CEREBROVASCULAR DISEASE-COGNITION (CVD-COG) PHASE-2 TRIAL IN NON-LACUNAR ISCHAEMIC STROKE WITH CEREBRAL SMALL VESSEL DISEASE

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Acronym:	CVD-Cog
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SYNOPSIS

Title	CerebroVascular Disease-Cognition phase-2 trial in non-lacunar ischaemic stroke with cerebral small vessel disease
Acronym	CVD-Cog
Short title	CerebroVascular Disease-Cognition
Chief Investigator	Professor Philip M Bath
Objectives	*To assess:* a) Feasibility: Recruitment of 400 patients from 25 UK sites at average recruitment rate of 0.9/site/month. b) Retention: >90% participants at end-of-trial/6-months. c) Adherence: ≥75% of participants are taking ≥50% trial dose at end-of-trial. d) Completeness of primary clinical outcome: >85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial. e) Safety: All cause death; serious adverse events; targeted drug-related adverse events. f) Proof-of-concept: Estimate of effect size and variance on DSM-5-7L ordinal cognition scale.
Trial Configuration	Partial factorial randomised controlled feasibility trial.
Setting	Secondary/tertiary care.
Sample size estimate	As a feasibility trial, there is no formal sample size calculation. However, recruitment of 400 participants will be sufficient to assess the feasibility, retention, adherence, safety and proof of concept aims.
Number of participants	400 participants
Eligibility criteria	***Inclusion****:* 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 anti-platelet 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 ⩾2. a. The relevant radiology report will be uploaded as part of eligibility and assessed for these criteria.

	9. Consent: a. Patient has capacity to give consent in the opinion of the PI or any delegated member of the research team; OR b. Patient lacks capacity and a legal representative is available to give proxy consent. 10. Likely to be available for follow-up at 6 months. 11. Women of childbearing potential and men with partners of child baring potential must be willing to use contraception providing they have capacity. ***Exclusion**:* 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. 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. 9. Planned surgery during the trial period including carotid endarterectomy. Note: Patient becomes eligible after planned surgery. 10. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg. 11. History of drug overdose or attempted suicide. 12. Person is a visitor to the hospital's region so cannot be followed, e.g. on holiday/from overseas. 13. 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. 14. Pregnancy, breast-feeding, or of child-bearing potential (a negative pregnancy test is needed prior to enrolment) and not using highly effective contraception. 15. Known renal impairment (most recent creatinine clearance <25 ml/min). 16. Known hepatic impairment (most recent transaminase >3 times upper limit normal). 17. Previously enrolled in CVD-Cog. 18. 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). 19. Women of childbearing potential and men with partners of child baring potential who lack capacity 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. 24. Bleeding tendency. 25. Uncontrolled high blood pressure: systolic BP >200 mmHg. ISMN exclusion criteria: 26. Definite indication for ISMN: i.e. already prescribed. 27. Definite contraindication to ISMN: see SmPC. 28. Prohibited medications to ISMN: see SmPC - phosphodiesterase type 5 inhibitors, e.g. avanafil, sildenafil, tadalafil and verdenafil.
Description of 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. Dose, formulation, brand and manufacturer must be recorded. Follow up calls to the participant will be conducted by the hospital site at 1-2 weeks, 3-4 weeks and Day 183. The research staff at the hospital site will check compliance and guide participants through the titration process. The research team will also check for any adverse events. A follow up call will be made by a blinded follow up coordinator at the coordinating centre (University of Nottingham) at Day 183 to complete cognitive, mood and function assessments with the participant. ***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 40-60mg daily. ***Patients on mono-platelet therapy (not an oral anticoagulant, OAC)***: Participants will also be randomised to cilostazol 50 mg bd po for two 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: • ISMN only; • Cilostazol only; • Both ISMN and cilostazol; • 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. Trial drug will be dispensed in original manufacturer's packaging from participating hospital pharmacies. 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 six-months supply will be dispensed.
Duration of study	The trial's funding is for 3 years. Participants will be treated and followed for 6 months in total.
Randomisation and blinding	Computerised randomisation to reduce bias with: 1) Stratify on 1. On oral anticoagulant i) If no: randomise ISMN+cil vs ISMN vs cil vs neither ii) If yes: randomise ISMN vs no ISMN 2) Minimise on: 1. Capacity no v yes 2. DSM5-7L >0 v 0 3. Index stroke v TIA 4. Age (years) >=70 v <70 5. mRS >1 v <=1 6. Systolic BP (mmHg) >140 v <=140 7. Time (days) >90 v <=90 8. Age leaving education <16 v >=16 9. WMH severe v mod 3) 5% randomisation Treatment is given open label (PROBE design).
Outcome measures	***Feasibility***: Recruitment of 400 patients from 25 UK sites. ***Retention***: >90% participants at end of trial/6-months. ***Adherence***: ≥75% of participants are taking ≥50% trial dose. ***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 (headache, loose stools, palpitations, nausea, dizziness, falls). ***Proof-of-concept***: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) 7-level ordinal cognition scale at end-of-trial. ***Health economics***: Not to be assessed. ***Process evaluation***: Not to be assessed.

Statistical methods	Tabulations of feasibility, retention, adherence, completeness of follow-up, safety and proof-of-concept. Data will be shown as number (%), median [interquartile range] or mean (standard deviation). Safety, symptoms and proof of concept will involve statistical comparisons between ISMN vs no ISMN, cilostazol vs no cilostazol and dual therapy vs no therapy. Comparisons will use adjusted binary logistic regression, Cox proportional hazards regression, ordinal logistic regression or multiple linear regression as appropriate. Primary analyses will use modified intention-to-treat (no imputation). There will be no adjustment for multiplicity.

ABBREVIATIONS

acOR	adjusted common odds ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
APT	Anti-platelet therapy
BD	Twice daily
BI	Barthel index
BNF	British National Formulary
CC	Coordinating Centre
CF	Informed Consent Form
CI	Chief Investigator overall
CRF	Case Report Form
cSVD	Cerebral small vessel disease
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DSM-5-7L	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, 7-level ordinal cognition scale
EOT	End of Trial
GCP	Good Clinical Practice
HR	Hazard ratio
ICH	Intracerebral haemorrhage
IMP	Investigational medicinal product
IS	Ischaemic stroke
ISMN	Isosorbide mononitrate
LACS	Lacunar syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin scale
NHS	National Health Service
NIHR	National Institute of Health & care Research
NIHSS	National Institutes Health stroke scale
OAC	Oral anticoagulant, e.g. apixaban, warfarin
OCSP	Oxfordshire community stroke project
OD	Once daily
OR	odds ratio
PACS	Partial anterior circulation syndrome
PDE5-i	Phosphodiesterase5-inhibitor

PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PO	By mouth
POC	Proof of concept
POCS	Posterior circulation syndrome
PROBE	Prospective randomised open-label blinded-endpoint
REC	Research Ethics Committee
RDN	Research Delivery Network (part of NIHR)
R&D	Research and Development department
Rx	Medical prescription
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
STUN	Stroke Trials Unit, Nottingham
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACS	Total anterior circulation syndrome
TIA	Transient ischaemic attack
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Cerebral small vessel disease (cSVD) causes or significantly contributes to 45% of dementia. cSVD involves endothelial,[1,2] smooth muscle, pericyte and blood brain barrier dysfunction and subsequent damages brain networks. Affected vessels are unable to vasoregulate and allow circulating toxins into brain tissue. cSVD is the commonest cause of vascular cognitive impairment (VCI) and vascular dementia (VaD), worsens the outcome of other dementia types such as Alzheimer's disease if they co-exist, and may also present with falls, apathy, fatigue and delirium.

cSVD causes lacunar strokes/acute cerebrovascular events (CVD, 25% of ischaemic strokes, IS) and most intracerebral haemorrhage (ICH) in older people. It also co-exists with non-lacunar IS, e.g. atherothrombotic large artery disease (LAD, 20% of IS), cardioembolism (CE, 20% of IS) [3] and stroke of undetermined type. When co-existing with stroke, cSVD more than doubles the risk of VCI/VaD, recurrent stroke and death.[3] It is a major cause of post-stroke cognitive impairment (PSCI, 8-39% at 1 year) and VaD (25% by 5 years).[4,5] cSVD is visible as WMH, either as white matter hypoattenuation on CT or white matter hyperintensities on MRI, lacunar infarcts and lacunes (CT/MRI), and microbleeds, perivascular spaces and cortical siderosis (MRI).[6] However, it is often missed or ignored. Critically, cSVD has no specific treatment or prevention [7] and yet affects ~750 million people/10% globally. In summary, cSVD is common in stroke, causes most VCI/VaD, worsens PSCI and yet has no treatment.

We will focus on patients with previous non-lacunar IS or TIA, i.e. those with atherothrombotic large artery disease (LAD, 25% of IS), cardioembolism (CE, 20% of IS) and stroke of undetermined type, who also have radiological evidence of cSVD. Our data showed that cSVD was present in 49-64% of 8,990 patients with non-lacunar IS.[8-11] Current secondary prevention of IS/TIA is based on blood pressure lowering, lipid lowering - typically with a statin, and antithrombotic therapy – oral anticoagulation (OAC) for CE and antiplatelet therapy (APT) for other IS.[12] LAD-IS/TIA may also need carotid endarterectomy. However, none of these prophylactics specifically target cSVD [7] nor the development of PSCI. Importantly, the Stroke Association-James Lind Alliance Priority Setting Partnership identified cognition as the major concern of patients after stroke (Figure 1, www.stroke,org,uk/psp).→ Extrapolation of results from LACI-2 raise the possibility that ISMN and/or cilostazol might reduce PSCI and functional dependence in people with previous non-lacunar IS/TIA and co-existing cSVD.

Fig 1. Top 6 concerns of 102 people with SVD

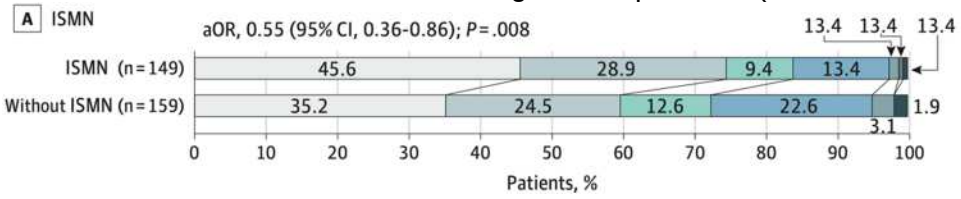
Rank	Concern	Frequency	Number of correspondents
1	**Cognitive problems**	70	43
2	**Healthcare services**	62	41
3	**Prognosis**	55	37
4	Sensory disturbances	38	27
5	Functional problems	32	24
6	Impact on daily life	31	24

and emotions expressed:

Following advances in Alzheimer's disease and stroke management, there is a world-wide drive to improve the management and treatment of cSVD and VaD. Following a search for potential agents that might delay or reverse cSVD,[13] we identified isosorbide mononitrate (ISMN) and cilostazol as candidate treatments worth exploring. ISMN (a nitric oxide donor) is widely used for angina prophylaxis. The role of NO donors in stroke and cSVD prevention is

unclear [13] although we have done large acute stroke trials of short-term transdermal glyceryl trinitrate (GTN) demonstrating safety but no effect on clinical outcomes.[8,11] Dipyridamole, a mixed phosphodiesterase-3/5-inhibitor that preserves the effects of NO, reduced stroke recurrence in our meta-analysis but data on PSCI were not collected.[14] Cilostazol (a phosphodiesterase-3-inhibitor, PDE3-i [13]) reduced recurrent stroke in Asia-Pacific trials in our meta-analaysis;[15] however, its effects in other populations are unclear with minimal data in PSCI/VCI.[15] ISMN and cilostazol have been studied in the LACI-1/2 2x2 factorial phase-2 trials in patients with previous lacunar stroke (see below). On the basis of the positive results in LACI-2, HTA have recently funded the phase-3 safety and efficacy LACI-3 trial in post-lacunar stroke – Chief Investigator = Wardlaw, Co-CI = Bath. Our aim here is to repeat LACI-2 but in non-lacunar stroke so that we could then perform a follow-on phase-3 trial, i.e. CVD-Cog-2. We are also considering whether LACI-2 and CVD-Cog could be repeated in other populations of cSVD including those attending memory/dementia clinics (who do not have Alzheimer's disease) and acute geriatric services (with falls or delirium).
TheLACI-1 phase-2a trial (ISRCTN12580546, n=57, 2 sites) was a partial factorial 2x2 study of 8 weeks of ISMN and/or cilostazol in participants with previous lacunar stroke from two centres.[16-18] The drugs were well tolerated and known side effects were not treatment-limiting (e.g. symptoms such as headache settled down).[16] There were no safety concerns (e.g. no bleeding or falls) and the treatments improved cerebrovascular function [17] and did not alter platelet function.[18]

In the LACI-2 phase-2b trial (ISRCTN-14911850, n=363) in lacunar IS,[19-21] 99% of participants were retained after 1 year of ISMN and/or cilostazol with 85% of participants taking half or more of their allocated dose. Safety events were uncommon with no increase in bleeding. ISMN vs no ISMN reduced recurrent stroke, cognitive impairment (DSM-5-7L ordinal scale [22] Figure 2 →), dependency (modified Rankin Scale, mRS [23]) and stroke impact and improved quality of life and combined global outcomes. Cilostazol vs no cilostazol reduced dependency and mood disturbance. Combining both vs neither improved all of these, demonstrating potential drug synergy.[21] Similar results were emerging at 6 months (WSC presentation 2023). But patient characteristics (e.g. age, severity), background vascular prophylaxis and outcome rates differ between IS types so we cannot simply assume that the LACI-2 results in lacunar IS/TIA will translate to patients with non-lacunar IS/TIA and cSVD.



