TITLE: Feasibility study: Can reducing periodontal infection (gum disease) slow the progression of cognitive impairment associated with Alzheimer's disease

SHORT TITLE: Oral Health for Brain Health (Mysmile)

STUDY PROTOCOL

Version 3.0, 15th December 2022

RESEARCH REFERENCE NUMBERS

Sponsor Number	DE/2021/7205
Funder Number	NIHR 203048
Project Registration	ISRCTN[XXXXXX]

PROTOCOL VERSION HISTORY

Amendment No.	Version No.	Version Date	Reasons for update
N/A	1.0	28/07/2022	N/A - Original version submitted for approval
N/A	2.0	24/10/2022	In response to provisional ethical opinion
NSA2	3.0	15/12/2022	Correction of RICE full name

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position: .....

Chief Investigator:

Signature: ..... Date: ...../...../.....

Name: (please print):

.....

CONTENTS

KEY STUDY CONTACTS

Chief Investigator	Professor Nicola West Dental Clinical Trials Unit Bristol Dental School Lower Maudlin Street Bristol, BS1 2LY n.x.west@bristol.ac.uk 07825 831352
Study Co-ordinator	Miss Nikki Hellin Dental Clinical Trials Unit Bristol Dental School Lower Maudlin Street Bristol, BS1 2LY Nikki.hellin@bristol.ac.uk Interim co-ordinator Dr Maria Davies Address and phone as above Maria.davies@bristol.ac.uk
Sponsor	University Hospitals Bristol and Weston NHS Foundation Trust Research and Innovation Education and Research Centre Level 3 Upper Maudlin Street Bristol, BS2 8AE R&Dsponsorship@uhbw.nhs.uk 0117 342 0233
Funder(s)	National institute for Health Research (Research for Patient Benefit): NIHR203048
Key Protocol Contributors	Prof Nicola West (n.x.west@bristol.ac.uk) Dr Shelley Allen-Birt (shelley.allen@bristol.ac.uk) Dr Liz Coulthard (elizabeth.coulthard@bristol.ac.uk) Dr Rosemary Greenwood (rosemary.greenwood@uhbw.nhs.uk) Dr Maria Davies (maria.davies@bristol.ac.uk)
Committees	Steering committee (N.X.West@bristol.ac.uk) Patient Advisory Group (Julie.Clayton@bristol.ac.uk) Trial Management Group (Nikki.Hellin@bristol.ac.uk)

LAY SUMMARY

Aim: To find out whether treatment which restores gum health in Alzheimer's patients with gum disease (periodontitis), slows down their rate of memory loss.

Background: Alzheimer's disease is an inflammatory disease of the brain causing memory loss, confusion and difficulties coping with daily life. It is the major cause of dementia, affecting 500,000 people in the UK with an estimated cost of £23 billion/year to the UK economy, including £3.2 billion to the NHS. It is estimated that any treatment which delays Alzheimer's disease onset by five years would reduce Alzheimer's sufferers by a third and benefit quality of life for patients and carers. Our research group and others have found links between Alzheimer's and gum disease. Gum disease occurs when certain bacteria thrive under the gum line causing inflammation and bleeding. There is good evidence these bacteria pass into the bloodstream and speed up, or cause development of other diseases (such as diabetes and heart disease).

Design and methods: We are a highly experienced research team of medical clinicians, dentists and scientists. This study monitors Alzheimer's patients treated for gum disease for 12-months to see if this also slows their rate of memory loss. We have already carried out a small study to see if Alzheimer's patients can cope with the treatment required to manage their gum disease. In most cases it showed gums can become, and stay healthy with a personalised dental plan for at least 1-year. The new study will compare two groups of patients who have both early Alzheimer's and gum disease. One group will continue to look after their teeth and attend their own dental practice as usual. The other group will receive a personalised mouth care plan with all treatment provided at Bristol Dental Hospital or an accredited General Dental Practice.

Patient and public involvement (PPI): We have had many discussions with patients, friends, carers and families at public and patient involvement meetings at venues such as Memory cafés. These conversations have not only helped us to design the study but have strengthened our belief in its importance. These meetings will continue throughout the trial to tell everyone about our progress and ask for advice about matters which call for PPI knowledge and awareness.

Dissemination: Throughout, we will keep everyone informed by means of talks, publications and social media posts. Slowing the progress of Alzheimer's by improving dental health could dramatically improve quality of life for sufferers and carers. If the study provides evidence to support a larger trial and shows the personalised dental care plan is helping, we would be able to strongly recommend the use of a personalised dental plan for the treatment of Alzheimer's patients within existing frameworks of care.

STUDY SUMMARY

Study Title	Feasibility study: Can reducing periodontal infection (gum disease) slow the progression of cognitive impairment associated with Alzheimer's disease
Short title	Oral Health for Brain Health
IRAS Number	315223
Sponsor ref. no.	DE/2021/7205
Study Design	An examiner blind, parallel, 2 arm randomised controlled trial in adults with early-stage-Alzheimer's Disease or Mild Cognitive Impairment (MCI), who also have periodontal disease. Participants will be randomised to an intensive or standard dental intervention.
Study Participants	Adults with early-stage-Alzheimer's Disease (AD) or Mild Cognitive Impairment (MCI), who also have periodontal disease
Planned Size of Sample (if applicable)	50
Follow up duration (if applicable)	Up to 18 months
Planned Study Period	September 2022 – May 2025
Research Question/Aim(s)	Overarching Aim: To show whether improved periodontal health can slow the progression of Alzheimer's Disease (AD). Aim of this feasibility trial: To assess the feasibility of conducting a Randomised Controlled Trial (RCT) of an Intensive Dental Care intervention (IDC), compared with the Standard Dental Care (SDC) provided in General Dental Practice, in AD patients to slow down decline in cognitive function
Key words	Alzheimer's Disease, cognitive decline, periodontal (gum) disease, oral health

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National institute for Health Research (Research for Patient Benefit): NIHR203048	Research costs: £261,791.00 NHS support and treatment costs: £11,443.00

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor is University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) and the funder the National Institute for Health Research (NIHR). The University of Bristol (UoB), as the substantive employer of the Chief Investigator, is responsible for protocol design and study co-ordination.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Steering Group

The Steering Group will meet approximately every six months during the study period, initially during study set up, and then at regular intervals throughout the study. The Group will be comprised of the PI, study co-ordinator, PPI representatives (PPI-lead, PPI-Co-Applicant and a study independent PPI member) and at least one further individual external to the study team together with other team members co-opted as appropriate. The Steering Group will review study procedures and documentation, study progress and conduct. Steering Group advice/direction will be sought regarding recruitment and other issues that are affecting study progress.

Patient & Public Involvement Group

A study specific Patient-Advisory-Group (PAG) will be recruited. An experienced PPI and Engagement (PPI&E) co-ordinator (the PPI-lead) will support the study team, and together with the PPI-Co-Applicant will recruit a diverse and inclusive study PAG, including people living with dementia and their carers who would also normally be expected to be involved in dental care decisions and attendance (10-12 members).

The PAG will meet approximately 5 times during the study, more if required, and be asked to provide advice/guidance on accessibility and clarity of study documentation; appropriate community awareness raising and recruitment methods; issues encountered such as slow recruitment rates/participant drop-out rates; interpretation of the significance of study results from a patient and carer perspective; dissemination of study data to ensure it reaches patients and carers in an accessible format.

The PPI-Co-Applicant will be the PAG key member and will liaise with the research team and the PPI lead regarding PAG meeting organisation, accessibility and agendas, ensuring that PPI contributors feel adequately supported in all aspects of work and that PPI has maximum impact. They will provide the link between the PAG and research team, attending the monthly Trial Management Group meetings in person, or providing input if they feel attendance is not necessary. They will take the lead on ensuring that the patient/carer perspective is represented at all study meetings and all stages and provide feedback to the PAG so they can see how their input has influenced the study.

A PPI impact log which records PPI involvement and outcomes/impact throughout the study will be kept and reported at the study-end.

Trial Management Group

This group is comprised of the key research team members including the PPI-Co-Applicant and will be led by Prof Nicola West or the study co-ordinator (Miss Nikki Hellin) in her absence. It will meet monthly and discuss the day to day running of the study.

