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A flexible initiative to test therapies for Alzheimer's disease

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Registration date 09/02/2026	**Overall study status** Ongoing	
Last Edited 09/02/2026	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Research into Alzheimer's disease is making progress, but big challenges remain. The proposed project, AD-SMART, is a quicker, more efficient way of identifying effective treatments for Alzheimer's. The trial will be for a period of about four years. It will test whether either of two existing medicines (atomoxetine and immediate-release (IR) metformin) can relieve and improve symptoms in patients with Alzheimer's. Currently, they are used for other illnesses and are known to be safe and effective for those diseases. It will also assess each treatment's side effects (if any), whether they improve quality of life, and offer the health service sufficient value for money.

Who can participate?
Patients with symptoms of Alzheimer's disease.

What does the study involve?
The trial will compare current standard care and each of two treatments with that care. There will also be a dummy treatment, known as a placebo. The drugs were chosen by an international panel review process, together with patient and public input.
A drug treatment will be considered successful in AD-SMART if, over 18 months, it is both safe and shows a meaningful difference to patients' quality of life in one or more of the following measures:
• cognitive symptoms (e.g. memory, problem solving).
• ability to perform daily activities (e.g. showering, cooking).
These will be tested in person at the start of the trial, and at intervals of six, twelve and eighteen months.
The research team will collect blood samples at the same time as these clinical tests to learn how changes in levels of certain blood markers are linked to the progression and severity of Alzheimer's. They will also conduct MRI scans at the start and end of the trial to look for changes in brain structure.
This information will allow us to improve our understanding of how the treatments work to reduce symptoms and affect the progression of the disease.

Following the screening and baseline appointments and once randomisation in the trial database is complete, participants will be contacted for follow-up visits with an additional weekly telephone call during the 4-week titration phase. Trial treatment should ideally be started within 2 weeks of randomisation. The screening, randomisation, week 26, week 52 and week 78 visits must be conducted in person at the AD-SMART trial site. All other study visits can be conducted remotely (via video or telephone). If bloods are required for a remote labelled visit, these can be collected via primary care or other phlebotomy clinics and results provided to the site team. Participants will only move up in titration if the dose is tolerated, there are no adverse events, or the clinician deems it appropriate to move up in titration if there is an adverse event reported, and only after the telephone assessment.

Prior to entering the study, the participant will be asked to have a blood test and an ECG for safety tests. Additional research blood samples for translational work will also be requested at baseline, week 26, week 52 and week 78 (final visit).
At the same time, the participant and their study partner will be asked to complete several assessments and questionnaires each visit to assess how they are living with AD, e.g. the EQ-5D-5L, ZBI, A-IADL-Q-SV (at baseline, week 26, week 52 and week 78).

What are the possible benefits and risks of participating?
It is hoped that participants will be helped by having any of the medications in this study, but this cannot be guaranteed. That is the reason the study is being conducted.
It is possible that the results may not help the participants, but the information obtained from this study will help us to improve treatment for future patients with AD.
The tests completed as part of the trial may find other health care concerns or illnesses that may be affecting the trial participants. If they do, the study team will follow their usual process to address these. This may include informing their GP so that they can follow up with them.
If benefit is shown, an application will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) with supporting documentation showing its effect. The MHRA will review this and ensure it meets the strict standards for quality, safety and effectiveness before licensing it for use within mild to moderate Alzheimer's Disease. This information will then be passed on to the National Institute for Health and Care Excellence (NICE), which will assess the cost-effectiveness for the NHS to fund the medication. If approved, the medication will then be available on the NHS as treatment for mild to moderate Alzheimer's Disease. Licensing may also be applied for in other countries around the world.

Questionnaires: Some of the questions asked may be upsetting, or the participant and their study partner may feel uncomfortable answering them.
Blood samples: Taking blood from a participant's arm may cause faintness and/or swelling, pain, redness, bruising, bleeding
at the collection site, or infection (infection rarely happens) at the site where the needle is inserted.
Electrocardiogram (ECG): Skin irritation is rare but could occur during an ECG from the electrode patches or gel that
is used.

Whilst MRI scans are part of standard care for AD, some people find it uncomfortable to have the scans due to the need to lie still or claustrophobia. Some people are unable to have an MRI due to other clinical reasons. If this is the case, the participant will not have to have an MRI test to take part in the study.

The AD-SMART trial treatments, atomoxetine and IR metformin, are repurposed drugs and therefore have a well-known safety profile. The participant might experience different or extra

side effects from the treatments that they take in this study. If a participant is experiencing adverse events, it is clinical discretion whether they should be assessed in person.

There is a potential risk that an analysis at stage 1 and 2 may result in a treatment arm being discontinued before it has a chance to have any cognitive effect. Against this has to be balanced the risk of continuing randomisation to a clinically ineffective treatment longer than necessary.

