Academic and Clinical Central Office for Research and Development

Study Protocol

LACunar Intervention (LACI) Trial-3: Assessment of efficacy and safety of cilostazol and isosorbide mononitrate to prevent adverse outcomes in patients with cerebral small vessel disease (lacunar) ischaemic stroke

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PROTOCOL APPROVAL SIGNATURE PAGE

LACunar Intervention (LACI) Trial-3: Assessment of efficacy and safety of cilostazoland isosorbide mononitrate to prevent adverse outcomes in patients with cerebral small vessel disease (lacunar) ischaemic stroke

LACI-3

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Joanna M Wardlaw			
Chief Investigator	**Signature**	**Date**	
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For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name				
Principal Investigator	**Signature**		**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
BP	Blood Pressure
CI	Chief Investigator
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CIL	Cilostazol
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
e-CRF	Electronic Case Report Form
ENOS	Efficacy of Nitric Oxide in Stroke
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
HE	Health Economy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISMN	Isosorbide Mononitrate

ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
mRS	Modified Rankin Score
MOCA	Montreal Cognitive Assessment
p-CRF	Paper Case Report Form
PDE3	Phosphodiesterase 3
PGI2	Prostaglandin Inhibitor 2
PI	Principal Investigator
PROBE	Prospective randomised open blinded end-point
PIS	Participant Information Sheet
NIMP	Non-Investigational Medicinal Product
QA	Quality Assurance
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SIS	Stroke Impact Scale
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPS3	Secondary Prevention of Small Subcortical Strokes Trial
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVD	Small vessel disease
TIA	Transient Ischaemic Attack
TICS	Telephone Interview for Cognitive Status
TMF	Trial Master File

TMG	Trial Management Group
tMOCA	Telephone Montreal Cognitive Assessment
UK	United Kingdom
TMT	Trail Making Test
TSC	Trial Steering Committee
WMH	White matter hyperintensity

TRIAL SUMMARY

Trial Title	LACunar Intervention (LACI) Trial-3: Assessment of efficacy and safety of cilostazol and isosorbide mononitrate to prevent adverse outcomes in patients with cerebral small vessel disease(lacunar) ischaemic stroke
Study Acronym	LACI-3
Clinical Phase	3
Trial Design	An investigator led, multicentre, prospective, randomised, controlled, open label, 2x2 factorial, blinded endpoint (PROBE) confirmatory trial. MHRA Scientific Advice has been incorporated into the trial design.
Trial Participants	LACI-3 will include independent adults (mRS ≤2), age ≥30 years with a clinical lacunar stroke diagnosed by brain imaging (CT or MRI), who can be recruited at least 24 hours after lacunar stroke symptom onset with no latest time limit after the stroke, who have capacity to give consent and no exclusion criteria. Randomisation cannot occur ≤24 hours after lacunar symptom onset, and in most cases ≤1 month, to avoid the period when guideline stroke secondary prevention advises prescription of dual antiplatelet drugs (aspirin, clopidogrel) for 28 days followed thereafter by single antiplatelet, usually clopidogrel in the UK. Once the dual antiplatelet phase is over, then participants meeting the criteria can be randomised
Planned Number of Participants	1300
Planned Number of Sites	≥ 60
Countries Anticipated to be Involved in Trial	UK (Scotland, England, Wales, Northern Ireland) LACI-3 is open to support international collaboration.
Treatment Duration	From within one day of randomisation until the end of trial follow-up.
Follow up Duration	18 months
Total Planned Trial Duration	52 months
Primary Objective	To determine if, in patients with symptomatic lacunar ischaemic stroke, the routine long-term administration of isosorbide mononitrate 50mg od or equivalent, and /or cilostazol 100mg bd, individually or together, in addition to continuing routine stroke prevention therapy, compared with continuing routine stroke prevention therapy alone, reduces cognitive impairment after lacunar ischaemic stroke, a marker of cerebral small vessel disease.

Secondary Objectives	To determine if the long-term administration of isosorbide mononitrate 50mg od or equivalent and/or cilostazol 100mg bd individually or together, in addition to continuing routine stroke prevention therapy, compared with continuing routine stroke prevention therapy alone, reduces dependency, recurrent stroke or TIA, MI, death, and improves mood, quality of life, and health economic resource usage and is safe and well tolerated in long term use in patients with lacunar ischaemic stroke, a marker of cerebral small vessel disease.
Tertiary Objective	To collect data on the antihypertensive drug prescriptions and blood pressure measurements made by participants or available from GP or hospital medical records as a part of the routine stroke prevention therapy.
Primary Endpoint	At 18 months: • 7-level ordinal cognitive impairment based on operationalisation of DSM-V criteria of cognitive impairment or dementia derived using subscores of the tMOCA, TICS, animal naming, clinical dementia diagnosis, as in LACI-2 and R4VaD.
Secondary Endpoint	At 18 months: • dependency (mRS>2) • tMOCA • TICS • Concentration (from MMSE) • Animal naming • Recurrent ischaemic stroke or TIA or haemorrhagic stroke • Fatal or non-fatal MI • Stroke Impact Scale (individual domains and global) • EQ5D-5L, EQ-VAS • Death, due to vascular and any cause; • Safety SAEs; • IMP Symptoms (headache; palpitations; loose stools; falls; etc); • Composite of recurrent stroke or TIA, MI, death, dependency (mRS>2), cognitive impairment. • Global Clinical Outcome of recurrent stroke or TIA, MI, death, mRS>2, cognitive impairment, QoL, mood (ZUNG) • Health economic usage
Tertiary Endpoint	• BP measures

IMP(s)	Any brand of isosorbide Mononitrate (ISMN) and cilostazol that is available in the hospital pharmacy can be used as IMP is defined by the active substance only. Participants will be randomised to start one of four treatments: • Isosorbide mononitrate slow release 50mg oral once daily • Cilostazol 100mg oral twice daily • Both ISMN and cilostazol • Neither ISMN nor cilostazol A target dose of ISMN is 40-60mg daily. If a slow release ISMN is not available, the non-slow release tablets may be used. All patients will continue their prescribed medications including guideline stroke prevention treatment (antiplatelet, antihypertensive, lipid lowering, lifestyle advice). Patients with contraindications to one drug can be randomised to the other drug; patients who develop a contraindication to one of the drugs during the trial can continue in the trial taking the other drug. 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. A maximum of six months supply will be dispensed at a time. Patients will be phoned by the local centre at one and three weeks after starting medication to check and advise on dose escalation.
IMP Route of Administration	Oral
NIMP(s)	Not applicable

Lay Summary of Trial	Background: Each year in the UK, about 35,000 people have a 'lacunar' or 'small vessel' stroke. It is different from other types of strokes, and caused by problems in tiny blood vessels deep in the brain that stop them from working properly. As well as causing stroke, it may also cause cognition (thinking) problems, lead to dementia and affect walking, and mood. Currently, there is no specific treatment to prevent more lacunar strokes, cognitive decline, or other problems. Drugs used to prevent other types of strokes do not work very well, or at all, in preventing bad outcomes after lacunar strokes. We looked hard for drugs that might improve small blood vessel function. We found two drugs, widely used to increase blood flow in the heart and legs: isosorbide mononitrate (ISMN) and Cilostazol (Cil). In two trials in people with lacunar stroke (LACI-1 with 57, LACI-2 with 363 people), we found that the drugs are tolerated, most people could take the drugs for 1 year, stayed in the trial, had no serious side effects, and the drugs might be helpful: ISMN reduced recurrent strokes, cognitive decline and improved quality of life; Cil reduced dependency on others day to day; both drugs together reduced dependency, cognitive decline, mood, and improved quality of life. We now need to do a similar but much larger trial, LACI-3, to prove if these drugs are helpful after lacunar stroke. Aims and Plan: With advice from patients, the public, and the LACI trials team, we propose to test ISMN and Cil in a large simple trial in people with lacunar stroke, LACI-3. We will give the tablets for 18 months (since they may work better if given for longer). We will collect information on cognition, dependency, new strokes, mood, quality of life, and safety, while not knowing which drug(s) the patient is taking. Based on LACI-2 results, we calculate that LACI-3 will need 1300 participants to confirm if ISMN and Cil, alone or together, help reduce recurrent stroke, dependency, impaired cognition, and improve quality of life. It will take 55-60 UK centres to recruit this many people, but we have many notes of interest from hospitals who are keen to offer this trial to their patients. We want to test the two drugs alone and together to confirm the effects of the two drugs individually, and to see if they work better together than alone. LACI-3 will be run from Edinburgh and Nottingham, by a team of experts who have worked together for over 10 years on small vessel disease, including on LACI-1 and 2. Importance: Currently there are few trials in lacunar stroke or vascular cognitive impairment and vascular dementia anywhere in the world and none at Phase 3. ISMN and Cil are off patent and inexpensive, have well-known modest side effects and are widely available. If LACI-3 confirms the LACI-2 results, then ISMN and Cil could be adopted widely into

	clinical practice quickly and inexpensively. Confirming if ISMN and CiI help lacunar stroke is also important since they could help patients with cognitive decline due to small vessel disease dementia and prevent future stroke and dementia before symptoms develop. NHS England Medicines Repurposing Programme are assisting LACI-3 in obtaining MHRA advice to facilitate a license extension if LACI-3 is positive.

1. INTRODUCTION

1.1 BACKGROUND

Burden of cerebral small vessel disease: Stroke and dementia rank among the most pressing health issues, show substantial co-morbidity and share many risk factors. Cerebral small vessel disease (SVD) has emerged as a central link between these two diseases.[1,2] SVD is the commonest cause of vascular dementia, the second commonest type of dementia, and combined with Alzheimer's disease, accounts for up to 45% of all dementias.[3,4] Dementia is a major Government target, is increasing in prevalence,[5] and has enormous economic and societal costs. SVD also causes 20-25% of clinical strokes (lacunar stroke),[6] about 35,000 per year in the UK, and leaves at least a 35-45% of these patients with cognitive impairment after the stroke.[7,8] Patients with lacunar stroke are often younger than for other stroke subtypes[6] and cognitive impairment restricts their return to work not just independence.[9] SVD is also the commonest cause of haemorrhagic stroke in older people, a devastating type of stroke.

SVD is easily detected on brain scanning, notably on magnetic resonance brain imaging (MRI), as white matter hyperintensities (WMH), lacunes, microbleeds, prominence of perivascular spaces and brain atrophy.[10,11] About 50% of 65 year olds and almost all 90 year olds, have imaging manifestations of SVD,[12] which build up insidiously and diffusely in the brain until of sufficient severity to cause symptoms. Individually, and when mild, these imaging features are often clinically 'covert' or unnoticed. However, when more severe, they increase the risk of developing dementia (2-fold) and of having a stroke (3-fold),[12] and substantially worsen outcomes after any acute stroke.[13,14]

Causes and pathology of lacunar stroke: Despite this profound impact on human health, there are no treatments with proven efficacy that prevent recurrent lacunar stroke, cognitive impairment or dependency, or progression of SVD and its clinical or imaging manifestations.[15] Although often assumed to have the same causes as other types of ischaemic stroke, less than 11% of clinically-evident lacunar ischaemic strokes are atherothromboembolic,[16] and lacunar stroke patients have less large artery atheroma (less ischaemic heart disease, carotid stenosis, peripheral vascular disease (PVD)), despite similar rates of hypertension and diabetes, than those with cardioembolic or atheromatous stroke.[6] Instead, most lacunar stroke is due to an intrinsic deep perforating arteriolar disease with arteriolar wall thickening, mural and perivascular inflammation, segmental arteriolar wall disintegration,[17] and perivascular brain damage.[2,18] The arteriolar damage is linked with cerebral endothelial dysfunction, causing impaired vasoreactivity,[19-21] increased blood-brain barrier (BBB) permeability,[22] and increased vascular stiffness,[23] all of which cause secondary brain damage.[2]

Secondary treatment to improve long term outcomes after lacunar stroke is suboptimal: There have been few RCTs specifically in lacunar stroke. The largest of these, the Secondary Prevention of Small Subcortical Stroke (SPS3) trial (3000+ lacunar stroke patients), tested aspirin+clopidogrel vs aspirin and target vs guideline BP reduction to prevent recurrent stroke and cognitive decline. The aspirin+clopidogrel vs aspirin arm stopped early due to increased bleeding and death[24] without reducing recurrent stroke or MI,[25] consistent with the non-atheromatous nature of SVD.[2] Target (vs guideline) BP lowering did not significantly reduce recurrent stroke,[26] and neither intensive vs guideline BP lowering nor aspirin+clopidogrel vs aspirin reduced cognitive decline.[27] The European Stroke Organisation (ESO) Guideline on Small Vessel Disease Part 1, Covert cSVD, examined antiplatelet drugs, BP lowering, statins, diabetes, dementia drugs and lifestyle interventions to prevent clinical outcomes in patients with cSVD.[28] It found that antiplatelet drugs in covert cSVD increased harm, intensive vs guideline BP reduction slightly reduced WMH progression but did not affect clinical outcomes, lifestyle interventions lacked data but should

be encouraged, diabetes should be managed as per diabetes guidelines, no benefit for dementia drugs, and limited information to support use of statins although large primary prevention trials show benefit and statins are unlikely to cause harm. The ESO Guideline on cSVD Part 2, lacunar ischaemic stroke, found similar results for patients with clinically-evident lacunar stroke.[29] The Guideline concluded that single antiplatelet drug should be administered long term although the evidence to support this was very limited. Blood pressure lowering should be to target 130/80, and that lipid lowering was reasonable despite a lack of direct evidence. This indicates that current guideline-based secondary prevention of lacunar stroke with antiplatelet, antihypertensive drugs and statins has a limited evidence base, may be ineffective, or even hazardous.