STUDY FLOW CHART

Screening

Screening study appointments will be at the Bristol Brain Centre, Southmead Hospital:

Participant and partner meet with cognitive assessor who takes informed consent (n=80)

↓

Cognitive assessor confirms eligibility based on clinical diagnosis MCI/early AD (n=65)

↓

Dentist confirms eligibility (dental inclusions/exclusions) and if periodontitis enrols the participant and performs the baseline dental measurements (n=50)

↓

Dentist collects saliva and blood (n=50)

↓

Additional cognitive assessment tests for baseline will be carried out (n=50)

↓

Dental nurse provides dental products including a general guide to oral hygiene (n=50)
Randomises participants to Standard/intensive dental care groups using the stratified randomisation schedule confirms how appointments for dental hospital visits for intensive dental care group (n=25) will be made

↓

An appointment for the 6-month cognitive and dental assessments together with sample collection at the Bristol Brain Centre, Southmead Hospital will be made (n=50)

Intervention phase

Standard dental care group The standard of care provided by general dental services (general guide to OH) (n=25)	Intensive dental care (IDC) group Treatment at Bristol Dental Hospital (BDH) or foundation training scheme dental practice by a dentist trained in the study protocol 3-5 visits (n=25)

6-month appointment

Cognitive and dental assessments, samples of blood and saliva (n=50)
Location: The Bristol Brain Centre, Southmead Hospital
At the 6-month assessment an appointment will be made for the 12-month study visit for cognitive and dental assessments together with sample collection

12-month appointment

Cognitive and dental assessments, samples of blood and saliva (n=50)
Location: The Bristol Brain Centre, Southmead Hospital
At the 12-month appointment those with periodontitis randomised to the standard dental care group (n=25) will be offered a course of intensive dental treatment at BDH (via the specialty training pathway) – this treatment is not assessed as part of the study

18-month appointment

Virtual (video-call) cognitive assessments (~n=35), not assessed in main analysis
IDC for those randomised to the standard dental care group (n=25) will be delayed until after this assessment

Post study Qualitative assessments:

Semi-structured interviews for 5-6 participants in each group and 8 dentists who delivered the intervention
This is to determine acceptability of the intervention

Figure 1: Patient flow through the study (OH = Oral Hygiene)

LIST OF ABBREVIATIONS

Abbreviation	Full text
Aβ	Amyloid beta
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale Cognitive
AWP	Avon and Wiltshire Partnership
BADLS	Bristol Activities of Daily Living Scale
BBB	Blood Brain Barrier
BDWS	Bristol Dementia Wellbeing Service
BDH	Bristol Dental Hospital
BOP	Bleeding On Probing
CC	Capacity and Capability
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
DFS	Dental Foundation Scheme
DFS-GDPr	Dental Foundation Scheme-General Dental Practice
ELISA	Enzyme-Linked Immunosorbent Assay
EME	Efficacy and Mechanism Evaluation
ES	Educational Supervisor
GDP	General Dental Practitioner
GP	General Practitioner
GWAS	Genome Wide Association Study
HRA	Health Research Authority
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
IDC	Intensive Dental Care
JDR	Join Dementia Research
LPS	Lipopolysaccharide
MacCAT-T	MacArthur Competence Assessment Tool for Treatment
MoCA	Montreal Cognitive Assessment
MCI	Mild Cognitive Impairment
NHANES	National Health and Nutrition Survey
NBT	North Bristol Trust
NHS	National Health Service
NIHR	National Institute for Health and Care Research
OH	Oral Hygiene
PAG	Patient Advisory Group
R&D	Research and Development
REC	Research Ethics Committee
RICE	The Research Institute for the Care of Older People
RES	Research Ethics Service
PAG	Patient Advisory Group
PI	Principal Investigator
PPI	Patient and Public Involvement
PPI&E	Patient and Public Involvement and Engagement
PIS/PIL	Participant Information Sheet/Participant Information Leaflet
R&I	Research and Innovation

RCT	**Randomised Controlled Trial**
SDC	**Standard Dental Care**
SOP	**Standard Operating Procedure**
UHBW	**University Hospitals Bristol and Weston NHS Foundation Trust**

STUDY PROTOCOL

Title: Feasibility study: Can reducing periodontal infection (gum disease) slow the progression of cognitive impairment associated with Alzheimer's disease (Oral Health for Brain Health)

1. BACKGROUND

Alzheimer's disease (AD) and its scale:

AD accounts for approximately 60-70% of dementia worldwide [1]. In the UK, ~885,000 individuals have dementia [2] with over 500,000 estimated to have AD. Dementia is the leading registered cause of mortality, accounting for 12.5% of deaths annually [3]. Early onset-AD (<65yrs), is reported at levels of 6-16% [4]. In late onset-AD (~90% of cases) symptoms often start in the mid-60s, with inability to learn new facts, gradual memory loss, confusion, behavioural changes including apathy and depression, resulting in inability for self-support, leading to death with an average survival of 8 – 12 years following diagnosis [5]. By the time diagnosis is given, the disease has advanced considerably, perhaps irreversibly, often over a period of 25-years [6].

No medication can currently reverse the disease process. Conventional AD treatment focuses on prescription drugs such as cholinesterase inhibitors and Memantine which, in general, provide short-to-medium term symptomatic relief in some patients [7,8]. New treatments had not been approved since 2004, however, a new drug Aducanumab (Aduhelm) administered via monthly intravenous infusion, is described as able to reduce amyloid protein build-up in the brain [9].

There is growing concern about the requisite costs, and societal care of dementia patients. The 2019 overall dementia-care cost to the UK-economy was ~£35 billion, with £4.9bn NHS costs [2] and the cost of the recently FDA-approved, Aduhelm treatment [9] is approximately $50,000/person/year. (currently priced at $28,200/person/year [10]. The current financial trajectory suggests there will be a need for substantial increases in future dementia care budgets [2] unless there are meaningful improvements in population health. Much overlooked also, is the loss of elderly family members who often fulfil social roles such as childcare, who now need care themselves (by families who would otherwise benefit from their support). It is estimated that delaying the emergence of AD symptoms by five years could reduce the case number by a third [11].

AD-a chronic neuroinflammatory disease:

In AD there is a build-up of amyloid peptide (usually amyloid beta 42 (Aβ42)) into amyloid-plaques, mainly outside neurones (nerve cells), and a hyper-phosphorylated misfolded form of tau-protein forms neurofibrillary tangles within neurones; both are directly responsible for the pathogenic progress of AD, which is overall, neuroinflammatory [12]. Because the brain is protected from the peripheral blood stream by the Blood-Brain-Barrier (BBB), it relies on its separate innate immune system. In AD, overactivity of the innate system is initiated, as shown from Genome-Wide-Association-Studies (GWAS), which indicate that many genetic variations (risk-loci) for late-onset AD are directly associated with the innate immune system [13].

The brain's innate immune system can be altered in various ways, and like the peripheral immune system, is responsible for preventing invasion of pathogens (microbes such as bacteria/viruses). Unlike the peripheral system there is no adaptive immune function (antibody production etc). Instead, microglial cells, which are generally supportive of neurones, alter their morphology when under attack, producing cytotoxins to destroy perceived pathogens.

Amyloid Aß-part of the brain's immune defence:

Part of the microglial remit is to routinely assist clearance of toxic Aβ42 from the brain. However, Aβ is now understood to be an antimicrobial peptide [14-16] with an important role in immune defence. Aβ triggers normally supportive microglia into an activated aggressive state against pathogens [17]. Activated microglia produce more cytotoxic molecules and activate inflammasomal processes which exacerbate both the amyloid and tau-pathology of AD, which, if continued long-term, results in chronic neuroinflammation [18-21].

Understanding the importance of the sustained immune response in AD and the consequent increase, rather than the normal restraint, of amyloid and tau-pathology, provides a possible method to halt the AD disease process.

Periodontitis: an inflammatory disease:

Periodontitis, like AD, is a chronic inflammatory disease, affecting 45-50% of all adults [22-23] and is the sixth most common disease of humankind [24]. The inflammation of periodontitis affects tissues around teeth and occurs as a result of an exaggerated and ineffective host-response to the continued presence of dental-plaque bacteria [25]. This leads to dysbiosis (an imbalance in the types of oral bacteria present), emergence of pathogenic strains, bleeding gums and ultimately, tooth-loss [26]. We have recently shown that predominantly oral, viable, bacteria are present in the bloodstream [27]. This can occur via the ulcerated bleeding gums of periodontitis, which allow bacteria to gain entry to the bloodstream (bacteraemia) which triggers an immune response [28] including the production of antibodies [29]. If the bacteraemia is sustained, the response of inflammatory cytokines to this results in chronic inflammation circulating around the body.

Considerable evidence for periodontitis as a causal factor or accelerator of other inflammatory conditions exists [30]. Oral bacteria are commonly associated with community-acquired native valve-infective endocarditis [31], whilst professional tooth-cleaning reduces the incidence of acute myocardial infarction and stroke [32]. In Type-2 diabetes, periodontal disease severity correlates with enhanced immune response [33,34] and treatment for periodontitis provides significant benefits for metabolic control and reduction of systemic inflammation [35].

