Participant Information Sheet

Assessment of efficacy and safety of cilostazol and isosorbide mononitrate to prevent adverse outcomes in patients with cerebral small vessel disease (lacunar) ischaemic stroke.

Local research team's NHS institution logo goes here

You are invited to take part in the LACI-3 study.

According to our records, you may be eligible for our study because:

- You have had a **lacunar stroke** in your brain.

- To help you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully.
- Talk to others about the study if you wish.
- Contact us if there is anything that is not clear.
- Let us know if you would like more information.
- Take time to decide whether or not you wish to take part.

If you are interested:

Please read this information sheet.

Do ask any questions you may have.

What is the purpose of the study?

Having a lacunar stroke increases your risk of another stroke, dementia and loss of independence.

- A quarter - 25% - of strokes, called lacunar strokes, are caused by disease of the smallest blood vessels in the brain.
- The lacunar strokes are caused when small blood vessels deep within the brain become damaged and do not supply oxygen and nutrients well.
- When there is an interruption in blood supply to part of the brain, the lacunar stroke happens. It affects about 35000 people per year in the UK.
- This 'small vessel disease' can also cause problems with thinking, balance and walking and can sometimes lead to dementia.
- There are no treatments yet to help the small blood vessels work better. As a result, damage to the brain may continue to build up.

We have found two drugs that may reduce damage to the small blood vessels in the brain and therefore could prevent strokes and thinking problems due to small vessel disease.

- The aim of this research is to test two possible new treatments for lacunar stroke in a clinical study called the 'Lacunar Intervention Trial 3' (LACI-3).

- The two drugs are widely used to treat other diseases but have not been used to treat small vessel disease before.

One drug, called **Cilostazol**, is most commonly used in the UK to treat problems with the blood supply to the legs, but is used to prevent more strokes from happening in many other countries.

The other drug, called **Isosorbide Mononitrate**, is commonly used all over the world including in the UK to treat angina (pains in the chest due to poor blood supply to the heart).

We want to test if these drugs can:

- help prevent the small vessel disease from causing another stroke or affecting the thinking skills
- if they can be used safely in patients with a lacunar stroke
- and if they can be taken over several years.

- LACI-2, the study before LACI-3, included about 363 participants and showed that both **Cilostazol** and **Isosorbide Mononitrate** were safe and well tolerated in patients.
- LACI-2's results are promising. But a bigger research study is needed to confirm if those drugs are better than standard care alone, and safe, for a wide range of lacunar stroke survivors.
- LACI-3 is a much larger study, with about 1,300 participants. Having more participants means that we can better understand the potential benefits of each drug and improve future patient care.

Why have I been invited to take part?

You have been asked to take part in the LACI-3 study as you have been diagnosed with a lacunar stroke either recently or at some time in the past.

Do I have to take part?

- No, it is up to you to decide whether or not to take part.
- If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.
- If you decide to take part you are still free to withdraw at any time and without giving a reason.
- Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive, or your legal rights.

What will happen if I take part?

Information and consent

You will be given **as much time as you need** to read the information and consider whether you would like to take part.

If you are interested in taking part in the study, you will be invited to talk to a study doctor or nurse and ask any questions.

If you decide to take part, a member of the research team from your local hospital will ask you to sign a consent form.

Collection of information about you, your diagnosis and your close contacts

A doctor or nurse in the research team will ask you some simple questions about your health and collect some information from your medical records about your previous and current health.

They will record information about your current drugs and allergies to check if you can take the study drugs.

The doctor will review your brain scans that were done as part of your normal stroke care.

The doctor will review your recent blood test results to determine if further lab testing is needed.

Your blood pressure will be checked to make sure that it is well controlled.

You will have a short test of your thinking skills and memory to find out about the effect your stroke has had on you.

They will record your contact details for future follow-up visits to monitor your progress and the contact details of a close personal contact you identify who has agreed to provide information about how you get on when you cannot be reached for safety if new information is available, or the study is stopped.

Everyone registered with a GP has their own unique number. This is known as a CHI number in Scotland and an NHS number in the rest of the UK. We will collect your CHI/NHS number and your GP contact details because it helps us to identify you correctly.

Random allocation to treatment

After your medical information is collected and a doctor confirms that you are eligible to take part in LACI-3, a computer will make a random choice as to which study drug(s) you will take or not.

- You will be randomly assigned to one of the four groups:

You may be given **cilostazol** only.

