Study Title: A randomised clinical trial of vitamin D to improve cognition in people at risk of dementia

Short Title: Vitamin D for people at risk of dementia

NHS Ethics & HRA Ref: 19/WA/0007

IRAS Ref: 247136

ISRCTN Number: 79265514

Sponsor Ref: 1718/40

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Sponsor:	University of Exeter
PICs:	Devon Partnership NHS Trust
	Royal Devon University Healthcare NHS Foundation Trust
	South London & Maudsley NHS Foundation Trust
Funder:	JP Moulton Foundation

Chief Investigator Signature:

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

SIGNATURE PAGE

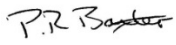
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor.

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

For and on behalf of the Trial Sponsor:

Signature: Date: 09/06/2023



Name (please print): Ms Pam Baxter

Position: Research Governance Manager (Health & Social Care)

University of Exeter Sponsor Representative

Chief Investigator:

Date: 09/06/2023

Signature: .....  .....

Name: (please print):

.....Anne Corbett.....

KEY TRIAL CONTACTS

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Committees	Trial Management Group: • Anne Corbett (chair) • Clive Ballard • Rod Taylor • David Llewellyn • Ellie Pickering • Kelly Hodge, Trial Administrator • Pam Baxter, Sponsor Representative • Mrs Diana Frost, Lay Member

i. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
CI	Chief Investigator
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee

SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

ii. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
JP Moulton Foundation 10 Buckingham Street London WC2N 6DF 0203 727 6609	**£265,272.00**

iii. ROLE OF TRIAL SPONSOR AND FUNDER

Trial Sponsor: The sponsor takes overall responsibility for the initiation, management and financing (or arranging the financing) of the research and must satisfy itself that appropriate arrangements are in place for management, monitoring and reporting of research activity. It is recognised that the sponsor can delegate specific responsibilities to any other individual or organisation where it is appropriate to do so. The University of Exeter undertakes to act as sponsor for the study.

Funder: The funder supports the financial requirements of the trial but has no role in the design, delivery or dissemination of the study. The research team will honour the Terms and Conditions of the funder, JP Moulton Foundation.

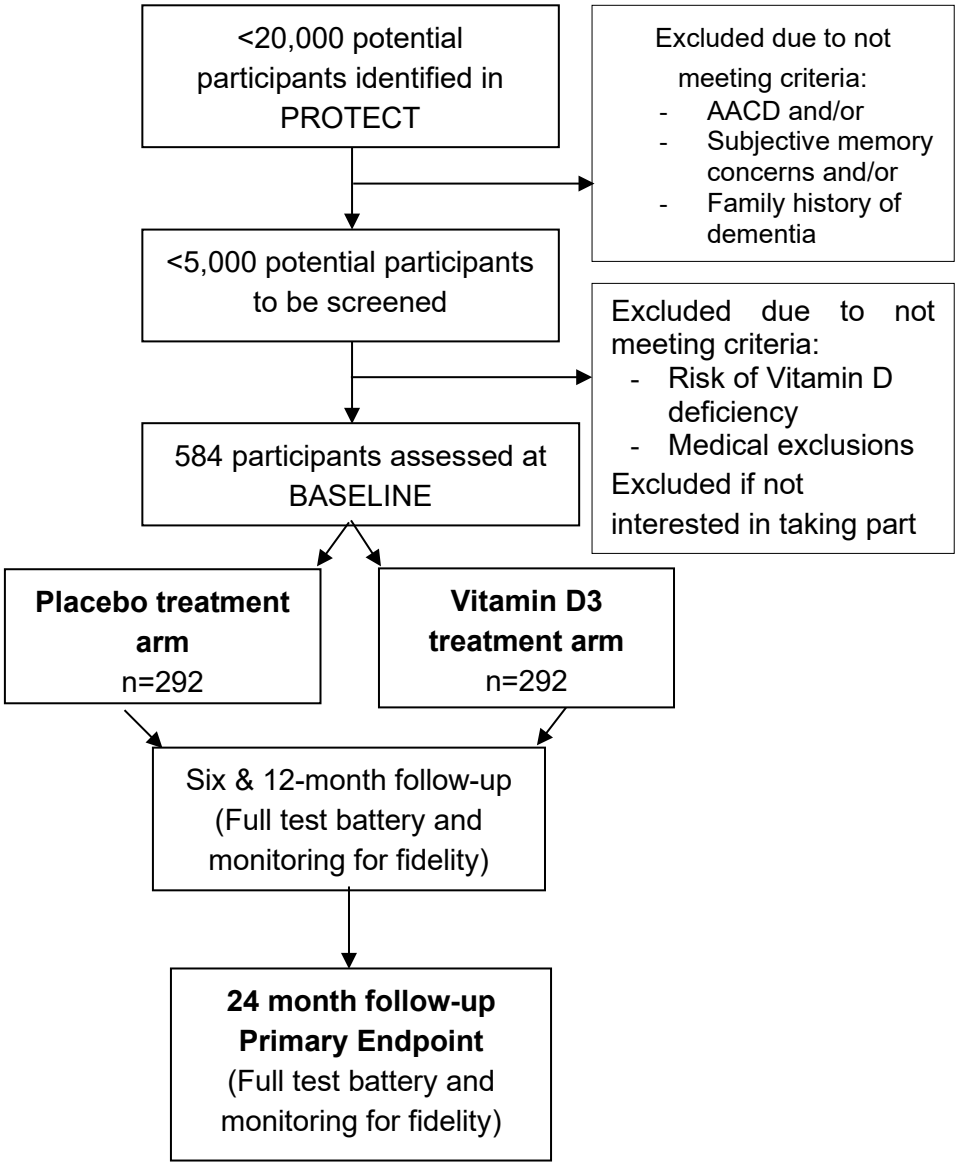
iv. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEE

Trial Management Group
The Trial Management Group will meet annually, with six-monthly teleconference to oversee the trial. Membership will consist of an independent statistician and two experts in the field. The TMG will have authority to end the trial early and will review any adverse events. A sub-group of the TMG will meet monthly to oversee the running of the trial and to coordinate interim reports from the study coordinator.

v. KEY WORDS: Vitamin D, online, Age-Associated Cognition Decline, Cognition, RCT

vi. TRIAL FLOW CHART

CONSORT Chart
The CONSORT chart below shows the proposed flow of participants through this study.



1 BACKGROUND

Dementia is a devastating condition that affects over 820,000 people in the UK[1]. It is characterised by the gradual loss of brain function which causes symptoms such as memory loss, changes in behaviour and difficulties with language. Dementia leads to loss of mobility, communication and independence, and eventually to death. Apart from the enormous emotional and personal impact, dementia exerts a considerable financial cost across society. This includes an additional substantial cost to individuals and their families who provide informal care for their loved ones, as well as an estimated cost of £26.3 billion each year to the UK health service[2]. Worldwide this figure reaches US$818billion.

While research continues to search for effective treatments there is increasing pressure to establish approaches to reduce the risk of cognitive decline and dementia, particularly in high risk groups who already have some degree of cognitive impairment. Cognitive decline is common amongst older adults. Whilst a degree of cognitive loss, or 'slowing down' of brain function, is a normal part of healthy ageing, it can also be a precursor to dementia. These more subtle forms of cognitive decline such as Mild Cognitive Impairment (MCI) are common in older adults. Between 5 and 10% of people with MCI develop dementia each year, making them a high risk group. Even more common is an earlier form of impairment known as Age-Associated Cognitive Decline (AACD). AACD is defined by subtle changes in key abilities, particularly problem-solving and memory, which indicate early changes in the brain that may lead to more severe changes later in life[3]. AACD can be detected in people who are otherwise completely healthy and functioning normally in daily life. There is no current diagnostic or treatment pathway for people with AACD, despite their high risk of developing dementia. Treatment for AACD is therefore a huge unmet need. Other key risk factors for the development of dementia later in life include a recorded family history of dementia in close family members and the recognition of subjective concerns of memory loss or cognitive change[4]. An approach that reduced risk of further decline would be an enormously powerful way of minimising dementia risk across a large sector of the population.

Reducing risk of dementia is now a major public health issue, and it has been highlighted in UK government strategy as well as by global health organisations[5,6]. The potential impact of a strategy to preserve cognition and delay the onset of dementia symptoms, even by a few months, could have a significant impact at a population level, and improve the health and wellbeing of older adults across the UK[7]. There is emerging evidence that prevention is a realistic way to reduce the burden of dementia which could result in improvements to society and individuals in the next decade[8]. There is also good evidence to support a number of different approaches for reducing the risk of dementia, of which one of the most promising is supplementation of key dietary elements[8]. There is good agreement amongst experts in the field that the most effective way to approach prevention is to tailor treatments to the needs of different groups rather than attempt a catch-all approach, due to the extreme complexity of cognitive health. This study therefore takes a 'precision medicine' approach and targets a specific, high priority group of at-risk individuals.

2 RATIONALE

A promising avenue for dementia risk reduction is through supplementation of dietary deficiencies, particularly with Vitamin D. A rapidly growing body of evidence strongly indicates that Vitamin D may play a role in brain health and cognition. We first identified Vitamin D as a potential intervention for dementia prevention in 2009 when we published the first large population study linking low vitamin D levels in 1,766 English older adults to cognitive impairment[9]. This was of considerable concern as a large proportion of older adults are vitamin D deficient[10]. Vitamin D receptors are found throughout the brain, and they are now thought to have several precognitive and neuroprotective effects. For example, vitamin D reduces the hallmarks of Alzheimer's disease including amyloid beta and phosphorylated tau[11]. We conducted the first large prospective study establishing that severe vitamin D deficiency (<25 nmol/L) increases the risk of substantial cognitive decline over six years by around 60%[12]. People with severe deficiency are around 120% more likely to develop dementia over a six-year period[13]. These landmark studies have been replicated by other groups and confirmed in a series of systematic reviews and meta-analyses[14,15]. Related animal studies have also been highly encouraging. For example, supplementing middle-aged rats for six months prevented cognitive decline and promoted hippocampal synaptic function[16]. If confirmed to be protective against dementia in humans, this would represent a major breakthrough that would have enormous impact worldwide.

