

# Research study for people who have cerebral small vessel disease (cSVD, damaged small blood vessels in the brain) and a stroke, which may lead to impaired memory and thinking and then dementia

<b>Submission date</b> 02/07/2025	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 29/08/2025	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 01/09/2025	<b>Condition category</b> Circulatory System	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

We intend to find new drug treatments for patients who have had a stroke and also have damaged small blood vessels in the brain, which are stiff and leaky. A stroke happens when a brain blood vessel blocks. Dementia can follow when stroke and small-vessel disease combine. We think that two drugs called cilostazol and isosorbide nitrate may be useful. Both are used in heart disease. We have already tested the drugs in lacunar (affecting the small vessels in the brain) stroke with promising results and are keen to see if we can perform a trial in other sorts of stroke.

### Who can participate?

Patients aged over 50 years with a stroke and small-vessel disease

### What does the study involve?

Patients will be randomly (like flipping a coin) given one or either drug, both drugs or neither, for a period of 6 months. We will then phone them to test their memory and thinking, and find out how much of the drugs they have taken and whether the drugs are safe and might reduce dementia.

### What are the possible benefits and risks of participating?

This study will tell us whether it is possible to do a trial in people with a stroke and small-vessel disease and whether the drugs might work and are safe. This will help plan a larger trial to give a definite answer. If the drugs work then we will have new treatments to help prevent dementia after a stroke.

6 months of IMP is given to the participant on discharge from hospital. The dose will be escalated over the first few weeks. There is a slight risk that patients may not take the medication as prescribed, but this method of drug administration was used in the MHRA-

approved LACI-2 trial and is now being used in the LACI-3 trial. There were no issues highlighted in the LACI-3 trials. The hospital research staff will be trained by the coordinating centre to follow up patients and identify any issues with compliance.

Research staff at the hospital will provide a drug information sheet at randomisation with clear instructions on how much and when medication should be taken. The drug information sheet will contain information on who to contact if there is an issue with the medication if they have side effects or take an overdose of the medication.

Research staff at the hospital will ring the participant at 1-2 weeks, 3-4 weeks and 6 months after the participant starts to take the medication to check whether the dosage has been increased and whether there have been any side effects.

At 6 months when the medication stops, a trained follow-up coordinator from the coordinating centre will ring the participant to ask a few questions about how they are, complete some assessments and check that they have not had any side effects of the medication.

Where is the study run from?  
University of Nottingham (UK)

When is the study starting and how long is it expected to run for?  
October 2025 to May 2028

Who is funding the study?  
Alzheimer's Society (UK)

Who is the main contact?  
1. Dr Philip Bath, philip.bath@nottingham.ac.uk  
2. Trial Manager, CVD-Cog@nottingham.ac.uk

## Contact information

### Type(s)

Scientific, Principal investigator

### Contact name

Dr Philip Bath

### Contact details

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## Additional identifiers

### Clinical Trials Information System (CTIS)

Nil known

## **Integrated Research Application System (IRAS)**

1011543

### **Protocol serial number**

25017, CPMS 67586

## **Study information**

### **Scientific Title**

CerebroVascular Disease-Cognition (CVD-Cog) Phase II trial in non-lacunar ischaemic stroke with cerebral small vessel disease

### **Acronym**

CVD-Cog

### **Study objectives**

#### **Feasibility:**

Recruitment of 400 patients from 25 UK sites at an average recruitment rate of 0.9/site/month

#### **Retention:**

>90% participants at end-of-trial/6 months

#### **Adherence:**

>75% of participants are taking >50% trial dose at end-of-trial

#### **Completeness of primary clinical outcome:**

>85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial

#### **Safety:**

All cause death; serious adverse events; targeted drug-related adverse events

#### **Proof-of-concept:**

Estimate of effect size and variance on DSM-5-7L ordinal cognition scale

### **Ethics approval required**

Ethics approval required

### **Ethics approval(s)**

notYetSubmitted, ref: 25/WM/0144

### **Study design**

Open randomized controlled parallel-group trial

### **Primary study design**

Interventional

### **Study type(s)**

Safety, Efficacy

### **Health condition(s) or problem(s) studied**

Clinical syndrome of cortical or large subcortical stroke or TIA (TACS, PACS or cerebellar POCS)

## **Interventions**

IMP is defined by the active substance only, so any brand of isosorbide mononitrate (ISMN) and cilostazol that are available in the hospital pharmacy may be used.

All patients: Participants will be randomised to ISMN 25 mg od po SR/MR for two weeks then 50 mg od po SR/MR for 5½ months, versus no ISMN. If a slow-release ISMN is not available, non-slow-release tablets may be used. The target dose of ISMN is 40-60 mg daily.

Patients on monoplatolet therapy (not an oral anticoagulant, OAC): Participants will also be randomised to cilostazol 50 mg bd po for 2 weeks then 100 mg bd po for 5½ months versus no cilostazol. Hence, participants on mono-antiplatelet therapy will be randomised to start one of four treatments:

1. ISMN only
2. Cilostazol only
3. Both ISMN and cilostazol
4. Neither ISMN nor cilostazol

Patients with contraindications to one drug may be randomised to the other drug versus control; patients who develop a contraindication to one of the drugs during the trial may continue taking the other drug.