Alternative therapies: We reviewed all potential drugs tested in preclinical models[30] and RCTs that included lacunar stroke and found many relevant drugs.[15] We particularly looked for available licensed drugs with relevant effects to stimulate the nitric oxide (NO)-cyclic GMP or Prostacyclin (PGI2)-cyclic AMP systems thereby improving vasodilatation, reducing inflammation and smooth muscle hypertrophy (to reduce stiffness) and improving cerebral endothelial integrity (prevent extra-vascular leakage) and neuroprotective effects,[2] and identified two drugs, both licensed in Europe for treatment of vascular diseases.
Cilostazol is a phosphodiesterase 3-inhibitor (PDE3-inhibitor) that enhances the PGI2-cAMP system. It has weak antiplatelet effects (so low bleeding risk),[31] reduces infarct size[30] and reduces ageing-related decline in myelin repair[32] in experimental models, has a UK license for treatment of peripheral vascular disease, and our systematic review found data from trials including more than 10,000 patients with stroke.[33] Amongst those, the trials where >50% of participants had lacunar stroke found long-term cilostazol (vs placebo or aspirin) reduced recurrent stroke (OR 0.62, 95%CI 0.49-0.77) without increasing haemorrhage (OR 0.52, 95%CI 0.36-0.75), or death (OR 0.90 95%CI 0.53-1.52) when given long term. Recent secondary analyses of the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) trial in patients with lacunar stroke found that cilostazol+aspirin or clopidogrel vs aspirin or clopidogrel alone reduced recurrent stroke without increasing haemorrhage.[34] However, there are few data on the effects of cilostazol on cognition, and most data on cilostazol in cerebrovascular disease are from Asia-Pacific region countries where the epidemiology, range of risk factors, stroke subtype profiles, and other vascular characteristics differ from those commonly seen in the West.
Isosorbide mononitrate (ISMN), is an NO donating organic nitrate that enhances vasodilation and has been widely used in ischaemic heart disease for decades. NO, an important regulator of cerebral haemodynamic function, is impaired in patients with stroke,[35] lacunar stroke and WMH,[20,36] and worsens outcome.[35] Replacing NO might improve vasoreactivity,[37] but drugs that increase NO availability are rarely used in stroke, particularly lacunar stroke (e.g. pre-stroke nitrates were used in <2% of patients randomised in the Efficacy of Nitric Oxide in Stroke (ENOS) trial including those randomised into the trial with lacunar syndromes[38] or in our lacunar stroke cohort studies[9,39] possibly because ischaemic heart disease is uncommon in patients with lacunar stroke.[40] The related drug, transdermal GTN, another organic nitrate, administered short term after acute stroke, improved cerebral perfusion,[41] but this short term administration did not improve cognitive outcomes.[42] An extensive search of the literature for any data from clinical trials or health data registries on cognitive, dementia or stroke outcomes in patients given organic nitrates for cardiovascular disease has failed to identify any data.

LACunar Intervention Trials 1 and 2. Based on knowledge of likely pathophysiology mechanisms of lacunar stroke and cSVD, that conventional stroke prevention has limited benefit, and having identified that ISMN and cilostazol had relevant modes of action, were licenced for other indications and had known safety profiles, we embarked on the LACunar Intervention Trials. The LACI approach was developed from discussion at a Workshop of experts in SVD stroke on 31st March 2014, funded by the UK National Institutes of Health Research Stroke Research Network. Use of two drugs with complementary actions that

affect different parts of the pathological pathway could provide more benefit than one drug alone.

The LACunar Intervention Trial 1 (LACI-1), was a small, 2-centre, trial testing the short term administration of ISMN and cilostazol for 10 weeks, funded by Alzheimer Society, registration EudraCT 2015-001953-33, ISRCTN 12580546.[43] LACI-1 enabled us to test dose implementation and escalation, determine symptoms, short term tolerability, safety and to assess some intermediary markers of efficacy.[43] LACI-1 compared ISMN vs cilostazol vs ISMN+cilostazol vs neither, in a partial factorial design, with all patients receiving guideline-based secondary stroke prevention. Tablets were masked by placing them in bottles marked 'A' and 'B' as no placebo was available and over encapsulation was not possible. LACI-1 recruited 56 participants between March 2016 and August 2017 and found no safety issues (no bleeding, falls, other concerning events), drugs were well tolerated (initial symptoms like headache settled down), and they improved brain blood vessel function.[44-46] LACI-1 enabled us to refine the trial methods preparatory to a larger feasibility, tolerability and safety trial, LACI-2.

The LACunar Intervention Trial 2 (LACI-2) trial was funded mainly by the British Heart Foundation (BHF) and was conducted in 26 centres in the UK between Feb 2018 and end of May 2021, (registration EudraCT 2016-002277-35, ISRCTN 14911850, MHRA 01384/0252/001-0004), aiming to recruit 400 patients.[47] LACI-2 was open label with blinded centrally-collected outcomes (PROBE) design since no placebo was available and overencapsulation was not possible. LACI-2 used the same partial factorial design as LACI-1 (ISMN vs cilostazol vs ISMN+cilostazol vs neither, in a partial factorial design, with all patients receiving guideline-based secondary stroke prevention) but the drugs were administered for 1 year. Drug was supplied by hospital pharmacies, via the AcoRD process, hence several generic brands could be used in LACI-2, as long as at the correct dose.
LACI-2 aimed to determine feasibility, tolerability, safety and recorded outcome event rates to determine event rates to power a larger trial and identify any efficacy signals to help justify a large phase 3 trial.[47] LACI-2 used a composite outcome of any recurrent stroke or TIA, MI, dependency (mRS>2), any cognitive impairment or death. LACI-2 also used an ordinal score of cognitive status based on DSM-5 definitions, using data from the tMoCA, TICS, animal naming, and any clinical dementia diagnosis, developed in a large UK study of cognitive impairment after stroke.[48] All analyses were adjusted for minimisation variables (baseline age, sex, NIHSS, mRS, sBP, smoking status, time after stroke, and years of education) and cognition was also adjusted for baseline MoCA.
LACI-2 recruited 363 of the planned 400, stopping at 363 since this was deemed enough to demonstrate feasibility, tolerability and safety and had been disrupted by COVID-19. The one-year follow-up ended in May 2022.[49] Recruitment stopped completely due to the Covid-19 pandemic for four months and delayed recruitment thereafter.
LACI-2 met its primary feasibility targets, recruiting 363/400 target patients (impact of COVID-19), median age 64 [interquartile range 56.0-72.0] years, 251/363 males (69.1%), at median 79 days after stroke, and baseline characteristics were well-balanced.
LACI-2 retained 358 (98.6%) at 12 months, and exceeded the tolerability target of 75% taking ≥50% of allocated drug, and indicating good drug tolerance.
There were no safety concerns, with only four deaths and four haemorrhages (all were systemic), and few SAEs of which only two were possibly related to either drug.
LACI-2 also provided efficacy signals. It showed that, in comparison with no drugs: neither ISMN nor cilostazol alone reduced the composite outcome (n=297; ISMN adjusted hazard ratio, aHR, 0.80, 95%CI 0.59-1.09, p=0.16; cilostazol aHR 0.77, 0.57-1.05, p=0.10). Individually, ISMN reduced recurrent stroke (adjusted odds ratio aOR 0.23, 0.07-0.74, p=0.014), and cognitive impairment (aOR 0.55, 0.36-0.86, p=0.008); cilostazol reduced dependency (aHR 0.31, 0.14-0.72, p=0.006); ISMN+cilostazol reduced the composite (aHR 0.58, 0.36-0.92, p=0.02), dependency (aOR 0.14, 0.03-0.59, p=0.008), any cognitive

impairment (aOR 0.44, 0.23-0.85, p=0.02), and improved QoL (aMD 0.10, 0.03-0.17, p=0.005).[49,50]
These findings were supported by the results of the patient-reported Stroke Impact Scale (global and individual domains) and an analysis of Global Clinical Outcome (recurrent ordinal stroke, ordinal MI, ordinal 7-level cognition, ordinal mRS, quality of life [full Health Status Utility Score of the EQ-5D], the Zung depression score full scale, and the binary status of alive or dead).
LACI-2 showed that the trial design was feasible, ISMN and cilostazol were well-tolerated and safe individually and in combination. They may reduce recurrent stroke, dependency, and cognitive impairment after lacunar stroke, improve QoL, and could prevent other adverse outcomes in SVD, and should be tested in large phase 3 trials.

1.2 RATIONALE FOR STUDY

The LACI-1 and LACI-2 trials were designed as part of an NIHR SRN-Portfolio Development Expert Writing Group. It considered experience from the USA NIH-funded SPS3 trial (3000+ lacunar stroke patients, CI Benavente; SRN Writing Group, LACI-2 International Advisor to TSC),[24,26,27] the CSPS, CSPS2 and CSPS.com trials (5619 patients CSPS [51,52] [51,53]) testing cilostazol to prevent stroke in Japan (PI Toyoda, International Advisor to TSC), the PRESERVE trial (CI Markus, SRN Writing Group),[54] and in monogenic SVD (Chabriat, SRN Writing Group, International Advisor to TSC).[55] The UKSRN Prevention CSG strongly supported trials testing cilostazol and ISMN in SVD prevention.

LACI-3 benefits from the experience gained in LACI-1 and LACI-2 which confirmed the feasibility of the approach. Additionally, there have been further expert initiatives considering ways to conduct trials in SVD such as the Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESS) in which the authors participated.[56] Many UK Stroke Research Network Centres have expressed interest in joining LACI-3.

LACI-2 showed that both cilostazol and ISMN are tolerated at the target dose for at least a year, provided data on outcome event rates, safety and efficacy. Both drugs cause headache, a marker of vasoreactivity[57] but this did not limit tolerance, and as with other side effects (palpitations, nausea), was minimised by starting at half dose, at night, escalating slowly to full dose over several weeks. In addition to providing confidence in trial procedures, event rates and recruitment, LACI-2 provided methods for balancing randomisation, and streamlining of follow-up to use in LACI-3.

Appropriateness of the research: LACI-2 showed that it is possible to improve cognitive (or other) outcomes after lacunar stroke, a form of cerebral small vessel disease. The improvement in cerebrovascular function seen in LACI-1,[46] and the improvement in cognitive and functional endpoints, the reduction in recurrent stroke, and improvement in mood and quality of life seen in LACI-2, across multiple analyses,[49] are consistent with the pathophysiological mechanisms of SVD identified in observational studies pointing to endothelial dysfunction leading to impaired vasoreactivity, increased vascular stiffness and blood brain barrier leakage.[2]
Since there is little good evidence that guideline stroke prevention improves outcomes in SVD[28] or in lacunar stroke[29,24,26,27] it is very important to confirm the results of LACI-2 in a large phase 3 confirmatory trial. The disparity between the apparent benefits of cilostazol in stroke prevention in the Asia-Pacific region[33] and its lack of use in the UK and other Western countries is striking and supports evaluation.

Treatment under investigation: The ways in which ISMN and/or cilostazol might improve cerebrovascular function by replacing NO which is deficient in SVD and stimulating the PGI2-cAMP system to reduce NO breakdown, amongst other effects, have been outlined

above. Notably, combined stimulation of the NO-cGMP and PGI2-cAMP systems potentially maximises the benefits of each drug, if it does not increase adverse effects. Indeed, the LACI-2 results seem to suggest that cilostazol and ISMN together may be more effective than either drug alone. Although both might also improve BP control, lower BP modestly, and reduce BP variability, we did not see any difference in BP between patients allocated ISMN, cilostazol, both or neither in patients at one year follow-up in LACI-2, nor did we see any increase in falls, dizziness or other symptoms that might be attributable to hypotension. Furthermore, we did not see any excess cranial or systemic bleeding from the combination of ISMN (no antiplatelet effects) and cilostazol (weak antiplatelet), or either drug alone in LACI-2,[49] when given with guideline clopidogrel or aspirin (both moderate-strong antiplatelet agents),[24] providing reassurance about safety. The lack of increase in bleeding with cilostazol including when given in combination with other antiplatelet drugs is consistent with the cilostazol trial data to date.[33,34]

Both ISMN and cilostazol are off patent, widely available as generics, and inexpensive.