Periodontitis as a potential causal factor or accelerator of AD

There is also good evidence that links periodontal bacteria with brain inflammation as seen in AD [36-48]. Strong associations between AD and oral bacteria have been seen in several different populations [45], including longitudinal studies in the USA (n=219) [50], Sweden (n=704) [51], and Japan (n=179) [52] which variously revealed increased cognitive decline [Mild Cognitive Impairment (MCI) and AD] associated with periodontitis. In a UK cohort (n=54) with mild-moderate AD, presence of periodontitis at baseline was associated with a six-fold higher rate of cognitive decline after 6-months [53]. Additionally, matched-cohort studies accessing a Taiwanese database (n=8828-27963) showed dementia risk was 1.17-2.54-fold higher in those with periodontitis [54-56] and the US, NHANESIII-survey data, linked to mortality and Medicare databases (n=9787, 1988-2014) indicated a consistent association between periodontitis and AD incidence at ≥65yrs [43].

Recently, a study in living, cognitively normal individuals evaluated levels and species of subgingival periodontal bacteria, as well as Aβ42 and ptau-levels, in cerebrospinal fluid (CSF). CSF-Aβ42 levels usually decline with AD progression indicating that this toxic protein is not being cleared from the brain tissue into the CSF. In this study, subgingival periodontal dysbiosis and lower CSF-Aβ42 levels were significantly associated [57]. The subgingival bacteria in the group with low CSF-Aβ (increased

brain amyloid load) was enriched in periodontal pathogens e.g. *Treponema, Porphyromonas, Tannerella,* whereas the group with high CSF-Aβ (low brain amyloid load) was enriched in health-related bacteria e.g. *Corynebacterium, Actinomyces*, *Capnocytophaga*. Further, many studies examining post-mortem brain tissue and CSF from AD patients have demonstrated the presence of periodontal pathogens [58-61], e.g. keystone *P.gingivalis*. Furthermore, lipopolysaccharide (LPS) from *P.gingivalis* was observed in AD but not control brain [60]. In mice, *P.gingivalis* oral inoculation exacerbated AD-pathology and impaired cognition [62]. Similar changes were demonstrated with intraperitoneal *P.gingivalis*-LPS injection [63] and oral gingipain application [64]. In *P.gingivalis* infected dogs neurodegeneration and AD-like pathology were blocked after oral administration of a small molecule gingipain inhibitor COR388 [65]. Notably, Cortexyme (San Francisco) is currently assessing gingipain inhibitors in the Phase-I/II clinical trials (https://www.cortexyme.com/pipeline/).

AD-pathology progresses slowly [66] thus where long-term neuroinflammation occurs, it is likely that microbial-triggers must remain largely undetected by the host, as for instance may occur from periodontal bacteria. Periodontitis is a silent disease which can instigate chronic inflammation at distant sites whilst initially producing little warning from pain or major discomfort. The constant circulation of inflammatory cytokines in response to this chronic inflammation may overload the peripheral adaptive immune system and cause BBB-failure [29].

2. RATIONALE

Most gum diseases are preventable [26] and patients with active disease can be treated and returned to oral health. Therefore, stabilising gum health manages an important risk-factor for inflammatory diseases, including AD [37-48,57]. The first evidence-based S3-level-guidelines for the treatment of periodontitis have now been published [67] focussing on optimising outcome-driven personalised, tailored oral health in a primary care setting.

If the emergence of AD symptoms were delayed by five-years [11], then up to one-third of cases (over-time) may not occur, providing considerable reduction in patient and carer suffering and economic burden. Considering late-stage costs alone, since 60% ≥65yrs have periodontitis [23], a potential saving of an estimated £1billion/year may be made if only one-third had their periodontitis treated and thus delayed their AD symptoms. Furthermore, because people with severe dementia need far more care than those with mild dementia, slowing dementia progression will lead to reduced total dementia-care costs [11].

This clinical study will test the feasibility of a large-scale trial aiming to demonstrate whether our intervention with intensive dental care for periodontitis [67], facilitating a lessening of bacteria-induced inflammation, can achieve oral health in AD patients and slow their AD-disease progression

3. RESEARCH AIM

Overarching Aim: to show whether improved periodontal health can slow the progression of Alzheimer's Disease (AD).

Aim of this feasibility study

To assess the feasibility of conducting a Randomised Controlled Trial (RCT) in AD patients with periodontitis to compare (1) the use of an Intensive Dental Care intervention (IDC) with (2) the Standard Dental Care (SDC) provided in General Dental Practice, to slow down decline in cognitive function.

3.1 Feasibility study objectives: show

- recruitment rates, retention rates and data completion rates
- improvement in oral health in the intervention arm patients at 12-months
- measures of cognitive decline show sensitivity to change over 12-months
- blood levels of inflammatory markers show sensitivity to changes in periodontal disease status over 12-months

3.2 Outcome

Outcome measures:

- Periodontal scores and cognitive scores
- Blood levels of two inflammatory markers
- Qualitive data regarding the perceived acceptability and success of the intervention

Feasibility outcomes measured:

- Recruitment rates
- Compliance rates-intervention
- Completion rates-data collection

If successful, and progression criteria are met sufficiently (recruitment and data completion targets are met) the study will proceed to a full trial (EME application) which would aim to confirm if improved periodontal health can slow the progression of Alzheimer's Disease (AD).

4. STUDY DESIGN

4.1 Overview

A feasibility study of a multi-site RCT of a dental care intervention for people with early-stage-AD or Mild Cognitive Impairment (MCI), who also have periodontal disease, in which the following definitive trial will investigate differences in rate of cognitive decline.

- Intervention group **(Arm1)**: treated with IDC.
- Control group **(Arm2)**: continue with SDC.

IDC **(Arm1)** comprises treatment for periodontitis, and oral hygiene instruction tailored for the individual, delivered using motivational techniques in general dental practice or secondary care by dentists on training pathways (up to 10 sites). SDC **(Arm2)** is the standard of dental care provided by the general dental services, participants in this group will be asked to continue with their normal dental care practices.

The 2 groups will be assessed at baseline, 6- and 12-months for cognitive and periodontal status by central research team study staff at study appointments that are independent of study intervention appointments. Patient flow through the study is shown in the study flow chart (Figure 1) above and the consort diagram (Figure 2), below.

Few RCTs have assessed adherence to oral hygiene regimens for longer than 6-months, but successful outcomes at 12-months have been reported [68]. In a pilot study of AD patients given an oral hygiene intervention similar to IDC (carried out by this research team), improvements in oral health were achieved and maintained at 12-months even though there was slow, steady cognitive decline indicating that this measure is sensitive to change in this timeframe. Within the 3-year funding timeframe it is not possible to collect data from all participants beyond 12-months, however cognitive data at 18-months will be collected from as many as possible (~75% participants).

