**Frequently-asked questions**

##### **Eligibility**

**Q: If participants presented with clinical lacunar syndrome but had no visible relevant lacunar infarct on brain scan, are they still eligible for LACI-3 trial?**
**A:** Yes, they are eligible if clinical symptoms fulfil the criteria AND no alternative causes on scan, i.e. no cortical infarct, tumour, or other structural finding.

**Q: If participants had lacunar stroke clinically and the visible small infarct is in posterior fossa (eg., pons, cerebellum) or cerebral white matter but close to cortex, are they eligible?**
**A:** Yes, they are eligible: a relevant (to time and symptoms) small subcortical infarct is eligible in these locations if there is no cortical involvement.

**Q: Are patients with atrial fibrillation eligible?**
**A:** Yes. Around 5–10% of patients with lacunar stroke also have atrial fibrillation. If they are taking anticoagulation, they can only be randomised to the Isosorbide Mononitrate (ISMN) or no-ISMN groups.

**Q: Can we recruit participants who were previously on other trials?**
**A:** Yes. Participants may be included if they have fully completed their previous trial and meet all eligibility criteria for the LACI-3 trial. If there are any uncertainties, please contact the LACI-3 central team (laci-3@ed.ac.uk).

**Q: Can we recruit participants who are still in another trial or study?**
**A:** This needs to be considered on a case-by-case basis. If you encounter such participants, please contact the LACI-3 central team (laci-3@ed.ac.uk) and liaise with the investigators of the other trial or study before proceeding.

**Q: How long after a previous stroke can a patient still be recruited into the trial?**
**A:** There is no strict time limit. However, the further back the stroke occurred, the greater the chance the patient may have had another event since. In practice, recruiting patients up to about 2–3 years after their stroke is usually reasonable.

**Q: If a patient struggles with side effects and is randomised to both drugs, can they choose to continue with only one of the drugs?**
**A:** Yes. In LACI-3, we first allow dose reduction to below the target dose. If participants cannot tolerate even the lowest dose, they may discontinue that drug while continuing with the other one.

**Q: Would a patient with a lacunar infarct but previous deep hypertensive intracranial haemorrhage (ICH) still be eligible to be enrolled into the study?**
**A:** Patients with any history of ICH (parenchymal, subarachnoid, or extradural) or other bleeding tendency are excluded from cilostazol randomisation. However, if the prior ICH is remote, the patient has made a good recovery, is not disabled, and fulfils all other eligibility criteria, they may still be randomised to ISMN vs no ISMN (see Protocol v3, p.26).

N.B.: Prior ICH refers to an old lesion unrelated to the current lacunar stroke symptoms. Recent ICH as the cause of the current presentation is excluded, since LACI-3 is focused on clinically evident lacunar ischaemic stroke.

##### **Imaging**

**Q: Do scans need to be performed specifically for the study or are routine scans used?**
**A:** No, we only collect scans that were performed as part of routine clinical care. For example, the initial diagnostic scan or any subsequent scans if the participant develops new potential stroke symptoms. We do NOT require additional scans solely for the study.

**Q: Do you need scan images sent to you or is the report sufficient?**
**A:** Yes, we do require the scan images themselves (not just the reports). These should be uploaded via our secure web-based system by a delegated team member who has completed the e-training and has access to the eCRF. Further details and instructions will be provided once your site is activated.

##### **Consent**

**Q: Is there any time limit between consent and randomisation? E.g., can we consent in hyperacute stroke unit before discharge and randomise later in clinic?**
**A:** Yes, formal written consent can be obtained prior to randomisation, or on the same day. Potential participants should be given adequate time to consider participation before giving formal consent and being randomised.

##### **Baseline Assessments**

**Q: Does patient need both MoCA and MMSE before commencing the trial drug?**
**A:** The MoCA is required before randomisation as it is part of the randomisation algorithm. After randomisation, the “spelling WORLD backward” task from the MMSE is collected at baseline.

##### **Follow-up**

**Q: For follow-ups, how should blood pressure be measured? Can participants take a reading at home if they have a machine, or do they need to attend in person?**
**A:** Blood pressure measurements are collected only if available - either from a reading the participant takes at home (if they have their own machine) or from a recent recording in their clinical notes.

##### **IMP**

**Q: Would you titrate the IMP dose based on BP recording?**
**A:** No. Dose escalation for the two LACI-3 drugs follows a standard schedule designed to minimise side effects and is not adjusted according to blood pressure. Blood pressure is recorded only when available, as a tertiary outcome measure. In cases of intolerance, the escalation schedule can be modified, but not in response to BP readings.

**Q: How is IMP re-supply organised? Is there funding for that?**
**A:** IMP re-supply is organised via courier at 6 and 12 months. The central trial team can provide pre-paid labels to courier via Royal Mail, or we can be invoiced for the cost of using your locally approved courier (funding covers up to £9 per package). Logistics for couriering will be discussed and agreed at your site initiation visit. The need to courier IMP outside the 6 and 12 month time points can be discussed with the central team on a case by case basis.