Our PODCAST trial (N=83 from 19 UK hospital sites) tested feasibility for preventing PSCI in a 2x2 factorial design of intensive versus guideline-based blood pressure and lipid lowering.[24-27] Although neutral for both interventions,[26] a *post hoc* analysis suggested that intensive lipid-lowering (primarily with atorvastatin) might improve global analyses of cognition and a wider group of clinical outcomes.[27]

Our R4VaD UK-wide observational study of PSCI (2018-late '24) recruited 2443 patients with any stroke/TIA type from 52 UK hospital sites.[22,28] Preliminary analyses suggest that PSCI is common, and cognition improves initially after stroke and then deteriorates. See recruitment details in the recruitment section of the protocol.

The population of patients with non-lacunar IS/TIA and radiological cSVD is substantial. Equally, ISMN/cilostazol are generic and are inexpensive (BNF: ISMN £6.75pm, cilostazol £35.98pm) and available in the UK (and many parts of the world). NHS England and MHRA have shown interest in licensing ISMN and/or cilostazol for cSVD management if LACI-3 shows beneficial effects on cognition. We believe guidelines will change on the basis of the LACI and CVD-Cog series of trials and so it would be easy to implement ISMN and/or cilostazol for the treatment of cSVD.

Specific background points

- The safety and efficacy of translating prophylactic interventions between different stroke types cannot be assumed and needs prospective testing. For example, non-lacunar stroke involves older, more severe and frailer patients who take different background guideline therapies. Hence, LACI-2/3 and CVD-Cog are complementary, and the positive findings of LACI-2 [21] should not be extrapolated to non-lacunar patients with cSVD.
- Provision of placebo is extremely expensive (over-encapsulation of different doses is needed for dose escalation), hence the PROBE design.
- Although LACI-2 [21] showed good adherence in lacunar stroke, CVD-Cog will assess this in non-lacunar IS/TIA with cSVD, e.g. headache, loose stools and palpitations may be more common in non-lacunar older more frail patients.
- We will use the DSM-5-7L cognition outcome,[22,28] as per LACI-2,[19-21] and widely used in dementia research. DSM-5-7L integrates multiple sources of data based on cognition (Montreal cognitive assessment), function (modified Rankin scale), disposition, dementia diagnosis, use of cholinesterase-inhibitors and death. Hence, it is not dependent on any one scale and so is more tolerant of missing data.
- Telephone follow-up of DSM-5-7L will be performed, as in LACI-2,[21] R4VAD and our previous large stroke trials. We will monitor the need for participants versus informants to complete outcomes.

CVD-Cog has been designed to address the above points and provide feasibility, tolerability, safety and proof of concept (PoC) information.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description

The IMP is defined by the active substance only; therefore, all authorised brands may be used. Oral ISMN slow release (or standard release) or cilostazol will be prescribed as per the brand available in the participating hospital pharmacy.

Isosorbide mononitrate (ISMN)

- Isosorbide mononitrate slow release, generic, as 25mg XL, 30mg XL, 40mg XL, 50mg XL or 60mg XL tablets to the target dose of 40-60mg daily; or
- Isosorbide mononitrate, standard release, as 20mg, 30mg or 40mg tablets to the target dose of 40-60mg daily. This preparation should be used in patients receiving feeding via an enteral tube. Sites will follow their own local policy and consult with their local pharmacists as needed and provide participants with instructions on how they should take this tablet at home via their enteral tube.

Most ISMN preparations are slow release in the UK. However, where slow-release preparations of ISMN are not available, non-slow release preparations may be used with the dose split with half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. The target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the study treatment sheet. See Table 2 & 4

Cilostazol – does not apply to participants taking oral anticoagulation
Cilostazol, generic, as 50mg or 100mg tablets with a target dose of 100mg twice daily See Table 3 & 4

Cilostazol and ISMN are both licensed products for treatment of vascular diseases in Europe, used outside of their licensed indication in this trial. Cilostazol is used for intermittent claudication and ISMN is used for prophylaxis of angina and as an adjunct in congestive heart failure. The example summaries of the product characteristics are appended to this trial protocol. Example Representative Summary of Product Characteristics (SmPC) (for ISMN slow release, ISMN generic and cilostazol) are provided and should be filed in the TMF.

For participants with an enteral tube, sites will follow their own local policy and consult with their local pharmacists as needed and provide participants with instructions on how they should take this tablet at home via their enteral tube.

Manufacture

No specific drug manufacturer is required for the trial. Both ISMN and cilostazol drugs are available from several providers in the UK. Pharmacies may provide the brand of each drug that is available to them.

Multiple doses and brands of ISMN are marketed in the UK. Two examples are:

- Isodur 50XL mg capsules (CAS 16051-787-7). Marketing authorisation holder: Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, UK. Marketing authorisation number: PL 27827/0022. SmPC updated 9 April 2024 - see https://www.medicines.org.uk/emc/product/11062/smpc.
- Isosorbide mononitrate 20 mg tablets (CAS 16051-787-7). Marketing authorisation holder: Dexcel Pharma Ltd, 7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK. Marketing authorisation number: PL 14017/0011. SmPC updated 1 January 2018 - see https://www.medicines.org.uk/emc/product/2698/smpc.

Several doses and brands of cilostazol is marketed in the UK. An example is:

- Cilostazol 100 mg tablets (CAS 73963-72-1). Marketing authorisation holder: Generics (UK) Ltd t/q Mylan [now part of part of Viatris], Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK. Marketing authorisation number: PL 04569/1427. SmPC updated 9 March 2020 – see https://www.medicines.org.uk/emc/product/2609/smpc.

There is no placebo and there are no modifications to the IMP.

Refer to the representative SmPC examples of the drug manufacturers provided for CVD-Cog investigators and as above.

Packaging and labelling

Standard pharmacy supplies will be used. The IMP will be clearly labelled for clinical trial use only with the trial specific label by the issuing pharmacist. The participant's trial ID number will be displayed on the study treatment pack. Each pack will be labelled in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices, with the primary and secondary packaging remaining together throughout the trial. They will include storage conditions for the drug, but no information about the patient.

Detailed prescribing and administration instructions will be provided with the study treatment pack. Dose initiation in first 2-4 weeks will be guided by a regular phone calls and instructions.

Medication labels will be in English and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

Storage, dispensing and return

Off-shelf trial drugs will be stored in participating hospital pharmacies as per requirements for the branded products. They will be stored in a restricted access area where temperature is monitored according to the storage instruction in the SmPCs. Drug will be delivered to hospital pharmacies as per Manufacturer's usual delivery practices.

Participants should store the cilostazol and ISMN at room temperature in a cool, dry place out of direct heat and sun.

Unused drug will be returned to community pharmacies by participants or to participating hospital pharmacies if more convenient for destruction as per usual practices at participating pharmacies. There are no special requirements for CVD-Cog.

Placebo

There is no placebo. The trial is open-label.

Known Side Effects

Isosorbide mononitrate
The SmPC describes the expected effects of isosorbide mononitrate in overdose and details measures for management of this.

Side effects: see Appendix for detailed list
Common or very common: Arrhythmias; asthenia; cerebral ischaemia; dizziness; drowsiness; flushing; headache; hypotension; nausea; vomiting.
Uncommon: Circulatory collapse; diarrhoea; skin reactions; syncope
Rare or very rare: Myalgia

Cilostazol: does not apply to participants taking oral anticoagulation
The SmPC for Cilostazol states that there is limited information on the effects of acute overdose in humans. It is anticipated to feature severe headache, diarrhoea, tachycardia and possibly cardiac arrhythmia. Management would be supportive care and gastric lavage as appropriate.

Side effects: see Appendix for detailed list
Common or very common: Appetite decreased; arrhythmias; diarrhoea; dizziness; gastrointestinal discomfort; gastrointestinal disorders; headache; increased risk of infection; nausea; oedema; palpitations; skin reactions; vomiting.
Uncommon: Anaemia; anxiety; congestive heart failure; cough; dyspnoea; haemorrhage; hyperglycaemia; hypotension; sleep disorders; syncope
Rare or very rare: Renal impairment; thrombocytosis
Frequency not known: Agranulocytosis; bone marrow disorders; conjunctivitis; fever; granulocytopenia; hepatic disorders; hot flush; hypertension; intracranial haemorrhage; leukopenia; paresis; severe cutaneous adverse reactions (SCARs); thrombocytopenia; tinnitus; urinary frequency increased.

Reference Safety Information: Safety and side effect information obtained from SmPC. The RSI for the following drugs:
ISMN slow release is taken from section 4.8 of the SmPC for Isodur 50XL capsules: latest revision 09/04/24
ISMN standard release is taken from section 4.8 of the SmPC for ISMN tablets 20mg: latest revision 01/01/18
Cilostazol is taken from section 4.8 of the SmPC for cilostazol 100mg tablets: latest revision 09/03/20

Other medications

Non-investigational medicinal products
Not applicable.

Permitted Medications
Patients should continue to take prescribed guideline stroke prevention treatment and may continue to take all other usual prescribed medication during the study except those listed immediately below or in the exclusion criteria. Investigators will record concomitant medications that the participant is taking at the time of enrolment or during trial follow-up in the eCRF.

Prohibited medications
Isosorbide mononitrate:
- Phosphodiesterase-5-inhibitors (PDE-5-i: tadalafil, sildenafil, vardenafil).

Cilostazol: – does not apply to participants already taking an oral anticoagulant
- Other strong inhibitors of metabolic enzymes CYP3A4 or CYP2C19, e.g. diltiazem.
- Erythromycin, clarithromycin, ketoconazole, itraconazole, omeprazole.
- Dual antiplatelet drugs, e.g. aspirin and clopidogrel simultaneously.
- Anticoagulants, e.g. warfarin, heparin, dabigatran, rivaroxaban, apixaban.

- Reduction of the dose to 50 mg twice daily is recommended in patients receiving omeprazole, erythromycin, clarithromycin, ketoconazole, and itraconazole.
- SmPCs for cilostazol indicate caution is advised with other strong inhibitors of metabolic enzymes CYP3A4 or CYP2C19, such as simvastatin, atorvastatin, lovastatin, carbamazepine, phenytoin, rifampicin.
- BNF notes caution with ISMN and hypotensive agents such as diltiazem, hydralazine, etc.
- No increase in symptoms or SAEs were observed in patients allocated both ISMN and cilostazol in the LACI-1 and LACI-2 trials.

Please refer to the SmPCs for full details.

