face to face or remotely permitting us to flexibly mitigate COVID-19 or future pandemics.

All visits to the patient's home should last no longer than two hours. All equipment and study materials will be collected from the participants when data collection has ended.

The cognitive tests will require mental effort on the part of participants. Participants are free to stop the test at any time and this will be re-iterated prior to the start of the test.

The sleep diary will only need to be completed each morning. This should take no more than 2 minutes to complete each day.

Venepuncture causes a brief stinging sensation that is usually well tolerated and occasionally triggers syncope in the minute or two afterwards, or causes a bruise later on. Participants will be seated during venepuncture and will be observed and offered suitable refreshments afterwards in case of any immediate syncope.

We will not be able to meaningfully feedback the blood biomarker or CSF/ plasma orexin results as we are using a research only laboratory without validated normal ranges which we will extrapolate from the clinic laboratory at UCL. Therefore we will not be able to disclose AD risk on the basis of blood biomarkers – thus avoiding potential participant burden to decide if they would like to know.

Similarly, we will not be able to meaningfully feedback the results of the *APOE* genotyping. The results will be for research purposes only and not performed as a clinical test. We are not undertaking the genetic testing in a validated clinical laboratory, and NICE guidelines specifically advise against disclosing the outcome. As we will not be disclosing AD risk on the basis of genotyping this avoids adding potential participant burden to decide if they would like to know.

If participants agree to an extra <5ml of CSF being taken for secondary validation of blood results, there is a low chance we may worsen a post-lumbar puncture headache. This can be mitigated in most cases by drinking fluids and lying flat and we will reinforce the advice already given to people having lumbar puncture to reduce the risk of post-LP headache.

12 ADVERSE EVENTS

This observational study does not involve administration of any medicinal product and utilises non-invasive passive monitoring devices only.

Due to the low risk nature of the project, and the comparatively long length of follow-up, only adverse events assessed as related to study procedures will be recorded. Participants will be asked at each contact if they have experienced any adverse events. Adverse events considered related to a protocol procedure will be recorded at site and entered into an eCRF. Serious adverse events will be reported to the Sponsor. Adverse event reporting will follow the research safety reporting standard operating procedure of University Hospitals Bristol and Weston NHS Trust who manage safety reporting on behalf of the Sponsor.

Adverse events that are judged to be possibly, probably, or definitely related to the EEG and meet one of the criteria for a serious adverse event will be reported to the Sponsor within 24 hours of the research team becoming aware of the event.

Serious adverse events are considered if any of the following criteria apply to an adverse event:

- Results in participant's death
- Is life threatening
- Results in hospitalisation or prolongs existing hospitalisation
- Results in a persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

13 OVERSIGHT ARRANGEMENTS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

14 QUALITY CONTROL AND ASSURANCE

14.1 Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible. This research study will be run in accordance with GCP. All investigators involved in any aspect of consenting and testing will have undertaken GCP training.

14.2 Quality Assurance

14.2.1 Accuracy of Case Report Forms

Paper case report forms (CRFs) and electronic patient-reported outcomes (PROs) are the primary data collection instruments for the study. The Principal Investigator, or a designee will record data collected on each subject. The Principal Investigator will be responsible for the timing, completeness, legibility and accuracy of the CRF and will retain a copy of each completed form.

For paper CRFs: All data requested on the CRF will be recorded and checked by a member of the study team. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be inserted. If the item is not applicable to the individual case, "N/A" will be inserted. All entries will be printed legibly in ink. If any entry errors are made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated. Pencil and correction fluid will not be used anywhere on the CRF. If it is not clear why the change has been made, an explanation will be written next to the change. Paper CRFs will be entered into a University of Bristol approved electronic data capture system.

Each participant enrolled into the study must have the correct CRFs completed and signed by the Principal Investigator (or designee). This also applies to those participants who failed to complete the study. All data submitted on CRFs must be verifiable in the source documentation or the discrepancies explained.

If a participant withdraws from the study during the experiment phase, the reason must be noted on the Withdrawal Form.

14.2.2 Case Report Form Sampling and Study Audit

At the conclusion of the data collection phase, a random sample of 20% of CRFs will be checked against relevant source data for quality purposes. This percentage will be increased if errors are found. Where necessary, corrective actions will be recorded and a re-audit is undertaken.