Taken together this evidence presents a compelling case to suggest that vitamin D supplements may reduce cognitive decline and delay or even prevent the onset of dementia. The supplements are known to be safe for older adults, are very affordable and widely available. Uptake of dietary supplements is limited however, perhaps due to a lack of clear evidence from clinical trials. Indeed, analysis of a cohort of over 9000 people revealed that only 11.8% of people report taking any supplements. In spite of the robust supporting evidence there have been no large clinical trials of Vitamin D in people at risk of dementia. This study seeks to address this gap and to conduct a definitive trial to determine whether

Vitamin D supplementation is an effective means of reducing risk of cognitive loss in people with AACD. The study will focus on people who are also at risk of Vitamin D deficiency in order to target the treatment to an appropriate group.

This study will be delivered through the existing online PROTECT cohort. PROTECT is an online cohort of >20,000 adults aged 50 and over who complete annual assessments of cognition, health and wellbeing. PROTECT is also an online clinical trials platform (www.protectstudy.org.uk), offering automated data collection and identification of eligible participants. The large, fully characterised PROTECT cohort, all of whom have provided consent for contact, offers a tailor-made recruitment source for clinical trials.

2.1 Assessment and management of risk

The medication to be tested in this trial is a dietary supplement, not presented as a medicine, in a dose already available to the public. As per the MHRA guidance the intervention is not a medicinal product and thus this trial is not classified as a CTIMP.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

This trial aims to establish the impact of dietary supplementation with Vitamin D on cognition and day-to-day function in at-risk older adults with vitamin D deficiency and Age-Associated Cognitive Decline (AACD), subjective memory concerns and / or family history of dementia.

3.1 Primary Research Question

Can Vitamin D supplementation result in benefits to executive function in adults with dementia risk and vitamin D deficiency over two years (Primary Outcome)?

3.2 Secondary Research Questions

1. Can Vitamin D supplementation result in benefits to cognitive functioning in adults with dementia risk and vitamin D deficiency over two years (Secondary Outcome)?
2. Can Vitamin D supplementation result in benefits to day-to-day functioning in adults with dementia risk and vitamin D deficiency over two years (Secondary Outcome)?

3.3 Outcome measures/endpoints

All outcome measures will be collected at six, 12, and 24 months.

3.4 Primary endpoint/outcome

The primary outcome measure will be Trails B as measured through the PROTECT online test battery. This measure has been used to assess cognitive change in adults with dementia risk extensively in the literature (e.g. Park 2022, Kim et al 2021.

3.5 Secondary endpoints/outcomes

Additional secondary outcome measures will be cognitive domains measured by the cognitive test battery (Paired Associate Learning, Digit Span, Self-Ordered Search Task [working / spatial memory tasks], Switching Stroop and Grammatical Reasoning [Executive Function Tasks]) and day-to-day functioning as measured by the well-validated Instrumental Activities of Daily Living Scale. Cost-effectiveness of the Vitamin D treatment will be measured through the widely adopted EQ5D scale. All assessments will be carried out online through the PROTECT study. Cognitive measures will be completed in one session to reduce the burden on the participant. At the end of the study an anonymous online survey will be completed to capture participant experience of the study.

3.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the effect of vitamin D supplementation on executive function	Trails-B measure, completed in one session online on the PROTECT website.	Baseline, six, 12, and 24 months Primary endpoint is 24 months
Secondary Objectives To compare the effect of vitamin D supplementation on cognition, function and behaviour To establish the cost-effectiveness of vitamin D supplementation	Cognitive Test Battery (Paired Associate Learning, Digit Span, Self-Ordered Search Task [working / spatial memory tasks], Switching Stroop and Baddeley Grammatical Reasoning [Executive Function Tasks Instrumental Activities of Daily Living Scale Mild Behaviour Impairment Scale EQ5D scale	Baseline, six, 12, and 24 months
Tertiary Objectives Example: To monitor safety and compliance of vitamin D supplementation in the trial cohort To explore participant experience of taking part in an online trial	Adverse Event and Serious Adverse Event reporting in response to email prompts, or proactively by participants through the website, telephone or email Anonymous survey	Quarterly 24 months (after study completion)

4 TRIAL DESIGN

A two-year two-arm placebo-controlled double-blinded randomised controlled trial in 584 participants.

5 TRIAL SETTING

The trial will be run remotely, with participants receiving study tablets at home, and completing all assessments online via the PROTECT website.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Age 50 and over
- Already registered as a participant on the PROTECT study
- Fulfilling research criteria for dementia risk: Either (1) Performing at least one Standard Deviation below age-matched population norms in one cognitive test as measured using the validated PROTECT and COGTRACK™ cognitive test batteries; and/or (2) Reporting subjective memory concerns; and/or (3) Reported family history of dementia
- Fulfilling criteria for vitamin D deficiency risk: Defined by a self-reported scale to be completed on registration.
- Access to a computer and the internet.