TRIAL OBJECTIVES AND PURPOSE

PURPOSE

To prepare for a phase-3 trial. This requires demonstration of site and participant recruitment at a necessary rate, participant retention, drug adherence over 6 months and evidence that the primary outcome can be collected. It also needs to assess safety and proof of concept with estimates of treatment effect to allow sample size estimation.

PRIMARY OBJECTIVE

Recruitment of 400 patients from 25 UK sites.

SECONDARY OBJECTIVES

To assess:

Feasibility
Retention of participants: >90% at end of trial.
Adherence to drugs: ≥75% of participants are taking ≥50% trial dose at six months.[19-21]
Telephone (or postal) follow-up of DSM-5-7L ordinal cognition scale:[22,28] >85%.
Safety: All cause death; serious adverse events; major bleeding; targeted drug-related adverse events (headache, loose stools, palpitations, nausea, dizziness, falls).
Proof of concept: Estimate of effect size and variance on DSM-5-7L ordinal cognition scale.[21]

TRIAL DESIGN

TRIAL CONFIGURATION

UK-wide hospital-based multicentre prospective randomised open-label blinded-endpoint (PROBE) 2x2 partial factorial trial.

Table *. Eligibility and randomisation possibilities.

	On oral anticoagulant	**Not on oral anticoagulant**
ISMN		
Must have ISMN	Ineligible for trial	Do not randomise to ISMN v no ISMN
Cannot have ISMN	Ineligible for trial	Do not randomise to ISMN v no ISMN
Otherwise	Randomise to ISMN v no ISMN	Randomise to ISMN v no ISMN
Cilostazol		
Must have Cil	Unlikely scenario Do not randomise to Cil v no Cil Ineligible if cannot take ISMN	Do not randomise to Cil v no Cil Ineligible if cannot take ISMN
Cannot have Cil	Do not randomise to Cil v no Cil Ineligible if cannot take ISMN	Do not randomise to Cil v no Cil Ineligible if cannot take ISMN
Otherwise	Do not randomise to Cil v no Cil Ineligible if cannot take ISMN	Randomise to Cil v no Cil

Cil: cilostazol; ISMN: isosorbide mononitrate

Participants on mono-antiplatelet therapy will be randomised to ISMN vs no ISMN, and cilostazol vs no cilostazol so 25% each of participants will be on both drugs, ISMN only, cilostazol only and neither drug (1:1:1:1) – see figure 4.

Participants on oral anticoagulation will only be randomised to ISMN vs no ISMN.

Primary endpoint

Recruitment of 400 patients from 25 UK sites.

Secondary endpoints

At six months by telephone (or post, e.g. if dysphasia):

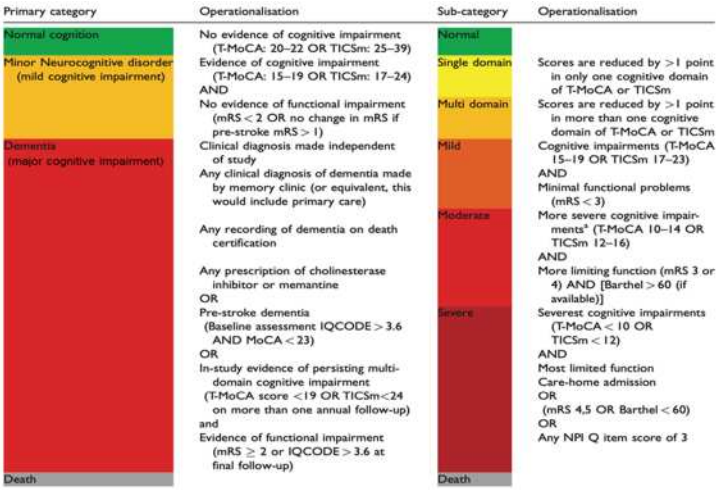
- Retention of participants: >90%.
- Adherence with drugs: ≥75% of participants are taking ≥50% trial dose.[21]
- Completeness of telephone/postal follow-up of DSM-5-7L ordinal cognition scale:[22] ≥85%.[21]

Safety endpoints

Safety by 6 months: All cause death; serious adverse events.
Drug-specific symptoms by 6 months: Headache, loose stools, palpitations, nausea, dizziness, falls.[16,21]

Safety assessments will occur at 2, 4 and 26 weeks after randomisation. The local hospital sites will ask participants by phone about the presence of symptoms that might be related to taking the trial drugs (e.g., headache, bleeding) during the first month after randomisation.

Proof of concept: Estimate of effect size/variance on DSM-5-7L ordinal cognition scale.[21,22] Figure 3 →



Local hospital sites will telephone participants at 2, 4 and 26 weeks to ask about IMP symptoms and adherence to trial medication.

Investigators from local hospital sites and central trial co-ordinators will record and report the outcome and safety events including SAEs, SARs and SUSARs between randomisation and 6-months based on the information from the follow-up questionnaires as well as alerts from hospital records. Safety reporting will include two weeks after the last dose of IMP is administrated when the hospital site and central coordinating centre call the participant for the 6-month follow up**T**his form of self-reporting was used successfully in the LACI-1 and LACI-2 trials, where telephone calls at weeks 1-3 and 3-4 were used to collect any SAEs/SARs and SUSARs information and remind participants to call the hospital site to report any side effects until the end of the treatment when a 6 month follow up call would also collect data on any side effects of the medication.

IMP symptoms, drug adherence, outcome, and safety events will be recorded in the eCRF. SAEs, SARs and SUSARs will be reported to the Sponsor.

Stopping rules and discontinuation

Individual participants: Participants, or their family if they lack capacity, may withdraw completely from the trial, from treatment or from individual assessments at any time without needing to give information as to why. Site principal investigators may also withdraw the participant from the trial or from treatment for medical reasons, e.g. need for palliation.

Trial: Since the trial is assessing feasibility, there is no stop-go assessment or interim analysis, subject to safety.

RANDOMIZATION AND BLINDING

Randomisation/concealment: Computerised randomisation to reduce bias:[16,21] with:
Stratification:

- . On oral anticoagulant
- i) If no: randomise ISMN+cil vs ISMN vs cil vs neither
- ii) If yes: randomise ISMN vs no ISMN

Minimisation:

- 1. Capacity no v yes
- 2. DSM5-7L >0 v 0
- 3. Index stroke v TIA
- 4. Age (years) >=70 v <70
- 5. mRS >1 v <=1
- 6. Systolic BP (mmHg) >140 v <=140
- 7. Time (days) >90 v <=90
- 8. Age leaving education <16 v >=16
- 9. WMH severe v mod

In 5% of randomisation, a random choice of assignment will take precedence over minimisation thereby preventing predictability.

Blinding of treatment: Outcome assessment at 6 months will be blinded with central follow-up to reduce bias. We will not use national data linkage since most of the outcomes are not routinely/reliably collected, data feeds can be slow, and linkage is complex and expensive.

Treatment is given open label with a PROBE trial design. Participants, their family, investigators and hospital pharmacists will know what treatment(s) the participant is taking. Most of the central trial-team, including chief investigator, blinded-outcome assessor, blinded SAE adjudicator and trial statistician, will be blinded to treatment assignment at telephone follow-up. The Trial manager will be unblinded so they can support sites with queries.

The data monitoring committee (DMC) and their support statistician will be unblinded to treatment and will review data by assigned group (ISMN vs, no ISMN, cilostazol vs. no cilostazol, both vs. neither).

Randomisation will use the Stroke Trial Unit's 'Bespoke' trial system as used in other ongoing stroke trials. Treatment assignment is stored in the system's separate secure vault.

Hospital delivery staff (research nurses/coordinators) will identify potential participants and brief them (and their families if they lack capacity) about the trial. This may be in hospital wards or clinics. Following at least 24 hours, principal investigators will further explain the trial, answer questions and obtain consent. The PI and delivery team will enter baseline information and obtain the resulting randomised treatment assignment. The PI will then prescribe the treatment which can then be collected from the hospital's pharmacy. Real-time stratification and minimisation will maintain allocation concealment.

Maintenance of randomisation codes and procedures for breaking code

The trial has a PROBE design and participants, their family, investigators and hospital pharmacists will know what treatment(s) the participant is taking. The central trial-team including CI, blinded-outcome assessor and trial statistician will be masked to treatment assignment at telephone follow-up. Since treatment is open-label and sites will know treatment assignment, there is no need to break the randomisation code.

TRIAL MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management and is the data custodian.

The trial will be overseen by a Trial Steering Committee (TSC) and independent Data Monitoring Committee (DMC) and run by a Trial Management Group (TMG). It will be managed from the Coordinating Centre (CC) based in the Stroke Trials Unit, Nottingham (STUN). Funded trial staff will be based at the CC. Sites will be trained on trial processes by the CC, slide sets on the website, via the protocol and trial manual and during the remote site initiation visit. Further details are given below.

Trial Steering Committee (TSC)

The TSC will lead the trial strategically reviewing participant and site recruitment rate, treatment delivery, data integrity and trial event rates. Any new data emerging from other trials will be discussed for their potential impact on CVD-Cog. The TSC will work according to a charter and meet twice yearly.
Independent members: Chair, Stroke neurologist, Stroke physician, Statistician, PPI member. The members will be appointed from non-recruiting institutions where possible.
Dependent member: Chief Investigator.
Observers: Co-applicants, Funder representative, Sponsor representative, Senior Trial Manager, Trial Manager.

Trial Management Group (TMG)

This will manage the trial daily and will meet monthly. The group will monitor trial accrual, site management (with local RDN research nurses/practitioners) and ensure recruitment strategy remains on target. Sites will be regularly contacted in the event of low recruitment.
Members: CI, Co-CI, Senior Trial Manager, Trial Manager, Follow up coordinator, Trial coordinator(s), Trial statistician and Trial programmer.

Independent Data Monitoring Committee (DMC)

This will review safety as well as the validity and scientific merit of the trial. Unblinded data will be provided by a statistician with no other role in the study and discussed at least twice yearly. A DMC Charter will be drawn up in line with the Damocles Study Group Guidance.[29] The Charter will define the schedule and format of twice-yearly meetings (or scheduled as necessary), the method and timing of interim reports and stopping rules:
Members: Chair, Stroke expert, Statistician.
Open blinded session: CI, Co-CI, Trial Manager.

Serious adverse events (SAE) adjudication

We will collect and then adjudicate all serious adverse events up to end of treatment/follow-up. Targeted drug related adverse events (headache, loose stools, palpitations, nausea, dizziness, falls [16,21]) will also be collected. Other adverse events (AEs) will not be collected since there are considerable safety data on ISMN and cilostazol already and these drugs are widely used including after stroke.

Adjudication will be performed by stroke medics, who will check whether adequate evidence has been entered to support the diagnosis and whether the information entered constitutes an SAE.

Sites, investigators and monitoring
Investigators will be trained in trial procedures via a site initiation videoconference after obtaining all the necessary regulatory approvals; this will include assessment of scans for eligibility. New investigators who join the study after site initiation training will be required to view the latest version of the site initiation visit (SIV) slides and make contact with the trial manager if they have any questions. All investigators must have good clinical practice (GCP) relative to their role in the study.

Central monitoring
The CC will perform central monitoring on consent forms, contact details and treatment allocation/compliance through the database for all participants, and primary endpoint data for a subset. Copies of the consent forms, contact details and treatment allocation/compliance will be uploaded to a secure vault at UoN. Central monitoring will be conducted on a daily basis. All monitoring will be conducted according to a trial specific monitoring plan.

Remote monitoring
All sites will be monitored remotely after 4 participants have been recruited, or at least once during the trial. In a proportionate approach, we will not perform local onsite monitoring unless triggered by concerns at the Coordinating Centre over data quality, integrity or low recruitment.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration: 6 months covering both treatment and follow-up.

Study Duration: 36 months comprising 3 months start-up, 24 months of recruitment, 6 months of follow-up of later recruited participants and 3 months of close-out.

End of the Trial

The end of the study will be the last follow-up performed for the last recruited participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Trial setting:
Secondary/tertiary care (district or teaching) hospitals that host comprehensive or acute stroke/TIA services.