You may be given **isosorbide mononitrate** only.

Both **cilostazol** and **isosorbide mononitrate** will be given.

No study drugs will be given.

- You and your doctors, including GP, will know which group you go into.
- If there is any medical reason why you cannot take one of the study drugs, then you can still join the study with the other drug.

- You will receive a 3 or 6-monthly supply of the study drug if allocated to this treatment group, to take home and to begin taking the following day with the instructions about when to take the tablets and how many.
- You will start on a low dose of the tablets and increase it as advised by your hospital team over the first 2-4 weeks until you reach the comfortable dose.
- You will continue taking your usual medicines unless told otherwise.

You will receive the standard best medical care in whichever group you are in, including guideline stroke prevention like: antiplatelet, antihypertensive and lipid-lowering drugs and lifestyle advice.

Checking how you get on in the future

We need to check how you get on so that we can work out whether or not LACI-3 drugs are better for people like you compared with standard best care alone. You will not need to come back to hospital for us to do this. You will be taking part in LACI-3 for about **18 months**. Within one month after randomisation, a study nurse or doctor will call you **2 times**:

1 Telephone call (around 7-14 days)

- After randomisation, the local research team will ask about your health, recent blood pressure records (if you own a BP monitor), and any side effects of drugs and advise about increasing the dose of study drug (if relevant).

2 Telephone call (around 21-30 days)

- The local research team will call you again to ask about your health, recent blood pressure records (if available) and any side effects of the drugs and advise about increasing the dose of study drug (if relevant).

- By the end of the first 30 days, most people will be taking the full dose, or the dose that they are most comfortable with if not the full dose, and will stay on this dose for the rest of the study.
- The study allows for some people to take a bit longer to get used to the drugs, and to stay on less than the full dose, if that suits them better but you need to tell the study staff what dose you are taking when they ask.

Follow-up visits

All participants will have **3 follow-up** visits at **6, 12** and **18 months**.

You will be followed-up by **two teams**:

Your local hospital team.

The central research teams from Edinburgh or Nottingham.

The follow-up visits will be done by:

phone

post

online which will be optional

We will ask you about your preferred ways to contact you during the follow-up period to check what is more convenient for all participants.

The local hospital team **will know** if you take study drugs or not and will:

Check new symptoms or problems that you have noticed.

Ask about the study tablets that you have been taking (dose and how many if relevant) and your other usual drugs

Send a new 3 or 6-monthly supply of the study drugs by post, if allocated to.

The central team **will not know** if you take study drugs or not and will ask about

New health problems like stroke, heart attack.

Mobility

Quality of life

Memory and thinking

This can be done by post, phone or online.

The questionnaires will take around **20 minutes** to complete.

Adherence to treatment

It is important that you take the treatment allocated to you regularly and as directed **during the 18 months** until your involvement in LACI-3 ends.

You should stick to the study's decision about whether to take an allocated drug until your participation in the study ends to make the study's results reliable.

Contact your local hospital team if you develop any side effect or would like to discuss any symptoms you experience.

- Your doctor may ask you to stop study allocated drug gradually or immediately if you develop a new health problem or you experience a side effect.
- If you lose the capacity to make decisions for yourself during the study, you will continue to take part in LACI-3 to the end of the study unless withdrawn by your doctor or relative.
- If you were allocated to the study drug, at the last visit, you will receive the instructions to reduce the dose of the study drug over a week and then stop. The study drug will no longer be provided to you. You will be asked to return the leftover tablets back to your local or hospital pharmacy.

Summary of commitment

Your participation in the LACI-3 will involve **1** or **2 visits** to the hospital and post, telephone calls or online for up to **18 months**.

The consent and randomisation visit can take place on the same day at your local hospital and will take approximately **2 hours**.

If consent and randomisation take place on the same day, you will visit hospital only once.

The rest of the follow-up visits will be done by phone, post or online. Each telephone call should last no longer than **20 minutes**.
The study team may call you more often if needed.
You will be able to phone the study team to ask any questions.

We can help with the cost of travelling to your appointments, please talk to a member of the study team about this.

Pregnancy

If you are a woman of childbearing potential and not breast feeding, you must have a negative pregnancy test before taking part in this study.

If you start study drugs:

- You have to use two highly effective methods of contraception from the time of screening until 34 days after discontinuing the study drug.
- Male participants must avoid unprotected sex with all sexual partners (by using condoms) until 3 months after the last dose of the study drug.
- If you or your partner become pregnant during the study you must notify the study team right away, and we will collect information about pregnancies.