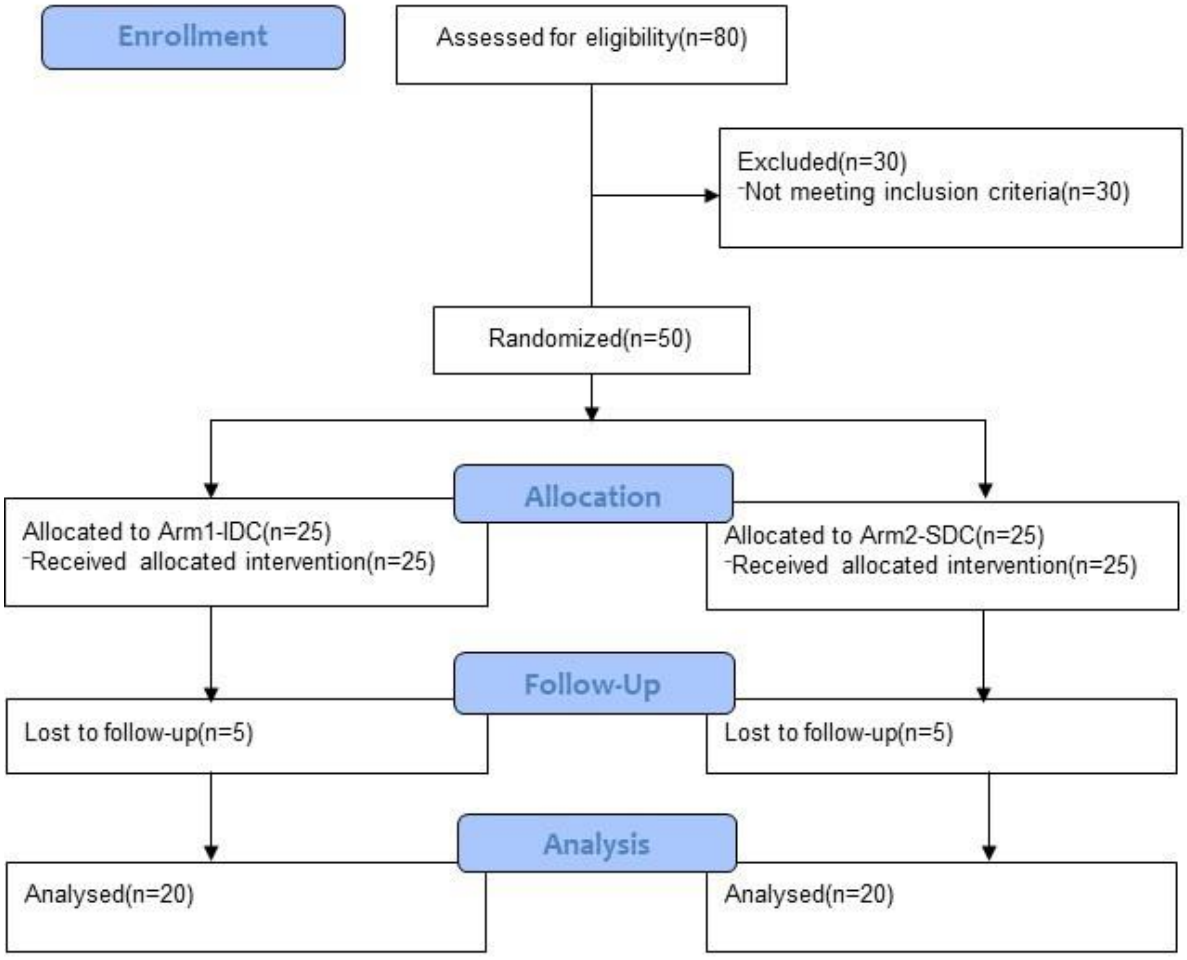

Figure 2: Consort diagram of patient flow through the study (data based on pilot study)

Samples of blood and saliva will be collected from all participants at screening/baseline, 6 and 12 months and analysed for inflammatory markers and bacterial composition and load.

Qualitative work to assess the acceptability of the IDC/study design to participants and dentists will also be undertaken.

Definition of End of Study

The end of the study is defined as the completion of the analysis of blood and saliva.

4.2 Study visits

4.2.1 Screening (post informed consent) and baseline assessment

Participants who have consented to take part in the study will first be assessed for eligibility against cognitive inclusion/exclusion criteria (in addition to the already assessed capacity to consent). The study dentist will then assess eligible volunteers for dental inclusion/exclusions. Participants meeting all inclusion criteria and none of the exclusion criteria will be enrolled. Baseline scores of cognitive and periodontal status will then be completed and samples of blood and saliva taken for inflammatory markers. All participants will receive oral and written oral hygiene education, toothpaste, a power toothbrush and an appointment to return to the Brain Centre after 6-months.

Immediately post the screening appointment, once baseline cognitive and periodontal status results can be combined, a Stratified Randomisation Schedule (computer-generated, concealed from recruiter until consent obtained) will be used to randomise participants to IDC(Arm1) or SDC(Arm2) stratified by cognitive status (MCI or early AD) and periodontal status (mild or severe). Participants will be contacted by their preferred method to confirm their randomisation to Arm1/Arm2.

As participants who do not meet screening criteria may be disappointed, they will be advised about other opportunities to become involved in research, such as participation in Patient Advisory Groups, or other studies that they may be eligible to take part in.

4.2.2 Intervention – IDC group

IDC (Arm1) participants will be informed they have periodontitis and invited to attend a series of visits (BDH or DFS-GDPr). These appointments may be at Bristol Dental Hospital (BDH), or at a Dental Foundation Scheme-General Dental Practice (DFS-GDPr) accredited to provide postgraduate training to Dental-Foundation-Trainees. Each DFS-GDPr has an appointed, accredited and salaried educational supervisor (ES) responsible for the training of the DFT. The study dental nurse will allocate the study participant to BDH or a DFS-GDPr taking travel time into account as far as possible. Periodontal treatment for these participants will be free of charge.

Dentists providing the intervention for the IDC (Arm1) participants (and ESs) will be given appropriate training/update training in the diagnosis, treatment planning and management of participants according to current UK guidelines [67], and the motivational techniques used successfully previously by the research team to improve participant compliance with oral hygiene regimes. A video of the intervention protocol (below) will also be made and provided for reference. Copies of dental charts taken as routine during the treatment of periodontitis will be provided to the study team.

Prior to implementing the IDC protocol a full periodontal assessment (<2 weeks post-randomisation) will determine the treatment plan and visits required to reach periodontal health (3-5 within the first 3-months).

IDC protocol:

1. Behaviour motivation and support for participants to attain and maintain effective plaque removal and reduce gum inflammation by a personalised, tailored oral hygiene regimen and motivational advice to maximise home-compliance [26,69].
2. Reduce/eliminate subgingival plaque and calculus with standard mechanical therapies and antibiotics if indicated clinically.
3. Address sites that respond poorly by repetition of standard mechanical treatment therapies and/or surgical interventions.
4. Deliver supportive periodontal care per current UK-guidelines [67] to maintain oral health

If participants in this arm (IDC) have a dentist we will inform the practitioner of their patient's participation in the study; the participant will attend our sites for the IDC, but their GDP for other routine care. The IDC will be free, and the patient should not incur any additional costs from their regular practice.

Participants will receive study-related 'reminders' throughout their participation, advice on the nature of these reminders will be sought from the PPI-lead/PAG.

4.2.3 Control – SDC group

SDC (Arm2) participants will be informed they have periodontitis and asked to continue their usual dental treatment, incurring the standard costs for their treatment. If they have a dentist the participant will already know they have gum disease and will be having treatment for it with the associated costs, they will not incur any additional costs due to study participation. If participants do not have a dentist they may choose to continue to abstain from dental treatment, in which case there will be no additional costs. If participants do not have a dentist but decide to see a dentist, their treatment costs will be no different to those normally incurred by patients.

Arm2 (SDC) participants who attend a dentist will be provided with periodontal treatment as part of usual dental care, however a recent NHS-GDP-practice survey showed active gum disease in 52.9% of patients even though 83.6% reported dental attendance in the previous year [70]. Without tailored personalised oral hygiene instruction, gum bleeding reduction is unlikely to be achieved [26,69].

With ethical consideration and PPI feedback, those in Arm2 will be offered free IDC after their 12-months on the trial. For those who can complete an 18-month cognitive assessment within the study timeframe, the IDC will be offered after this has taken place.

In addition, at the end of the study we will contact participants' regular dentists to share the IDC treatment regime performed and support its uptake in practice.

4.2.4 Visits at 6, 12 and 18 months

All participants will be invited to return to the Brain Centre, Southmead Hospital at 6 and 12 months for cognitive and periodontal assessments and to donate samples of blood and saliva. For those participants who remain in the study to 18 months, the 18-month assessment will be cognitive only and conducted over video if possible, with face-to-face assessment used if participants are unable to use a video link.

4.3 Assessments

Baseline, 6 and 12 months:

- Cognitive assessment: Clinical Dementia Rating Sum of Boxes (CDR-SB): an appropriate and widely used primary outcome measures for early and late dementia [71]. Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog11) [72], and Bristol Activities of Daily Living Scale (BADLS), measuring functional ability [73].
- Periodontal assessment: Bleeding on Probing (BOP) (yes/no); periodontal pocket depths (mm)-four gingival sites/tooth; dental plaque- O'Leary plaque index (yes/no)-four surfaces/tooth [74].
- Blood/saliva (laboratory research): Assessed for inflammatory response and bacterial load to confirm that bacteraemia and that pathogens have been reduced by the treatment.

18-months (cognitive only):

- Cognitive assessment: ADAS-Cog assessment over video. This assessment has been adapted and used successfully by the team in a recent previous study during the covid-19 pandemic. There is a precedent for comparing video and face-to-face ADAS-Cog, although this is not yet validated or mainstream. This assessment will not be audio-recorded, the assessor will record scores in the same way as they would in a face-to-face scenario.

Both the study dentist and cognitive assessor will be blinded to the treatment received by the participant.