Comparator: None (PROBE design).

Standard of care: UK guideline-based stroke prophylaxis with antithrombotic, blood pressure lowering, lipid-lowering, carotid endarterectomy, lifestyle etc and recorded.

The trial drug will be dispensed in the original manufacturer's packaging from participating hospital pharmacies. The drug will be supplied in a treatment pack marked with the participant ID and including instructions on how to take the tablets, including the dose initiation and escalation phase. Patients will be phoned by the local centre at one to two weeks and three to four weeks after starting medication to check and advise on dose escalation. A maximum of 6 months' supply will be dispensed.

Randomisation - Computerised randomisation to reduce bias with:

Stratification:

No oral anticoagulation - ISMN: cilostazol: both: neither 1:1:1:1.

On oral anticoagulation - ISMN: no ISMN 1:1.

Minimisation:

Age, sex, premorbid mRS, stroke impairment (NIHSS), age of leaving education, cognition (DSM-5 7L), time from stroke/TIA onset to randomisation, systolic blood pressure, smoking.

## **Intervention Type**

Drug

## **Phase**

Phase II

## **Drug/device/biological/vaccine name(s)**

Cilostazol, isosorbide mononitrate

## Primary outcome(s)

Feasibility: Recruitment of 400 patients from 25 UK sites at 6 months, information collected from the trial database.

## Key secondary outcome(s)

1. Retention: >90% participants at end of trial/6 months, information collected from database following the Day 183 follow-up.
2. Adherence: >75% of participants are taking >50% trial dose, information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.
3. Completeness of primary clinical outcome: >85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial, information collected from database following the Day 183 follow-up.
4. Safety: All cause death; serious adverse events targeted drug-related adverse events (headache, loose stools, palpitations, nausea, dizziness, falls), information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.
5. Proof-of-concept: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) 7-level ordinal cognition scale at end-of-trial, information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.

## Completion date

01/05/2028

## Eligibility

### Key inclusion criteria

1. Adult, age >50 years, with no upper limit.
2. Clinical syndrome of cortical or large subcortical stroke or TIA (TACS, PACS or cerebellar POCS).
3. At least 7 days after the index event.
4. Stable medically according to the PI.
5. Has completed any phase of dual antiplatelet therapy.
6. Independent functionally or requires only limited help (mRS 0-3).
7. Able to swallow or has established enteral feeding route.
8. Brain imaging (CT or MRI scan) at the time of the index stroke/TIA shows moderate-severe white matter hyperintensities, Fazekas Score periventricular and deep  $\geq 2$ .
9. The relevant radiology report will be uploaded as part of eligibility and assessed for these criteria.
10. Patient has capacity to give consent in the opinion of the PI or any delegated member of the research team; OR Patient lacks capacity and a legal representative is available to give proxy consent.
11. Likely to be available for follow-up at 6 months.
12. Women of childbearing potential and men with partners of childbearing potential must be willing to use contraception, provided they have the capacity.

## Participant type(s)

Patient

## Healthy volunteers allowed

No

## Age group

Adult

### **Lower age limit**

50 years

### **Sex**

All

### **Key exclusion criteria**

1. Lacunar infarct (LACS; so is eligible for LACI-3 trial).
2. Brain stem-only posterior circulation stroke syndrome (POCS). Note: cerebellar POCS are eligible.
3. Known monogenic cerebral small vessel disease.
4. Index event was an intracranial haemorrhage. Note: a past history of ICH before the index event is eligible.
5. Other active brain disease, e.g. brain tumour, multiple sclerosis, Parkinson's disease, recurrent seizures, neurodevelopmental disorder. Note: well-controlled epilepsy present prior to the stroke, a single seizure at onset of the stroke, or provoked seizure, is not an exclusion.
6. Clinical diagnosis of dementia, e.g. letter from a memory clinic and/or taking acetylcholinesterase inhibitor or memantine.
7. Contraindication to both trial drugs
8. Indication for both trial drugs. Planned surgery during the trial period including carotid endarterectomy. Note: Patient becomes eligible after planned surgery. 'Prior and apparently successful carotid endarterectomy (or other surgery) is not an exclusion criterion and patients who would otherwise be eligible but require endarterectomy first may be randomised after recovery from successful endarterectomy
9. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100 mmHg.
10. History of drug overdose or attempted suicide.
11. Person is a visitor to the hospital's region so cannot be followed, e.g. on holiday/from overseas.
12. Unlikely to comply with study procedures and follow-up procedures for whatever reason (e.g. history of poor medication compliance) in the opinion of the randomising physician.
13. Pregnancy, breastfeeding, or of child-bearing potential (a negative pregnancy test is needed prior to enrolment) and not using highly effective contraception.
14. Known renal impairment (most recent creatinine clearance <25 ml/min).
15. Known hepatic impairment (most recent transaminase >3 times upper limit normal).
16. Previously enrolled in CVD-Cog.
17. Enrolled in a study that does not have an agreement with CVD-Cog allowing co-enrolment (see up-to-date list of trials allowing co-enrolment on CVD-Cog website).
18. Women of childbearing potential and men with partners of childbearing potential who lack capacity
19. Cilostazol exclusion criteria - still allows randomisation to ISMN:
20. Definite indication for cilostazol: i.e. already prescribed.
21. Definite contraindication to cilostazol: see SmPC.
22. Prohibited medications to cilostazol: see SmPC.
23. Active cardiac disease, e.g. atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure.
24. Bleeding tendency, e.g. known platelets <100, active peptic ulcer, history of intracranial haemorrhage such as subdural haematoma, subarachnoid haemorrhage, intracerebral