Other drug studies

If you enrol in LACI-3, you may not be able to enrol in randomised controlled studies of other drugs unless both studies agree that you may take part in them at the same time.

Is there anything I need to do or avoid?

There are some drugs which are not allowed in LACI-3. The doctor will ask you about your current drugs before you can go into the study. Your doctor will consider whether any of your current drugs need to be changed if LACI-3 assigns you to the group taking study drugs. If not, you can continue to take your usual drugs.

- If you have lactose intolerance, then you will not be able to take one of the study drugs.

- You cannot take drugs for impotence, such as Viagra (or tadalafil, sildenafil, vardenafil), while taking some of the study drugs.
- Drugs containing nitrates, e.g., which are used for treating angina or chest pain and are available on prescription only, may interfere with some of the study drugs.

What are the possible benefits of taking part?

There are no direct benefits to you from taking part in this study. The results from this study will help us to treat others in the future.

What are the possible disadvantages of taking part?

Disadvantages of study drugs

There is a chance that you may experience side effects from the study drugs.

- Both drugs have been used for many years to treat other conditions, so the side effects are well known.

The most common side effects include:
headache, loose bowel motions, changes to your heart rate or blood pressure, dizziness, nausea/vomiting, runny nose, sore throat, fever, changes to the skin (e.g., rash/itch /bruising), chest pains, swelling and loss of appetite.

- If any of these occur, they are usually noticed when first starting the tablets and usually settle after a few days. You will start on a low dose of the tablets to help minimise these symptoms.

- You will be asked about side effects at each phone call, and you can reduce, or if necessary, stop, the tablets at any time you wish. If you develop any side effects that you are worried about, please contact the research team using the details at the end of this information sheet.
- If your symptoms are urgent, then you should contact your GP or go straight to hospital.

Disadvantages of the study

You may find the time you spend completing study visits inconvenient.

What if there are any problems?

If you have a concern about any aspect of this study, please refer to the contact details at the end of this document to identify the most appropriate person to answer your question.

- In the unlikely event that something goes wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the NHS organisations at the end of this document but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What will happen if I don't want to carry on with the study?

Your decision to take part in LACI-3 is entirely voluntary.

You are free to withdraw at any time and without giving a reason.

- The study doctor may withdraw you from the study early and will discuss the reasons e.g., when you develop a new health problem.
- Your representative may withdraw you from the study early when you develop a new health problem and cannot make decisions for yourself.

Any decision to withdraw will not affect your standard medical care.

- We would like to keep you in the study if you are allocated to starting a study drug but you stop taking it. You will be asked to return all leftover tablets to the hospital or pharmacy where you obtained them.
- We would like to keep you in the study if you do not want to engage in the six-monthly telephone calls and we can collect information about your health from central NHS records or GP.
- We would like to continue to follow you to the end of the study if you stop taking your study tablets, or stop the follow-up visits, and keep collecting data from your health records to help answer our research question.

If you decide to withdraw from all aspects of the study, please contact your hospital team. We will retain data collected about you before you withdrew.

What happens when the study is finished?

Anonymised information about you will be kept indefinitely so that researchers can look at them again.

This will enable us to study the effects of **cilostazol** and **isosorbide mononitrate** in the long-term. It will also enable us to address other relevant research questions that we might not have thought of now without having to repeat this research all over again.

Your local hospital will archive study information about you for 5 years.

Will my taking part be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

How will we use information about you?

We will need to use information from you and your medical records for this research project.

We will collect your Community Health Index (CHI) number or NHS number. Note that the CHI is a population register, used in Scotland for health care purposes. The CHI number uniquely identifies a person on the index and is personal identifiable information. Your CHI number or NHS number is being collected to allow us to identify you in your medical records and with your GP. Other personal identifiable information collected will include your:

- Name and initials
- Date of birth
- Sex assigned at birth
- Ethnicity
- Years of education and occupation
- Address, telephone number and email

- GP contact information
- Contact information for a nominated close personal contact whose permission you have obtained - they will not leave your NHS organisation.

Only authorised people will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. **Your data will have a code number assigned instead.**

LACI-3 is run by a team at the University of Edinburgh and the University of Nottingham who will keep all information about you safe and secure.