Qualitative assessments (measuring impact on participants/dentists)
These assessments will be undertaken by the central research team at 12-month visit(participants), or on-line via Zoom/similar once the treatment course(s) is/are complete for their participants (dentists who delivered IDC):

In-depth, semi-structured, qualitative interviews will be carried out with 10-12 participants (5-6 from the control and 5-6 from the intervention group) as well as up to 8 of the dental teams who delivered the intervention. Interviews will follow a topic guide that will assess participants' acceptability of the intervention, barriers and facilitators to participation, the ingredients of the intervention that they felt had positively or negatively impacted on their behaviour and overall perceptions about the feasibility of the study. Dental teams will be asked similar questions, in addition to questions aimed to assess treatment fidelity with regard to the motivational intervention. Interviews will be audio-recorded and fully transcribed. It is expected that these will take about 30 minutes for each patient participant and 15 minutes for each dental practitioner.

Data will be thematically analysed using an inductive approach and following Braun and Clarke's (2006) [75] 6-stage process.

4.4 Statistics and Data Analysis

At randomisation participants will be stratified according to whether they have MCI or early AD as follows: Cognition stratification will be based on the Clinical Dementia Rating Sum of Boxes (CDR-SB): score with scores above 0.5 classed as early AD [71]. In the full trial the randomisation will also be stratified by periodontal disease classed as mild for periodontal pockets >4mm and <6 mm with bleeding on probing and severe: one or more periodontal pocket(s) ≥6 mm [67].

After data lock a CONSORT-diagram will be produced showing recruitment/consent/follow-up rates and treatment compliance with reasons for loss to follow-up. Progression rates for MCI/AD will

include all participants. The 80% confidence interval for all effect sizes (laboratory data/periodontitis scores/MCI or AD progression) will be calculated to assist with planning the full trial, illustrating proof of concept for sensitivity to change, ensuring effect sizes used in planning the definitive trial are plausible.

5. STUDY SETTING

Participant appointments for screening/baseline, 6, 12 and 18 months will take place at the Bristol Brain Centre, at Southmead Hospital, North Bristol NHS Trust (NBT), and is a building operated in partnership between NBT and the University of Bristol.

Participants allocated to the IDC will be treated either at Bristol Dental Hospital (UHBW NHS Foundation Trust), or at a general dental practice that is part of the South West Dental Foundation Scheme, or the dental practice of co-Applicant Nicholas Claydon. Up to 10 different sites will deliver the intervention.

Qualitative work will be undertaken on-line via Zoom/Teams or similar.

Laboratory analysis of blood and saliva samples will be undertaken in University of Bristol laboratories.

6. RECRUITMENT

6.1 Eligibility criteria

6.1.1 Inclusion Criteria:

1. Adults with amnesic or multidomain MCI [76] or early-stage AD [77] diagnosed using standard diagnostic criteria [76-78]. Participants are expected to have an Addenbrooke's, Montreal Cognitive Assessment (MoCA) or equivalent cognitive score in the typical range for early-AD/MCI (60- 94yrs)[79-80]. For Addenbrook's the typical range is 65-92 and for MoCA, 16-28. However, if participants clinically diagnosed with AD, meet test requirements, retain capacity and perform better or worse on Addenbrooke's Cognitive Examination (ACE-III) than expected, trial inclusion may proceed (case-by-case basis) as assessed by Dr Coulthard/another team dementia expert. This will make the trial as inclusive as possible and not exclude people with, e.g. prominent visual disturbance that disproportionately affects cognitive test performance such that scores do not reflect true cognitive ability or those with particularly high baseline function.
2. People who retain capacity to consent: Determined by a fully trained assessor. Where there is doubt about capacity, we will utilise a formal decision-making tool built around UK-legislation (MacCAT-T Brief screening tool [81]) and the decision taken by Dr Coulthard/another team dementia expert–in line with guidance [82].
3. A project partner (e.g. carer/friend) to attend at least the first appointment with participant (In our pilot study we amended the protocol to allow participants to attend thereafter without their partner as requested by some volunteers).
4. $\geq$6 teeth for adequate assessment of periodontitis
5. Aged 60yrs+
6. Periodontal pockets >4mm with Bleeding on Probing (BOP).

6.1.2 Exclusion criteria:

1. Uncontrolled diabetes
2. Uncontrolled dental disease other than periodontitis
3. Scores ≥3 on the American Society of Anaesthesiologists Physical-Status-Classification-System.

6.2 Sample size

The sample size is set to 50 participants for both allowing sufficient precision around the recruitment and follow-up percentages that will appear in the consort statement, and for the parameters to show the potential proof of concept for the underlying hypothesis using the surrogate end point of blood markers of inflammation.

50 participants with 25/group will allow us precision within 10% to predict follow-up data completion rates with 80% proof of concept confidence intervals such that a data completion rate of 80% would have the 80% confidence intervals of [71%, 87%]. Effect sizes for MCI/AD progression (n=50) will have 90% power to show 80% confidence intervals do not contain zero if the effect size is larger than 0.4 standard deviations. For the 25 in the intervention arm there is 90% power to show that periodontal improvement and blood markers of inflammation have 80% confidence intervals which do not contain zero if the effect size is larger than 0.6 standard deviations.

6.3 Recruitment

6.3.1 Identification of potential participants

Participants with MCI or early AD will be recruited via various avenues as follows:

Via co-applicants: Liz Coulthard (Research into Memory Brain Sciences and Dementia, Southmead Hospital); Vanessa Bishop (The Research Institute for the Care of Older People (RICE, Bath, UK)); Shaun Popel (Bristol Dementia Wellbeing Service (BDWS)); Phillip Loughnane (NHS General Dental Practices participating in Dental Foundation Training salaried schemes (DFS-GDPr's; 25 Bristol-region)); Nick Claydon (General Dental Practitioner (GDP)). These individuals will identify potential participants in their databases or who are in their care and provide them with study information if they are interested in taking part.

Via Avon and Wiltshire Mental Health Partnership (AWP) NHS Trust: Join Dementia Research (JDR) and the North Somerset Memory Service. JDR is an opt-in database where those with dementia or who are interested in acting as controls for dementia studies leave their details. The study details will be posted on this site and those who express an interest through the site will be contacted by study staff following JDR protocols. The AWP North Somerset Memory Service is a clinic for those with a dementia diagnosis. Study information will be provided to the site in formats such as posters and leaflets and the Service will pass these to potential participants identified either at clinic appointments or through database searches by AWP staff.

Via Great Minds (for Dementia): Similar to JDR this is an opt-in database where volunteers willing to contribute to dementia research register their interest. Great Minds is hosted by the Dementias Platform^{UK} (Medical Research Council), and an application to Great Minds to access individuals meeting study criteria will be made.

Via GP practices: using database searches and providing information in an appropriate form for potential participants who are visiting their GP. GP practices will identify potential participants

through data base searches to identify those who have a diagnosis of AD or MCI, and be provided with study information to send to these individuals in a form that appropriate for their practice. The GP practices will also be provided with brief information about the study for their waiting rooms in appropriate formats such as posters and leaflets. Interested participants will be directed to contact the study team for more details

Via Dhek Bhal (South Asian community group), Bristol Black Carers and other community groups: We will provide study information for websites or display in their premises, or that can be communicated by text message/email by the group co-ordinators using the methods agreed with the group co-ordinators/leads. Interested participants will be directed to contact the study team for more details, and we will encourage eligible individuals in this community to participate and will support translation needs.

Appropriate formats of study information prepared with the input of the PPI-Co-app and the study Patient Advisory Group (PAG) will be disseminated to locations/organisations as above, as well as memory cafes and their online equivalents, relevant community boards, clubs with an older demographic (with their permission), online-platforms including online and any other platform/by any other media suggested by the PPI-Co-app/PAG. If the opportunity presents itself study team members will attend memory cafes and/or their online equivalents to talk about the study its aims and what it involves. Easy-read versions of information sheets and consent forms are supplied with this application. These will be used to help explain the study to those who for whatever reason, such as language or literacy level, will find them helpful, however all participants will be provided with the full participant information sheet, all this information will be conveyed prior to consenting, using an interpreter if necessary.

Initial contact:

Interested participants/participant carers will be asked to contact the study team using details on displayed/distributed study information or to leave contact details at the leaflet/information source (e.g. GP practices), or will be approached directly by research nurses at memory clinics/by GP-letter/ by letter from Participant Identification Centres such as the BDWS, RICE, AWP North Somerset Memory Service). During an initial phone-call, the study team will provide more information about the study and answer any questions. If the individual remains keen to take part, the team member will establish if patients have a diagnosis, ask some basic eligibility questions to minimise unnecessary travel where a person could have been identified as unsuitable over the phone, take contact details and send full study information. A follow-up phone-call/email/letter as agreed with the potential participant/carer will answer any questions and a screening appointment booked if appropriate. A letter/email/text will be sent to the patient/carer confirming details.