6.2 Exclusion criteria

- Already taking part in another active interventional clinical trial
- Regularly take any supplement containing vitamin D. If the supplement is prescribed for a pre-existing condition the participant will be excluded. If the supplement is bought over the counter the participant will have the option of stopping the supplement and re-registering for the trial after a 28-day washout period.
- Diagnosis of dementia
- Taking the medication Digoxin (Lanoxin)
- History of physiological condition that specifically necessitates the avoidance of Vitamin D supplementation e.g. risk of renal stones

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

Recruitment of participants will be achieved through the PROTECT study cohort. The study operates entirely online, with existing participants receiving email reminders to log in and complete outcome assessments or register for new trials. All participants have given consent for contact and have full datasets for pre-screening. The PROTECT study has existing ethical approval (Ref: 13/LO/1578) and has been running since April 2015.

Participants with dementia risk will be identified anonymously through pre-screening of the existing PROTECT database. This will involve identification of people fulfilling the criteria for AACD through screening of cognitive test scores, those fulfilling criteria for family history through self-reported data provided on family history of dementia and those with subjective concerns about their cognitive health. Participants in the PROTECT study will be contacted via email and invited to take part in VitaMIND. The email will contain a link to the dedicated trial section of the site. Individuals known to fulfil the AACD and family history criteria will be automatically flagged for eligibility by the online system. Participants will also be asked if they have subjective concerns about their cognitive health in order to capture this third eligibility criterion. In the event that additional recruitment is required new participants will be approached through NHS Trust memory clinics, the Exeter 10,000 cohort of older adults (existing approval and consent for contact), through partner platforms such as Join Dementia Research (an online self-registration service that enables volunteers with memory problems, carers of those with memory problems and healthy volunteers to register their interest in taking part in research), and through national publicity.

10% of the study cohort will be randomly selected for compliance testing via a finger prick blood test. Participants in this sub-group will confirm their willingness to participate in the blood testing during registration and those selected will be sent a blood test kit in their welcome pack.

7.1.2 Screening

A series of screening steps will be completed to confirm eligibility. This will consist of:

- Confirmation of eligibility criteria (defined above) – Where possible these criteria will be screened by filtering of existing PROTECT data prior to participant contact but will be confirmed at registration using a tick-box process. New criteria will be screened at registration by completion of yes/no tick-box questions, covering:
    - Family history of dementia: Participants will be asked whether they have a family history of cognitive impairment or dementia.
    - Subjective concerns about cognitive health: Participants will be asked whether they are currently worried about their memory or other aspects of brain health.
    - Contra-indicated medication: Participants will be asked to state whether they are currently taking Digoxin. If so, they will be excluded.
    - Existing Vitamin D supplementation: As described above, participants taking existing vitamin D supplements will be offered the opportunity to re-register after a 28-day washout period, unless the supplements are prescribed by a medical practitioner.
    - Contraindication for vitamin D supplements: Participants will be asked if they have been advised by a medical practitioner not to take Vitamin D supplements due to an existing medical condition, for example due to risk of kidney stones. If so, they will be excluded.
    - Involvement in an ongoing interventional study
- Dementia Risk: Increased dementia risk will be a pre-requisite for invitation to the study. Participants will be identified as described in section 61. The risk profiles included in this protocol are still exploratory, and relevant to research purposes only. Therefore, participants will not be informed if they fulfil this criterion since communications of early cognitive impairment (which are too early for any clinical detection, treatment or support) carry an extremely high risk of unwarranted distress.
- Vitamin D deficiency risk: Participants will complete a screening questionnaire during the registration and consent process. This will involve completion of a tick-box list of the following pre-set risk factors:
    - BMI
    - Age
    - Smoking status
    - Self-rated health
    - Outdoor/physical activity
    - Osteoporosis
    - Marital status
    - Ethnicity
    - Alcohol consumption
    - Month of assessment

  Participants fulfilling criteria for vitamin D deficiency will continue into the trial. Any participants not fulfilling criteria will be informed and excluded at this point.

7.2 Consent

Consent will be given by participants following the approved online, electronic processes in place within the PROTECT study. This process is already ethically approved and occurs as follows:

1. Participants first access the Participant Information Sheet via their PROTECT study homepage. The PIS will be presented in online and printable format, and participants are required to tick a box to confirm they have read and understood the document.
2. Participants will then be presented with a new website page with each consent item in the approved Informed Consent Form. They will have to tick each item individually before they can proceed.
3. Once complete, participants then tick a further tick-box on the same consent page to confirm they consent to take part in the study.
4. Finally, a separate confirmation page appears for participants to confirm that they are consenting on purpose. This process ensures consent cannot be given in error.

5. Consents are time- and date-stamped electronically and stored on the PROTECT study database, linked to study ID and pseudo-anonymised to allow for linkage to personal details in the event this information is required for future contact.