14.2.3 Trial Steering Committee

The investigators will be responsible for data quality, which will be monitored as described below. A Trial Steering Committee will be formed, which will meet with the researchers during the planning and the execution of the project to monitor the progress of the study, including data analysis.

14.2.4 Study Monitoring

Study monitoring will be undertaken on behalf of the Sponsor, University of Bristol. The University of Bristol (UoB) has a Service Level Agreement in place with a local NHS Trust (UH Bristol). As part of this, UH Bristol will undertake monitoring of research projects where UoB is fulfilling the responsibilities of a research sponsor. A minimum of 10% of UoB Projects will be monitored.

Before the study

The CI will work with the Sponsor to develop a risk-based monitoring plan.

The CI will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

During the study

The CI will allow the sponsor to:

- Inspect the site, the facilities and the material used for the study
- Meet all members of his/her team involved in the study
- Consult all of the documents relevant to the study
- Check that the CRFs have been filled out correctly
- Directly access source documents for comparison of data therein with the data in the CRFs
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements
- Carry out study monitoring at regular intervals, depending on the recruitment rate, and arranged between the CI and monitor
- All information dealt with during these visits will be treated as strictly confidential
- Respond to monitoring report

14.2.5 Access to Source Data / Documents

The CI will allow monitors (from UH Bristol on behalf of the Sponsor), persons responsible for monitoring, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data/documents. This is reflected in the PIS.

14.2.6 Measures and Tests

The validation and quality control of memory test is the responsibility of the study team. These tasks will have been piloted extensively prior to commencing recruitment for this study.

14.3 Patient and Public Involvement (PPI)

Patient and public involvement was sought from our dedicated Patient Involvement in Memory Studies (PIMS) group during the development of this protocol. This group were consulted on the planning and design of the study, as well as actively shaping key study documents including the protocol, information sheets and recruitment materials. We will arrange further PPI involvement in the future to support effective dissemination of our findings.

15 END OF STUDY

The end of the main study is defined as the last participant's last visit. The follow up medical records checks will occur at 2 and 5 years after the last participant visit.

The Investigators or the sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the main study will be reported to the REC, and R+D Office(s) within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC within 1 year of the end of the main study.

The end of the follow up period will also be reported in line with the above, and a further summary report provided.

16 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites

concerned. The sponsor require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

17 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

The findings of the current trial will be reported in conferences, as a student thesis and as an article(s) in a high-ranking scientific journal(s). A brief summary of the results will also be published in the Health Research Authority public database for UK clinical trials, as well as on the research group's website at http://remembrgroup.com/. All the investigators listed at the top of this protocol will be included as authors on any publications, with additional authors determined by the CI and PI. Only non-identifiable data will be available in the public domain.

18 AUTHORSHIP POLICY

An author is considered to be someone who has made substantive intellectual contribution to any publication drawn from this study. Many journals consider it best practice that everyone who is listed as an author should have made a substantial, direct, intellectual contribution to the work. Honorary or guest authorship is not acceptable.

19 GLOSSARY

AD	Alzheimer's Disease
AES	Apathy Evaluation Scale
CI	Chief Investigator
COM-B	Capability, Opportunity, Motivation, Behaviour Model
CRF	Case Report Form
CSD	Consensus Sleep Diary
CSF	Cerebrospinal Fluid
DCFS	Dementia Cognitive Fluctuation Scale
DH	Dreem Headband
DLB	Dementia with Lewy Bodies
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
GAD-7	Generalised Anxiety Disorder - 7 Item
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
ICD-10	International Classification of Diseases - 10th Version
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IRLSSG	Restless Legs Syndrome Rating Scale
JDR	Join Dementia Research
LBD	Lewy Body Dementia
LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
NBT	North Bristol NHS Trust
NREM	Non-Random Eye Movement
OSA	Obstructive Sleep Apnoea
PDD	Parkinson's Disease Dementia
PI	Principal Investigator
PIS	Participant Information Sheet
PLMS	Periodic Limb Movements
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Random Eye Movement
RESTED	Remote Evaluation of Sleep To enhance understanding of Early Dementia
SWS	Slow Wave Sleep
u-MCTQ	Ultra-Short Munich Chronotype Questionnaire
UoB	University of Bristol