Where is the study run from?
University College London.

When is the study starting and how long is it expected to run for?
January 2026 to March 2031.

Who is funding the study?
1. UK Dementia Research Institute, UK.
2. The National Institute for Health and Care Research, UK.

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
1012878

Protocol serial number
ND003

Study information

Scientific Title
Alzheimer’s Disease - Systematic Multi-Arm Adaptive Randomised Trial (AD-SMART)

Acronym
AD-SMART

Study objectives
The main objective is to demonstrate therapeutic benefit, on clinically oriented outcome measures, of selected compounds when compared with standard-of-care plus placebo.
For the first 2 treatment arms, selected compounds will be repurposed medications tested over several years using the multi-arm multi-stage (MAMS) trial design, so that new research treatments can be added when appropriate. Novel drug treatments, including compounds developed and proposed by industry, will be considered for future arms.
The primary objective for the analyses of activity at the end of interim analysis stages 1 and 2 and the final analysis of efficacy at the end of stage 3 will be to detect a difference in the rate of change in score over 18 months on at least one of the co-primary outcomes: the rate of change in Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the rate of change in score on the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q).

To assess the effects of candidate drugs over 18 months on:
• Neuropsychiatric symptoms (NPI)
• Quality of life
• Caregiver burden
• Thinking ability and cognitive impairment
• Establish the safety profile of the IMPs in Alzheimer’s Disease.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/01/2026, Fulham Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 020 7104 8000; fulham.rec@hra.nhs.uk), ref: 25/LO/0919

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking

Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Treatment

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Medical condition: Symptomatic Alzheimer's Disease (Mild Cognitive Impairment, Mild Dementia, Moderate Dementia)
Medical condition in lay language: Alzheimer's disease (AD)
Therapeutic areas: Diseases [C] - Nervous System Diseases [C10]

Interventions
The AD-SMART trial will test whether either Atomoxetine or Immediate Release (IR) Metformin can relieve and improve symptoms in patients with Alzheimer's.
Currently, they are used for other illnesses and are known to be safe and effective for those diseases. We will also assess each treatment's side effects (if any), whether they improve quality of life, and offer the health service sufficient value for money. The trial will compare current standard care and each of two treatments with that care. There will also be a dummy treatment, known as a placebo.
Randomisation will be performed centrally at MRC CTU. Each participant will be randomised using their unique participant identification number that was allocated sequentially at screening. Eligibility and consent will be verified before each participant is randomised. If participants are ineligible for a specific research arm, they can be assessed for eligibility and randomised to other open arms.
Trial treatment should be started within 2 weeks of randomisation and will continue over the course of 18-month follow up. Follow up will continue until the study ends, regardless of whether participants discontinue treatment (either temporarily or permanently).
An electronic prescription will be produced and approved by a delegated staff member at the participant's site. The electronic prescription will be provided to the central pharmacy, which will dispense and courier the IMP to the participant's home address. There will be a 4-week titration phase, and participants will be dispensed 1 bottle containing 100 pills. Participants will only move up in titration if the dose is tolerated, there are no adverse events, or the clinician deems it appropriate to move up in titration if there is an adverse event reported.
Following completion of the titration phase and confirmation of tolerability, participants will receive 200 capsules per bottle, 2 bottles received every 3 months, if the participant is on dose 3 or dose 4. They will only receive 1 bottle if they are on dose 1 or dose 2.
Arm A participants will receive placebo capsules with microcrystalline cellulose or pregelatinized starch, Arm B participants will receive Atomoxetine 25mg capsules, over-encapsulated in DBCaps capsules with pregelatinized starch as a backfill. Arm C participants will receive over-encapsulated immediate-release metformin: 500mg in week 1, 1000mg in week 2, 1500mg in week 3 and 2000mg from week 4 to week 78, in the form of 500mg capsules in addition to their usual SoC.

A drug treatment will be considered successful in AD-SMART if, over 18 months, it is both safe and shows a meaningful difference to patients' quality of life in one or more of the following measures:
(i) cognitive symptoms (e.g., memory, problem solving).
(ii) neuropsychiatric symptoms (e.g., mood, anxiety, apathy).
(iii) ability to perform daily activities (e.g., showering, cooking).
These will be tested in person at the start of the trial, and at intervals of 6, 12 and 18 months. Our research teams will collect blood samples at the same time as these clinical tests to learn how changes in levels of certain blood markers are linked to the progression and severity of Alzheimer's.
We will also conduct MRI scans at the start and end of the trial to look for changes in brain structure. This information will allow us to improve our understanding of how the treatments work to reduce symptoms and affect progression of the disease.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Metformin [Metformin Hydrochloride] , Atomoxetine 25 mg hard capsules [Atomoxetine Hydrochloride] , Metformin [Metformin Hydrochloride]