Participants
Participants will be recruited from hospital stroke service wards, stroke follow-up clinics, TIA clinics and from the R4VaD study. (Patients were consented for recontact including recruitment into PSCI trials and we will contact them to assess their interest in CVD-Cog. The University of Edinburgh hold the contact details of participants who agreed to be re-contacted for future stroke trials. The coordinating centre at the University of Nottingham will send out names and contact details via @nhs.net to the recruiting hospital site of R4VaD participants who agreed to be contacted. The hospital site will do a GP contact to check the status of the participant. The hospital site will make contact with the participant to check

eligibility and present the trial and address questions. If agreeable, the hospital site researcher can send out the consent form for signature and PIS for written information).

The initial approach will be from a member of the patient's usual care team (which may include the investigator or stroke research nurses/coordinators). REC approved information about the trial will be on display in the relevant clinical areas.

The investigator or their designee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their legal representative, of all aspects pertaining to participation in the study. The legal representative will also be asked whether any advance decisions may have made about participating in research as this should take precedence.

Historically, women and patients from ethnic minority communities have been underrepresented in stroke trials. Our pragmatic inclusion criteria have no exclusions based on protected characteristics (including age, sex, ethnicity, religion, socioeconomic status) or geography and this should increase inclusivity and fairness (and negates the need for an Equality Impact Assessment). Recruiting staff will be reminded about the importance of inclusivity and fairness. The baseline eCRF will collect information on these and other participant characteristics.

The British National Formulary recommends that women who are, or could become, pregnant should not take ISMN ("manufacturers advise avoid unless potential benefit outweighs risk") or cilostazol ("avoid – toxicity in *animal* studies"). Hence, women who could potentially become pregnant will not be eligible unless are prepared to use a contraceptive. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Detailed information on women of childbearing potential is given later in the protocol.

There are no healthy volunteers in the trial.

Co-enrolment will be on case-by case basis for each trial but will be limited to CTIMP or device trials with interventions having a known safety record and already in clinical use in the UK.: the rationale being that if shown to be effective, they will become standard care and thus will be used together in future. Thus, co- enrolment with such trials will be considered by the chief investigators and sponsors of both studies: the decision will be guided by CVD-Cog Sponsor's comprehensive checklist covering safety, participant burden, and the potential for bias, with a risk/benefit assessment to the patient and the integrity of the trial. Only if deemed permissible under that guidance, will a contract be signed by the chief investigators and the sponsors of both studies to permit co-enrolment. Patients who are in non-interventional studies are permitted to be enrolled in the trial. Studies, where co-enrolment is permitted will be listed and added the TSC and DMC report. TSC permission will also be sought.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. However, if the participant decides to withdraw, it would be discussed with the participant to understand their reason(s) for withdrawal and to establish if they can be supported to remain in the trial. . In the event of their withdrawal, it

will be explained that their data collected so far cannot be erased and will be available for analysis.

Eligibility criteria

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 anti-platelet therapy (so avoiding increased risk of bleeding with triple APT [9]).
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 ≥2 (Appendix *).[30]
    a. The relevant radiology report will be uploaded as part of eligibility and assessed for these criteria.
9. Consent:
    a. Patient has capacity to give consent in the opinion of the PI or any delegated member of the research team, OR
    b. Patient lacks capacity and a legal representative is available to give consent on their behalf.
10. Likely to be available for follow-up at 6 months.
11. Women of childbearing potential and men who have a partner of childbearing potential must be willing to use contraception providing the participant has capacity – see later section which details this.

Acceptable contraceptive methods include established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

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

Exclusion criteria

Any one or more of the following:

1. Lacunar stroke (LACS; so is eligible for LACI-3 trial).
2. Brain stem-only posterior circulation stroke syndrome (POCS).
    a. Note: cerebellar POCS are eligible.
3. Known monogenic cerebral small vessel disease.
4. Index event was an intracranial haemorrhage.

    a. Note: a past history of ICH before the index event is eligible for randomisation to ISMN vs no ISMN but not to cilostazol vs no cilostazol.
5. Other active brain disease e.g. brain tumour, multiple sclerosis, Parkinson's disease, recurrent seizures, neurodevelopmental disorder;
    a. 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 dementia, e.g. letter from a memory clinic and/or taking acetylcholinesterase inhibitor or memantine.
7. Contraindication to both trial drugs (as per SmPC);
8. Indication for both trial drugs (as per SmPC);
9. Planned surgery during the trial period including carotid endarterectomy;
    a. 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.
10. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg.
11. History of drug overdose or attempted suicide.
12. Person is a visitor to the hospital's region so cannot be followed, e.g. on holiday/from overseas.
13. 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.
14. Pregnancy, breast-feeding, or of child-bearing potential (a negative pregnancy test is needed prior to enrolment) and not using highly effective contraception. (Women of childbearing potential and men with partners of childbearing potential must be willing to use contraception)
15. 15. Known renal impairment (most recent creatinine clearance <25 ml/min).
16. Known hepatic impairment (most recent transaminase >3 times upper limit normal).
17. Previously enrolled in CVD-Cog.
18. 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).
19. Women of childbearing potential and men who have a partner of childbearing potential who lack capacity

Cilostazol exclusion criteria - still allows randomisation to ISMN only vs standard care only:

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, any other bleeding diathesis.
25. Uncontrolled high blood pressure: systolic BP >200 mmHg

ISMN exclusion criteria - still allows randomisation to cilostazol only vs standard care only:

26. Definite indication for ISMN: i.e. already prescribed.
27. Definite contraindication to ISMN: see SmPC.
28. Prohibited medications to ISMN: see SmPC – phosphodiesterase-5-inhibitor, e.g. sildenafil, tadalafil and verdenafil.

Expected duration of participant participation

Study participants will be participating in the study for 6-months.

Removal of participants from therapy or assessments

Discontinuation and withdrawal

Once enrolled, participants, their relative (if the participant still lacks capacity), the site PI, or the CI, may:

- Temporarily discontinue the trial drugs, e.g., if the participant transiently deteriorates;
- Permanently discontinue the trial drug(s):
    - e.g., if they suffer an adverse event and decide they no longer want to take further trial treatment(s);
    - If they become pregnant.
- Temporarily discontinue follow-up, e.g., refuse follow-up at a particular timepoint;
- Withdraw from the trial, including from further drug treatment(s) and from all further follow-up, e.g., if they withdraw consent from the trial. Participants must be withdrawn from study and discontinue trial drugs if they withdraw consent. Site and trial staff should discuss with the participant the importance of collecting the primary safety and clinical outcomes so limiting the effect of withdrawal. Participants should be told that withdrawal:
    - Will not affect their future care.
    - Will not affect data collected up to the date of withdrawal, i.e., data cannot be erased and may still be used in the final analysis.

eCRF forms will record (temporary) discontinuation of drug treatment(s) or follow-up, or withdrawal from the trial.

Notes:

- A participant who develops dementia does not need to be withdrawn for this reason.
- Participants who withdraw after randomisation will be replaced if there is still time to do this within the funding envelope of the trial.
- Abrupt termination of treatment will not lead to any rebound or affect patient safety.

Lost to follow-up

Participants will be deemed to be lost to follow-up once at least four attempts to make contact at 6 months, e.g., involving texts, phone calls and letters, have been fruitless.

Informed consent

Consent and legal representative consent

The investigator (or delegated medical colleague) is responsible for performing consent procedures for each patient enrolled in the study. Informed consent will be sought from patients after full and adequate oral and written information about the design and purpose of the trial, potential risks and benefits, and the right to refuse and to withdraw at any time has been provided. As we are recruiting patients with moderate strokes to this study, it is anticipated that some will be unable to give fully informed consent due to confusion, anxiety or potential cognitive impairment from the stroke. In cases where the patient does not have

capacity to consent, consent will be sought from a legal representative. All consent will be recorded in writing.
In England, Wales and Northern Ireland, consent will be sought from a personal legal representative, that is, a family member or friend who is suitable to act as the participant's legal representative by virtue of their relationship with the participant, and if no relative can be identified, a doctor unrelated to the trial. A professional legal representative will only be approached for consent only after every attempt has been made to contact a personal representative. They will be asked whether they know of any advance decisions by the patient with regards to participating in research as these should take precedence.
In Scotland consent from a legal representative will be sought where potential participants lack capacity, in the first instance this will be an appointed guardian or welfare attorney, following which the participant's nearest relative, and if no relative can be identified, a doctor unrelated to the trial. A professional legal representative will only be approached for consent only after every attempt has been made to contact a personal representative.

As the personal legal representative may equally be stressed by the situation a short, pictorial version of the information sheet and consent form will be used for patient and their representative to facilitate explanation and gain initial consent. However, a longer, more detailed information sheet will also be offered at a later date for a fuller evaluation of the trial.

Since patients with cortical or large subcortical stroke often have cognitive or language (dysphasia) problems, it is vital that legal representative consent is sought where the patient lacks capacity, an approach we have frequently used in previous stroke trials whether of phase-2 (GTN-1/2/3, STEMS-1/2, SPEED, TICH, RIGHT, DASH,[31-39] EXCITES – submitted for publication) or phase-3 (e.g. STEPS, TARDIS, TICH-2, RIGHT-2, PHAST-TRAC, PHADER [9-11,40-42]) design. Participant consent will be sought if the participant regains capacity.

There will be a separate information sheet and consent forms for informants of all participants to give their consent to completing some of the cognition questionnaires. The informant will be someone who is close to the participant i.e. relative or carer and can complete the IQ code questionnaire, which is used to assess cognitive decline in older adults. Participants who do not have an informant will be allowed to participate in the trial as they will be completing cognitive questionnaires as part of the 6-month follow up.

Information
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The investigator (or designated doctors) will all be trained in consent and assessing capacity. Capacity will be assessed by the Investigator or designate to ensure the potential participant understands the purpose, procedures and potential risks of the study. If the patient is deemed by the Investigator or designate to lack capacity (e.g. due to confusion, cognitive impairment or severe dysphasia), an opinion will be obtained from their legal representative. The Investigator or designate will then provide the patient or legal representative an Information Sheet and explain the research study and then answer any questions that may arise. If the legal representative cannot attend the hospital, the legal representative may discuss the trial over the telephone and have time to consider whether the patient would want to be enrolled in the trial. Consent will be obtained from the legal representative when they visit the hospital. The Participant Information Sheet and consent form may be sent by email or post if the legal representative is unable to attend the hospital in person to sign the consent form during the participants hospitalisation.

If a legal representative gives consent for a patient to take part in the trial and the patient regains capacity, re-consent must take place for continued participation in the trial.

Consent will be explicit and cover both participation and use and retention of the trial data. A verbal explanation will be provided in terms suited to the patient's or legal representative's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Pictures and simplified written language will be used in the form of a short, pictorial version of the information sheet and consent form where relevant, to facilitate comprehension of information e.g. relevant to patients with dysphasia/cognitive impairment. Patients or legal representatives will have the opportunity to carefully review the written consent/declaration forms and ask questions prior to signing. Patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The patient or legal representative will sign the consent form prior to any procedures being done specifically for the study. Consent will be witnessed by a third party (unrelated to the study) if the patient lacks the ability to write a signature (e.g., due to dominant hand weakness). Written informed consent will be obtained for all participants before they undergo any interventions related to the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. One copy of the consent form will be kept by the participant or legal representative, one will be kept by the Investigator, and a third will be retained in the patient's hospital records and a copy will be sent to the coordinating centre. The informed consent process will be conducted and documented in the patient's medical notes. The rights and welfare of the patients will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Should there be any subsequent amendment (e.g., to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant or their legal representative.