7.3 The randomisation scheme

Randomisation of participants will be achieved through a purpose-built algorithm embedded in REDCap Cloud. This functionality exists within the REDCap Cloud architecture and will be tailored to account for the specific randomisation and stratification requirements of the VitaMIND study. This will occur after a participant has consented to take part in the trial. The randomisation algorithm will allocate participants randomly, but will stratify them by:

- Age (age brackets of five years)
- Gender
- Vitamin D deficiency severity (mild-moderate (< 50 nmol/L) or severe (< 25 nmol/L) Vitamin D level)

7.4 Blinding

Treatment allocation of participants will be recorded electronically in REDCap Cloud which is hosted by the University of Exeter's Clinical Trials Unit. This will ensure that both participants and research team will be blind to allocation, thus removing any bias. Administrative staff on the overall PROTECT study team that have direct participant contact will not be involved in any data analysis in order to avoid any unconscious bias as a result of their contact.

7.5 Emergency Unblinding

Emergency unblinding will be overseen by the authority of the TMG. In the event that emergency unblinding is required the linked dataset will be accessed by an independent administrator from the PROTECT study team (outside of the VitaMIND study team) using the participant identifier via the administration portal on the PROTECT site to reveal treatment allocation of the individual participant. Access permissions for the administration portal will be restricted to the VitaMIND trial coordinator and supporting administrator in the PROTECT team (who will act as the independent administrator in the event of unblinding). Access to the portal does not automatically provide access to personal details, as this is password-protected in a separate database. Passwords will be held by the Trial Coordinator, under the supervision of the Chief Investigator, and will only be approved for use where required for safety and unblinding procedures.

7.6 Baseline data

Participant data will be pulled from the PROTECT main dataset to populate the baseline data point. This will include:

- Age
- Gender
- Education level
-
- Use of brain training games prior to randomisation (not an eligibility or randomisation factor – for us in analysis only)
- Lifestyle factors as captured by the PROTECT lifestyle questionnaire (not an eligibility or randomisation factor – for use in analysis only)

Cognitive Assessment data and all other trial-specific measures will be collected within the trial areas as part of the scheduled assessment at baseline.

7.7 Trial assessments

Assessments will be conducted at baseline, 26, 52, and 104 weeks. Participants will receive weekly automated emails notifying them that assessments are available to complete until they are completed or no longer available. The assessments will become available for completion two weeks before the assessment point and remain open for completion during the week of the assessment point and a further five weeks, making them available for eight weeks in total. Missing data or late data will be accounted for within the analysis plan.

Assessments will follow the set online assessment protocol described below.

1. scale Trail-making B (primary outcome measure)
2. PROTECT Cognitive Tests: Switching Stroop Test, Baddeley Grammatical Reasoning , Self-ordered Search, Digit Span, and Paired Associate Learning Tasks (secondary outcome measures)
3. Instrumental Activities of Daily Living
4. EQ5D measure of health and wellbeing
5. Mild Behaviour Impairment Scale

An anonymous survey will be completed at the end of the study to provide a process measure and to capture participant experience.

7.8 Withdrawal criteria

Withdrawal by participant
Participants are free to withdraw from the trial at any point without giving a reason. This can be achieved by selecting the withdrawal option on the study website or by contacting the study team by email or telephone.

Withdrawal due to non-compliance
Any participant not fulfilling criteria for compliance after one week will be withdrawn from the trial. Compliance will be established by a telephone call at the one-week time point in which participants will be asked to confirm they are taking their Vitamin D study tablets. This will be recorded in REDCap Cloud by the study administrator.

Withdrawal due to loss of capacity
Cognitive status would usually be monitored by a medical practitioner at a clinical visit using a clinical assessment tool such as the Mini-Mental State Examination (MMSE) or similar. Since this study is conducted remotely, cognitive ability of participants will be monitored through an existing algorithm which is built into the PROTECT system. It is based on completion of the cognitive tests described above which are considerably more sensitive to change than the MMSE. Any participant flagging as performed more than one standard deviation below age-matched norms on two cognitive tests in two consecutive assessments will be reviewed by one of two named study doctors (Dr Sue Dyson / Professor Clive Ballard). If concerns are considered to be valid the participant and their GP will be contacted by the study doctors to recommend further assessment, and the participant will be withdrawn from the trial.

Withdrawal procedure
At the point of withdrawal participants will receive notification by email. Anonymised data will be retained. Participants will have the option to remove all personal data with the exception of the minimum required for record of consent. Participants will be sent a pre-paid envelope to return any unused tablets for disposal.

7.12 End of trial participation

End of trial is defined as the last assessment point completed by the last participant to enrol in the study or six weeks after the last participant's last time point if the last assessments are not completed.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

Vitamin D capsule single dose (4000IU)

8.3 Product Characteristics

Composition: Microcrystalline cellulose [*bulking agent*], Vitamin D3 preparation (Maltodextrin, Starch, Sucrose, Cholecalciferol), Hydroxypropyl methyl cellulose [*Capsule*], Magnesium stearate [*anti caking agent*], Silicon dioxide [*anti caking agent*]

Preparation: Two-piece HPMC capsules, provided in blister packs of 28 capsules stamped with the day of the week to aid compliance

8.4 Supplement storage and supply

Vitamin D tablets and placebo will be manufactured by HealthSpan Ltd and packaged in blister packs of 28 pills, with days of the week marked on the packet. The shelf life of capsules is a conservative two years, but to ensure dosing capsules will be delivered quarterly unless the government COVID-19 alert is level 2 or higher in which case a larger supply will be sent to mitigate against the risk of site closure due to a lockdown. Capsules can be stored at room temperature with no additional special requirements.