Primary outcome(s)
1. Severity of cognitive symptoms of dementia measured using the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) at baseline, month 6, month12 and month18 (end of study)

2. Functional impairment for instrumental activities of daily living measured using the Amsterdam IADL Questionnaire (A-IADL-Q short version) at baseline, months 6, 12 and 18 (end of study)

Key secondary outcome(s))
1. Neuropsychiatric and behavioural symptoms measured using the Neuropsychiatric Inventory (NPI), a structured, informant-based interview at baseline, months 6, 12 and 18 (end of study)

2. Participant health-related quality of life measured using the EQ-5D-5L at baseline, months 3, 6, 12, 15 and 18 (end of study)

3. Caregiver burden measured using the Zarit Burden Interview (ZBI) at baseline, months 6, 12 and 18 (end of study)

4. Safety Profile of IMPs, including all adverse events, serious adverse events, adverse reactions, and suspected unexpected serious adverse reactions, measured using the systematic collection, assessment, and analysis of safety data throughout the study, from the first dose until the end of follow-up at one time point

5. Use of health and social care resources measured using a structured Resource Use Questionnaire at baseline covering preceding 6 months, and months 6, 12 and 18

Completion date
31/03/2031

Eligibility

Key inclusion criteria
Patient Core Inclusion Criteria:
1. Adults aged ≥55 years on the day of screening, no upper age limit
2. Either:
2.1. Confirmed clinical diagnosis of Alzheimer's Disease (AD)
2.2. Confirmed clinical diagnosis of Mixed Dementia consisting of Alzheimer's Disease and Vascular Dementia
3. Mini Mental State Examination score of ≥17
4. Confirmatory blood biomarker testing (pTau-217) (positive or intermediate via validated assays) ≤ 365 days prior to screening or between screening and randomisation or a positive amyloid PET scan (if available) or a positive amyloid CSF test (if available)
5. Randomisation should ideally take place within 4 weeks of the screening visit but no later than 8 weeks after the screening visit
6. Must be able and willing to comply with the treatment and assessment schedule and requirements including being able to start trial treatment ≤ 2 weeks after randomisation
7. Willing and able to have MRI scans in accordance with the assessment schedule unless participant is clinically contraindicated due to:
7.1. Pacemakers or defibrillators (unless MRI-conditional models)
7.2. Aneurysm clips, stents or metal implants (unless MRI safe)
7.3. Cochlear implants (unless MRI-conditional models)
7.4. Metal fragments in the body
7.5. Severe claustrophobia
8. Negative pregnancy test ≤4 weeks prior to randomisation for women of child-bearing potential
9. Normal liver function at screening consisting of all the following:
9.1. Total serum bilirubin <1.5 x ULN (except for participants with Gilbert's disease, for whom the upper limit of total serum bilirubin is 51.3 µmol/l or 3mg/dl)
9.2. Alanine aminotransferase (ALT) <3 x ULN;
9.3. Alkaline phosphatase <3 x ULN
10. Documented participant and study partner informed consent
11. If a participant is being re-randomised into the trial, additional timing of entry requirements must also be met:
11.1. For participants being re-randomised after completing 18 months' follow-up and the arm was not closed due to lack of activity, a 12-week washout period from last dose of IMP must be completed before their screening visit. If the efficacy analysis indicates that the IMP was ineffective then this washout period can be reduced to 6 weeks.
11.2. For participants being re-randomised following treatment arm termination due to lack of activity, a 6-week washout period from their last dose of IMP must be completed prior to screening assessment. See Section 5.4 of the main Protocol for further details on the re-randomisation process.

Study Partner inclusion criteria:
1. Participant that meets the AD-SMART eligibility criteria has consented to participation in the trial
2. Has at least twice-weekly contact with participant
3. Be 18 years or older at the time of providing consent

4. Willing to complete study partner questionnaires as outlined in visit schedule
5. Willing to attend remote and in-person study visits with participant
6. Documented informed consent