TRIAL TREATMENT AND REGIMEN

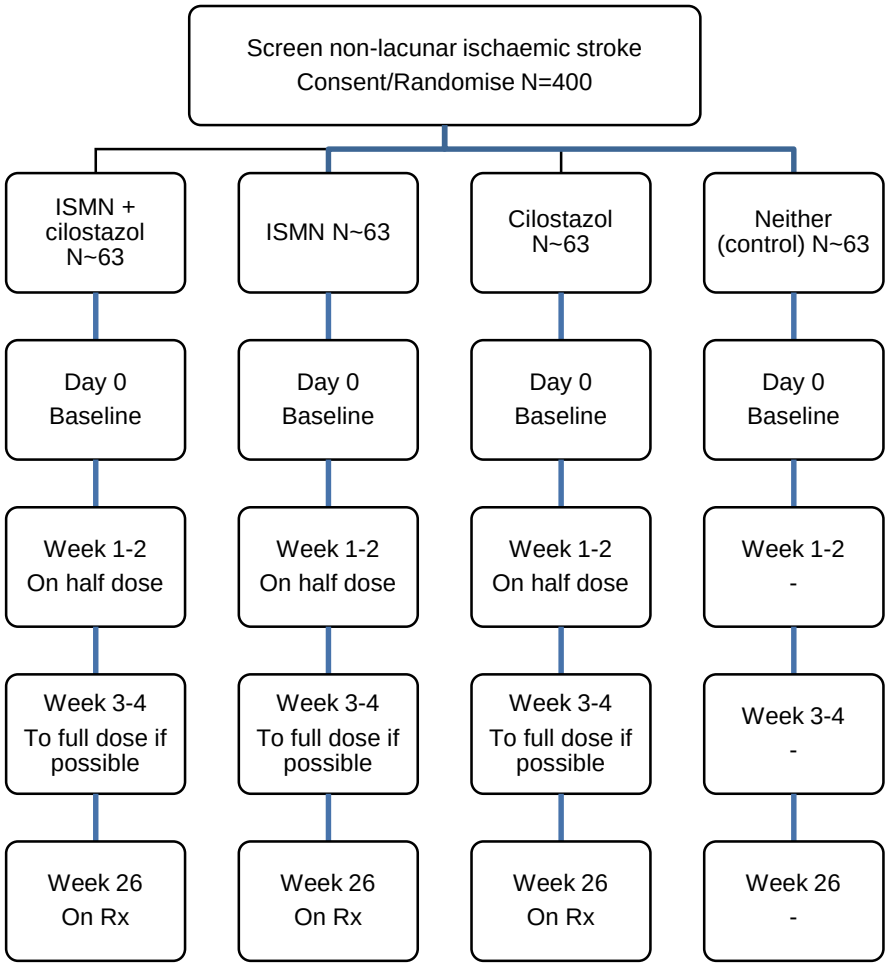
Design

UK-based prospective randomised open-label blinded-endpoint (PROBE) partial-factorial feasibility and proof-of-concept phase-2c trial of ISMN vs no ISMN and, in patients not on an oral anticoagulant, ISMN/cilostazol vs ISMN only or cilostazol only or neither drug in patients with previous cortical or large subcortical ischaemic stroke.

Trial flow

Figure 4: Flow of treatment/follow-up. Example is for participants randomised to ISMN, cilostazol, both or neither. Patients only randomised to ISMN vs no ISMN are represented by columns 2 and 4 and patients only randomised to cilostazol vs no cilostazol are represented by columns 3 and 4.

Following week 26, reduce then stop drug and return unused drug to community pharmacy.



Patient flow

Table 1. Flow of participants.

	Screen	Base-line	Days 1-14	Day 7-14	Days 15-183	Day 21-28	Day 183	Day 183
Location	Ward-clinic	Ward-clinic	Home	Home	Home	Home	Home	Home
Assessment by	Site	Site		Site: phone		Site: phone	CC: phone	Site: phone
Eligibility	+							
Consent or assent	+							
Demographics		+						
NIHSS		+						
Cognition: MoCA, semantic/phonemic verbal fluency, TICS-M, trail-making B, ZDS		+					+	
BI, CFS, EQ-5D-5L, EQ-		+					+	

VAS, mRS, SIS								
Calculated DSM-5-7L		+					+	
Informant: IQCODE		+					+	
Concomitant medications		+						+
Randomisation †		+						
Prescription for 6 months		+						
Half-dose(s)			<>					
Full-dose(s)					<>			+
Adherence, targeted drug related adverse events,‡ major bleeding				+		+		+
SAEs: fatal/non-fatal				+		+		+
Dementia diagnosis				+		+	+	+
All-cause mortality				+		+		+
Disposition							+	+
GP contacted for status							+	

BI: Barthel index;[43] CC: coordinating centre (blinded to treatment assignment); CFS: clinical frailty scale;[44] EQ-5D-5L: EuroQoL 5-dimension 5-level; EQ-VAS: EuroQoL visual analogue scale; DSM-5-7L: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition 7-level ordinal cognition scale; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly;[45] MoCA: Montreal Cognitive Assessment;[46] mRS: modified Rankin scale;[47] NIHSS: National Institutes of Health stroke scale;[48] SIS: stroke impact scale;[49] TICS-M; telephone interview cognition scale-modified;[50] Ward-clinic: Hospital stroke ward or stroke/TIA clinic; ZDS: Zung depression scale.[51]

†: Point of inclusion
‡ Targeted drug related adverse events: headache, loose stools, palpitations, nausea, dizziness, falls

Data to be collected at each time-point:

Randomisation form: in ward/clinic by hospital site

- Date/time
- Who: participant/carer and investigator
- General eligibility criteria confirmation
- ISMN criteria confirmation
- Cilostazol eligibility criteria confirmation
- Investigator confirming eligibility and their role
- Informed consent details: date of the ICF, date of PIS given to participant or surrogate, version of PIS and ICF, Investigator taking consent details and their role
- Participant details: initials, date of birth, NHS/CHI number
- Contact details, participant: name, address, telephone, email
- Contact details, next of kin: name, address, telephone, email
- Contact details, informant: name, address, telephone, email
- Contact details, GP: name, address, telephone, email
- Demographic: age, sex assigned at birth, disposition (home, residential care, nursing home, hospital), years of full-time education
- Index event: severity (NIHSS [48])

- Cognition/mood: MoCA,[46] TICS,[50]
- Function: dependency (mRS [47]), disability (Barthel Index [43])
- CT/MRI scan report (cut & paste from PACS): stroke lesion size, white matter CT hypodensities/MRI hyperintensities severity, lacunes, atrophy, old lesions
- Who completed form

→ calculated ordinal cognition from MoCA, mRS, disposition [22]

Baseline form: in ward/clinic by hospital site

- Date/time
- Who: participant/carer and investigator
- Demographic: ethnicity, education attainment (i.e. premorbid peak cognitive ability), occupation, employment status
- Lifestyle: smoking, alcohol
- Medical history: Previous ischaemic stroke/TIA/intracerebral haemorrhage, myocardial infarction, treated hypertension, treated hyperlipidaemia, diabetes mellitus, previous falls
- Index event: date, OCSP[52]
- Concomitant medications: antiplatelet, antihypertensives, lipid lowering, anti-diabetes
- Cognition/mood: concentration (MMSE), semantic and phonemic verbal fluency,[53] trail making B,[54] mood (Zung [51])
- Function: impairment (NIHSS), frailty (clinical frailty scale, CFS [44]), quality of life (EQ-5D-5L, EQ-VAS), fatigue (severity scale, FSS), global (Stroke Impact Scale)
- Haemodynamics (record measurements 2 and 3): blood pressure, heart rate
- Informant: IQCODE [45]
- Randomised drug(s): date, drug, dose, formulation, frequency, brand

- All contact details and NHS/CHI number will be encrypted and stored separately from the anonymised trial data in compliance with data protection regulations. The nominated close personal contact details collected on the paper Contact form will be stored securely by the local hospital NHS research team and uploaded to the Coordinating Centre secure vault to allow central follow-up.

- ***Neuroimaging scan upload***:
- Date/time of scan after index
- Brain scan type: CT, MRI
- Upload scan facility

- ***Day 7-14 form***: telephone by hospital site
- Date/time
- Status: available, lost, declined, withdrawn, died
- Who: participant/carer and investigator
- Targeted drug adverse events: headache, loose stools, palpitations, nausea, dizziness, falls [16,21]
- Serious adverse events
- Drug(s): Current dose, formulation, frequency, brand
- Decision to increase dose if drug(s) tolerated: if so new drug(s): date, drug, dose, formulation, frequency, brand

- ***Day 21-28 form***: telephone by hospital site – in response to dose increase
- Date/time
- Status: available, lost, declined, withdrawn, died
- Who: participant/carer and investigator
- Targeted drug related adverse events: headache, loose stools, palpitations, nausea, dizziness, falls [16,21]
- Serious adverse events
- Drug(s): Current dose, formulation, frequency, brand
- Decision to decrease dose if drug(s) not tolerated: if so drug(s): date, new drug, dose, formulation, frequency, brand

Day 183: telephone by coordinating centre (blinded to treatment assignment)
- Date/time
- Status: available, lost, declined, withdrawn, died
- Who: participant/carer and investigator
- Disposition (home, residential care, nursing home, hospital)
- Vascular events since randomisation: stroke, MI
- Cognition/mood: MoCA, TICS, concentration (MMSE), semantic verbal fluency, phonemic verbal fluency, mood (Zung)
- Function: mRS, BI, frailty (clinical frailty scale, CFS [44]), quality of life (EQ-5D-5L, EQ-VAS), fatigue (severity scale, FSS), global (Stroke Impact Scale, SIS [49])
- New dementia diagnosis: letter from dementia/memory clinic, taking acetylcholinesterase inhibitors and/or memantine
- Informant: IQCODE

→ calculated clinical primary outcome - ordinal cognition from MoCA, mRS, disposition, dementia diagnosis, dementia drugs [22]

Day 183: telephone by hospital site (unblinded to treatment assignment)
- Date/time
- Status: available, lost, declined, withdrawn, died
- Who: participant/carer and investigator
- Disposition (home, residential care, nursing home, hospital)
- Concomitant medications (focussed on vascular secondary prevention)
- Targeted drug related adverse events: headache, loose stools, palpitations, nausea, dizziness, falls [16,21]
- Serious adverse events
- New dementia diagnosis: letter from dementia/memory clinic, taking acetylcholinesterase inhibitors and/or memantine
- Randomised drug(s): drug, dose, formulation, frequency, brand

Note: If participant is an inpatient at day180 the follow up can be completed by staff at site face to face.

Dosing regime

Patients will be supplied with trial drug in its usual (marketing) packaging, i.e. unaltered. Patients will be issued with instructions reflecting the allocated dosing schedule which will instruct them what tablets they have to take initially and how to increase the dose. Cilostazol should be taken 30 minutes before meals. They will receive a phone call after 1 to 2 and 3 to

4 weeks post randomisation as per the schedule above (Table 1) to guide dose escalation. The research staff conducting the telephone follow up will be under the supervision of, and contact, the site Principal Investigator. If a participant encounters intolerable side effects, they will be asked to return to the highest previously tolerated dose, and this will be recorded in the eCRF and hospital records. They will be given clear instructions by phone or in person (depending on the stage of the trial). Patients will also receive instruction on how they should decrease the dose of trial drug incrementally at the end of the study. Patients are asked to contact the hospital research staff between the follow up calls if they experience any adverse events whilst on the IMP. This form of telephone follow up was used successfully in the LACI-2/3 trials (EudraCT 2016-002277-35/ ISRCTN44436843). Dosing and compliance with treatment were not deemed to be an issue.
All decisions to change the dose to be administered, increase or decrease, will be made by a medically qualified doctor in the research team, and this decision will be documented in the medical notes and study records.

Table 21: Patients randomised to Isosorbide Mononitrate alone - either XL or non-XL preparations, example. If a slow-release preparation is not available, then a non-slow-release preparation may be used, but the dose should be split with half given in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Does not apply to patients with a contra-indication to ISMN.

Week	ISMN XL [1/2] Morning	Evening
Study start		
1 and 2	25mg [3]	Nil
3 and 4	50mg [4]	Nil
5 to 25	50mg [4/5]	Nil
Study end		
26	25mg [3]	Nil
27	Nil	Nil

Week	ISMN-standard release [1] Morning	Evening
Study start		
1 and 2	Nil	20mg
3 and 4	20mg	20mg
5 to 25	20mg [5]	20mg
Study end		
26	20mg	Nil
27	Nil	Nil

Notes:
1. A long-acting formulation of ISMN should be used if available; if not then use a standard-release formulation.
2. LA, Retard, SR, XL are considered the same, i.e. a long-acting formulation requiring a single dose given daily.
3. 25mg XL may be substituted for 20mg or 30mg depending on local availability.
4. 50mg XL may be substituted for 40mg or 60mg depending on local availability.
5. Participants should contact their hospital site at any time if they have questions about dosing or concerns about adverse events. The full doses given here (50mg XL daily or 20 mg standard release twice daily) may be halved if adverse events are problematic.
6. The protocol here follows that in the published LACI-2 trial (EudraCT 2016-002277-35, ISRCTN14911850 [21]) and ongoing LACI-3 trial (ISRCTN44436843).