8.5 Preparation and labelling of Supplement

Blister packs of study supplements will be labelled with the participant ID and batch number. The Clinical Trials Unit at the University of Exeter will provide recording and mail-out services. The CTU is fully registered and qualified as a research facility and is fully compliant in participant confidentiality procedures. Postage will comply with regulations pertaining to mailing of research/hazardous materials, using pre-labelled envelopes, sealed boxes and tracked delivery. The randomisation schedule will be directly accessed through REDCap Cloud by the Clinical Trials Unit staff member who will be unblinded to treatment allocation. This staff member will be responsible for labelling and sending out trial tablets, recording dispensing and reporting back to the VitaMIND team to ensure dispensing activity is recorded in the study database.

8.6 Dosage schedules

Participants will be instructed to take one tablet per day for two years. For the active supplement each dose will contain 4000IU of Vitamin D3.

8.7 Known drug reactions and interaction with other therapies

Possible severe interaction with Digoxin. Participants taking this medication will be excluded from the trial.

Guidance on taking supplements: Participants will be instructed to take one tablet per day. There are no known side effects of vitamin D supplementation within the dose used in this study. In the event of an extreme overdose (usually occurring after taking consistent high doses of 60,000IU per day for several months) symptoms include nausea and vomiting, weakness and frequent urination, followed by osteopain and kidney complications. This is extremely unlikely to occur within this trial but participants will be guided to be aware of symptoms in case of an overdose and provided with clear signposting to contact their GP for support if this occurs, in addition to reporting the event to the study administrator.

8.11 Assessment of compliance with treatment

Compliance Monitoring: Monitoring of participant use of the tablets will be achieved through a 'medication diary' on the PROTECT site which will ask participants to provide a quarterly tablet count, both of which will be entered online. This will also be supported through reminder emails and regular newsletters from the PROTECT study. This process is anticipated to be highly effective. However, since it is reliant on participant adherence and fidelity, an additional sub-group of compliance testing will also be performed (see below).

Sub-group Compliance Monitoring: In addition a sub-group of 10% of the total cohort (n = 58) will be recruited to complete a finger prick test to analyse blood levels of Vitamin D3 metabolites at baseline and primary endpoint (24 months) as a further compliance measure. This process will be delivered through partnership with the Sandwell and West Birmingham NHS foundation Trust test facility. This process will involve:

- Sub-group compliance participants allocated to the first 10% of randomised participants
- Study administrator attaches participant identifier label to test kit and posts kit to participant
- Participants will receive a test kit to complete at home, involving a short finger prick test
- Participants use pre-addressed envelope to send their completed test to the Sandwell and West Birmingham NHS Foundation Trust test laboratory
- Laboratory completes Vitamin D3 analysis according to published protocols using anonymised sample identifiers. No sample is retained after analysis
- Laboratory returns anonymised test results to study team

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect

	Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

Adverse Event

An AE is defined as any medical event occurring to a participant during the two-year study that requires medical intervention.

Serious Adverse Event

An SAE must fulfil the following criteria:

- Hospitalisation, excluding admission for scheduled and elective surgery
- Death
- Life-threatening condition, excluding conditions already in an unstable state at registration

9.3 Recording and reporting of AEs and SAEs

All AEs and SAEs occurring from the time of **start of trial treatment** until the end of the trial will be reported by participants using an online form. Participants will be prompted to enter any details of events at each login event (quarterly) and encouraged to report any event proactively using the online form or by contacting the study team by telephone and email. All AEs will be logged in REDCap Cloud.

Receipt of an AE or SAE on the system will prompt review by the study team. AEs will be reviewed by at least two members of the TMG. SAEs will be reviewed by a study clinician within

24 hours. The participant, and their GP where appropriate, will be contacted for follow-up and recommended action. The Sponsor will also be informed.

AE and SAE actions and monitoring will be recorded electronically, including the following information

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information will be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Absent participant follow-up

In the event that a participant who has entered the intention-to-treat cohort fails to complete any online activity on two consecutive timepoints they will be contacted by telephone by a study administrator. The purpose of the call will be to verify the health and wellbeing of the participant. If any suspected AE is detected this will prompt an AE report.

9.4 Responsibilities

Principal Investigator (PI), Trial Coordinator and clinical delegate (TMG member):

Initial review of any AEs when reported by a participant

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.
4. Central data collection and verification of AEs and SAEs
5. Reporting safety information to the oversight committees identified for the trial (Trial Management Group) according to the Trial Monitoring Plan.
6. The unblinding of a participant for the purpose of expedited reporting

Trial Management Group (TMG):

In accordance with the Trial Terms of Reference for the TSG, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The sample size calculation is based on a published study of online cognitive training in adults over 50, which showed significant change in executive function in adults with AACD (Corbett, et al. 2015b). Based on an effect size of 0.3, which is clinically meaningful and has been achieved through similar trials in this field, 234 participants would be required for each group to provide 90% power at a two-sided 0.05 significance level and assuming a conservative drop-out rate of 20%. Therefore, a total of 584 participants (293 per group) will be recruited.