Benefits to participants: About 35000 patients experience lacunar stroke each year in the UK. Currently they receive UK guideline secondary stroke prevention treatment (an antiplatelet drug usually clopidogrel, antihypertensive treatment, a statin and lifestyle advice), but two ESO guidelines (in prep and[28]) show that these approaches have limited benefit in patients with lacunar ischaemic stroke, reflecting that the mechanism of SVD differs from that of other types of ischaemic stroke.
LACI-3 aims to determine if ISMN and/or cilostazol are effective in reducing cognitive impairment, dependency, recurrent stroke and improve mood and quality of life long term after lacunar ischaemic stroke, without increasing harm. If LACI-3 confirms the signals of benefit seen in LACI-2, without harm, then firstly, patients with lacunar ischaemic stroke, i.e. a quarter of all ischaemic strokes, can expect better outcomes including lower risk of cognitive impairment, a main problem after lacunar stroke,[7] as confirmed in LACI-2.[49] In addition, secondly, large proportions of patients with stroke or cognitive impairment dementia may benefit as SVD is such a common cause of these conditions. For example, LACI-2 findings are also highly relevant to treatment of other clinical presentations of cSVD, all of which share the same underlying mechanism.[2] These include vascular cognitive impairment and vascular dementia, SVD found on a scan done for other reasons,[12] patients with other types of stroke who have a lot of SVD on their scan and who are known to have worse outcomes than similar patients who do not have SVD on their scan,[14] and patients with mobility and mood presentations of SVD, for whom there is no effective specific treatment for SVD at present. However, LACI-3 will focus on patients with lacunar ischaemic stroke presentations of SVD.

Both drugs are licensed in the UK and Europe and available in generic form, therefore both interventions will be inexpensive to the NHS. Both drugs are taken orally, once or twice daily, so are easy to administer. The long-term impact of successful treatment is difficult to quantify but potentially, a reduction of 10-20% in the combined stroke, cognitive or physical consequences of SVD, consistent with the LACI-2 results, would benefit several tens of thousands of patients per year in the UK.

Relevance to current policies: Dementia remains a UK Government priority, as well as a priority for other Governments and Health Organisations, with major investments in the UK Dementia Research Institute, the Dementia Platform UK and the Barbara Windsor Dementia Initiative. Stroke is also a Government priority,[58,59] in the UK and many other countries.[60] Preventing dementia through preventing stroke is a major focus of the World Stroke Organisation.[3] Long term consequences of stroke including cognitive impairment are priorities for patients (personal communications) and amongst the top ten research priorities identified by the James Lind Alliance.[59] The trial is informed by the Medicines and Health Care Regulatory Agency, assisted by NHS England Medicines Repurposing Programme, at

a Scientific Advice Meeting on 2nd July 2024. All MHRA guidance has been incorporated into the design of LACI-3.

2. STUDY OBJECTIVES & ENDPOINTS

2.1 PRIMARY OBJECTIVES

2.1.1 Primary Objective

To determine if, in patients with symptomatic lacunar ischaemic stroke, the routine long-term administration of isosorbide mononitrate 50mg od or equivalent, and /or cilostazol 100mg bd, individually or together, in addition to continuing routine stroke prevention therapy, compared with continuing routine stroke prevention therapy alone, reduces cognitive impairment after lacunar ischaemic stroke, a marker of cerebral small vessel disease.

2.1.2 Primary Endpoint

At 18 months:

- 7-level ordinal cognitive impairment, based on operationalisation of DSM-V criteria of cognitive impairment or dementia derived using subscores of the tMOCA, TICS, animal naming, clinical dementia diagnosis, as in LACI-2 and R4VaD.

2.2 SECONDARY OBJECTIVES

2.2.1 Secondary Objectives

To determine if the long-term administration of isosorbide mononitrate 50mg od or equivalent and/or cilostazol 100mg bd individually or together, in addition to continuing routine stroke prevention therapy, compared with continuing routine stroke prevention therapy alone, reduces dependency, recurrent stroke or TIA, MI, death, and improves mood, quality of life, and health economic resource usage and is safe and well tolerated in long term use in patients with lacunar ischaemic stroke, a marker of cerebral small vessel disease.

2.2.2 Secondary Endpoints

At 18 months:

- dependency (defined as mRS>2)
- tMOCA
- TICS
- Concentration (from MMSE)
- Animal naming
- Recurrent ischaemic stroke or TIA or haemorrhagic stroke
- Fatal or non-fatal MI
- Stroke Impact Scale (individual domains and global)
- EQ5D-5L, EQ-VAS
- Death, due to vascular and any cause;
- Safety SAEs;
- IMP Symptoms (headache; palpitations; loose stools; falls; etc);
- Composite of recurrent stroke or TIA, MI, death, dependency (mRS>2), cognitive impairment.
- Global Clinical Outcome of recurrent stroke or TIA, MI, death, mRS>2, cognitive impairment, QoL, mood (ZUNG)
- Health economic usage

2.3 TERTIARY OBJECTIVES

2.3.1 Tertiary Objectives

To collect data on the antihypertensive drug prescriptions and blood pressure measurements made by participants or available from GP or hospital medical records as a part of the routine stroke prevention therapy.

2.3.2 Tertiary Endpoints

- BP measures

3. STUDY DESIGN

LACI-3 will be an investigator-led, Phase III, prospective, randomised, controlled, 2x2 partial factorial, open label, blinded outcome trial performed in multiple UK hospital-based centres. LACI-3 is open to support international collaboration. The trial received Scientific Advice from the Medicines and Health Care Regulatory Agency assisted by NHS England Medicines Repurposing Programme at a meeting on 2nd July 2024. All MHRA guidance has been incorporated into the design of LACI-3.

Duration: The trial will last for 52 months with the treatment phase for each participant starting from within one day of randomisation until the end of trial follow-up at 18 months.

Participants meeting inclusion/exclusion criteria will be randomised at participating hospitals.

Participants will be randomised to start one of four treatments; ISMN only; cilostazol only; both ISMN and cilostazol; or neither ISMN nor cilostazol. Patients with contraindications to cilostazol can be randomised to ISMN versus no ISMN arms only; patients with contraindications to ISMN can be randomised to cilostazol versus no cilostazol arms only. The partial factorial design allows testing of both drugs when given alone and together. As in LACI-2, the doses will be escalated until participants are on their full dose by 1 month. If a patient encounters intolerable side effects at full dose, then they will be able to remain on the highest dose regime that they can tolerate and this dose will be recorded. The total duration of the trial drug administration will be 18 months. After the end of follow-up, the patients will reduce the tablets over about two weeks and then stop the trial medication. They will return any unused drug to their local community pharmacy or the hospital pharmacy if more convenient for destruction.

Drug supply: Trial drug will be dispensed by hospital pharmacies. The first drug supply will be given at the randomisation visit if allocated to the IMP. The IMP re-supply for the follow-up at 6 and 12 months will be posted to participants. Participants can collect the IMP re-supply in person from the recruiting site.

Participants should continue their allocated treatment until the end of 18-month follow-up.

Discontinuing the allocated treatment by the participant's direct clinical care team due to the occurrence of an outcome event does not constitute withdrawal.

Throughout the trial, patients will continue to take their normal prescribed medication which will include guideline stroke secondary prevention prescribed since their event as per national guidelines/usual post-stroke care in participating centres and including lifestyle advice.

Measurement of outcomes: The trial follow-up visits will be done remotely by phone, post or web-based. The outcome measurement after randomisation and from 6 months onwards until the last follow-up at 18 months will be assessed by the local hospital sites teams and the central trial coordinators located in Edinburgh and Nottingham.

Stopping rules for the trial by Data Monitoring Committee:

The trial will not stop unless asked to do so by the Data Monitoring Committee (DMC).

The DMC will review un-blinded data at regular intervals and, in the light of these analyses, will advise the chair of the TSC and Sponsor (via the chief investigator) if, in their view, the randomised comparisons in LACI-3 have provided both (i) “proof beyond reasonable doubt” that for all, or for some, specific types of patient, a LACI-3 treatment is clearly indicated or clearly contraindicated, and (ii) evidence that might reasonably be expected to materially influence future patient management by many clinicians who are already aware of the results of any other relevant trials. Appropriate criteria of ‘proof beyond reasonable doubt’ cannot be specified precisely.

The stopping rules for effectiveness are based on the combination of presence of ‘proof beyond a reasonable doubt’ and the likelihood that the results would change clinical practice. The possible DMC recommendations at any assessment are:

1. Stop enrolment if the treatment is negative, i.e. treatment is hazardous: statistical evidence that intracerebral haemorrhage, systemic bleeding, or fatal SAE rates are significantly higher in the ISMN vs no ISMN or cilostazol vs no cilostazol or both vs neither groups ($p<0.01$), on safety data assessed at any of 6, 12 or 18 months of treatment;

2. Stop enrolment if the study is positive, i.e., treatment is beneficial: the combination of statistical evidence that cognitive function is significantly better in the patients allocated ISMN, or cilostazol, or both, vs not allocated that treatment “beyond reasonable doubt” (i.e. at least 3 standard errors difference in magnitude1) and the overall trial results will lead to a change in clinical practice, e.g. by also taking account of evidence that at least some secondary outcomes are also being benefitted, for example, some of less dependency (mRS), less recurrent stroke, better individual cognitive scale scores, and/or better quality of life.

3. Continue enrolment if the study is neutral: or if conditions 1 and 2 are not present.

4. Modify study design – if it appears that:

    i. Sample size calculation assumptions were incorrect, e.g., if OR of cognitive impairment is much less than 0.7;

    ii. Apparent study design aspects will lead to incorrect study conclusions;

    iii. Specific clinical procedures, e.g. change in usual stroke prevention drugs, might jeopardise the safe execution of the study.

Formal statistical analyses will be used as “stopping guidelines” rather than absolute rules. In the light of interim data, and other evidence from relevant studies (including updated overviews of relevant randomised controlled trials), the DMC will inform the TSC, if in their view there is proof beyond reasonable doubt that the data indicate that the intervention is either clearly indicated or contra-indicated, either for all or for a particular subgroup of study participants. A decision to inform the TSC will in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt are not specified precisely. A difference of at least 3 standard errors in the primary endpoint may be needed to justify halting, or modifying, the study prematurely. This approach has the practical advantage that the exact number of analyses are of little importance, and so no fixed schedule is proposed. The DMC may also consider supporting evidence from secondary outcomes in their decision making, but the overall guidance remains that the results should be sufficiently convincing to change practice.

Stopping rules for the trial by funder:

There will be two trial phases with no break in recruitment unless LACI-3 meets stopping criteria

Table 1: Trial progression criteria – target recruitment rate 1.1pt/site/month

Table 1 Progression criteria	Red	Amber	Green
% Threshold	≤35%	65%	100%
Trial Recruitment	110	205	300
Recruitment rate/site/month	1.1	1.1	1.1
Number of sites opened	24	35	48
Total number of participants recruited	110	205	300

Amber actions 1: Increase recruitment – protocol review, identify/remove barriers, re-train sites, increase recruitment at active sites/close inactive sites, increase number of sites.

Red actions 2: as for amber + acceleration plan as per HTA.

We will review recruitment of sites and participants monthly and commence mitigation measures if it becomes clear that the study is behind schedule.

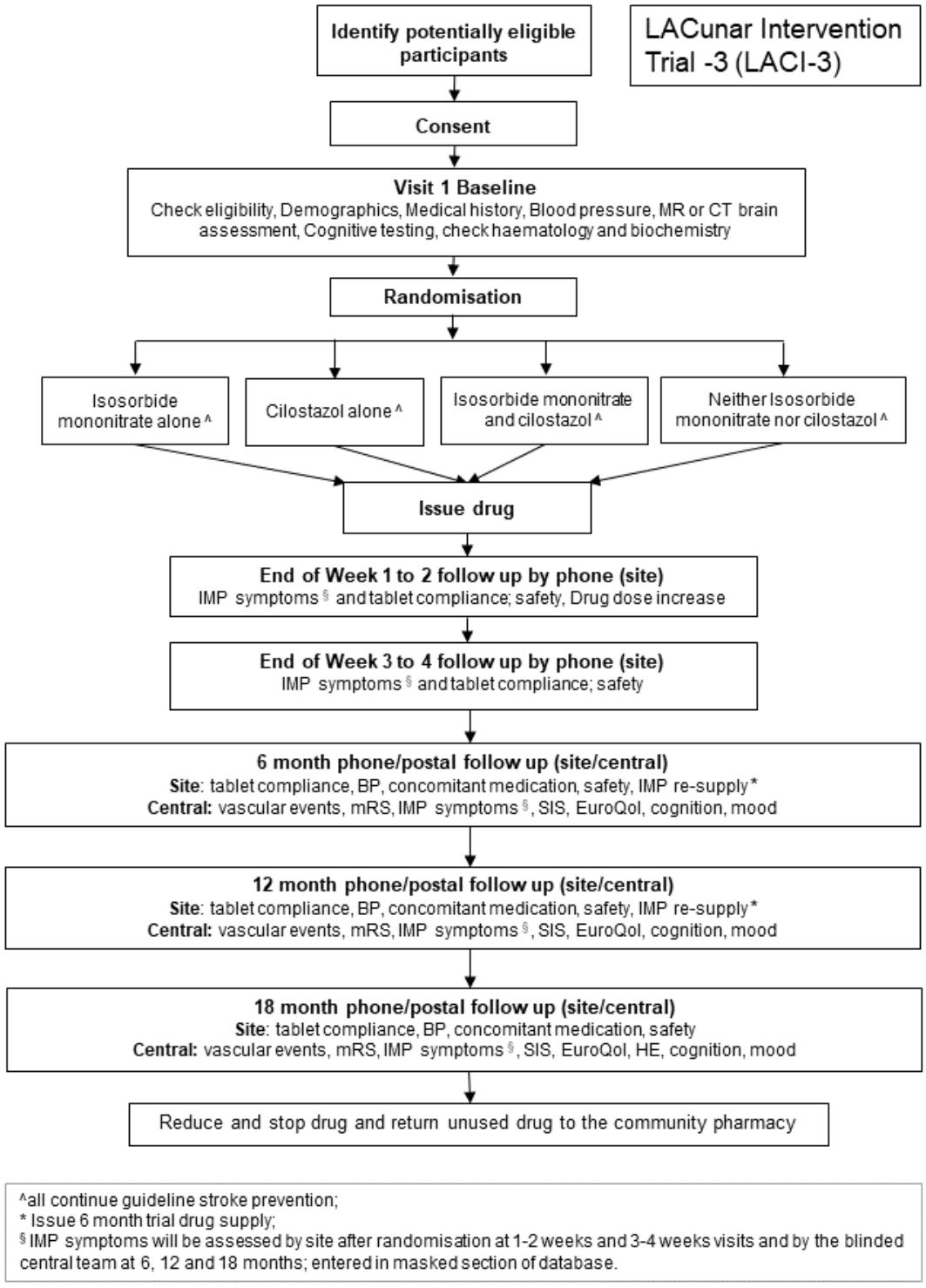
There will be no break in recruitment between phases unless recommended by the DMC.