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
55 years

Upper age limit
120 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Patient exclusion criteria:
1. Fazekas Score =3 reported from an MRI taken at any time prior to randomisation, if an MRI is not clinically contraindicated (reasons specified in Inclusion Criteria 7)
2. MRI does not need to be repeated if Fazekas score = 0, 1 or 2 reported from an MRI performed ≤365 days to screening visit (if Fazekas score has not been reported, refer to Section 7.4)
3. MRI should be conducted if participant is not clinically contraindicated to MRIs and previous MRI where Fazekas score = 0, 1 or 2 was >365 days or previous MRI scan is not available for Fazekas score reporting or participant has never had an MRI (refer to Section 7.4)
4. Clinical diagnosis of Dementia with Lewy bodies
5. Clinical diagnosis of Parkinson's disease
6. Clinical diagnosis of Frontotemporal Dementia
7. Cardiac failure (American Heart Association Stage C or D)
8. Significant respiratory comorbidity (hospitalisation within the previous ≤6 months due to respiratory comorbidity)
9. Renal failure (CKD IV or eGFR ≤45 mL/min/1.73m^2) at any time point prior to randomisation
10. Malignancy (except if in complete remission) e.g. solid organ or haematological or melanoma
11. Individuals without an identified study partner (refer to Section 4 for further details on study partners)
12. Individuals who have an Alzheimer's Disease or Central Nervous System medication (e.g. antidepressant) change or dose change ≤28 days prior to screening
13. Use of an Investigational Medicinal Product (IMP) or Investigational Medical Device (IMD) ≤26 weeks prior to randomisation (except for AD-SMART participants that are being re-randomised. See Section 5.4 for further information).
14. Receiving antibody-based amyloid clearing treatment for Alzheimer's Disease within 6 months prior to randomisation
15. Unable or unwilling to comply with study procedures
16. Unable to swallow whole capsules
17. Individuals who are living in the same household as an AD-SMART participant who is actively

taking trial medication
18. Female participants that are pregnant or breastfeeding
19. Women of child-bearing potential (WOCBP) who are unwilling or unable to use an acceptable method of contraception (see Appendix 1) whilst on trial treatment and up to 12 weeks after the last dose of study drug
20. Male participants with a partner of child-bearing potential unwilling or unable to use an acceptable method of contraception whilst on trial treatment and up to 12 weeks after the last dose of the study drug.
21. Male participants unwilling to desist from sperm donation during the trial and for 12 weeks after the last dose of trial treatment
22. Current or previous exposure to any of the currently recruiting AD-SMART IMPs ≤26 weeks before randomisation.
23. History of alcohol and/or drug abuse and/or dependence within the 5 years prior to screening visit.
24. Any concurrent medical condition, abnormal laboratory tests or uncontrolled, clinically significant systemic disease that, in the opinion of the Investigator, could cause study participation to be detrimental to the participant.
25. Participants who are not eligible for any of the trial IMPs, according to the eligibility criteria listed in the individual drug appendices. Please note that participants can enter the trial if they are eligible for at least one of the trial treatment arms, but do not need to be eligible for all.

Information on repeating screening tests due to abnormal results and re-completing the screening visit can be found in Section 3.5.5 of the main Protocol.

If a treatment arm is stopped early following interim analysis, or a new treatment arm is introduced to the trial, the overall and treatment-specific inclusion/exclusion criteria will be reassessed and updated as needed.

Arm-specific eligibility criteria:
Atomoxetine-specific exclusion eligibility criteria:
In addition to the core inclusion and exclusion criteria, refer to section 2.2 of AD-SMART Appendix 1 Atomoxetine' for the arm-specific exclusion eligibility criteria for the Atomoxetine arm which must also be met.

Metformin-specific exclusion eligibility criteria:
In addition to the core inclusion and exclusion criteria, refer to section 2.2 of AD-SMART Appendix 2 Metformin' for the arm-specific exclusion eligibility criteria for the metformin arm which must also be met.

Date of first enrolment
01/03/2026

Date of final enrolment
30/09/2029

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type

Funder Name
UK Dementia Research Institute

Alternative Name(s)
UK DRI Ltd, UK DRI

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Research teams may approach the MRC CTU (mrcctu.adsmart@ucl.ac.uk) with a formal data-sharing request detailing the specific requirement, proposed research, qualification of researchers and publication plan if they are interested in using AD-SMART data. The request will

be reviewed by the trial committees.
Data and/or samples will be available for sharing following the end of a trial arm and the unblinding of participants. Researchers wishing to access the AD-SMART Trial data should contact the Trial Management Group in the first instance. Following trial completion, requests for data and/ or sample sharing will be reviewed by an AD-SMART access committee, which will include the trial's Chief Investigators.
Data and/ or samples will be shared during the trial according to the CTU's controlled access approach, based on the following principles:
1. No data and/or samples should be released that would compromise an ongoing trial or study.
2. There must be a strong scientific or other legitimate rationale for the data and /or samples to be used for the requested purpose.
3. Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data and /or samples before key trial data are made available to other researchers.
4. The resources required to process requests should not be underestimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
5. Data and/ or sample exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
6. Data and/ or sample exchange is only provided following the execution of a valid material transfer agreement (MTA).
Anonymised study data will be made available on appropriate data-sharing platforms.

IPD sharing plan summary

Available on request