Participants will be reimbursed standard class travel fares, fuel or taxis to a maximum of £20/visit for attendance at study appointments, travel costs above this threshold will be reimbursed where possible.

6.3.2 Consent

Participants who have expressed an interest in taking part in the study will be sent a copy of the participant information sheet prior to their study appointment in the format that they prefer (paper, electronic). At screening participants will attend Southmead Hospital (Brain Centre) so that dental and cognitive assessments can be performed in a single visit. Prior to any study procedures the cognitive assessor will go through the participant information sheet and take informed consent from the participant with the project partner/carer present, excluding individuals lacking capacity. Informed consent will be captured in written form, and captured on the Easy-read consent form where participants have initially received the Easy-read PIS due to language.

This study involves adults with AD, however we will only enrol those with capacity to consent. While a project partner will be recruited, they will not have to attend every study appointment as this is often not practical or necessary for those with early-stage cognitive-decline; in the pilot study project partners and participants requested that the requirement for the project partner to be present at all participant visits was removed. The project partner will be required to attend the screening appointment before capacity to consent has been confirmed. During the consent process the participant's capacity to consent and ability to (1) retain information long enough to make a decision, (2) understand what the decision relates to and consequences of not deciding, (3) understand the benefits, risks and inconveniences of study-participation, (4) communicate their decision, will be assessed. An autonomous informed and written consent form documenting the patient's decision to participate in the study will be completed prior to screening for study inclusion.

Where the individual's capacity to consent is in doubt, every effort will be made to maximise capacity using simple language/leaflets/drawings. Consent will only be obtained if the clinical psychologist believes the individual is competent to consent.

The project partner(carer/friend) will be involved in all aspects of the consent process and similarly asked to consent to support the participant in the study. Support will include reminding and aiding the participant when attending appointments, and with home-care dental-protocols. Should the carer/friend or participant wish to discuss any matters alone with the clinician this will be arranged.

6.4 Discontinuation/Withdrawal of participants

Each participant has the right to withdraw at any time and information relating to all withdrawals will be recorded. If a participant wishes to discontinue, data collected up until that point will be kept and included in the analysis.

Participants who have initially consented to participate and then lose capacity will be withdrawn from further study procedures. Data collected up until that point will be kept and included in the analysis.

7. SAMPLES – STORAGE AND ANALYSIS OF CLINICAL SAMPLES

Samples of blood and saliva will be collected from each participant at the Brain Centre in Southmead at screening, 6 and 12 months. At each of these visits one standard size tube of blood will be taken (approx. 5-8ml) and saliva will collected by asking the participant to swill a small amount of mouthrinse around their mouth and spit this into a collection pot – maximum 5-10 ml). These samples are taken for the research study only and not as part of any standard care and are for analysis under this protocol to determine bacterial load and variety in the saliva, and levels of immune markers in the blood. Consent for storage and future use of any anonymised unused samples will be sought.

Samples will be collected by the University research team members and stored on University premises frozen pending analysis. Analysis will be undertaken by the University team. Bacterial DNA will be amplified using standard techniques to allow quantification of total bacterial content and identification of key species. Proteins will be extracted from the blood using standard techniques and levels of inflammatory markers determined by ELISA or other similar standard technique for quantifying specific proteins. For the duration of the study only study staff will have access to the

samples, but consent for storage and future use of any anonymised unused samples will be sought. At the end of the study any unused samples with consent for future use will be stored in the research team's laboratories, storage will be indefinite as there is a Human Tissue Licence in place (12200), and the DI will permit storage on their licence pending an NHS REC application to use the samples in a future study.

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

The qualitive assessments (semi-structured interviews) will be undertaken by staff trained by the senior qualitative researcher, questions will not be of an upsetting or disturbing nature, they will simply explore the perceptions of participants receiving the intervention and dentists providing the intervention of its success. Participants will be asked to consent to be approached to take part in the qualitative research when they give informed consent at the start of the study, and both groups will give informed consent for the qualitative research prior to taking part in this. It is highly unlikely that the researcher would come into information that has safeguarding implications.

As indicated in '6.3.2 consent' above, this study will recruit those who have cognitive decline, but clear consent procedures are in place to ensure only those with capacity are recruited, and there are also procedures that will be followed if participants lose capacity to consent during the study. Participants must have a project partner who will consent to this role and support the participant with the study procedures.

The study intervention uses standard dental techniques and will be carried out by qualified dentists in dental practice. Dental assessments by the study team will be carried out by qualified dentists assisted by the dental nurse in appropriate facilities within the Brain Centre. None of the dental treatment should pose any risk above that posed by normal dental care.

The cognitive assessments will be carried out by a trained assessor.

8.2 Safety Reporting

Although unexpected, any adverse events will be recorded and reported in accordance with University Hospitals Bristol's Research Safety Reporting SOP if necessary.

8.3 Research Ethics Committee (REC) and other regulatory review and reports

8.3.1 Authorisations

The study will be performed subject to favourable opinion/ authorisation/permission or equivalent from all necessary regulatory and other bodies. This includes but is not limited to REC, HRA, NHS Trusts.

UHBW NHS Foundation Trust will be the study sponsor. With their input an application for NHS Research Ethics Committee and Health Research Authority approval will be prepared and submitted. This application will include the study protocol, all patient-facing material, insurance and indemnity confirmation, organisation-information-documents and SoECAT cost-assessment to enable

participating NHS sites to assess capacity and capability (CC), appropriate approval from non-NHS sites will be obtained where required. The chief investigator will ensure that the study will not start until approvals, CC, non-NHS site approvals (as appropriate) and sponsorship are in place. The study will be carried out in accordance with Good Clinical Practice guidelines.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will complete the amendment tool and following sponsor sign off, submit this for review to the bodies indicated by the tool. Information will be cascaded to study sites according to the HRA categorisation indicated. Once approved, the Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended. Amendments will not be implemented until all approvals that the amendment tool indicates are required are in place, and at a specific sites only after they have confirmed they can deliver the amendment.

All NHS REC correspondence will be retained by the Chief investigator in the study site file. Annual Progress reports will be submitted to the NHS REC until the study ends. At the end of the study the Chief Investigator will complete and submit an end of study declaration.

8.3.2 Research Governance Statement

This study will be conducted in accordance with:
- The principles of Good Clinical Practice, as set out in the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- The UK Policy Framework for Health and Social Care Research.

8.3 Peer Review

This study has been peer reviewed by panel members of the Research for Patient Benefit NIHR scheme and funding awarded.

8.4 Patient and Public Involvement

The Bristol-Dementia-Wellbeing-Service User-Group and our pilot-study design group (facilitated by the PPI & Engagement (PPI&E)-co-ordinator, provided feedback on this application. In response we have added GP and on-line platforms as recruitment routes, vetoed lumbar puncture and MRI as screening procedures, will include telephone pre-screening, and included IDC for those in Arm2-SDC at the study.

Study PAG meetings will be organised and run by the study team and the PPI co-app with the help of the PPI&E co-ordinator. The PPI co-app and PAG (10-12 members) will be re-imbursed (NIHR rates). Meetings will be held 5-times during the study, virtually if necessary and advice sought on things such as study documentation/slow recruitment rates/participant drop-out rates/accessible dissemination of study data. The PPI co-app supported by the PPI&E co-ordinator will be a key member of the PAG, liaising with the research team/setting PAG agendas and linking the PAG and research team providing bi-directional feedback.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time, any that occur will be documented such that the participant ID, date on which the deviation occurred, date on which it was resolved and a description of the deviation are captured. Protocol deviations will be reported to the Chief Investigator immediately and for any other than minor deviations also to the sponsor. Where procedures can be amended to improve protocol compliance, these will be implemented.

Deviations from the protocol which recur frequently will not be acceptable, and once identified action to minimise impact will be taken immediately. Such breaches could potentially be classified as serious.

8.6 Data Management

Where applicable a random sample of at least 30% of CRFs will be checked, by the study Research Team, against entries within the database and with the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. In addition, the first set of recruitment data collected from a new site will be scrutinized.

8.7 Data protection and patient confidentiality

The database and randomisation system will be designed so as to protect patient information in line with the General Data Protection Regulation. Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the study centres (as relevant) in line with the Ethics approval. All documents will be stored securely and only accessible by study staff and authorised personnel. Data will be collected and retained in accordance with the General Data Protection Regulation.

All investigators and study site staff will comply with the requirements of the UK 2018 Data Protection Act 2018 and General Data Protection Regulation (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Personal information to recruit participants will only be accessed by the patient's clinical care team, or if recruiting through a community group such as Dhek Bhal, accessed by the group in line with GDPR.