Vanguard phase: Recruitment of 300 participants from up to 48 sites by month 12 after recruitment starts (1.1 ppm) which will be 16 months after the grant starts (Figure X). These sites will necessarily include those of the applicants and some larger hospitals with existing LACI trial experience.

Main phase: Recruitment of 900 participants over 32 months from 60 sites, (1.1 p/pm/site) (Figure 1). The expected recruitment rate is slightly lower than in the pilot phase since there will be a higher proportion of lower volume stroke sites. The reason for this difference is to ensure the main protocol works in experienced sites before expanding out to sites where PES-training will be key.

Figure 1: Planned recruitment rate.

The trial flow diagram (Figure 2) summarises the study design:



4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit 1300 participants, over about 30 months who will be followed up to 18 months. Recruitment will take place in two phases at the request of the funder: a vanguard or 'internal pilot' phase and a 'main' phase. The vanguard phase will be assessed at 16 months after the grant starts, i.e., after 12 months of recruitment, and run seamlessly into the main phase assuming that recruitment is to target (300 patients by 12 months of recruitment).

LACI-3 will include patients who are independent in activities of daily living (modified Rankin ≤2) with symptoms and brain imaging compatible with a recent lacunar ischaemic stroke, aged >30, who can be recruited at least 24 hours after lacunar stroke symptom onset with no latest time limit after the stroke, who have capacity to give consent and no exclusion criteria.

4.2 INCLUSION CRITERIA

Inclusion criteria:

- Age ≥30 years;
- Clinical stroke syndrome compatible with a lacunar stroke and brain imaging (MRI preferred but CT allowed) at the time of the stroke shows a relevant recent small subcortical infarct, or if no relevant infarct then no other explanation for symptoms is seen;
- Genetic forms of SVD (e.g. CADASIL) may be included if they present with a lacunar stroke.
- Capacity to give consent in the opinion of the PI or any delegated member of the research team;

4.3 EXCLUSION CRITERIA

General exclusion criteria:

- Less than 24 hours since onset of the lacunar stroke or patient on dual antiplatelet drugs;
- Stroke mechanism with definite treatment indication (e.g. cardioembolism, ipsilateral carotid stenosis);
- Other explanation for the lacunar stroke symptoms (ie recent cortical infarct, haemorrhage or tumour);
- Other active neurological disease (e.g. brain tumour, multiple sclerosis, recurrent seizures, neurodevelopmental disorder - well-controlled epilepsy present prior to the lacunar stroke, a single seizure at onset of the stroke, or provoked seizure, is not an exclusion);
- Contraindication to both trial drugs in section 4.3 of the SPCs (patients with a contraindication to one trial drug may still be randomised to the other trial drug);
- Indication for either trial drug (patient already prescribed one trial drug may still be randomised to the other trial drug);
- Dependent (mRS>2);
- Clinical diagnosis of dementia;
- Planned surgery during the trial period including carotid endarterectomy. Note 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;
- Unable to swallow;
- Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg;
- History of drug overdose or attempted suicide

- Unlikely to be available for follow-up at 18 months;
- Unlikely to comply with study procedures and follow-up procedures for whatever reason (eg history of poor medication compliance) in the opinion of the randomising physician;
- Pregnant, breast-feeding, or of child-bearing potential and not using highly effective contraception as stated in section 10.9 (Pregnancy);
- Renal impairment (creatinine clearance <25 ml/min)
- Hepatic impairment
- Currently prescribed dual antiplatelet treatment (single antiplatelet is not an exclusion); patients can be randomised into the trial once the 28-day period of dual antiplatelet for guideline secondary prevention following the acute lacunar ischaemic stroke has completed;
- Previously enrolled in LACI-3;
- Enrolled in a study that precludes co-enrolment with LACI-3.

Cilostazol exclusion criteria (still allows randomisation to ISMN):

- Definite indication for (i.e. already prescribed) Cilostazol, or definite contraindication to Cilostazol as per SPCs section 6.1.8.
- Prohibited medications to Cilostazol (see sections 4.5 of the appended SPCs and protocol section 6.7.3).
- Active cardiac disease (atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure).
- 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)

ISMN exclusion criteria (still allows randomisation to Cilostazol):

- Definite indication for (i.e. already prescribed) ISMN, or definite contraindication to ISMN as per SPCs.
- Prohibited medications to ISMN (see sections 4.5 of the appended SPCs and protocol section 6.7.3).

4.4 CO-ENROLMENT

Co-enrolment in LACI-3 and another research study will be assessed case-by-case following the Sponsor's co-enrolment policy (POL008 Co-enrolment Policy).

Co-enrolment assessment between LACI-3 and another CTIMP or interventional non-CTIMP (e.g., surgical, or implantable device) will consider the safety of study participants, the interventions involved, the participant burden, and the potential impact on the LACI-3 outcomes.

Before the co-enrolment begins, the permission for co-enrolment must be documented according to the Sponsor's policy.

Co-enrolment in LACI-3 with non-interventional research (e.g., sample only, questionnaire studies) will not require any formal documentation or authorisation from the sponsor. The chief investigators and sponsor should be consulted for guidance if required.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The investigators from the patient's direct clinical care team at participating hospital sites will identify potential participants for LACI-3. These investigators may include delegated doctors, nurses, or other research staff undergoing specific trial training. Potentially participants may be identified when presenting for the first time with a new stroke or recurrent stroke during hospital attendance in the everyday clinical practice of investigators. Potential participants who presented to the stroke services of participating sites in the past may also be identified through screening of hospital record systems, outpatient's clinic appointments, local audit and other registries as are available at participating hospitals. Potential participants can be referred to the investigators for the eligibility assessment by the clinical staff or they can self-refer to the recruiting hospital team. Potential participants may also be identified from other relevant trials and observational studies where consent has been given for re-contact for future relevant research e.g., from the Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD) Study.

The first LACI-3 approach will occur after the delegated investigator reviews the patient's medical records, diagnostic scan, and medication list and confirms eligibility.

This initial contact will occur in person, via phone, or post following local clinical practice by the delegated investigator. If the potential participant is interested in LACI-3, the Facts Sheet will be given with a short summary about the trial, followed by the Participant Information Sheet and verbal explanations, as required. The Facts Sheet can be included in the Invitation letter.

The potential participants can be approached for consent at least 24 hours after lacunar stroke symptom onset.

Randomisation cannot occur ≤24 hours after lacunar symptom onset, and in most cases ≤1 month, to avoid the period when guideline stroke secondary prevention advises prescription of dual antiplatelet drugs (aspirin, clopidogrel) for 28 days followed thereafter by single antiplatelet, usually clopidogrel in the UK. Once the dual antiplatelet phase is over, then participants meeting the criteria can be randomised.

There is no upper time limit after the lacunar stroke onset when the potential participants can be approached, recognising that lacunar stroke is a sign of small vessel disease which is a long-term condition, enabling the recruitment of participants who have had their stroke in the past, and helping to optimise the equity of access to the research. Although lacunar stroke is more common in men than women,61 and LACI-2 included more males than females as is typical of lacunar stroke, nonetheless we aim in LACI-3 to include a more balanced male to female sample.

5.2 CONSENTING PARTICIPANTS

The potential participants will be given as much time as they need to decide if they want to join the LACI-3 before signing the informed consent. Consent will only be taken from potential participants who, in the opinion of the delegated Investigator, have capacity to understand each aspect of the trial. Only investigators delegated by the local Principal Investigator can obtain the consent from potential participants.

After allowing time for consideration, clarifying any questions and emphasizing that patients may withdraw their consent to participate at any time without affecting their medical care, potential participants will be asked by the delegated investigator to sign the informed consent form. The written consent must be signed by the participant and a delegated investigator. The investigator is responsible for ensuring that the consent form is completed,

signed and dated by all parties prior to any protocol specific procedures being carried out. The consent must be obtained in person.

The participant will be asked as a part of the consent form to name on a contact form an additional contact who has given permission to the participant to provide the information during the follow-up visits, in the event the research teams cannot contact the participant directly, to monitor the participant progress, IMP symptoms, IMP resupply and for safety e.g., to follow-up on the reported events (outcomes, SAEs) and if new information is available or the study is stopped. The contact information for the nominated additional contact whose agreement participant have obtained will be stored only at the local hospital NHS research team.

The participant should receive a copy of the consent form and a copy of the contact form, a copy of the consent form and contact form should be filed in the patient's medical records whether paper or electronic (a PDF will be uploaded to the medical record on sites where medical records are only held electronically) and the original consent and contact form filed in the Investigator Site File (ISF).

The whole consent process should be documented in the medical notes for any future source data verification. This must include the information on when eligibility was confirmed and by whom, when consent was obtained, and the version of the PIS. Obtaining consent must be recorded in the trial database. The site research staff should upload a copy of the consent on the e-CRF.

5.3 SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Confirmation of eligibility will be recorded within the participants' medical records.

A delegated investigator (Principal investigator or other doctor) will review the brain scan and/or its report that diagnosed the lacunar stroke to confirm eligibility before approaching a potential participant for the informed consent.

The baseline information obtained after consent and required for randomisation will be recorded in the eCRF.

Screening logs will not be used as part of the data collection for this study.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Participants who have been approached for the study and subsequently found to be ineligible but not consented will be informed of the reasons why and continue under the care of their physician. Patients found to be ineligible after signing the informed consent form will be recorded as 'consented but not randomised', will therefore not constitute part of the intention to treat population, will be excluded from the primary analysis and will not be followed for AEs.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Randomisation cannot occur ≤24 hours after lacunar symptom onset, and in most cases ≤1 month, to avoid the period when guideline stroke secondary prevention advises prescription of dual antiplatelet drugs (aspirin, clopidogrel) for 28 days followed thereafter by single antiplatelet, usually clopidogrel in the UK. Once the dual antiplatelet phase is over, then participants meeting the criteria can be randomised.

Randomisation can take place on the same day as the consent visit at the clinic after obtaining the consent, if all required tests for eligibility criteria and the baseline information are available.

Investigators with delegated responsibility will collect and enter pre-randomisation baseline data on the web-based trial database.

The electronic randomisation system and trial database are hosted by the University of Nottingham as in LACI-2. Randomisation will be stratified by baseline MoCA score (≥26, 22-25, ≤21) and minimised on the key prognostic variables of age, sex, NIHSS, mRS, time since index stroke, years of education, systolic BP (≤/>140), smoker (current/ex/never) similar to LACI-2.[47,49] Years of education give an estimate of pre-morbid cognitive ability and predicts post-stroke cognitive impairment; BP and smoking predict recurrent stroke; delay since stroke reflects disease activity; age, sex and stroke severity are standard minimisation variables. This approach ensures concealment of allocation, minimises differences in key baseline prognostic variables, and improves statistical power. Randomisation will not be minimised by Centre because this may result in high rates of allocation prediction, but a pre-specified post-hoc analysis by centre will be performed to investigate and adjust for heterogeneity of treatment effect by centre.

Randomisation will allocate a trial treatment, which will be prepared by the local participating Pharmacy.

Note that randomisation will be performed during normal office hours (09.00 – 17.00) and the trial allows for randomisation to occur any time beyond 24hrs after the stroke (if the eligibility criteria are met) with no upper time limit after the stroke. Therefore, in the event of computer failure (for example: server failure), the investigator will wait until the computer system is re-established to perform the randomisation. Normally, this would only be a few minutes to two hours. However, if this delay requires the patient to return on a separate occasion to collect the drugs, then a separate appointment will be made and the patient's travel expenses covered as per other trial visits or the drug supply may be sent by post for the next day delivery.

Patients will be randomised to one of the following at a 1:1 ratio as per Section 6.3:

- cilostazol versus no cilostazol
- ISMN versus no ISMN

resulting in a partial factorial comparison of cilostazol versus ISMN versus both drugs versus neither drug.

All participants will continue their usual prescribed guideline stroke prevention medication.