Table 3: Patients randomised to cilostazol alone. Does not apply to patients with a contra-indication to cilostazol, including participants taking oral anticoagulation.

Week	Cilostazol Morning	Evening
Study start		
1 and 2	50mg	50mg
3 and 4	100mg	100mg
5 to 25	100mg	100mg
Study end		
26	50mg	Nil
27	Nil	Nil

Notes:

1. Participants should contact their hospital site at any time if they have questions about dosing or concerns about adverse events. The full doses given here (100 mg twice daily) may be halved if adverse events are problematic.
2. The protocol here follows that in the published LACI-2 trial (EudraCT 2016-002277-35, ISRCTN14911850 [21]) and ongoing LACI-3 trial (ISRCTN44436843).

Table 4: Patients randomised to both Isosorbide Mononitrate and Cilostazol. Does not apply to patients with a contra-indication to ISMN or cilostazol including participants taking oral anticoagulation.

4a) If using ISMN XL

Week	ISMN XL [1/2] Morning	Evening
Study start		
1 and 2	25mg [3]	Nil
3 and 4	50mg [4]	Nil
5 to 25	50mg [4/5]	Nil
Study end		
2726	25mg [3]	Nil
27	Nil	Nil

Week	Cilostazol Morning	Evening
Study start		
1 and 2	50mg	50mg
3 and 4	100mg	100mg
5 to 25	100mg	100mg
Study end		
26	50mg	Nil
27	Nil	Nil

4b) If using ISMN standard release

	ISMN-standard release [1]				Cilostazol	
Week	Morning	Evening		Week	Morning	Evening
Study start				Study start		
1 and 2	Nil	20mg		1 and 2	50mg	50mg
3 and 4	20mg	20mg		3 and 4	100mg	100mg
5 to 25	20mg [5]	20mg		5 to 25	100mg	100mg
Study end				Study end		
26	20mg	Nil		26	50mg	Nil
27	Nil	Nil		27	Nil	Nil

Notes for tables 4a and 4b:

1. A long-acting formulation of ISMN should be used if available; if not then use a standard-release formulation.
2. LA, Retard, SR, XL are considered the same, i.e. a long-acting formulation requiring a single dose given daily.
3. 25mg XL may be substituted for 20mg or 30mg depending on local availability.
4. 50mg XL may be substituted for 40mg or 60mg depending on local availability.

5. Participants should contact their hospital site at any time if they have questions about dosing or concerns about adverse events. The full doses given here (ISMN: 50mg XL daily or 20 mg standard release twice daily; cilostazol 100 mg twice daily) may be halved if adverse events are problematic.
6. The protocol here follows that in the published LACI-2 trial (EudraCT 2016-002277-35, ISRCTN14911850 [21]) and ongoing LACI-3 trial (ISRCTN44436843).

Table 5: Patients randomised to neither Isosorbide Mononitrate nor Cilostazol

Week	No ISMN Morning	Evening
Study start		
1 and 2	Nil	Nil
3 and 4	Nil	Nil
5 to 25	Nil	Nil
Study end		
26	Nil	Nil
27	Nil	Nil

Week	No cilostazol Morning	Evening
Study start		
1 and 2	Nil	Nil
3 and 4	Nil	Nil
Study start	Nil	Nil
Study end		
26	Nil	Nil
27	Nil	Nil

Dose changes
Doses will be initiated as per the example regime in section 6.3. Patients will be allowed to increment the dose more slowly, or to stay at a previously tolerated dose where their symptoms preclude reaching the target dose stated in Tables 2-5. Such variation of dose will not count as a protocol deviation. Patients will be able to stay on the dose they can tolerate. This will be done under close guidance of the researcher under the guidance of the principal investigator. There will be no other changes to the doses described in Table 2-5.

Concomitant and Rescue Medications and Treatments

Permitted medications
Patients should continue to take prescribed guideline stroke prevention treatment and may continue to take all other usual prescribed medication during the study except those listed immediately below and in the exclusion criteria as above. Investigators will record concomitant medications that the participant receives at the time of enrolment or during the trial follow-up in the eCRF. These will be recorded before and at end of trial treatment(s).

Prohibited medications
ISMN:
If a participant develops an indication for ISMN (e.g. angina) or a phosphodiesterase-5 inhibitor (PDE5-i, e.g. benign prostatic hypertrophy or erectile dysfunction), ISMN should be ceased immediately.

Cilostazol:
If a participant develops an indication for oral anticoagulation (e.g. warfarin, heparin, dabigatran, rivaroxaban, apixaban) or requires treatments comprising other strong inhibitors of metabolic enzymes CYP3A4 or CYP2C19 (e.g. diltiazem) or requires erythromycin, clarithromycin, ketoconazole, itraconazole, omeprazole, dual antiplatelet drugs (e.g. combined aspirin and clopidogrel/ticagrelor), cilostazol should be ceased immediately.

There are no rescue interventions save stopping ISMN and/or cilostazol as appropriate.

Compliance

Compliance will be monitored by the local hospital sites by phone. Symptoms that might be related to either drug will be assessed using a structured questionnaire given as per the follow-up visit schedule.

Participants will be asked to contact the local hospital investigator if they experience adverse symptoms, or concerns about taking the tablet(s); they may also contact the central team. Once patients are established on their steady dose of tablets, they will be asked to contact the local hospital or the central team if they experience untoward symptoms (in addition to contacting their GP or other relevant hospital service). Such episodes of contact will be recorded in the eCRF or AE form or reported as SAEs as appropriate.

The target adherence is $\geq$75% of participants are taking $\geq$50% trial dose at end-of-trial.[19-21]

Accountability for drugs & placebos

Randomised treatment(s) will be prescribed by the principal investigator or their designate in the hospital ward or stroke/TIA clinic. The prescription will be for 6 months of treatment(s) and account for the weaning-up period in the first month. Prescriptions will be taken to the hospital site for dispensing. Research staff at the hospital site will telephone the participants at 1-2 weeks and 3-4 weeks post randomisation. During the telephone call the research staff will ensure that the participant is taking the correct dose of medication and will explain any dose escalation, or reduction if the participant is experiencing side effects of the medication. Research staff will be under the direction of the principal investigator and will be trained is advising participants regarding dose escalation/reduction. Any concerns raised during the telephone call will be discussed with the principal investigator. Following the day 183 telephone call by the hospital site, participants will be asked to take any unused medications to a local community pharmacy for destruction.

Prescription, date of changing from half to full dose(s), dose at end of treatment and the request for destruction will be recorded in the eCRF.

Management of study drug overdose

The risk of overdose will be mitigated by follow-up phone calls by the hospital research teams at weeks 1-2 and 3-4 as well as minimised by excluding patients with a history of overdose or attempted suicide. In the case of an overdose participants will be informed to seek medical assistance immediately. Also, if participants accidentally take more medication that they should, they will be advised to contact the hospital research staff as soon as possible. Of note, these drugs are widely used in various parts of the world.

***Isosorbide mononitrate*:**
The SmPC describes the expected effects of isosorbide mononitrate in overdose and details measures for management.

***Cilostazol*:**
The SmPC for Cilostazol states that there is limited information on the effects of acute overdose in humans. It is anticipated to feature severe headache, diarrhoea, tachycardia

and possibly cardiac arrhythmia. Management would be supportive care and gastric lavage as appropriate.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant.

The trial treatment(s) may be stopped at any time. Investigators must immediately report any urgent safety measure to the Coordinating Centre who will then report this to the Sponsor; the Sponsor will report this immediately by telephone to the MHRA Clinical Trials Unit safety scientist and follow this with a written notification.

Protocol Deviations and Violations

Protocol Deviation:
These are minor deviations from the protocol that affect the conduct of the trial in a minor way. This includes any deviation from the trial protocol that is not listed as a Protocol Violation. Deviations will be collected, via the online electronic case report form. The list of deviations is not exhaustive and so there will be a drop-down menu as well as a free text box. The Chief Investigator will be informed of protocol deviations via the online electronic case report form.

Protocol violation:
These are a major deviation from the trial protocol, for example where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria, or where deviations from the protocol could affect participant safety, the trial delivery or interpretation significantly: Listed protocol violations are:

1. Enrolment without consent.
2. Enrolment but ineligible.
3. Failure to prescribe the randomised drug(s).
4. Non-reporting of primary outcome measure.
5. Primary outcome not recorded between days 170 and 210.
6. Non-reporting of safety outcomes once known, death, serious adverse event (SAE), serious unanticipated serious adverse event (SUSAR), major bleeding or targeted drug adverse events.
7. Any other major violation of the trial protocol or GCP.

All protocol violations must be reported immediately to the Chief Investigator, via the online electronic case report form. The CI will notify the Sponsor if a violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious GCP breach, internal audit of the trial and seeking counsel of the trial committees.

Criteria for terminating trial

The overall trial may be terminated following advice from the Trial Steering Committee or Data Monitoring Committee, or by the sponsor or the funders if there is overwhelming evidence of major safety concerns, new information on the interventions, or issues with trial conduct (e.g. poor recruitment, loss of resources).

The trial may be stopped at individual centres due to unacceptable performance in recruitment and/or failure to comply with protocol.

Sites should archive all trial materials.

FERTILITY AND PREGNANCY

Women of childbearing potential are defined as fertile following menarche (having not been free from menses for >1 year) and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) unless permanently sterilised by hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy.

Women of childbearing potential must use a highly effective method of contraception from the time of screening until 34 days after discontinuing the trial drug (duration of the study drug clearance from the body plus 30 days duration of one ovulatory cycle). Highly effective birth control methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
    - For female participants, the vasectomised male partner should be their sole partner, and the vasectomised partner must have had medical assessment of surgical success
- Sexual abstinence - refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments
    - True sexual abstinence when this is in line with the preferred and usual lifestyle of the patient.
    - Periodic abstinence (calendar, symptom-thermal, post-ovulation methods) or withdrawal are not acceptable methods of contraception.

All methods of contraception must be used in combination with the use of a condom by the male sexual partner for intercourse, from the time of screening until 34 days after discontinuing study treatment.

Male participants must avoid unprotected sex with all heterosexual partners (by use of condoms) during the trial, and for a washout period of 3 months after the last dose of trial drug.

Women of childbearing potential must have a negative urine pregnancy test done as a part of the screening on the day of randomisation. If applicable, the central team will send the urine pregnancy test with the central follow-up paper questionnaire to do the pregnancy test after 4 days of discontinuing the trial drug.

Although pregnancy is not considered an AE or SAE, for safety purposes, Investigators will be required to record any female participant's pregnancy or any pregnancy of a female partner of a male participant, who became pregnant while participating in the study, and for up to 34 days after the last dose. The Investigator will need to record the information on an electronic Pregnancy Notification Form within 14 days of being made aware of the pregnancy. The participant will be withdrawn from the trial medication(s). The participant will be followed up to 6 months in the trial and long-term via the GP for safety.

All pregnant female participants and pregnant partners of male participants must be followed up until the outcome of the pregnancy.

STATISTICS and DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN

General

The DMP will be written as a separate document. It will cover:

- Contact details for relevant trial staff including roles and responsibilities with regard to data management, indicate access controls and restrictions.
- Details of the flow of data from investigator site to archiving.
- Trial database to be used, including data audit trail, maintenance, disaster recovery plans and data backup system.
- Data coding.
- Data monitoring plans e.g. frequency, source data verification.
- Data protection procedures, including electronic transfer requirements.
- Data storage.

