

# A study of the anti-inflammatory medication colchicine for people with blocked arteries of the legs

<b>Submission date</b> 09/07/2024	<b>Recruitment status</b> Recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 07/08/2024	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 01/05/2025	<b>Condition category</b> Circulatory System	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Atherosclerosis is a disease that causes narrowing of the arteries including those in the heart, brain and legs. It is caused by chronic inflammation and may lead to heart attack, stroke and removal of the leg (amputation). Atherosclerosis in the legs is called peripheral arterial disease (PAD). The main treatment for people with PAD is to try to reduce further damage to the arteries throughout the body, thereby preventing artery complications such as stroke, heart attack and amputation. These treatments include living a healthier lifestyle, statin medication, aspirin and blood pressure medication. Unfortunately, despite these treatments, people with PAD still have a high risk of developing further artery complications. Because people with atherosclerosis have chronic inflammation of the arteries, researchers think that a commonly used medication called colchicine that reduces inflammation (an anti-inflammatory) may prevent further artery damage and artery complications. Research conducted on individuals with atherosclerosis in the heart's arteries has shown that colchicine can lower the incidence of artery-related complications by approximately 20%. This is a large study to find out whether colchicine can be taken by people with PAD and whether it will prevent further artery damage and complications. If colchicine was shown to be effective in preventing artery complications, it could be a really important treatment to offer people with PAD. The study is part of an international project being led by a team of researchers at Hamilton Health Sciences and McMaster University in Canada. The study will be conducted in other countries including Canada, Australia and the Netherlands. The project as a whole aims to enrol 6,150 adults with PAD. Around 1,500 of these participants will be from the UK. Half of the participants will receive tablets containing the study medication colchicine and half will receive tablets containing a placebo (inactive medicine).

### Who can participate?

Patients aged 18 years old and over with symptomatic atherosclerotic lower extremity PAD

### What does the study involve?

Patients referred to vascular department clinics or hospitalised with PAD will be eligible for the study. Participants who consent will be given colchicine for 2-3 weeks to make sure they can

tolerate it and don't experience unwelcome side effects. Participants who tolerate colchicine will then be randomly assigned to colchicine or a dummy pill (placebo). People in the study will not know which type of pill they are taking. Participants will take the tablets daily and have follow-up visits or phone calls with the clinical team, every 6 months for up to 4 years. Information about hospital admissions, blood tests and PAD symptoms will be collected at the follow-up visits. Participants will be asked to complete quality-of-life questionnaires annually. Where blood test results are unavailable for full blood count these may be requested annually.

What are the possible benefits and risks of participating?

Colchicine is a well-tested drug with a long and safe history. It has been extensively used at a larger dose for the treatment of gout. Its safety has been well described in these patients, with the most common side effect being tummy upset (diarrhoea, nausea, vomiting). Colchicine at a lower dose than is being used in this study, has been studied in trials of more than 10,000 people with heart disease. At this dose, there was no difference in the rates of tummy upset in those receiving colchicine compared with those taking a dummy medication (placebo). The study protocol includes a 2-3 week run-in phase during which patients will receive colchicine to ensure that they can tolerate it. Patients will be given a prescription for 20 tablets for the run-in phase. Patients who take a minimum of 11 tablets, who are happy to continue with the trial and whose study doctor assesses them as tolerating colchicine will be randomised. People who have PAD frequently come to the hospital for a variety of assessments and procedures. The number of follow-up visits in the trial has been kept to a minimum; enough to ensure safety without placing excess burden on the participants. Some of the follow-up may be delivered in the form of questionnaires or phone calls that can be completed at home without the need for travelling.

Where is the study run from?

The University of Bristol, UK  
Hamilton Health Sciences, Canada

When is the study starting and how long is it expected to run for?

May 2021 to October 2028

Who is funding the study?

In the UK, the study is funded by the British Heart Foundation

Who is the main contact?