As participants are enrolled on the study they will be allocated a study ID. Information recorded about enrolled participants and for research purposes will be link anonymised using this study ID. The study co-ordinator will hold the study link in a password protected location behind the University of Bristol's fire wall. Participant contact details will also be held by the study team in a password protected location behind the University of Bristol's fire wall.

8.8 Storage of Records

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All essential documents, including patient records and other source documents will be retained for a period of 5 years following the end of the study. Where study related information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 5 years after the last patient last visit. Where electronic records are in use, trust policy will be followed.

Paper copies of consent forms will be held which contain the participant's name. These will be held in a secure locked cabinet in the dental clinical trials office and only accessible to study team members.

Participant contact details will be held only as long as is needed to complete participant follow up. Study documentation (link anonymised), and associated consent forms will be kept for 5 years in line with guidelines for RCTs, however if consent for future use of tissue is granted, consent forms relevant to this will be kept as long as the tissue is held and will be transferred at the end of the archiving period to the University of Bristol.

8.9 Indemnity

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Bristol's Public Liability insurance policy provides an indemnity to our employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including a Trust's responsibility for University of Bristol employees acting in connection with their NHS honorary appointments).

8.10 Access to the final study dataset

All study team members will have access to the full dataset. The data set will be stored in a data repository in anonymised form and will be available for use by bone fide researchers whose application for the use of the data will be assessed by a data access committee. Participants will be informed of the potential use of their anonymised data in future studies by means of the participant information sheet and consent will be sought, however if consent for future use of anonymised data is not granted the participant can still take part in the study, and their data will be removed prior to submission to the data repository.

8.11 Monitoring and Audit

The study will be monitored in accordance with UHBW's Monitoring SOP. All study related documents will be made available on request for monitoring and audit by UHBW, the relevant Research Ethics Committee and for any other regulatory authorities.

9 DISSEMINATION POLICY

9.1 Dissemination policy

The data arising from the study will belong to the study sponsor. Study data will be analysed by the research team and a final study report prepared. The Chief Investigator will co-ordinate the drafting

of the study report and the first publication. Credit to both sponsor and research team will be given, and the funding body will be acknowledged on all publications.

Following PAG review, at the end of the study a study synopsis and short video explaining the outcomes and their clinical relevance will be provided to study participants.

The study will be registered on the ISRCTN clinical trials website from which the protocol and links to study publication will be available to the general public.

9.2 Authorship eligibility

Publications will be drafted by the research team and individually named authors will be identified based on the criteria outlined by The International Committee of Medical Journal Editors.

10 REFERENCES

[1] World_Health_Organization, World Health Organization Fact Sheet for Dementia https://www.who.int/news-room/fact-sheets/detail/dementia 2020.

[2] Wittenberg R, H.B., Barraza-Araiza L, Rehill A, Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040. Care Policy and Evaluation Centre, London School of Economics and Political Science CPEC Working Paper 5. , 2019. https://www.alzheimers.org.uk/sites/default/files/2019- 11/cpec_report_november_2019.pdf.

[3] ONS.Gov, Deaths registered in England and Wales: 2019. Office for National Statistics, 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2019.

[4] Wattmo, C. and A.K. Wallin, Early- versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. Alzheimers Res Ther, 2017. 9(1): p. 70.

[5] Dementia care central 2021 Life Expectancy Calculator for Alzheimer's Disease & Dementia. https://www.dementiacarecentral.com/aboutdementia/life-expectancy-calculator/

[6] Bateman, R.J., et al., Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med, 2012. 367(9): p. 795-804.

[7] Knapp M, P.A., Burns A., Medications for treating people with dementia: summary of evidence on cost-effectiveness 2017. https://www.england.nhs.uk/wpcontent/uploads/2018/01/dg-medications-for-treating-people-with-dementia.pdf.

[8] (WAS 26) Dementia: Assessment, management and support for people living with dementia and their carers. London: National Institute for Health and Care Excellence (NICE); 2018 Jun. (NICE Guideline, No. 97.) 11, Cholinesterase inhibitors and memantine for dementia. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536484/

[9] Alzforum, Aducanumab Approved to Treat Alzheimer's Disease. https://www.alzforum.org/news/research-news/aducanumab-approved-treat-alzheimersdisease, 2021.

[10] https://www.neurologylive.com/view/biogen-50-percent-drop-aducanumab-price-feedback-costs)[

[11] Lewis F, S.S., O'Neill P, Cockcroft L, The Trajectory of Dementia in the UK – Making a Difference Office of Health Economics Consulting, 2014. https://www.alzheimersresearchuk.org/wp-content/uploads/2015/01/OHE-report-Full.pdf.

[12] Kinney, J.W., et al., Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y), 2018. 4: p. 575-590.

[13] Griciuc, A. and R.E. Tanzi, The role of innate immune genes in Alzheimer's disease. Curr Opin Neurol, 2021. 34(2): p. 228-236.

[14] Soscia, S.J., et al., The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One, 2010. 5(3): p. e950

[15] Kumar, D.K., et al., Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med, 2016. 8(340): p. 340ra72.

[16] Moir, R.D., R. Lathe, and R.E. Tanzi, The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement, 2018. 14(12): p. 1602-1614.

[17] Michelucci, A., et al., Characterization of the microglial phenotype under specific pro-inflammatory and anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta. J Neuroimmunol, 2009. 210(1-2): p. 3-12.

[18] Kempuraj, D., et al., Neuroinflammation Induces Neurodegeneration. J Neurol Neurosurg Spine, 2016. 1(1).

[19] Labzin, L.I., M.T. Heneka, and E. Latz, Innate Immunity and Neurodegeneration. Annu Rev Med, 2018. 69: p. 437-449.

[20] Heneka, M.T., et al., Neuroinflammation in Alzheimer's disease. Lancet Neurol, 2015. 14(4): p. 388-405.

[21] Dansokho, C. and M.T. Heneka, Neuroinflammatory responses in Alzheimer's disease. J Neural Transm (Vienna), 2018. 125(5): p. 771-779.

[22] Chapple, I.L., Time to take periodontitis seriously. BMJ, 2014. 348: p. g2645.

[23] White, D.A., et al., Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. Br Dent J, 2012. 213(11): p. 567-72.

[24] Kassebaum, N.J., et al., Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res, 2014. 93(11): p. 1045-53.

[25] Hajishengallis, G., T. Chavakis, and J.D. Lambris, Current understanding of periodontal disease pathogenesis and targets for host-modulation therapy. Periodontol 2000, 2020. 84(1): p. 14-34.

[26] Chapple, I.L., et al., Primary prevention of periodontitis: managing gingivitis. J Clin Periodontol, 2015. 42 Suppl 16: p. S71-6.

[27] Emery, D.C., et al., Comparison of Blood Bacterial Communities in Periodontal Health and Periodontal Disease. Front Cell Infect Microbiol, 2020. 10: p. 577485.

[28] Rutter-Locher, Z., et al., Association between Systemic Lupus Erythematosus and Periodontitis: A Systematic Review and Meta-analysis. Front Immunol, 2017. 8: p. 1295.

[29] Dickstein, J.B., H. Moldofsky, and J.B. Hay, Brain-blood permeability: TNF-alpha promotes escape of protein tracer from CSF to blood. Am J Physiol Regul Integr Comp Physiol, 2000. 279(1): p. R148-51

[30] Hirschfeld, J., Chapple, ILC (Editors), Periodontitis and Systemic Diseases: Clinical Evidence and Biological Plausibility. Quintessence Publishing 2021. ISBN 978-1-78698-100-4.

[31] Gaetti-Jardim, E., et al., Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. J Med Microbiol, 2009. 58(Pt 12): p. 1568- 1575.

[32] Chen, Z.Y., et al., The association of tooth scaling and decreased cardiovascular disease: a nationwide population-based study. Am J Med, 2012. 125(6): p. 568-75.

[33] Mesia, R., et al., Systemic inflammatory responses in patients with type 2 diabetes with chronic periodontitis. BMJ Open Diabetes Res Care, 2016. 4(1): p. e000260.

[34] Acharya, A.B., et al., Systemic Cytokines in Type 2 Diabetes Mellitus and Chronic Periodontitis. Curr Diabetes Rev, 2018. 14(2): p. 182-188.

[35] Baeza, M., et al., Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. J Appl Oral Sci, 2020. 28: p. e20190248.

[36] Kamer, A.R., et al., Periodontal dysbiosis associates with reduced CSF Abeta42 in cognitively normal elderly. Alzheimers Dement (Amst), 2021. 13(1): p. e12172.

[37] Nadim, R., et al., Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis. Eur J Epidemiol, 2020. 35(9): p. 821-833.