The randomisation algorithm will allocate a unique participant identifier which will be used to label the treatment pack containing the appropriate drug made up for the patient and dispensed by the local Pharmacy.

Participants with an indication for or contraindication to one of the trial drugs may still be randomised to the other trial drug. If a participant allocated to both trial drugs develops a contraindication to one of the trial drugs after randomisation into the trial, then they should discontinue that drug but continue to take the other trial drug. If a patient has to discontinue either or both drugs, they should continue to be followed up in the trial as planned (unless they withdraw from the trial). Patients should remain in follow up until the end of the trial follow up period, even if they discontinue trial drug, unless they withdraw from the trial. Drug discontinuation will be recorded.

The study will be performed open label. Placebo tablets are not available and masking by encapsulation is too complicated and expensive. However, blinding of outcomes is important to obtain unbiased information about tolerability, safety, and efficacy. As such, IMP adherence structured questionnaire and prescribed medications will be taken by site staff who are already unblinded to trial allocation, while ascertainment of the main cognitive and

clinical outcomes will be collected by central follow-up co-ordinators who are masked to treatment allocation. During the first month after the randomisation, when the IMP dose will be increased, the local hospital sites will ask about the IMP symptoms using structured questionnaire at one-two and three-four weeks. The central blinded trial co-ordinators will continue to ask participants about the IMP symptoms at 6, 12, and 18-months follow-up visits. A web-based system into which the participant can enter information directly may also be available for participants who are willing to use this method.

5.5.2 Treatment Allocation

Participants randomised to start drug will be provided with their allocated drug/s after randomisation at the baseline visit, which they will start on the next day (i.e., day 1, week 1). In the event that there is any delay between receiving the trial tablets and starting the treatment, then the patient will receive a reminder telephone call shortly before the day that the medication should be commenced. The first day of treatment defines day 1, week 1. Delay between randomisation and receipt of IMP will not be a deviation but will be recorded in the CRF.

Participants will be supplied with trial tablets from the hospital pharmacy to cover a maximum period of six months. Detailed dated instructions on dosing will be provided in the patient pack. The participant will be telephoned between the end of weeks 1 and 2 and between the end of weeks 3 and 4 by the site staff, and other times during drug introduction as necessary, as well as routine follow-up time points, to ensure they are taking the medication correctly.

Drugs will be provided in their packs as marketed and licensed (i.e. unaltered) and dispensed by the participating hospital pharmacy under research protocols.

5.5.3 Emergency Unblinding Procedures

If the patient develops a contraindication to the trial medications, the medication should be stopped in line with SPC guidance. Similarly, if the patient develops a definite indication for the trial medications the study medications should be stopped as per the SPC.

As this is an open label trial, it should not be necessary to unblind the allocated treatment. If identification of the trial drug is considered necessary, the tablets can simply be examined and identified as cilostazol or ISMN as they will be dispensed in their licensed packaging.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data;

(ii) study medication and follow-up visits (or study procedures) with continued collection of clinical and safety data from medical notes

(iii) Consent to be contacted about other research studies

(iv) all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be retained.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and

another participant will be recruited to replace them. Data on the original participant will be kept on the CRF/database if the participant agrees to this.

Trial medication may be stopped at any time by the Investigator or treating physician if deemed advisable. Stopping trial medication on its own does not necessarily equate with withdrawal from the trial, and follow-up procedures will continue unless the participant withdraws consent. Participants who wish to withdraw from follow-up will not be able to continue on the IMP. Participants may wish to withdraw from active participation in follow-up by central co-ordinators but agree that relevant information can be obtained from their hospital or GP records. Participants may withdraw consent to be contacted about other research but this will not affect their continued participation in LACI-3. These scenarios will be documented and kept up to date in the CRF.

If after randomisation into LACI-3, a participant subsequently is found to have a condition which would have made them ineligible for recruitment, these participants will be retained in the trial, at least for the purposes of follow-up, to protect the 'intention to treat' principle of analysis, and a decision for the continuation of the IMP will be made by the Principal Investigator or designee with the participant (or their relatives in the event of loss of capacity) on the basis of safety.

A recurrent event, such as stroke or other outcome, or SAE s not of itself a reason for withdrawal or discontinuation of IMP. In legal terms, consent to participate is assumed to remain valid if mental capacity is lost during the trial. Hence, the participant who loses capacity will remain in the trial unless their doctor or representative considers it necessary to withdraw some or all aspects of their participation. In making such decisions, the doctor or representative will consider the participant's wishes and feelings before the loss of capacity.

Delegated research team members will follow the appropriate local regulations (Mental Capacity Act 2005 for England and Wales and Adults with Incapacity (Scotland) Act 2000 for Scotland) and guidance regarding loss of mental capacity in research to determine if the consent remains valid after loss of capacity. If it is agreed that the participant should be withdrawn from the study medication, follow-up or all aspects of the trial, a delegated research team member will record it on e-CRF.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

The IMP is defined by the active substance only, therefore all authorised brands may be used.

Oral cilostazol or ISMN slow release will be prescribed as per the brand available in the participating hospital pharmacy.

Cilostazol, generic, as 50mg or 100mg tablets.

Isosorbide mononitrate slow release, generic, as 25mg XL, 30mg XL,50mg XL or 60mg XL tablets to the suggested target dose of 40-60mg daily

Isosorbide mononitrate, generic, as 20mg or 40mg tablets to the suggested target dose of 40-60mg daily.

Most isosorbide mononitrate preparations are slow release in the UK. However, where slow release preparations of isosorbide mononitrate are not available, then non-slow release

preparations may be used, but the dose should be split 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. A target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the study treatment pack.

Several doses and brands of these drugs are marketed in the UK, examples are given below as listed in the representative SPCs in section 6.1.3.

- Cilostazol
    - Cilostazol 100 mg Tablets (Generics [UK] Ltd t/a Mylan, Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK
- Isosorbide mononitrate
    - Isodur 25XL Capsules (Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, UK.
    - Isosorbide Mononitrate Tablets 20 mg (Dexcel Pharma Ltd, 7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK)

Cilostazol and ISMN are both licensed products for treatment of vascular diseases in Europe and the example summaries of the product characteristics are appended to this trial protocol.

6.1.2 Study Drug Manufacturer

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

Refer to the separate document of the representative SPC example of the drug manufacturers provided for LACI-3 investigators and section 6.1.1 above

6.1.3 Marketing Authorisation Holder

The representative SPCs for Cilostazol (Cilostazol 100mg Tablets; marketing authorisation number PL 04569/1427) and Isosorbide mononitrate (Isodur® 25 mg XL capsules; marketing authorisation number PL 27827/0021 and (Isosorbide mononitrate (ISMN) 20mg tablets; marketing authorisation number PL PL 14017/0011) are provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Co-Sponsors) and filed in the trial master file (TMF). Please refer to the representative SPCs.

- Cilostazol
    - Cilostazol 100 mg Tablets
        - Marketing authorisation number PL 04569/1427
- Isosorbide mononitrate
    - Isodur 25XL Capsules
        - Marketing authorisation number PL 27827/0021
    - Isosorbide Mononitrate Tablets 20 mg
        - Marketing authorisation number PL PL 14017/0011

6.1.4 Labelling and Packaging

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 remain 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 the local language 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.

6.1.5 Storage

The 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 SPCs. Drug will be delivered to hospital pharmacies as per Manufacturer's usual delivery practices

6.1.6 Regulatory Release to Site

Not applicable. Off-shelf IMP use from the hospital pharmacies.

6.1.7 Destruction of Trial Drug

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 LACI-3.

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The Representative Summary of Product Characteristics (SPC) (for cilostazol, isosorbide mononitrate slow release, and isosorbide mononitrate, generic) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Co-Sponsors) and is filed in the TMF.

6.2 PLACEBO

There is no placebo.

The comparator will be a standard care alone including guideline stroke secondary prevention prescribed post-stroke as per national guidelines.

6.2.1 Labelling and Packaging

Not applicable. Off-shelf IMP use from the hospital pharmacies.

6.2.2 Storage

Not applicable.

6.3 DOSING REGIME

Patients will be supplied with trial drug in its usual (marketing) packaging 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. They will receive a phone call after 1 to 2 and 3 to 4 weeks as per schedule below to guide dose escalation. If a patient 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 notes. 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.

Table 1: 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 given half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs)

ISMN XL Dosing Regime		
Day	**ISMN XL 25mg**	
	Morning	**Evening**
1-5	25mg	nil
6-10	50mg	nil
11-15	50mg	nil
16-20	50mg	nil
At end of study		
Week	**Morning**	**Evening**
79	25mg	Nil
80	Nil	Nil

ISMN non-XL Dosing Regime		
Day	**ISMN non-XL 20mg**	
	Morning	**Evening**
1-5	nil	20mg
6-10	20mg	20mg
11-15	20mg	20mg
16-20	20mg	20mg
At end of study		
Week	**Morning**	**Evening**
79	20mg	Nil
80	Nil	Nil

Table 2: Patients randomised to cilostazol alone

Cilostazol Dosing Regime		
Day	**Cilostazol**	
	Morning	**Evening**
1-5	Nil	50mg
6-10	50mg	50mg
11-15	50mg	100mg
16-20	100mg	100mg
At end of study		
Week	**Morning**	**Evening**
79	50mg	50mg
80	Nil	Nil

Table 3: Patients randomised to both Isosorbide Mononitrate and Cilostazol

ISMN XL/Cilostazol Dosing Regime				
Day	**Isosorbide Mononitrate XL 25mg**		**Cilostazol**	
	Morning	**Evening**	**Morning**	**Evening**
1-5	25mg	nil	Nil	Nil
6-10	50mg	nil	Nil	Nil
11-15	50mg	nil	Nil	50mg
16- 20	50mg	nil	50mg	50mg
21-25	50mg	nil	50mg	100mg
26-30	50mg	nil	100mg	100mg
At end of study				
Week	**Morning**	**Evening**	**Morning**	**Evening**
79	25mg	Nil	50mg	50mg
80	Nil	Nil	Nil	Nil

ISMN non-XL/Cilostazol Dosing Regime				
Day	**Isosorbide Mononitrate 20mg**		**Cilostazol**	
	Morning	**Evening**	**Morning**	**Evening**
1-5	nil	20mg	Nil	Nil
6-10	20mg	20mg	Nil	Nil
11-15	20mg	20mg	Nil	50mg
16- 20	20mg	20mg	50mg	50mg
21-25	20mg	20mg	50mg	100mg
26-30	20mg	20mg	100mg	100mg
At end of study				
Week	**Morning**	**Evening**	**Morning**	**Evening**
79	20mg	Nil	50mg	50mg
80	Nil	Nil	Nil	Nil

Table 4: Patients randomised to neither Isosorbide Mononitrate or Cilostazol

Neither ISMN/Cilostazol Dosing Regime				
Day	**Isosorbide Mononitrate**		**Cilostazol**	
	Morning	**Evening**	**Morning**	**Evening**
1-4	Nil	Nil	Nil	Nil
5-8	Nil	Nil	Nil	Nil
9-12	Nil	Nil	Nil	Nil
13, 14	Nil	Nil	Nil	Nil
At end of study				
Week	**Morning**	**Evening**	**Morning**	**Evening**
79	Nil	Nil	Nil	Nil
80	Nil	Nil	Nil	Nil

6.4 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 6.3. Variation of dose like this will not count as a protocol deviation. Patients will be able to stay on the dose they can tolerate. If necessary, this will be done under close guidance of the researcher. There will be no other changes to the doses described in section 6.3.

6.5 PARTICIPANT COMPLIANCE

Adherence 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.

As indicated in 7.2 below, during the first month after randomisation, participants will be asked to contact the local hospital investigator if they experience adverse symptoms, or 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.

6.6 OVERDOSE

Cilostazol: The SPC 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.

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

The risk of overdose will be mitigated by follow-up phone calls by the hospital research teams at weeks 1-2 and 3-4 and at 6, 12, and 18 months as well as minimised by excluding patients with a history of overdose or suicide.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Not applicable.

6.7.2 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 in section 6.7.3 and in the exclusion criteria in section 4.3.

Investigators will record the concomitant medications that the participant receives at the time of enrolment or during the trial follow-up in the eCRF.

6.7.3 Prohibited Medications

Isosorbide mononitrate:

Phosphodiesterase 5’ inhibitors (tadalafil, sildenafil, vardenafil).

Cilostazol:

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 (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.

Although not noted in the BNF, SPCs 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 isosorbide mononitrate and hypotensive agents such as diltiazem, hydralazine, etc. No increase in symptoms or SAEs were observed in patients allocated both ISMN and cilostazol in LACI-1 or LACI-2.
Please refer to the SPCs for full details.STUDY ASSESSMENTS

6.8 SAFETY ASSESSMENTS

Safety assessments for the trial drug will occur at 2-weekly intervals in the first month after randomisation and six-monthly intervals thereafter during the 18 months duration of the trial.

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

The central blinded trial co-ordinators will continue to ask participants about the IMP symptoms as a part of the postal questionnaire at 6, 12 and 18-months follow-up visits.

The local hospital sites will phone-visit participants at 2-weekly intervals in the first month, and at 6, 12, and 18-month follow-up visits to ask about adherence to trial medication.