In the UK, the main contact is Miss Lucy Ellis, [leaderpad-trial@bristol.ac.uk](mailto:leaderpad-trial@bristol.ac.uk)

## Contact information

### Type(s)

Scientific, Principal Investigator

### Contact name

Prof Robert Hinchliffe

### Contact details

Department of Vascular Surgery, 2nd Floor, Learning and Research Building, Southmead Hospital  
Bristol  
United Kingdom

BS10 5NB  
None provided  
robert.hinchliffe@bristol.ac.uk

### **Type(s)**

Public

### **Contact name**

Miss Lucy Ellis

### **Contact details**

Bristol Trials Centre, 1-5 Whiteladies Road  
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United Kingdom  
BS8 1NU  
None provided  
leaderpad-trial@bristol.ac.uk

## **Additional identifiers**

### **EudraCT/CTIS number**

Nil known

### **IRAS number**

1009217

### **ClinicalTrials.gov number**

NCT04774159

### **Secondary identifying numbers**

2023-2851, IRAS 1009217, CPMS 61099

## **Study information**

### **Scientific Title**

Low dose colchicine in patients with peripheral artery disease to address residual vascular risk: a randomized trial (LEADER-PAD)

### **Acronym**

LEADER-PAD

### **Study objectives**

The overall objective is to examine the efficacy and safety of colchicine 0.5 mg daily in reducing the incidence of cardiovascular death, myocardial infarction, stroke or severe limb ischemia requiring an intervention including major vascular amputation in patients with peripheral artery disease.

In addition to the primary objective, outcome data will be collected and analysed:

- To examine the effects of colchicine 0.5 mg/daily on quality of life in PAD patients (assessed via patient questionnaires).
- To examine side effects of colchicine 0.5 mg/daily in PAD patients.

## **Ethics approval required**

Ethics approval required

## **Ethics approval(s)**

1. Approved 07/05/2021, Hamilton Integrated Research Ethics Board (237 Barton Street East, Hamilton ON, L8L 2X2, Canada; -, fspence@mcmaster.ca), ref: CTO Project ID: 3520

2. Approved 25/09/2024, North West - Greater Manchester South Research Ethics Committee (3 Piccadilly Place, Manchester, M1 3BN, United Kingdom; +44 (0)207 104 8014, 207 104 8065, 208 104 8051; gmsouth.rec@hra.nhs.uk), ref: 24/NW/0235

## **Study design**

Randomized placebo-controlled double-blind parallel-group study

## **Primary study design**

Interventional

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Home, Hospital, Medical and other records, Telephone

## **Study type(s)**

Safety, Efficacy

## **Participant information sheet**

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

Peripheral artery disease

## **Interventions**

Eligible participants who consent to take part in the study will undergo a 2-3 week test period when they will take colchicine 0.5 mg daily. Participants who tolerate colchicine (are not sensitive to medication side effects) and have taken at least 11 tablets will then be randomised to either colchicine or a placebo tablet in a 1:1 ratio. Randomisation will be carried out using an online system.

Group 1: Colchicine 0.5 mg daily

Participants will take a colchicine tablet by mouth daily for the duration of study participation. Study medication will be dispensed every year.

Group 2: Placebo

Participants will take a placebo tablet by mouth daily for the duration of the study participation. Study medication will be dispensed every year.

Colchicine drug and placebo are of the same appearance and are indistinguishable. All investigators, study personnel and participants will be blinded to drug treatment assignment.

Participants in each group will be followed up every 6 months for evaluation of clinical outcomes, including major cardiovascular and limb adverse events or hospitalisation for vascular complications or revascularisation. Participants will be asked to complete quality-of-life questionnaires annually. In the first year, participants will be contacted at months 3 and 9 to discuss any challenges in taking study drugs, and as needed, they will be re-contacted to address adherence issues.

### **Intervention Type**

Drug

### **Pharmaceutical study type(s)**

Prophylaxis, Therapy

### **Phase**

Phase III

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

Colchicine

### **Primary outcome measure**

The rate of major adverse cardiovascular and limb events (MACE or MALE). This composite outcome consists of cardiovascular deaths, myocardial infarction, stroke, and severe limb ischemia that requires a vascular intervention (i.e., pharmacological reperfusion, endovascular or surgical revascularisation) or a major vascular amputation (defined as ankle/transtibial amputation or higher). Details of these events will be collected at 6 monthly follow-up visits for the duration of participation via participant reports and using information in participant medical records. The trial is event-driven with the final analysis planned once 731 primary events have occurred.

### **Secondary outcome measures**

Major adverse cardiovascular events, major adverse limb events (MALE), extended MALE, cardiovascular deaths, myocardial infarction, stroke, hospitalisation, acute or chronic limb-threatening ischemia, all revascularisation (defined as coronary or cerebrovascular or lower limb or other peripheral revascularisation), total vascular amputation, overall mortality, all thrombosis or thromboembolism (arterial and venous), Fontaine Stage. Details of these events will be collected at 6 monthly follow-up visits using for the duration of participation via participant reports and using information in participant medical records.