Data Capture and Data Queries

Data will be captured using an electronic case record form (eCRF) built using Stroke Trials Unit Bespoke system as used by our ongoing trials (MACE-ICH, RECAST-3, TICH-3). Data can be added directly into the database, however at hospital sites where this is not possible, the eCRF can be downloaded and completed on paper for later transcription into the database. All paper CRFs should be stored in a locked cupboard in a locked office, with access only granted to those on the trial delegation log.

The Data Management Plan will detail the CRFs to be used, how these will be disseminated to sites, how sites should send completed forms to the trial coordinating centre or staff and within what timeframes. A record will be kept by the co-ordinating centre or central trial staff of all data queries sent out to participating sites and replies received. Participating sites should be given clear instructions on how to respond to data queries and how to change local records. All alterations to trial data will only be made by personnel authorised to do so and recorded as such on the Site Responsibility/Delegation Log.

Investigators will access the electronic database over the internet using an encrypted link and via a log-in/password/PIN system. The database is backed up daily by the University of Nottingham. Investigators will be trained via a training slide set and manual, this covering the eCRF. The database will check and query in real time for logic and range errors. Essential fields will require mandatory data entry. This approach will reduce missing and incorrect data and prevent protocol violations related to inclusion/exclusion criteria. Any remaining protocol violations will lead to exclusion of the participant from the per protocol data set.

If discrepancies are found during 6-monthly statistical reports (done for DMC/TSC), the Trial Manager will follow-up with the site who will amend incorrect data.

Description of Data Entry Validation

The STU Bespoke system will be used to collect clinical and trial data. Test data will be entered for validation purposes. Logic checks (e.g., MoCA cannot differ by more than 20 over 6 months) and range checks (e.g., age>=30) will be built in to reduce errors. Regular assessments of exported pseudo-anonymised data will test for incorrect data; identified errors will be passed back by trial staff to the recruiting site for correction. Data corrections will be recorded.

Data Cleaning and Database Lock

The database will be regularly downloaded and assessed for logical or range inaccuracies. The same will be performed after data lock. Database lock will comprise changing the file from read-write to read-only and so preventing further changes. Anonymised data will be archived and shared for legitimate tertiary analyses and meta-analyses. Where sites have not used a paper CRF, a copy of their entered trial data will downloaded by the site prior to database lock.

Monitoring

Remote monitoring will be carried out with analyses of data logic and range checks by sites, and assessment for unusual data patterns (e.g., digit preference, non-random data). Where there is uncertainty about the veracity or accuracy of data, or low recruitment rates, a site will be visited and monitored by the Trial Manager with data comparison against source data.

STATISTICS

Methods

The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines. A full Statistical Analysis Plan (SAP) will be developed and published prior to database lock.

Tabulations:
Characteristics of randomised participants will be presented for the two pairs of trial arms at baseline, i.e. ISMN vs no ISMN and cilostazol vs no cilostazol, using appropriate descriptive statistics: number %, median [interquartile range] or mean (standard deviation). The publication supplement will have a table comparing both drugs versus neither.

Similarly, the main trial objectives will be tabulated:

- Participant feasibility: Number of participants recruited
- Site feasibility: Number of sites recruited
- Retention: Number of participants with data recorded at 6 months
- Adherence: Number of participants taking at least half the drug(s) dose, i.e. ISMN XL 25mg od or ISMN non-XL 20mg od; cilostazol 50mg bd
- Outcome feasibility: Number of participants with a record of the primary clinical outcome (DSM-5-7L ordinal cognition scale)

Safety outcomes will be tabulated by drug treatment: ISMN vs no ISMN and cilostazol vs no cilostazol:

- Primary safety: All-cause death
- SAEs
- Major bleeding
- Targeted drug related adverse events

Proof-of-concept outcomes will be tabulated by drug treatment: ISMN vs no ISMN, cilostazol vs no cilostazol and both ISMN/cilostazol vs neither:

- Primary clinical: DSM-5-7L ordinal cognition scale
- Other cognition measures: MoCA, TICS, concentration (MMSE), semantic verbal fluency, phonemic verbal fluency, mood (Zung), dementia diagnosis, IQCODE
- Functional measures: mRS, BI, CFS, EQ-5D-5L, EQ-VAS, FSS, SIS

Comparisons:
Analyses of safety and clinical proof-of-concept variables will be performed by intention-to-treat using:

- Binary logistic regression: for binary events, e.g. major bleeding
- Cox proportional hazards regression for time-to-event outcomes, e.g. death
- Ordinal logistic regression: e.g. DSM-5-7L, mRS
- Multiple linear regression: e.g. for BI
- Wei-Lachin test, assessment of global outcomes: e.g. 1) combining DSM-5-7L, recurrent ordinal stroke, ordinal MI, mRS, EQ-5D-5L, ZDS, death; and 2) global SIS, using individual SIS domain scores.[21]

Apart from the Wei-Lachin test, analyses will be adjusted for stratification (on anticoagulation) and minimisation factors (age, premorbid mRS, NIHSS, age of leaving education, sex, onset from stroke to randomisation; systolic BP, smoking). Absolute and relative measures of effect and 95% confidence intervals will be presented for each analysis. A worst score will be assigned at day 183 for people who die (e.g. mRS = 6, BI = -1, EQ-5D-5L = 0) to avoid losing participants in analyses and missing a “kill or cure” effect, and to anchor analyses, as we did in ENOS, TARDIS and RIGHT-2. All analyses will be fully specified in the SAP.

The primary clinical outcome, DSM-5-7L, will be assessed in pre-specified subgroups using interaction tests to identify responder subgroups including all stratification and minimisation factors as well as: anterior vs posterior circulation, lesion side (right, bilateral, left). Since the trial is not powered for statistical comparisons between groups, these analyses will be regarded as hypothesis generating.

The trial statistician will perform statistical analyses using code written in SAS and the R language. Analyses will be compared as randomised without imputation of missing data. Due emphasis will be placed on the confidence intervals for the between arm comparisons. No formal interim analyses will be performed.

Stopping rules:
As a feasibility trial, there are no formal stopping rules for effectiveness or futility. However, the DMC may recommend to the TSC that the trial should be stopped on the basis of hazard:

- Stop enrolment if the study is negative: statistical evidence that DSM-5-7L or fatal SAEs is worse in the ISMN vs no ISMN group or cilostazol vs no cilostazol ($p<0.01$);

Hence, the DMC will inform the TSC, if in their view there is proof beyond reasonable doubt that the data indicate that the negative intervention is clearly contra-indicated. Recruitment and treatment will continue in the non-hazardous intervention arms.

Sample size and justification

As a feasibility trial, there is no formal sample size calculation. However, recruitment of 400 participants will be sufficient to assess the feasibility, retention, adherence, safety and proof of concept aims. The sample size is not designed to assess efficacy but rather to obtain an estimate of the effect size and variance necessary to plan a definitive study and protocol.[55] We assume n~250 on Anti-platelet therapy (APT) (or none),and n~150 on OAC.

Assessment of efficacy

The primary clinical measure to be assessed in proof-of-concept analyses will be the DSM-5-7L ordinal measure of cognition at 6-months and presented as an adjusted common odds ratio (acOR). Secondary outcomes will include cognition and functional measures as listed above.

Assessment of safety

The primary safety outcome is all-cause death by 6-months. This will be ascertained through a check via the GP prior to any telephone. At end of trial, death will be validated against the office for national statistics and equivalents across UK. Secondary outcomes include serious adverse events, major bleeding and targeted drug-related adverse events as reported to the recruiting site or coordinating centre.

Procedures for missing, unused and spurious data

Many fields in the electronic case report form will be mandatory, especially those relating to baseline covariates, treatment and primary and secondary outcomes; further, the primary and most secondary outcomes include a value for death. Hence, there should be minimal missing data in the primary and key secondary analyses, and we will not impute data. A sensitivity analysis of the primary outcome will use regression imputation of missing data.

Definition of populations analysed

Three analysis populations will be defined for assessment of safety and proof of concept.

Safety set:
All randomised participants. This accounts for participants randomised to one or both drugs or nether.

Full Analysis set:
All randomised participants who have at least one follow-up assessment, i.e. in the first month or at 6-months.

Per protocol set:
All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

ADVERSE EVENTS

Definitions

Adverse events:
An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study. Since ISMN and cilostazol have been licensed for many years, not all non-serious adverse events will be recorded. The presence of the following targeted drug adverse events will be collected explicitly in the eCRF: headache, loose stools, palpitations, nausea, dizziness, falls, as present in the previous LACI-1/2 trials in stroke;[16,21] these cover both ISMN and cilostazol. If these targeted AEs are considered serious, they will also be reported as an SAE.

Reference Safety Information of Isodur 50XL
Known side effects of ISMN slow release (ISODUR 50XL) are based on the SmPC of Galen Ltd section 4.8 (latest revision 09/04/24) and are listed in Appendix 1

Reference Safety Information of cilostazol 100mg
Known side effects of cilostazol 100mg are based on the SmPC of Mylan section 4.8 (latest revision 09/03/20) and are listed in Appendix 2.

Reference Safety Information of ISMN
Known side effects ISMN 20mg standard release are based on the SmPC of Dexcel Pharma Ltd section 4.8 (latest revision 01/01/18) and are listed in Appendix 3.

Serious Adverse Events (SAEs):
A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death.
2. A life-threatening adverse event.
3. Inpatient hospitalisation or prolongation of existing hospitalisation.
4. A disability / incapacity.
5. A congenital anomaly in the offspring of a participant.

6. An important medical event: these may not result in death, be life-threatening, or require hospitalisation but may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A SAE does include a / an:
1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

A SAE does not include a / an:
1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure may be a SAE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

All SAEs will be assessed for seriousness, expectedness and causality. A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Serious adverse events (SAEs):

The list below are associated with the index stroke or underlying co-morbid conditions associated with stroke and so are expected and will not be reported as AEs. These may include, but are not limited to, the following and will be reported as an SAE if considered serious:

- Agitation
- Anaemia
- Angina/myocardial infarction/cardiac ischaemia
- Anxiety
- Atrial fibrillation/flutter
- Bradycardia
- Bruising/bleeding of skin
- Cardiac arrest
- Cardiac dysrhythmia
- Carotid artery stenosis
- Cellulitis
- Cerebral oedema
- Cerebral herniation
- Cerebral infarct extension/recurrence
- Chest infection

- Coma/diminished level of consciousness
- Confusion
- Congestive heart failure/heart failure
- Constipation
- Death
- Decubitus ulcer
- Deep venous thrombosis
- Dehydration
- Delirium
- Diarrhoea
- Dyslipidaemia
- Dyspepsia
- Dysphagia
- Dyspnoea
- Epistaxis
- Extracranial bleeding
-
- Fever
- Fractures
- Gastritis or gastric/duodenal ulcer
- Gastrointestinal bleed
-
- Haemorrhagic transformation of cerebral infarct
- Hydrocephalus
- Hypokalaemia
- Hyperglycaemia/hypoglycaemia
- Hypertension
- Hypoxia
- Ileus
- Insomnia
- Intracerebral haemorrhage expansion
- Intraventricular haemorrhage
- Ischaemia, intestinal
- Joint pain (arthralgia)
- Malignant cerebral oedema
- Musculoskeletal pain
- Neurologic worsening
- Oesophagitis
- Peripheral vascular disorder
- Peripheral oedema
- Pneumonia
- Pressure sore
- Pulmonary oedema
- Pulmonary embolism
- Renal impairment
- Seizure
- Sepsis
- Shoulder pain
- Sleep apnoea
- Skin rash
- Limb spasticity

- Transient ischemic attack
- Urinary incontinence
- Urinary tract infection
- Vomiting

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners. SAEs will be reviewed by the CI and subsequently adjudicated (blinded to treatment assignment) by an independent medical monitor. The medical monitor will determine whether the event fits the criteria of an SAE and whether enough information has been supplied to support the diagnosis. The medical monitor cannot downgrade an assessment of seriousness or causality made by the site PI, if there is a disagreement on this a conservative approach to reporting should be taken and both opinions should be included on the report.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring. Where it is the partner of trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant.

The trial treatment(s) may be stopped at any time. Investigators must immediately report any urgent safety measure to the Coordinating Centre who will then report this to the Sponsor; the Sponsor will report this immediately by telephone to the MHRA Clinical Trials Unit safety scientist and follow this with a written notification.