Investigators from the 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 the last follow-up visit at 18 months based on the information from the follow-up questionnaires as well as alerts from the hospital records. The safety reporting will include two weeks after the last dose of IMP is administrated.

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

6.9 STUDY ASSESSMENTS

Study assessments (see Table 2) include the maximum of the six planned study visits.

The first study visit includes consent, baseline information collection and randomisation. After eligibility confirmation and obtaining the informed consent, investigators will collect the baseline medical history data required for randomisation. The randomisation visit can take place on the same day as the consent visit at the clinic, if all required tests for eligibility criteria and the baseline information are available.

Baseline information will include the confirmation of eligibility and informed consent details, demographic information such as date of birth, sex assigned at birth, ethnicity, years of full-time education [62, 63] and occupation.

The medical history will contain details of incident stroke, past medical history, vascular risk factors, concomitant medications and the characteristics of the lacunar stroke and SVD features (white matter hyperintensities/hypoattenuation, and/or lacunes) on brain imaging.

Baseline brain MR (preferred wherever possible) or CT: To identify the index stroke or exclude other causes of symptoms, and assess the burden of SVD – this is the clinical scan with MRI (T2, FLAIR, T1, T2* or SWI and diffusion imaging) or CT obtained soon after the presentation with stroke to diagnose the stroke. Brain imaging in eligible patients with lacunar ischaemic stroke may show either:

- a recent, relevant (in time and location) acute small subcortical (lacunar) infarct,

- or, if no visible acute lacunar infarct, there is no other competing pathology as a cause for stroke (e.g. no acute cortical infarct, no intra-cerebral haemorrhage, no stroke mimic such as tumour, or subdural haematoma)... Investigators will post scans to the LACI-3 Imaging office in Edinburgh for central reading in DICOM format or upload them online to the database according to the imaging acquisition guidance.

In participants whose lacunar stroke occurred more than six months previously, or in whom there have been further neurological symptoms, any brain MRI or CT imaging performed in the interval between the index lacunar stroke and recruitment should also be sent for central reading.

Cognitive baseline testing: Participants will be assessed at baseline using the Montreal Cognitive Assessment (MoCA), and the timed Trail Making Test B for processing speed/executive function, and for the concentration, the backwards spelling from the MMSE.

The lifestyle risk factors for vascular disease such as cigarettes and alcohol use as well as blood pressure, weight and height will be collected as a part of the baseline information.

Participants will be asked about health-related quality of life (using the EuroQol Group EQ-5D-5L/ EQ-VAS instrument).

Haematology and biochemistry: Full blood count, urea and electrolytes and renal function results will be obtained and collected on e-CRF from the most recent standard of care results sample since the time of the index stroke. If there is a clinical reason to expect change since this last sample, the full blood count and biochemistry should be repeated prior to randomisation. These samples will be analysed in the hospital haematology or biochemistry labs in the centre in which the patient has been recruited as a part of the standard clinical care.

Clinical outcomes: Information on recurrent ischaemic stroke, TIA, major systemic or brain haemorrhage, non-fatal MI, and dementia will be assessed by phone or post questionnaire at 6, 12, and 18 months as well as by checking the participant's medical notes. Patients will be encouraged to seek medical advice if they develop new neurological events during the trial. The death of any cause will be detected, reported and recorded by the investigators based on the information from the medical notes.

Functional outcome: modified Rankin Scale to assess dependency at 6, and 12, 18 months. If participants are unable to be contacted, the central assessor will obtain the most recent modified Rankin Score from the local staff (if available) or estimate from the relative/carer.

Cognitive and mood outcomes: Telephone MoCA (tMoCA), The Telephone Interview for Cognitive Status (TICS), animal naming, Concentration (from the MMSE), the ZUNG and Stroke Impact Scale (SIS), will be collected remotely at 6, 12 and 18 months by the central trial team.

Drugs symptoms: Will be assessed by site investigators after randomisation at 1-2 weeks and 3-4 weeks visits and by the blinded central team at 6, 12 and 18 months using a short simple validated questionnaire to assess for symptoms potentially related to trial tablets as part of safety monitoring, including headache, dizziness, palpitations, altered bowel habit, falls, bruising and bleeding, as in LACI-2. The participant will be asked whether any symptoms were severe enough to interfere with normal daily activities. Participants will also be able to report any other symptoms and describe them in detail.

Drug adherence: Will be assessed by site investigators at each follow-up visit by phone. Participants will be asked about adherence to medication using a very short structured question. These contacts will be timed around prescribing for the next batch of IMP.

Blood pressure: Will be collected by the site hospital teams as a part of the baseline visit. BP measurements, if available, will be collected by sites as a part of the site phone follow-up at each follow-up visit. Sites can use self-recorded BP by the participant using their own BP monitor or self-reported from routine GP or other hospital measure. The medication list including antihypertensive drugs will be collected at each visit by the hospital team as a part of the data collection on the continuing routine stroke prevention therapy.

Health economics: EQ-5D-5L, EQ-VAS will be collected at 6, 12 and 18 months and measures to assess health economic usage and impact of trial drug (contact with health care, place of residence, return to work, etc) will be collected centrally at 18 months.

Repeat Brain CT or MRI: any repeat scanning performed to assess a recurrent neurological event during the trial will be anonymised and sent to Edinburgh for central blinded adjudication.

Follow-up:

After randomisation, all participants will be followed up for outcome and safety events until the end of their follow-up at the 18 months visit.

The follow-up includes five visits. Participants will be followed up remotely by phone and post for 18 months by two teams: the local site and the central research team. Each time, a questionnaire will be completed by a participant by telephone or on paper or both to collect trial outcomes.

Local site:

- Contact at one-two and three-four weeks by phone to advise on dose escalation, check symptoms and drug adherence, BP, outcomes and safety.

- Contact at 6, 12, 18 months by phone to check drug adherence; BP, medication history and supplements, outcomes and safety; arrange IMP re-supply by post if applicable

Central:

- Contact at 6, 12 and 18 months by post to collect recurrent vascular events, cigarettes and alcohol use, mRS, drug symptoms, Stroke Impact Scale, EQ-5D-5L, EQ-VAS, and health economic parameters only at 18 months; outcomes and safety
- Contact at 6, 12 and 18 months by phone to collect cognitive outcomes: tMoCA, TICS, Concentration (from MMSE), Animal naming, Zung, outcomes and safety

Central follow-up at 6, and 12, 18 months will be by post and telephone, blinded to allocated treatment. A trained assessor who is part of the central trial team and based either at the University of Edinburgh or University of Nottingham and who is blinded to treatment and baseline clinical information, will first confirm with the local site team and/or GP that the participant is contactable. They will then contact the participant by post and phone to administer the questionnaires following a standardised script.

About three weeks before the anniversary of the participant's randomisation or the last follow-up visit, the site hospital team will contact a participant by phone to conduct the 6, 12, or 18 months follow-up visit and to arrange the IMP re-supply if relevant.

If the site hospital team confirms that the participant is still alive, the participant will be sent a postal central follow-up questionnaire (followed by a telephone reminder if no response is received).

The central follow-up paper questionnaire can be obtained by phone during the cognitive outcomes collection. If the follow up information cannot be obtained by either postal or telephone questionnaire the local research team will be asked to provide follow up information from the medical records or by contacting the GP.

If, after at least 5 attempts, a participant fails to complete the phone visit done by the hospital site or return the paper questionnaire or will not complete the cognitive testing done centrally, this will be recorded as lost to follow-up in the e-CRF and reviewed by the TSC and DMC.

Table 2 Study Assessments

Assessments	Consent	Random	Follow-up[b]											
	V1		V2	V3	V4				V5				V6[c]			
Timelines	0		1-2 week	3-4 week	6 months				12 months				18 months			
Team	Site		Site	Site	Site		Central		Site		Central		Site		Central	
Visit window (weeks)			+/- 1 week		+/- 3 weeks				+/- 3 weeks				+/- 5 weeks			
Type of visit	Clinic		Phone	Phone	Phone	Post	Post	Phone	Phone	Post	Post	Phone	Phone	Post	Post	Phone
Baseline Procedures																
Eligibility criteria	●															
Informed consent	●															
Demographics		●														
Medical History		●														
Diagnostic scan check[d]		●														
Occupation/ education		●														
Weight and height		●														
Pregnancy test[m]		●													●	
Blood test[e]		●														
MOCA		●														
Timed Trail Making Test B		●														
Concentration (MMSE)		●														
Blood pressure[f]	●		●	●	●				●				●			
Medications																
Concomitant medications	●				●				●				●			
1st study drug		●														
Drug dispense[g]		●				●				●						
Drug dose increase			●													
Drug re-supply						●				●						
Drug - dose decrease													●			
Drug symptoms			●	●			●				●				●	
Drug adherence			●	●	●				●				●			
Clinical Outcomes[h]		●	●	●			●				●				●	
Functional outcome																
Modified Rankin Scale[i]	●						●				●				●	
Cognitive Outcomes[j]								●				●				●
Safety Outcomes[k]		●	●	●			●				●				●	
Health economics[l]	●						●				●				●	

[a] Randomisation visit can take place on the same day as the consent visit at the clinic, if all required tests for eligibility criteria and the baseline information are available.
[b] Participants will be followed up remotely by phone and post for 18 months by two teams: local site and the central research team.
[c] End of Study Visit is a follow-up visit at 18 months.
[d] Copy of the diagnostic scan (CT or MRI) will be sent for central reading.
[e] Full blood count, urea and electrolytes and renal function will be obtained from the most recent sample since the time of the index stroke.
[f] Blood pressure collection is optional depending if a participant has access to the BP monitor or GP or hospital measure is available.
[g] Dispensing in 3-monthly intervals is allowed. IMP re-supply to be sent to the participants home address.
[h] Recurrent ischaemic stroke, TIA, major systemic or brain haemorrhage, fatal or non-fatal MI, death of any cause, dementia
[i] Modified Rankin Scale can be obtained from the relative/carer or the local site if a participant is unable to be contacted.
[j] Stroke Impact Scale (SIS), Telephone MOCA, Telephone Interview for Cognitive Status (TICS), concentration (from MMSE), Animal naming, ZUNG
[k] SAE - Serious Adverse Event; SAR - Serious Adverse Reaction, SUSAR - Suspected Unexpected Serious Adverse Reaction
[l] EQ5D5L, EQ-VAS - quality of life questionnaires will be done at baseline and each follow-up visit. The NHS and social service use will be done at 18 months visit
[m] Women of childbearing potential must have negative urine pregnancy testing on the day of randomisation. If applicable, the central team will send the urine pregnancy test with the central follow-up paper questionnaire.

6.10 COMPLIANCE ASSESSMENTS

Tablet adherence: Will be assessed by site staff at each visit by the simple structured questionnaire. This will allow to monitor safety and maintain blinding of central trial staff.

Participants who stop all of their trial-allocated IMP for more than four weeks and so not restart the IMP will be classed as non-compliant.

Participants will be asked to return any packs of unused tablets to the local community pharmacy (or hospital pharmacy if more convenient) at the end of their participation in the trial. All returned tablets will be destroyed.

6.11 LONG TERM FOLLOW UP ASSESSMENTS

Participants will not be followed up long term after the end of the treatment period. Participants who consented at enrolment to further contact for future research may be contacted as new research opportunities arise.

6.12 STORAGE AND ANALYSIS OF SAMPLES

Full blood count, urea and electrolytes and renal function will be analysed and stored as a part of the standard clinical care according to the routine NHS methods.

7. DATA COLLECTION

Section 7.2 (study assessments) details data to be collected, including time points and who will collect data.

7.1 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

Study data will be recorded on source documents (patient’s paper and electronic medical records), trial documents (signed consent and completed follow-up questionnaires) and on study specific CRFs (paper and electronic).

The Source Data Plan will specify the location where all the trial data points are documented for the first time and how investigators will report and record study data into CRFs.

If the study data is first collected on a paper trial document, such as completed consent or paper CRFs, investigators must file all the completed documents in the ISF. If the study data is entered directly into electronic CRFs, the CRF will act as the source for the specified study data points.

The Source Data Plan must be completed before each site activation.

7.2 CASE REPORT FORMS

The electronic case report forms (eCRF) will be used to collect trial data. The web-based trial database will require user authentication with user-specific access rights for data entry, editing, and password protection. A separate database will be used to encrypt and store participants' personal identifiable data required to perform the follow-up. Paper versions of the

eCRF will assist with data collection when interviewing patients at baseline and during follow-up visits by phone or post. Research staff will file all completed paper CRFs in the ISF or TMF if data have not been entered directly on e-CRF.

Section 7.2 (study assessments) details data to be collected, including time points and who will collect data.

Baseline case report forms will include pre-randomisation and post-randomisation data collection.