- Your personal information will be stored securely in a database hosted by the University of Nottingham for the duration of the study to contact you for follow-up visits. The database will be compliant with the relevant regulations and Sponsor Standard Operating Procedures.
- Only trained and approved members of the study team will be given password-protected access to the study database.

Identifiable data about you will be kept separate from your health information and removed before data are analysed.

We comply with the GDPR and Data Protection Act 2018 and Caldicott principles when sharing or processing their data within the NHS and other organisations involved in the study. The University of Edinburgh/NHS Lothian is the data controller. Hospitals involved in LACI-3 may be required to provide information for official inspections of research conduct made by the sponsor of the study or other regulatory bodies.

Data sharing

De-identified information about you will be kept indefinitely so that researchers can look at them again. Where data are being shared with a third party, there will be an appropriate data sharing agreement between organisations to ensure your information is safe.

- Once we have finished the study, we will keep some of the data so we can check the results.
- Researchers who analyse the data will not be able to identify you and find out your personal information.
- We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records/ your hospital/ your GP. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will also have the option to allow the research team (within the sponsoring organisation) to securely store your contact details and agree to be contacted about other ethically approved

research studies. You will only be contacted by a member of this research team to determine if you are interested in taking part in another research study. Your verbal consent may then be sought to pass your contact details to another research team within the University of Edinburgh and/or NHS Lothian. Agreeing to be contacted does not oblige you to participate in further studies. You can withdraw from being contacted for the future research.

Where can you find out more about how your information is used?

You can find out more about how we use their information:

- at www.hra.nhs.uk/information-about-patients
- in a leaflet available at www.hra.nhs.uk/patientdataandresearch
- by asking one of the study team (see the last page of this sheet)
- by sending an email to dpo@ed.ac.uk (University of Edinburgh Data Protection Officer)

What will happen to the results of the study?

The results of the study will be submitted for publication in professional journals.

We will also make the results available in a format appropriate to the general public on our www.laci-3.ed.ac.uk website.

The results of LACI-3 study will be publicly accessible on the research registry:

- ISRCTN number: 44436843

We would be very happy to send you a newsletter twice yearly about the progress and results of the research by post or email, if you wish. When the results of our study are published, we will not include any individual information that identify you. If LACI-3 results show that taking study drugs is beneficial for patients after lacunar stroke, it may change the standard practice and you may re-start again or start taking those drugs.

Who is organising and funding the research?

accord Academic and Clinical Central Office for Research and Development NHS Lothian

NIHR | National Institute for Health Research

THE UNIVERSITY of EDINBURGH

The University of Nottingham

The University of Edinburgh and NHS Lothian jointly sponsor the LACI-3 study and take on overall responsibility for this research study.

- The National Institute for Health and Care Research funds the conduct of LACI-3 by a grant to the University of Edinburgh.
- The LACI-3 is run by the University of Edinburgh and the University of Nottingham.
- Professor Joanna Wardlaw is the Chief Investigator in charge of the LACI-3.
- Professor Philip Bath is the Co-Chief Investigator of the LACI-3.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee.

Research Ethics Committee protects the interests of the participants.

This study has been reviewed and given a favourable opinion by the Scotland B Research Ethics Committee. All participants are covered by The University of Edinburgh's insurance policy, which needs to be in place before the study starts.

In designing this study, we have taken into account patients' opinions on what's involved in the study. The Patient and Public Involvement (PPI) panel, and other patients/carers with lived experience of stroke, cerebral small vessel disease and vascular dementia, have reviewed and commented upon this participant information sheet.

Who to contact for more information?

You can contact your **local research team** about your participation:

Insert name

Insert job title

Insert address, address, address, address, address, address, address, address, address, address, address, address, address address, address, address, address, address, address, address

Telephone: insert

You can contact **central research team** if you have any question:

Dr Fergus Doubal

Reader and Consultant Stroke Physician and Geriatrician

Telephone: 0778979220007814 296434 **Helpline:** 0131 465 9592

Please refer to our website: www.laci-3-ed.ac.uk

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You can obtain **independent advice** about this study by contacting:

Professor Susan Shenkin

Professor of Healthcare for Older People, Ageing and Health

Telephone: 0131 242 6481

The contact for complaints in your NHS region is:

Enter text

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The contact for formal complaints is: NHS Lothian Patient Experience Team, Waverley Gate, 2-4 Waterloo Place, Edinburgh. EH1 3EG.

Telephone: 0131 536 3370; Email: feedback@nhslothian.scot.nhs.uk