SUSARs:

A serious adverse event that is either sudden in its onset (anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator. The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's ICSR Submissions web site.
- Shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required.

Trial Treatment Related SAEs:

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator. The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or legal representative informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their

nominee and the participant or legal representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms, and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial. A copy should also be sent to the coordinating centre, via upload to the secure vault.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by the local hospital's Pharmacy.

The investigator and the local site pharmacist shall maintain records of tthe study drug's distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF).

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on eCRFs other trial documents and the electronic database. The documents and database will also use the site number, participant initials (first and last names separated by a hyphen or a middle name initial when available) and trial participant number.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS/CHI number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A eCRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below. Source documents should be kept in a locked cupboard in a locked office with access only granted to those on the delegation log for the trial.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made always be available for review by the Chief Investigator or their designate, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Manager, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly, and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; drug prescription chart data storage and data transfer procedures.The Trial Manager, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Presentations and publications will comprise:

- Ongoing trial presentations as an abstract/poster at UK Stroke Forum, and possibly at European Stroke Organisation Conference, International Stroke Conference and World Stroke Conference as appropriate.
- Protocol, statistical analysis plan and baseline characteristic publications in open access journal (e.g. International Journal of Stroke, European Stroke Journal, Stroke & Vascular Neurology).
- Primary results: Oral presentation at UK Stroke Forum or a large international stroke conference (as listed above) depending on proximity to trial completion and readiness of results. Open access publication in high impact journal to ensure maximum impact and rapid dissemination.
- Secondary/tertiary/post hoc analyses: In appropriate journals (e.g. Stroke).
- Subsequent presentations to inform UK, European and International guidelines.
- Data sharing with the VISTA Stroke archive.[56]

USER AND PUBLIC INVOLVEMENT

A Patient-Public Involvement (PPI) representative (who is a stroke survivor) contributed to the development of the grant application leading to funding of this trial through participating in planning meetings and then leading on the development of PPI text for this application. They provided guidance on issues related to consent and consent with family member legal representatives, and the need for separate information sheets and consent forms for these. A second PPI member (to be appointed) will be added as an independent member of the TSC.

The PPI applicant, with support from the Senior Trial Manager, will work with the Independent PPI member of the Trial Steering Committee on areas where there is no conflict of interest. Their focus will be on the writing of the participant and family-facing materials, including participant/legal representative information sheets, consent forms (paper for participants and legal representatives) and trial leaflets. They will also support development of participant and relative-facing materials on the trial website, including a PowerPoint

training slide set. At trial end, they will lead on PPI dissemination of the results.

STUDY FINANCES

Funding source

This study is funded by Alzheimer's Society (AS-PG-24-075 *Check).

Participant stipends and payments

Participants will not be paid to participate in the trial. There are no additional hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) Professor Philip M Bath

Signature: _____

Date: _____

Trial Statistician: (name) Dr Lisa Woodhouse

Signature:_____

Date: _____

Trial Pharmacist: (name) *

Signature:_____

Date: _____

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APPENDICES

APPENDIX 1: Undesirable effects of isosorbide mononitrate (Isodur 50XL) - from Galen Ltd SmPC

Very common, >1-in-10:
Headache

Common, 1-in-100 to 1-in-10:
Asthenia
Dizziness (including dizziness postural)
Postural hypotension
Somnolence
Tachycardia

Uncommon, 1-in-1,000 to 1-in100:
Allergic skin reactions (e.g. rash)
Angina pectoris aggravated
Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
Flushing/flushed skin
Nausea
Vomiting

Rare, 1-in10,000 to 1-in-1,000:
/

Very rare, <1-in10,000:
Heartburn

Not known:
Abdominal discomfort
Angioedema
Blurred vision
Cold perspiration
Dermatitis exfoliative
Excitation
Fatigue
Hypotension
Palpitations
Restlessness
Sweating
Syncope
Vertigo

Side effects, further information:
- Headache may be minimised by starting with the lower dose and gradually increasing the dose.
- Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration.

- Temporary hypoxaemia may occur during treatment with isosorbide-5-mononitrate due to a relative redistribution of blood flow in hypoventilated alveolar areas. This may lead to myocardial hypoxia, particularly in patients with coronary artery disease.

APPENDIX 2: Undesirable effects of cilostazol - from Generics [UK] Ltd t/a Mylan SmPC

Very common, >1-in-10:
Abnormal faeces
Diarrhoea
Headache

Common, 1-in-100 to 1-in-10:
Abdominal pain
Angina pectoris
Anorexia
Arrhythmia
Dizziness
Dyspepsia
Ecchymosis
Flatulence
Nausea
Oedema (peripheral, face)
Palpitations
Pharyngitis
Rhinitis
Tachycardia
Ventricular extrasystoles
Vomiting

Uncommon, 1-in-1,000 to 1-in100:
Abnormal dreams
Allergic reaction
Anaemia
Anxiety
Atrial fibrillation
Chills
Congestive heart failure
Cough
Diabetes mellitus
Dyspnoea
Epistaxis
Eye haemorrhage
Gastritis
Gastrointestinal haemorrhage
Haemorrhage, unspecified
Hyperglycaemia
Insomnia

Malaise
Myalgia
Myocardial infarction
Orthostatic hypotension
Pneumonia
Supraventricular tachycardia
Syncope
Ventricular tachycardia

Rare, 1-in10,000 to 1-in-1,000:
Bleeding time prolonged
Renal failure
Renal impairment
Thrombocythaemia

Very rare, <1-in10,000:
/

Not known:
Agranulocytosis
Aplastic anaemia
Bleeding tendency
Blood creatinine increased
Blood urea increased
Cerebral haemorrhage
Conjunctivitis
Eczema
Granulocytopenia
Haematuria
Hepatic function abnormal
Hepatitis
Hot flushes
Hypertension
Hypoaesthesia
Hypotension
Interstitial pneumonia
Jaundice
Leukopenia
Muscle haemorrhage
Pain
Pancytopenia
Paresis
Pollakiuria
Pulmonary haemorrhage
Pyrexia
Respiratory tract haemorrhage
Skin eruptions
Stevens-Johnson syndrome
Subcutaneous haemorrhage
Thrombocytopenia

Tinnitus
Toxic epidermal necrolysis
Uric acid level increased
Urticaria

Side effects, further information:

- An increase in the frequency of palpitation and peripheral oedema was observed when cilostazol was combined with other vasodilators that cause reflex tachycardia e.g. dihydropyridine calcium channel blockers.
- The only adverse event resulting in discontinuation of therapy in ≥ 3% of patients treated with cilostazol was headache. Other frequent causes of discontinuation included palpitation and diarrhoea (both 1.1%).
- Cilostazol *per se* may carry an increased risk of bleeding and this risk may be potentiated by co administration with any other agent with such potential.
- The risk of intraocular bleeding may be higher in patients with diabetes.
  An increase in the frequency of diarrhoea and palpitation has been found in patients older than 70 years.

APPENDIX 3: Undesirable effects of isosorbide mononitrate 20 - from Dexcel Pharma Ltd SmPC

Very common, >1-in-10:
Headache

Common, 1-in-100 to 1-in-10:
Bradycardia
Cutaneous vasodilation
Hypotension
Dizziness
Drowsiness
Flushing
Reflex tachycardia
Weakness

Uncommon, 1-in-1,000 to 1-in100:
Allergic skin reaction
Flushing
Nausea
Vomiting

Rare, 1-in10,000 to 1-in-1,000:
Angina symptoms
Bradyarrhythmia
Collapse
Excessive sweating
Nausea
Pallor
Restlessness

Severe hypotension
Syncope
Vomiting

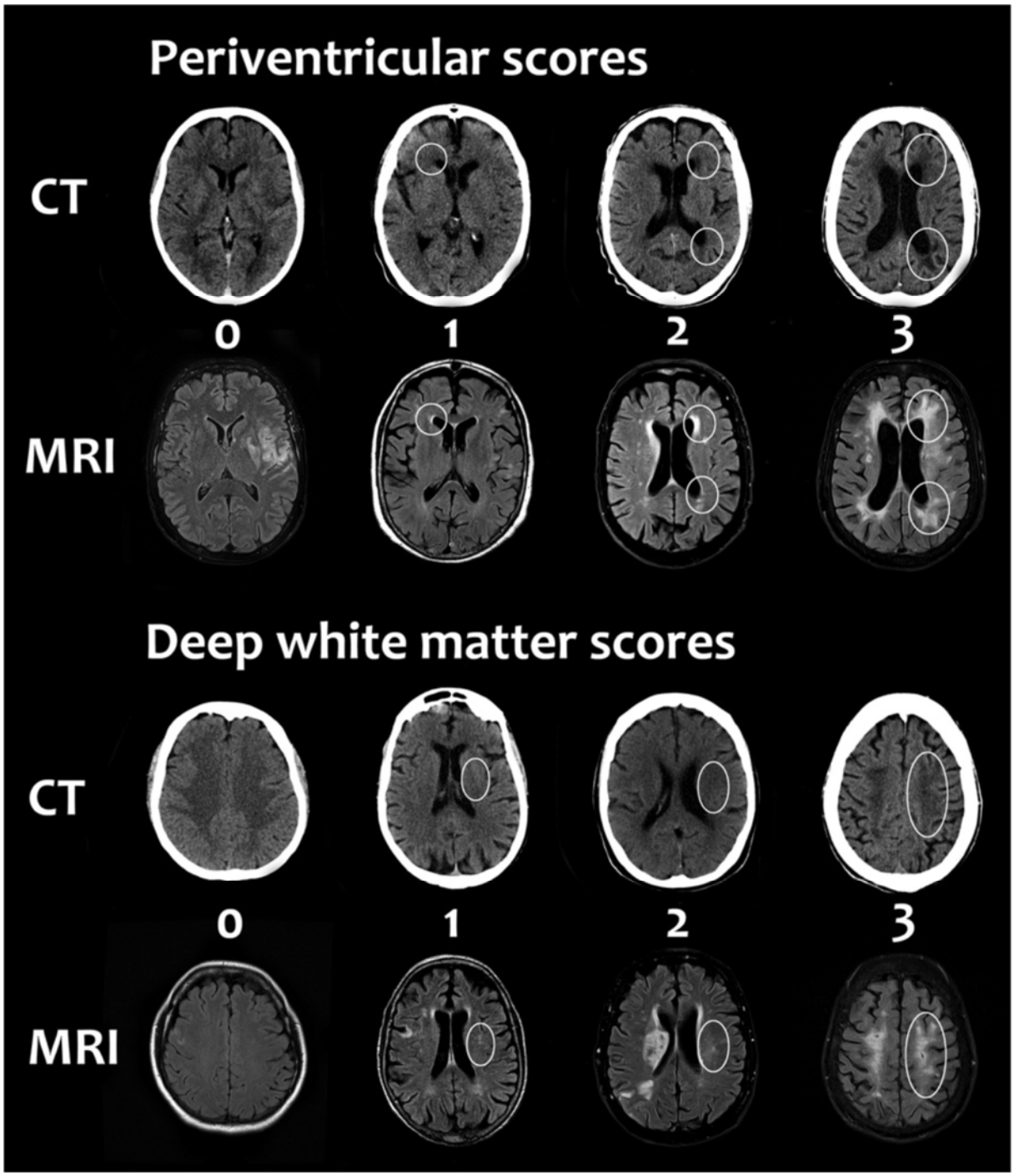
Very rare, <1-in10,000:
Myalgia

APPENDIX 4. Fazekas scoring of CT and MRI scans.

Periventricular (PV) and deep white matter (DWM) CT hypodensities and MR hyperintensities are scored separately using the Fazekas four-point scales.[30]

Periventricular scoring:
0 – absence
1 - caps or pencil-thin lining
2 - smooth halo
3 - irregular PV lesions extending into the deep white matter

Deep white matter scoring:
0 – absence
1 - punctate foci
2 - beginning confluence of foci
3 - large confluent areas



Images from Rudilosso *et al*. *Clinical Imaging* 2017; 46:24-7. Evaluation of white matter hypodensities on computed tomography in stroke patients using the Fazekas score.[30]