Baseline eCRFs will contain:

- General eligibility criteria confirmation
- Cilostazol eligibility criteria confirmation
- ISMN criteria confirmation
- Investigator confirming eligibility and their role
- Informed consent details (date of the ICF, date of PIS given to participant, version of PIS and ICF, Investigator taking consent details and their role)
- Participant details (initials, date of birth, sex assigned at birth, ethnicity, years of full-time education and occupation, employment status)
- Medical history (details of incident stroke, past medical history, vascular risk factors, concomitant medications and the characteristics of the lacunar stroke and SVD features on brain imaging.
- Medication list
- Lifestyle risk factors (smoking cigarettes and alcohol use)
- Falls
- Blood pressure, weight, and height
- Quality of life (5D-5L/ EQ-VAS)
- Cognitive testing (MOCA, Trail Making Test B, concentration – MMSE)
- Participant contact details (name, postal address, telephone, email)
- Participant CHI/NHS Number
- GP contact details (name
- Optional: Participant close personal contact details to be used when the participant is uncontactable during follow-up (name, postal address, telephone, email, relationship)
- Date and time of randomisation

The participant, GP, and participant's CHI/NHS Number will be encrypted and be 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 only at the local hospital NHS research team.

Prescription eCRF will include:

- Date of prescription
- Duration of prescription (3 or 6 months)
- Tables dispensed (name of the drug and dose)
- Brand

Follow-up CRFs will include:

- **Week 1-2** telephone follow-up form - completed by the local site team:
    - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
    - IMP symptoms
    - IMP compliance
    - Blood pressure
    - Outcome and safety events

- **Week 3-4** telephone follow-up form - completed by the local site team:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - IMP symptoms
  - IMP compliance
  - Blood pressure
  - Outcome and safety events
- **Month 6** telephone follow-up - completed by the local site team:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - IMP compliance
  - Blood pressure
  - Medication list
  - Supplements
  - Outcome and safety events
  - Details of the investigator who completed the phone questionnaire
- **Month 6** postal follow-up - completed by the central blinded trial co-ordinators:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - Type of accommodation
  - Vascular events
  - mRS
  - Smoking cigarettes and alcohol use
  - IMP symptoms
  - Falls
  - Stroke Impact Scale
  - Quality of life (5D-5L/ EQ-VAS)
  - Details of the person who completed the postal questionnaire
- **Month 6** telephone follow-up - completed by the central blinded trial co-ordinators:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - tMOCA
  - TICS-M
  - Concentration (MMSE)
  - Animal naming
  - Zung (mood)
  - Outcomes and safety events
- **Month 12** telephone follow-up - completed by the local site team:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - IMP compliance
  - Blood pressure
  - Medication list
  - Supplements
  - Outcome and safety events
  - Details of the investigator who completed the phone questionnaire
- **Month 12** postal follow-up - completed by the central blinded trial co-ordinators:
  - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
  - Type of accommodation
  - Vascular events
  - mRS
  - Smoking cigarettes and alcohol use
  - IMP symptoms

    - Falls
    - Stroke Impact Scale
    - Quality of life (5D-5L/ EQ-VAS)
    - Details of the person who completed the postal questionnaire
- **Month 12** telephone follow-up - completed by the central blinded trial co-ordinators:
    - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
    - tMOCA
    - TICS-M
    - Concentration (MMSE)
    - Animal naming
    - Zung (mood)
    - Outcomes and safety events
- **Month 18** telephone follow-up - completed by the local site team:
    - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
    - IMP compliance
    - Blood pressure
    - Medication list
    - Supplements
    - Outcome and safety events
    - Details of the investigator who completed the phone questionnaire
- **Month 18** postal follow-up - completed by the central blinded trial co-ordinators:
    - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
    - Type of accommodation
    - Vascular events
    - mRS
    - Smoking cigarettes and alcohol use
    - IMP symptoms
    - Falls
    - Stroke Impact Scale
    - Quality of life (5D-5L/ EQ-VAS)
    - Health economic parameters
    - Employment status
    - Details of the person who completed the postal questionnaire
- **Month 18** telephone follow-up - completed by the central blinded trial co-ordinators:
    - Status of the participant (available, lost to follow-up, declined, withdrawn, died)
    - tMOCA
    - TICS-M
    - Concentration (MMSE)
    - Animal naming
    - Zung (mood)
    - Outcomes and safety events

Follow-up data will be collected on paper and electronic CRFs. If a participant needs help completing the follow-up questionnaires due to, e.g., visual or hearing impairment, a carer or relative may assist with it, and it will be recorded on the e-CRF. **Outcomes and Serious Adverse Events CRF** will include any clinical trial outcome reported from the moment of randomisation until the last follow-up at 18 months and any SAE reported from randomisation until up two weeks after the last dose of IMP is administrated.

Outcome events will be reported on the e-CRF and reviewed by the members of the trial management group. The event adjudication process will include checking for duplicates as

reported events may come from several sources (site research team, participant, follow-up questionnaire, GP or carer, friend, or relative). The relevant clinical, radiographic or pathological information about the reported event will be obtained from the site hospital research team, e.g., Outpatient clinic letter, Discharge summary, brain imaging and radiological report, and blood results. Patient identifiers will be redacted from these documents before sending for internal adjudication to confirm if the event is classified as the outcome. Any potential SAEs or SUSARS identified during the review process will be reported to the sponsor using online e-CRF.

The anonymised **brain scans** that diagnosed the qualifying lacunar stroke and any reported clinical outcomes will be stored in a separate imaging database described in section 8.3. The central research staff will check each brain scan to confirm that it relates to the correct participant, correct time of the event, includes the required imaging sequences, does not show other explanations for the symptoms and will make scan available for the readers.

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

NOTE: All electronic case report forms are subject to Co-Sponsor approval (see section 8.3).

7.3 TRIAL DATABASE

The Stroke Trials Unit, Nottingham (STUN) will provide a bespoke trial database with electronic case report forms. It will contain one database for the pseudonymised data and one to encrypt and store participants' personal identifiable data.

The data will be held on the University of Nottingham’s servers/storage, which are based at the King's Meadow campus and protected by regular security updates and firewall software.

Data will be entered into the eCRF by site investigators and central follow-up co-ordinators who are fully trained and delegated to access e-CRFs. Each research team member will receive unique login credentials to access only relevant parts of the database.

The Systematic Image Review System Tool (SIRS) will be used as a web-based imaging database to assess the brain scans. The SIRS is comprised of the imaging database, which will be accessed only by the members of the central team and will be hosted by the servers located at the University of Edinburgh Data Centre on the King’s Buildings Campus, and the web application that scans readers will use to access their assigned cases. The web application accesses rendered views of imaging and not the imaging database itself. Scan reads are transferred to the University of Nottingham to link with the eCRF for statistical analysis.

Trial database will be achieved after the end of trial and stored on University of Edinburgh servers for a minimum of five years.

8. DATA MANAGEMENT

8.1 Data Management Plan

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving will be detailed in a separate Data Management Plan (DMP).

8.2 Personal Data

All investigators and the central trial staff must comply with the Data Protection Act and the General Data Protection Regulation (GDPR). Access to identifiable participant data will be limited to the research team, sponsor representatives, and regulatory authorities.

The following personal identifiable data will be collected as part of the research:

The following personal identifiable data will be collected as part of the research: forename, surname, initials, date of birth, sex assigned at birth, ethnicity, socioeconomic information (years of education, occupation), home address, telephone numbers, email addresses, contact information for the close personal contacts, GP address, unique healthcare identifiers like CHI/NHS Number and medical history.

The participant's name and contact details will help to facilitate contact during the follow-up by phone and post. The local investigators and central trial coordinators will collect the information on safety, outcomes and drug adherence. The local research teams will post a study drug if applicable to the participant's home address.

A patient's initials, age, sex and years of education are part of the electronic baseline data and are required for randomisation procedures. Patient initials alone will be recorded as a safeguard against duplicate entries on e-CRF.

Demographic information such date of birth, sex assigned at birth, ethnicity, socioeconomic information (years of education, occupation) will help to study whether those characteristics influence the effects of the tested drugs.

Participant's GP address is required to inform about the participant's involvement in LACI-3 and the treatment allocation. The GP letter will include participant's name, address, date of birth and CHI/NHS Number to verify that we are communicating about the correct participant with GP.

Participant's relatives, carers, or close personal contacts information will be used if the participant cannot be contacted or the participant no longer has the mental capacity to make decisions for themselves during the follow-up.

The site investigators and central trial teams at the University of Edinburgh and the University of Nottingham will process personal data. Research teams will store personal data on password-protected computers at sites kept in locked offices. The trial documentation containing personal data will be stored and kept in locked and secured filing cabinets within secure alarmed buildings. Access to trial documentation will be restricted to the trial team exclusively.

Published results will not contain any personal data that could allow identification of individual participants.

8.3 Data Information Flow

The data collection and access will occur through Case Report Forms (CRFs). The site investigators will upload participant data into the trial database, where the data will be stored. During the follow-up, the local research teams and the central trial coordinators will access data to enable contact with participants and collect information for the follow-up visits. They will record and report data on electronic CRFs. The access to the database will be locked after the trial is compete and ready to be archived. Anonymised and de-identified data may be available for data sharing after obtaining applicable approvals.

8.4 Data Storage

Personal data will be physically stored by the research teams within locked filing cabinets in locked offices, with swipe card access for authorised personnel only.

The research teams will digitally store personal data using password-protected database logins to access the trial database. The database servers are hosted in a secure server room within the King's Meadow Campus at the University of Nottingham. Access to the secure server room is restricted to authorised individuals with swipe card access and pin codes.

8.5 Data Retention

Personal data will be stored for a minimum of five years and destroyed only with permission from the chief investigator and sponsor. The anonymised dataset will be securely stored in the Data Vault, the University of Edinburgh's archival storage platform.

Trial documentation may be destroyed only after the minimum retention period with permission from the chief investigator and the Sponsor.

8.6 External Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s) and the University of Nottingham.

8.7 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

The LACI-3 is run by the University of Edinburgh and the University of Nottingham who provides the trial database and acts as data processor.

8.8 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

The primary outcome, cognitive impairment assessed using the DSM-5 7-level ordinal score, will be compared between ISMN vs no ISMN, cilostazol vs no cilostazol, and ISMN+cilostazol vs no ISMN or cilostazol using ordinal logistic regression adjusted for stratification and minimisation variables. The null hypothesis is that ISMN, alone or with cilostazol, will not reduce long-term cognitive impairment in patients with lacunar ischaemic stroke.

A sample of N=1300 is needed (650 ISMN, 650 no ISMN) assuming alpha 5%, power 90%; distribution of DSM-5 7-level ordinal score in the control (standard of care) group is: level 1 (normal): 35%, 2: 24%, 3: 12%, 4: 20%, 5: 3%, 6: 3%, 7 (dead):3% (as in LACI-2); DSM-5 7-level unadjusted odds ratio 0.70 (the risk reduction exceeds the minimal clinically important

difference [MCID] of 0.27), standard deviation 1.33; losses/cross-overs 15%; no covariate adjustment; sample rounded up

Notes:

1. We chose OR 0.70 because it represents a 'small' treatment effect and so is of relevance to the large lacunar stroke cSVD population; a readily available, easy to administer and inexpensive intervention, albeit with small (or better) effect, would be very valuable clinically. The odds ratio=0.70 is more conservative than that seen in LACI-2: ISMN vs no ISMN aOR 0.55 (95% CI 0.36, 0.86) and ISMN+cilostazol aOR 0.44(95%CI 0.23-0.85).[49]
2. The MCID assumption of 0.27 lies in the range of 0.17 to 0.69, which is based on plausible values from anchor, distribution and expert opinion in dementia and stroke studies,[61-64] and calculated from LACI-2[49] and R4VaD, a large UK cohort study, n=2441, of post-stroke cognitive impairment.[48] The distribution-based MCID of 0.27 is based on pooled standard deviation (SD) of 1.33 in LACI-2, multiplied by 0.2, as appropriate for low cost drugs.[61] The anchor-based MCID for DSM-5 7-level cognition at 1year in LACI-2 was 0.41 for ISMN v no ISMN,[49] and was 0.69 for severe vs. mild stroke in R4VaD, but this is less relevant to lacunar stroke (1^{ry} results in prep).[48] A survey of experts (n=48, ongoing) suggested an MCID of median 0.4-0.5.
3. LACI-2 showed no differential loss between treatment groups using telephone/postal follow-up,[49] a common issue in cognition trials. We assume losses of up to 15%, within rates seen previously (8-15%).[27,49] We do not expect cross-overs since ISMN and cilostazol are rarely used in the UK after lacunar stroke.
4. We and others have shown that adjustment for co-variates improves statistical power[65] and so can reduce sample size; we have not taken account of this in the above sample size calculation since the relevance of these findings to analysis of ordinal cognitive scales remains unclear. However, covariate adjustment will likely improve statistical power so that the final power will probably be greater than assumed here.
5. The number needed to treat is 6.1 (95%CI 3.7, 17.2) which is very potent for a prevention trial.
6. The power varies by the final achieved sample size (Table 2)

Table **Power**	**95%**	**90%**	**85%**	**80%**	**75%**	**70%**	**65%**
Total sample size ISMN vs no ISMN	1521	1229	1052	918	812	723	644

9.2 PROPOSED ANALYSES

All analyses and presentation of the results will be in accordance with CONSORT guidelines including on factorial trials.[66] All analyses will be intention to treat. A full statistical analysis plan will be developed and published prior to database lock including use of imputation or complete case analysis and sensitivity analyses. Numbers (%), median [interquartile range] or mean (SD) will be used as appropriate to summarise data, with 95% confidence intervals (CI). Main outcomes will be presented for the whole population and by sex. Participants who die will be included in the DSM-5 7 level ordinal cognitive and mRS scores, and for scores without a category for death will have a score worse than any living score assigned to maintain power and prevent missing any 'kill or cure' effect. Multiple testing adjustments will be used where relevant.