[38] Sadrameli, M., P. Bathini, and L. Alberi, Linking mechanisms of periodontitis to Alzheimer's disease. Curr Opin Neurol, 2020. 33(2): p. 230-238.

[39] Leblhuber, F., et al., Knock-on effect of periodontitis to the pathogenesis of Alzheimer's disease? Wien Klin Wochenschr, 2020. 132(17-18): p. 493-498.

[40] Dioguardi, M., et al., The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review. J Clin Med, 2020. 9(2).

[41] Kamer, A.R., et al., Periodontal disease as a possible cause for Alzheimer's disease. Periodontol 2000, 2020. 83(1): p. 242-271.

[42] Genco, R.J. and M. Sanz, Clinical and public health implications of periodontal and systemic diseases: An overview. Periodontol 2000, 2020. 83(1): p. 7-13.

[43] Beydoun, M.A., et al., Clinical and Bacterial Markers of Periodontitis and Their Association with Incident All-Cause and Alzheimer's Disease Dementia in a Large National Survey. J Alzheimers Dis, 2020. 75(1): p. 157-172.

[44] Choi, S., et al., Association of Chronic Periodontitis on Alzheimer's Disease or Vascular Dementia. J Am Geriatr Soc, 2019. 67(6): p. 1234-1239.

[45] Cerajewska TL, A.-B.S., West NX, Periodontitis and neurodegenerative diseases (Chapter 9). In: Periodontitis and Systemic Diseases, Quintessence Publishing UK, Hirschfeld & Chapple (Eds) 2021.

[46] West N, S.D., Davies M, Allen-Birt S., Associations between Periodontal Disease and Alzheimer's Disease: Can brushing your teeth affect Alzheimer's disease? Periodoncia Clinica, 2017. 8, 63-76.

[47] Shoemark, D.K. and S.J. Allen., Bacterial burden in disease, aging and Alzheimer's disease. In: Handbook of Infection and Alzheimer's Disease Miklossy,J (Ed.). pp. 133-149 IOS Press, 2017.

[48] Shoemark, D.K. and S.J. Allen, The microbiome and disease: reviewing the links between the oral microbiome, aging, and Alzheimer's disease. J Alzheimers Dis, 2015. 43(3): p. 725-38.

[49] Cerajewska TL, A.-B.S., West NX, Periodontitis and neurodegenerative diseases (Chapter 9). In: Periodontitis and Systemic Diseases, Quintessence Publishing UK, Hirschfeld & Chapple (Eds) 2021.

[50] Noble JM, Scarmeas N, Celenti RS, et al. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PloS One 2014;9:e114959

[51] Nilsson H, Sanmartin Berglund J, Renvert S. Longitudinal evaluation of periodontitis and development of cognitive decline among older adults. J Clin Periodontol 2018;45:1142–1149

[52] Iwasaki, M., et al., Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study. J Periodontal Res, 2019. 54(3): p. 233-240.

[53] Ide M, Harris M, Stevens A, et al. Periodontitis and cognitive decline in Alzheimer's disease. PloS One 2016;11:e0151081

[54] Tzeng, N.S., et al., Are Chronic Periodontitis and Gingivitis Associated with Dementia? A Nationwide, Retrospective, Matched-Cohort Study in Taiwan. Neuroepidemiology, 2016. 47(2): p. 82-93.

[55] Lee, Y.T., et al., Periodontitis as a Modifiable Risk Factor for Dementia: A Nationwide Population-Based Cohort Study. J Am Geriatr Soc, 2017. 65(2): p. 301-305.

[56] Chen, C.K., Y.T. Wu, and Y.C. Chang, Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther, 2017. 9(1): p. 56.

[57] Kamer, A.R., et al., Periodontal dysbiosis associates with reduced CSF Abeta42 in cognitively normal elderly. Alzheimers Dement (Amst), 2021. 13(1): p. e12172.

[58] Dominy, S.S., et al., Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv, 2019. 5(1): p.eaau3333.

[59] Emery, D.C., et al., 16S rRNA Next Generation Sequencing Analysis Shows Bacteria in Alzheimer's Post-Mortem Brain. Front Aging Neurosci, 2017. 9: p. 195.

[60] Miklossy, J., Bacterial Amyloid and DNA are Important Constituents of Senile Plaques: Further Evidence of the Spirochetal and Biofilm Nature of Senile Plaques. J Alzheimers Dis, 2016. 53(4): p. 1459-73.

[61] Poole, S., et al., Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis, 2013. 36(4): p. 665-77.

[62] Ishida, N., et al., Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. NPJ Aging Mech Dis, 2017. 3: p. 15.

[63] Wu, Z., et al., Cathepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide from Porphyromonas gingivalis in mice. Brain Behav Immun, 2017. 65: p. 350-361.

[64] Ilievski, V., et al., Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One, 2018. 13(10): p. e0204941.

[65] Arastu-Kapur, S., et al., Treatment of Porphyromonas gulae infection and downstream pathology in the aged dog by lysine-gingipain inhibitor COR388. Pharmacol Res Perspect, 2020. 8(1): p. e00562.

[66] Beason-Held, L.L., et al., Changes in brain function occur years before the onset of cognitive impairment. J Neurosci, 2013. 33(46): p. 18008-14.

[67] West, N., et al., BSP implementation of European S3 - level evidence-based treatment guidelines for stage I-III periodontitis in UK clinical practice. J Dent, 2021. 106: p. 103562.

[68] Jönsson, B., et al., The effectiveness of an individually tailored oral health educational programme on oral hygiene behaviour in patients with periodontal disease: a blinded randomized-controlled clinical trial (one-year follow-up). J Clin Periodontol, 2009. 36(12):1025-34.

[69] PHE, Delivering better oral health: an evidence-based toolkit for prevention. https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention/chapter-3-behaviour-change

[70] PHE, Oral health survey of adults attending dental practices 2018. 2020: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/891208/AiP_survey_for_England_2018.pdf

[71] Cedarbaum, J. M., et al., Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trial. Alzheimers Dement, 2013. 9(1 Suppl):S45-55

[72] Samtani, M. N., et al., Alzheimer's disease assessment scale-cognitive 11-item progression model in mild-to-moderate Alzheimer's disease trials of bapineuzumab. Alzheimers Dement, 2015. 1(3):157-169

[73] Bucks, R. S., et al., Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale Age Ageing, 1996. 25(2):113-20

[74] O'Leary, T. J., et al., The plaque control record. J Periodontol, 1972. 43(1):38-8.

[75] Braun, V. and Clarke, V., Using thematic analysis in psychology. Qual Res Psychol, 2006. 3(2) 77-101.

[76] Albert, M. S., et al., Diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease Alzheimers Dement, 2011.7(3): 270-9.

[77] McKhann, G. M., et al., Diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease Alzheimers Dement, 2011. 7(3):263-9.

[78] Petersen, R. C., et al., Mild cognitive impairment due to Alzheimer disease in the community Ann Neurol, 2013. 74(2):199-208

[79] Mathuranath, P. S., et al., A brief cognitive test battery to differentiate Alzheimer’s disease and frontotemporal dementia. Neurol, 2000. 55(11):1613–1620.

[80] Nasreddin, Z. S., et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc, 2005. 53(4):695-699.

[81] Grisso, T., et al., MacCAT-T:a clinical tool to assess patients’ capacities to make treatment decisions. Psychiatr Serv, 1997. 48(11):1415-9

[82] Pennington, C., et al., Tools for testing decision-making capacity in dementia. Age Ageing, 2018. 7(6):778-84.

APPENDICES

Appendix 1 Schedule of Procedures

Procedures	Visits						
	Screening at the Brain centre	Treatment visits in general dental practice (IDC group only)[1]			6 Month assessment at the Brain centre	12 Month assessment at the Brain centre	18 Month assessment (virtual if possible)
		1	2	3			
Informed consent	X						
Demographics	X						
Medical history	X						
Cognitive Inclusion/Exclusion	X						
Dental Inclusion/Exclusion	X						
Provision of electric toothbrush	X						
Provision of oral healthcare leaflet	X						
Cognitive Assessments	X				X	X	X
Dental Assessments	X				X	X	
Blood sample	X				X	X	
Saliva sample	X				X	X	
Randomisation	X[2]						
Intervention treatment (IDC group only)		X	X	X			
Motivational reminders (IDC group only)		X[3]	X[3]	X[3]			
Feedback interview						X	

[1]It isn't possible to be entirely prescriptive as to the number of treatments will depend on treatment need and there will be a personal approach. Three is the predicted average number.
[2]This will actually occur the day after this visit, and the participant contacted by their preferred means to let them know which group they are in and allocate a dental practice if they are in the treatment group
[3]These will actually be sent regularly until study participation ends