haemorrhage (but not asymptomatic haemorrhagic transformation of infarction or a few microbleeds), taking anticoagulant medication).

25. Uncontrolled high blood pressure: systolic BP >200 mmHg

ISMN exclusion criteria:

7. Definite indication for ISMN: i.e. already prescribed.

8. Definite contraindication to ISMN: see SmPC.

9. Prohibited medications to ISMN: see SmPC – phosphodiesterase-5-inhibitor, e.g. sildenafil, tadalafil and verdenafil.

**Date of first enrolment**

01/12/2025

**Date of final enrolment**

01/12/2027

## **Locations**

**Countries of recruitment**

United Kingdom

England

Northern Ireland

Scotland

**Study participating centre**

**Aberdeen Royal Infirmary**

Foresterhill Road

Aberdeen

United Kingdom

AB25 2ZN

**Study participating centre**

**Royal United Hospital Bath**

Combe Park

Bath

United Kingdom

BA1 3NG

**Study participating centre**

**Royal Victoria Hospital**

274 Grosvenor Road

Belfast

United Kingdom  
BT12 6BA

**Study participating centre**  
**Good Hope Hospital**  
Rectory Road  
Sutton Coldfield  
United Kingdom  
B75 7RR

**Study participating centre**  
**Southmead Hospital**  
Southmead Road  
Westbury-on-trym  
Bristol  
United Kingdom  
BS10 5NB

**Study participating centre**  
**Fairfield General Hospital**  
Fairfield General Hospital  
Rochdale Old Road  
Bury  
United Kingdom  
BL9 7TD

**Study participating centre**  
**Craigavon Area Hospital**  
Lurgan Rd  
Craigavon  
United Kingdom  
BT63 5QQ

**Study participating centre**  
**Royal Derby Hospital**  
Uttoxeter Road  
Derby  
United Kingdom  
DE22 3NE

**Study participating centre**

**Dorset County Hospital**

Dorset County Hospital

Princes Street

Dorchester

United Kingdom

DT1 1TS

**Study participating centre**

**Royal Infirmary of Edinburgh at Little France**

51 Little France Crescent

Old Dalkeith Road

Edinburgh

Lothian

United Kingdom

EH16 4SA

**Study participating centre**

**Northwick Park Hospital**

Watford Road

Harrow

United Kingdom

HA1 3UJ

**Study participating centre**

**Victoria Hospital**

Hayfield Road

Kirkcaldy

United Kingdom

KY2 5AH

**Study participating centre**

**Leeds General Infirmary**

Great George Street

Leeds

United Kingdom

LS1 3EX

**Study participating centre**

**Leicester Royal Infirmary**  
Infirmary Square  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**Charing Cross Hospital**  
Fulham Palace Road  
London  
United Kingdom  
W6 8RF

**Study participating centre**  
**University College London Hospital**  
250 Euston Road  
London  
United Kingdom  
NW1 2PG

**Study participating centre**  
**Luton and Dunstable University Hospital**  
Lewsey Road  
Luton  
United Kingdom  
LU4 0DZ

**Study participating centre**  
**The James Cook University Hospital**  
Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

**Study participating centre**  
**Royal Victoria Infirmary**  
Queen Victoria Road  
Newcastle upon Tyne  
United Kingdom  
NE1 4LP

**Study participating centre**

**Northampton**

Northampton General Hospital  
Cliftonville  
Northampton  
United Kingdom  
NN1 5BD

**Study participating centre**

**Queens Medical Centre**

Derby Road  
Nottingham  
United Kingdom  
NG7 2UH

**Study participating centre**

**Royal Hallamshire Hospital**

Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre**

**Royal Stoke University Hospital**

Newcastle Road  
Stoke-on-trent  
United Kingdom  
ST4 6QG

**Study participating centre**

**Royal Cornwall Hospital (treliste)**

Treliske  
Truro  
United Kingdom  
TR1 3LJ

**Study participating centre**

**Ulster Hospital**

Upper Newtownards Rd

Dundonald  
Belfast  
United Kingdom  
BT16 1RH

## Sponsor information

### Organisation

University of Nottingham

### ROR

<https://ror.org/01ee9ar58>

## Funder(s)

### Funder type

Charity

### Funder Name

Alzheimer's Society

### Alternative Name(s)

alzheimerssoc

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Associations and societies (private and public)

### Location

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date

### IPD sharing plan summary

Data sharing statement to be made available at a later date