10.2 Planned recruitment rate

Based on recruitment to trials previously delivered through PROTECT we anticipate a recruitment rate of at least 300 per month. A three-month recruitment window has been defined but will be extended following recruitment review if required.

10.3 Statistical analysis plan

All statistical analyses will be undertaken according to a predefined detailed statistical analysis plan (SAP) agreed in advance with the trial management group, trial steering committee.

Baseline sociodemographic and outcome variables will be reported and compared descriptively by treatment arm.

The primary analysis will be conducted on an intention-to-treat basis comparing both primary and secondary outcomes between treatment and control groups in those with complete data at week 104 follow up. Linear regression models will adjust for baseline score and stratification variables.

Secondary analyses will include: between group comparisons at all follow up time points using mixed model repeated measures approach; between group comparison of primary and secondary outcomes at primary outcome time point based on imputed outcome data (using multiple imputation models based on an assumption that data is missing at random); per-protocol analysis using an estimated complier average causal effects analysis (CACE) of the primary outcome at the primary outcome follow-up data; and an exploratory assessment of subgroup effects using interaction terms based on subgroup effects. Prior to analysis and to be defined in the SAP, the trial management group will pre specify the per-protocol definition and subgroup.

All analyses will be undertaken by a statistician blinded to group allocation. Results will be reported means and 95% CIs.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

All data will be collected online via the PROTECT platform, which conforms to all UK GDPR regulations and the Data Protection Act 2018. Trial data will be stored in a bespoke fully encrypted trial database in a linked anonymised format. The database will be stored online on University of Exeter servers and in cloud-based storage provided by Microsoft Azure (UK site). Full details are available in the PROTECT study specification documentation.

Some of the participants' personally identifiable (PII) and some sensitive data will be manually entered into REDCap Cloud for randomisation and stratification for treatment allocation. Password protected Excel spreadsheets stored within the secure trial management files on the University of Exeter shared drives will be used to manage dispensing, log Adverse Events and record the outcome of the compliance telephone call.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

11.4 Data Recording and Record Keeping

All data collected on the PROTECT platform for VitaMIND will be stored in Microsoft Azure UK region SQL databases. Personally identifiable data will remain in the PROTECT cohort database using a unique and independent ID and held on a separate database from the non-identifiable trial results data. There will be no means of linking the two data sets via the databases. Backup instances of the data will be created daily.

Only approved database developers will have access to personally identifiable data through the electronic database. A combination of the management portal and REDCap Cloud will give the approved administration team access to the information required to liaise with participants, extract randomisation information for dispensing and follow up any Serious Adverse Events. The administration portal and REDCap Cloud require username and password login.

Data may also be downloaded from the data portal and stored alongside other study documents in password-protected databases, which only the study team will have access to. Any paper records (copies and/or original documents) deriving from or belonging to the study will be kept in a locked filing cabinet, in a locked room, in a secure building the University of Exeter Medical School. Where applicable, these records will be pseudonymised by physically obscuring any PII and replacing it with the participant's Results ID.

The anonymised dataset will be retained for 10 years after the end of the trial. Where data is part of the overall PROTECT dataset this will be retained for the length of the PROTECT longitudinal study. Data will be made available for reuse based on the University of Exeter's Open Research Exeter (ORE) policy for open access. Investigators wishing to access study data will complete a data access application. This is required since some trial data is also held as PROTECT study data.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects.

13.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3 Approvals

This trial is subject to full NHS REC and HRA review. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All documentation relating to ethics and approvals will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended

It is the Chief Investigator's responsibility to produce the annual reports as required and to notify the REC and Sponsor of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC and Sponsor, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

13.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5 Participant Confidentiality

Data protection processes will be fully compliant with the UK General Data Protection Regulation 2018 and Data Protection Act 2018. All investigators and staff will comply with UK GDPR with regards to the collection, storage, processing and disclosure of any personally identifiable information (PII) and will uphold the regulation's core principles.

All PII will be stored as per in a separate and encrypted participants database, stored on a cloud-based server provided by Microsoft Azure and held within the UK region. Unique participant IDs will be created for each participant, using an unrelated sequence of characters, and this will not be linked to the pseudo-anonymised results data held in a separate database.

Only approved database developers will have access to personally identifiable data through the master electronic database. A management portal will give the Chief Investigator, Prof. Anne Corbett, and the delegated administration team, access to personal information where required for the trial. Access to PII will be limited to the administrator responsible for sending out trial capsules, welcome packs and blood test kits, and this role will occur in a secure room at the University of Exeter Medical School. To achieve this, the minimum required PII will be extracted from the participants database (name and address), access to a portal that requires authorised login from which an authorised member of staff can use the unique participant ID to look up the name and address held for the participant and print straight from the portal so no data leaves the database or is stored outside the database. PII may also be stored in password-protected databases located on University of Exeter shared drives, which only the study team at the University will have access to.