Analyses will use, as appropriate: binary logistic regression (BLR, presented as adjusted odds ratio, aOR), Cox proportional hazards regression (CPHR, adjusted hazard ratio, aHR), ordinal logistic regression (OLR, presented as aOR), or multiple linear regression (MLR, presented as adjusted mean difference, aMD). 95% confidence intervals (CI) will also be given.

Analyses will be adjusted for stratification (MoCA) and minimization variables (baseline age, sex, NIHSS, mRS, SBP, smoking status, time after stroke, years of education). Additional adjustments will be used where relevant and feasible, e.g. treatment duration, visible infarct y/n and SVD burden.

The Primary outcome is an ordinal adjusted analysis of the DSM-5 7-level cognitive score at 18 months.

Secondary outcomes will be analysed including all available data, using:
-*MLR*: 7-level ordinal mRS, 4-level DSM-5 cognitive score, cognitive tests individually (MoCA, TICS); Quality of Life (EQ-5D, Health Status Utility Value and VAS); mood (Zung); Stroke Impact Scale individual domains and overall score;
-*BLR*: dependency [mRS>2] vs no dependency; death; recurrent ischaemic or haemorrhagic stroke or TIA, or MI, individually; systemic haemorrhage; symptoms; SAEs, SARs, SUSARS – events that meet these definitions as per protocol and that are not already reported as formal outcomes;
-*CPHR*: death; and a Composite Outcome (recurrent stroke or TIA, MI, dependency [mRS>2], any cognitive impairment, death) using patients with complete data for all required variables, adjusted for baseline variables;
-and the *Wei-Lachin test* (unadjusted), reported as *Mann-Whitney difference (MWD)*: a Global Clinical Outcome (recurrent ordinal stroke, ordinal MI, ordinal 7-level cognition, ordinal mRS, quality of life (full Health Status Utility Score of the EQ-5D), the Zung depression score full scale, and the binary status of alive or dead) using all patients; and a Global SIS score.

Subgroup analyses: Prespecified subgroups include all minimisation variables (baseline age, sex, NIHSS, mRS, SBP, smoking status, time after stroke, and years of education), hypertension, diabetes, prior stroke/TIA, index infarct on imaging, WMH score, SVD score, duration of treatment, for 7-level ordinal cognition, ordinal mRS, recurrent stroke or TIA. We will assess cognitive and dependency outcomes, recurrent vascular events, safety, QoL and HE usage at 6 and 12 months, using repeated measures where relevant. Subgroup analyses will be adjusted for cilostazol in ISMN models and for ISMN in cilostazol models to assess interactions. Other exploratory subgroup analyses may be performed.

Sensitivity analyses: Imputation analysis of primary outcome. Baseline characteristics of participants with versus without long term outcome cognition data (DSM-5 7 level ordinal score, tMoCA, TICS) and/or long-term dependency (mRS) to assess for drop-out bias. Composite Outcome, including all patients with any data for the required analysis, regardless of whether missing.

Missing data: The primary outcome (DSM-5) incorporates data from multiple sources and so suffers from less loss of data than when using a single outcome scale; Death is a valid outcome in DSM-5 and is not missing data; The sample size includes an inflationary adjustment for up to 15% missing primary outcome data; Baseline data and adherence will be compared for those with versus those without missing DSM-5 data.

A full Statistical Analysis Plan will be prepared and published during LACI-3 prior to data softlock, as was done for LACI-2, and will describe analysis procedures and procedures for missing, unused or spurious data, and definitions of populations analysed.

10. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet for cilostazol and isosorbide mononitrate.

Participants will be instructed to contact their Investigator at any time after being randomised if any symptoms develop. All adverse events (AE) that occur after randomisation until death or completion of active trial follow-up (two weeks after the last dose of IMP is administrated) must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

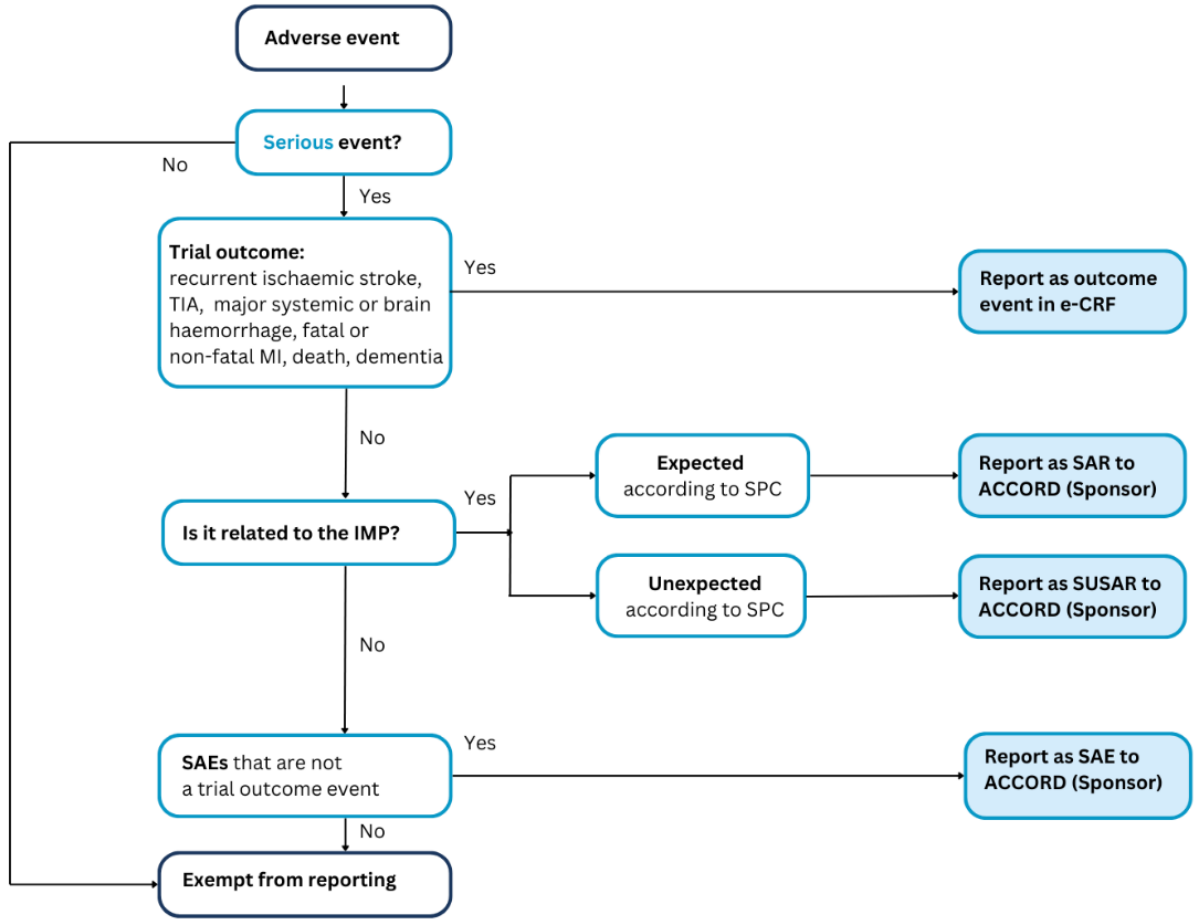
The main factor in assessing the safety of cilostazol and isosorbide mononitrate is the collection of the trial secondary outcomes:

- recurrent ischaemic stroke
- TIA
- major systemic or brain haemorrhage
- fatal or non-fatal MI
- death of any cause
- dementia.

These outcomes should be reported as trial outcomes in the e-CRF and are exempt from the safety reporting as SAEs. Any other adverse events that fulfil the seriousness criteria of the adverse event should be reported as SAE to the Sponsor.

Both cilostazol and isosorbide mononitrate have a known safety profile. The IMP symptoms that are not serious adverse reactions (AR), such as headache or loose stools, will be collected and reported on the e-CRF at each follow-up visit. The SARs and SUSARs will be reported to the Sponsor.

Figure 3: Trial reporting flowchart



10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

10.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

10.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

Adverse events that are not outcome events, SAEs, SARs, and SUSARs and align with the anticipated progression of the underlying disease should not be recorded or reported, including:

- Consequences of lacunar stroke
- Consequences of outcome events that happen during trial follow-up
- Consequences of pre-existing co-morbidities at the time of consent or during the trial follow-up.

10.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

10.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet. – section 4.8 of the document where the info can be found. The event may be classed as either:

- **Expected**: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet.
- **Unexpected**: the AR is not consistent with the toxicity in the SPC Booklet.

Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log.

10.6 REPORTING OF SAEs/SARs/SUSARs

*Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

The SAEs, which are defined as secondary outcomes (section 11), will be captured as endpoint data on e-CRF and not reported to the sponsor as SAEs.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

10.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the Co-Sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial) of SUSARS. Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility

of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

10.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

10.9 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 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).

The 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; the vasectomised partner must receive medical assessment of the 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, symptothermal, post-ovulation methods), 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 sexual 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; as a matter of safety, the Investigator 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. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

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

11. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager, follow-up coordinator, programmer, data manager, statistician, trial medic, administrative assistant and other investigators and trial staff as necessary

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

11.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

11.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

11.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the Co-Sponsors, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the Co-Sponsors direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the Co-Sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

11.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study

management audits and facility (including 3rd parties) audits as necessary (delete where not required).

12. GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

12.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Co-Sponsors.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

12.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

12.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

12.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.3.6 Data Protection Training

Research staff are responsible for completing mandatory data protection training in accordance with local policy.

12.3.7 Information Security Training

Research staff are responsible for completing mandatory information security training in accordance with local policy.

12.3.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Co-Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.3.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13. STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Co-Sponsors for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

13.2 PROTOCOL NON COMPLIANCE

13.2.1 Definitions

- **Deviation** - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.
- **Violation** - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

13.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Co-Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

13.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Co-Sponsors every 3 months. Each protocol violation will be reported to the Co-Sponsors within 3 days of becoming aware of the violation.Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

13.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

13.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Co-Sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Co-Sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

13.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Co-Sponsors.

13.6 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee and/or the Co-Sponsors have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and Co-Sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Co-Sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Research Study Report will be provided to the Co-Sponsors (QA@accord.scot) and REC within 1 year of the end of the study.

Within one year of the end of trial, the Investigator will publish summary results on the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to the public registry. The subject line of the email notification must state:'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX and/or IRAS ID XXXXXXX'. The Co-Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

13.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

It is not currently envisaged that the trial drug will be continued beyond the end of the trial follow-up.

13.8 INSURANCE AND INDEMNITY

The Co-Sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Co-Sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place

(which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Co-Sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

14. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the Co-Sponsors although the study team will be responsible for retaining data, publishing findings and submitting necessary reports derived from the data. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

14.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors, within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

14.3 DATA SHARING

Researchers may apply to use a de-identified version of the dataset for prospective individual patient data meta-analysis and a data dictionary after one year of the publication of the results. A LACI-3 data sharing committee will assess the written proposals and decide whether data use is appropriate. A data sharing agreement must be in place before any data sharing.

We plan a prospective individual patient data meta-analysis (IPDMA) of cilostazol trials (Cilostazol Trials Collaboration) to which the data from LACI-1, LACI-2 and LACI-3 (once completed) can contribute. An IPDMA of nitric oxide donor drugs like isosorbide mononitrate

is also planned, as well as an IPDMA of all three LACI trials and of other SVD trials testing other related agents.

After the trial is completed and the main results have been published, anonymised data from consented patients will be made available to researchers involved in LACI-3 and other researchers outside LACI-3 including outside the UK. The data may contribute to international data repositories and collaborations (e.g., VISTA, META-VCI, STROKCOG, Cilostazol trials collaboration, amongst others).

14.4 PEER REVIEW

The protocol outline was peer-reviewed by the co-applicants listed in the grant application and by the NIHR HTA when submitted for the funding programme. The trial design received Scientific Advice from the MHRA to facilitate license extension in the event that LACI-3 is positive and confirms the results of LACI-2. The TSC has reviewed the finalised protocol before the start of the trial.

The trial design was informed by a Stroke Research Network-funded NIHR Stroke Research Network Writing Workshop, held in Nottingham, 31 March 2014 and attended by 20 experts on small vessel disease, stroke, dementia and imaging. The workshop proposal underwent peer review prior to securing funding.

The LACI-1 and 2 trials each underwent peer review during their funding applications and subsequent presentation of results and publications. The LACI-3 trial underwent several cycles of peer review during its funding application, which also included many discussions with stroke and dementia trials experts and participant representatives.

A paper describing potential drugs to prevent SVD progression was peer reviewed and is now published in the International Journal of Stroke.[16]

The concepts described in this protocol have been presented at several Stroke and Dementia conferences and discussed. The LACI-2 trial provided proof of feasibility and a practical pragmatic approach to conducting trials in lacunar stroke and SVD and has informed LACI-3.

The Stroke Research Network Prevention Studies Group reviewed the proposal in 2014 and supported the work.

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