20 APPENDICES

20.1 Appendix 1

SleepAD Sleep Questionnaire

Lifestyle *Please provide answers based on a normal or average day.*

Q1	Do you drink any caffeinated drinks? *If 'No' please go to Q2*	Yes		No	
	a) How many cups / bottles / cans do you drink per day?				
	b) What time do you drink your final caffeinated drink?	:			

Q2	Do you drink any alcohol? *If 'No' please go to Q3*	Yes		No	
	a) How often?	Every Day		Most Days	
		Some Days		Rarely	
	b) Please estimate how many units per week (1 unit is a small glass of wine, a half-pint of beer or a measure of a spirit)	units			

Q3	Do you smoke?	Yes		No	

Q4	What is your occupation? (if retired please specify main previous occupation)				
Q5	Do you currently do shift work?	Yes		No	
Q6	If no, have you ever done shift work in the past?	Yes		No	

Environment *These questions refer to the place that you usually sleep*

Q7	Do you find that your sleep is frequently disturbed by noise?	Yes		No	
Q8	Do you find that your sleep is frequently disturbed by excessive light?	Yes		No	
Q9	Do you share a bed? *If 'No' please go to Q10*	Yes		No	
	Does your partner regularly disturb your sleep?	Yes		No	
Q10	Are there any other environmental factors that regularly affect your sleep? (please specify)				

Sleep history

Q11	Have you been diagnosed with any sleep conditions in the past?	Yes		No	
	If yes, please specify:				
Q12	Do you have any current sleep problems?	Yes		No	
	If yes, please specify:				
Q13	Are you currently satisfied with your sleep?	Yes		No	
	If no, please specify:				
Q14	Have any of your immediate relatives been diagnosed with a sleep condition? (E.g. Including obstructive sleep apnoea, narcolepsy or other sleep disorder)	Yes		No	

	If yes, please specify:				
Q15	When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?	Yes		No	

Daytime napping behaviours

Q16	Do you regularly nap during the day?	Yes		No	
Q17	Are your naps mostly intentional (you deliberately sit/lie down for a nap) or unintentional (you fall asleep without meaning to)?	Intentional		Unintentional	
Q18	In an average week, how often do you nap?	Every Day		Most Days	
		Some Days		Rarely	
Q19	In an average day, how long during the day do you nap in total?		minutes		
Q20	What time of day do you usually nap?	Morning (before 12pm)		Afternoon (12pm – 5pm)	
		Evening (after 5pm)			

Sleep hygiene

Q21	Do you keep a regular sleep routine?	Yes		No	
Q22	Do you wake up naturally or use an alarm clock?	Naturally		Alarm	
Q23	Do you take regular exercise in daylight	Yes		No	
	If yes, please specify time of day as morning, afternoon, or evening:				
Q24	Do you get regular good exposure to daylight?	Yes		No	
Q25	Do you do any of the following activities regularly in bed? Read, use a phone/ smart device, watch TV, work/ study	Yes		No	
	If yes, please specify				

Comments

Q26	Do you have any additional comments regarding your sleep?	

Appendix 2

Sleep AD experience questionnaire The questionnaire is designed using the Unified Theory of Acceptance and Use of Technology (UTAUT) model to determine the factors that determine user acceptance of technology these include performance expectancy, effort expectancy, social influence, attitude, and facilitating conditions.

Question	Response format
How did you feel about taking part in the SleepAD study?	*Free text*
Did your experience of wearing the EEG match your expectations (or was it better or worse)?	*Free text*
What did you think about wearing the EEG device before testing?	*Free text*
Did you encounter any difficulty or notice benefits from using the EEG device?	*Free text*
Do you think it's a good/interesting idea to use an EEG device to measure your sleep and do blood testing?	*Free text*
Did anyone encourage you to continue the study?	*Free text*
What did your family/friends think about you getting involved in this study?	*Free text*
How did you find the process of blood testing?	*Free text*
Would anything make the process easier for you in the future?	*Free text*

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