Access to PII outside of the master electronic database and management portal (i.e. paper copies and participant email correspondence to the PROTECT helpdesk) will be limited to the Chief Investigator and the delegated administration/ managerial team. PROTECT study clinicians may gain access to PII for the purpose of reviewing cognitive performance data (please see section 9.2).

In the event of a subject access request (SAR), the individual will be provided with the UoE Data Subject Request Form including the contact details for the designated Data Protection Officer and will be advised to submit their request in writing.

No PII data will be transferred to any other third party without written participant consent, and PII will not be included in any analysis files or study disseminations. PII will be stored for three years after the study has ended. It will then be destroyed. Pseudonymised and anonymised information will be kept indefinitely and up until the study objectives have been achieved. If the participant continues to be involved in the overall PROTECT host cohort their PII will be retained in the core PROTECT study participants database as per study protocols.

The data custodian for this trial is the Chief Investigator, Prof Anne Corbett (*a.m.j.corbett@exeter.ac.uk*).

13.6 Public and Patient Involvement

This study has benefitted from a number of PPI activities including consultation with the NIHR Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC) PPI Group, who prioritised the study, and a PPI workshop with volunteer carers hosted by Alzheimer's Society. The protocol has also been refined following consultation with a lay focus group. PPI will be delivered for this study through the existing lay advisory group for PROTECT, which is a group of older adults including carers and former carers of people with dementia. The group will meet at key points throughout

the study and will be consulted on major issues such as recruitment and retention strategies. Members of the PPI group will be invited to raise any discussion points with investigators, and a member of the group will be a permanent member of the Project Management Group to ensure full representation across the study. Where wider discussion with lay groups is deemed necessary the PPI group at the PenCLAHRC group, hosted at the University of Exeter, will be consulted and online channels available through the PROTECT study will be utilised.

13.5 Protocol compliance

Protocol compliance will be monitored by the Trial Coordinator and reviewed by the TMG. Deviations will be documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

None

13.9 Indemnity

Indemnity will be covered by the standard insurance cover produced by the University of Exeter as Sponsor and as detailed in separate documentation.

13.10 Amendments

Substantial amendments will be approved by the TMG prior to request for Sponsor sign off and subsequent submission to the REC and notification to the HRA Amendments Team. Non-substantial amendments will be signed off by the Sponsor prior to submission to the HRA Amendments Team. No amendment will be actioned until full approval has been confirmed from local sites supporting the trial. Amendments will be recorded in Appendix A.

13.12 Access to the final trial dataset

Access to the trial dataset will be restricted to the TMG members. Applications for access to the dataset will be considered on a case-by-case basis by the TMG. There are no specific terms set by the funder for data access.

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16 APPENDIX A: AMENDMENTS HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	**4.0**	**10th July 2019**	**Anne Corbett**	**Addition of REDCap Cloud to manage dispensing records; clarification of vitamin D deficiency level scale; removal of CogTrack cognitive tests; follow-up for missing participants**
2	**5.0**	**28th Oct 2019**	**Anne Corbett / Ellie Pickering**	**Broadening of eligibility criteria to include family history of**

				dementia and/or subjective memory concerns; removed stratification of AACD, Assessment scheduling change following TMG; addition of memory clinics as recruitment channel; updated end of trial definition; updated a few inconsistencies in text resulting from changes made in previous amendment; clarification that baseline assessments will be done at registration, prior to tablets being sent
3	**6.0**	**7th Sept 2020**	**Ellie Pickering**	**Aligning definition of AACD to more standard definition requiring performance of 1 standard deviation below the age matched norm on one or more PROTECT cognitive test; clarifying "online cognitive tests" refers to COGTRACK™ cognitive tests; addition of partner platforms such as Join Dementia Research for participant identification; mitigating against the risk of a COVID-19 lockdown by sending larger supply of tablets when government Covid-19 alert levels are 2 or higher; update key references section; update trial administrator due to staff change; aligning email assessment reminder schedule to existing scheduling rules on PROTECT platform to avoid confusing participants or sending too many reminders**
4	**7.0**	**9 Sept 2022**	**Anne Corbett**	**Added anonymous end-of-study survey as process measure**
5	**8.0**	**5 May 2023**	**Anne Corbett**	**Change length of trial to two years from three due to a review of the study design by the TMG which gave confidence in the primary outcome measure at 2**

				years, and the confirmation that power has already been achieved for the two-year outcome. In addition, ending at two years will reduce participant burden and avoid the need for further expenditure on study tablets. **Update to technical description to database to accurately reflect its design.** **Change to primary outcome measure from one cognitive test measuring executive function (Grammatical Reasoning) to another cognitive test of executive function (Trails-B). Trails-B is a widely used test in Alzheimer's research and because it is presented first in the online cognitive test battery, the completion rate is expected to be higher, allowing more data points to be included in the analysis of primary outcome measure.** **Change to power calculation to reflect the amended executive function primary outcome measure**