EQ-5D-5L, VascuQOL-6 and Standard Assessment of Global Everyday Activities (SAGEA) will be completed by participants at randomisation, and every 12 months for the duration of participation.

### **Overall study start date**

06/05/2021

### **Completion date**

31/10/2028

# Eligibility

## Key inclusion criteria

Patients need to meet the following criteria for inclusion:

1. Age > 18 years old
2. Symptomatic atherosclerotic LE PAD fulfilling at least one of the following:
  - 2.1. Intermittent claudication with ankle/arm blood pressure ratio\* ( $ABI \leq 0.90$ ) or artery stenosis  $\geq 50\%$  plus one of
    - 2.1.1. >1 vascular bed affected by atherosclerosis.
    - 2.1.2. Diabetes
    - 2.1.3. Heart failure
    - 2.1.4. Chronic kidney disease ( $eGFR < 60 \text{ mL/min/1.73 m}^2$ )
  - 2.2. Rest pain (mostly in the foot) OR necrosis of limb OR gangrene of limb (corresponding to either Fontaine stages 3 or 4 OR Rutherford Classification categories 4 to 6). All must have an ankle/arm blood pressure ratio\* ( $ABI \leq 0.90$ ) OR artery stenosis  $\geq 50\%$ .  
\*In cases of incompressible ankle arteries, the presence of toe pressure  $\leq 60 \text{ mm Hg}$  or toe-brachial index  $\leq 0.70$  is acceptable
  - 2.3. Revascularization, defined as limb bypass surgery or endovascular revascularization procedures (irrespective of the specific device used), including percutaneous transluminal angioplasty/stent of iliac or infra-inguinal arteries or extra-anatomical bypass surgery.
  - 2.4. Leg or foot amputation for arterial vascular indications
3. Written or verbal informed consent from the patient

## Participant type(s)

Patient

## Age group

Adult

## Lower age limit

18 Years

## Sex

Both

## Target number of participants

6150

## Key exclusion criteria

1. Contraindication to colchicine
2. Long-term requirement for colchicine for another clinical indication
3. Active diarrhoea
4.  $eGFR < 30 \text{ mL/min/1.73 m}^2$  (based on the local method for estimating eGFR)
5. Cirrhosis or severe chronic liver disease
6. Woman who is pregnant, breast-feeding or of child-bearing potential not protected by reliable contraception or is planning conception during the study
7. Current or planned long-term use of cyclosporine, verapamil, HIV protease inhibitors, azole antifungals, or macrolide antibiotics (except azithromycin)
8. Patients who are deemed unlikely to return for follow-up
9. Patients with life expectancy < 1 year

**Date of first enrolment**

07/05/2021

**Date of final enrolment**

01/08/2027

## **Locations**

**Countries of recruitment**

Argentina

Australia

Brazil

Canada

Ecuador

England

Italy

Mexico

Netherlands

Switzerland

Türkiye

United Kingdom

**Study participating centre****Addenbrookes Hospital**

Hills Road

Cambridge

United Kingdom

CB2 0QQ

**Study participating centre****Royal Infirmary of Edinburgh at Little France**

51 Little France Crescent

Old Dalkeith Road

Edinburgh

Lothian  
United Kingdom  
EH16 4SA

**Study participating centre**  
**Musgrove Park Hospital (taunton)**  
Musgrove Park Hospital  
Taunton  
United Kingdom  
TA1 5DA

**Study participating centre**  
**Glenfield Hospital**  
Groby Road  
Leicester  
United Kingdom  
LE3 9QP

**Study participating centre**  
**Leeds General Infirmary**  
Great George Street  
Leeds  
United Kingdom  
LS1 3EX

**Study participating centre**  
**Bradford Royal Infirmary**  
Duckworth Lane  
Bradford  
United Kingdom  
BD9 6RJ

**Study participating centre**  
**John Radcliffe Hospital**  
Headley Way  
Headington  
Oxford  
United Kingdom  
OX3 9DU



**Study participating centre**  
**Southampton General Hospital**  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

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

**Study participating centre**  
**Northern General Hospital**  
Northern General Hospital NHS Trust  
C Floor, Huntsmnan Building  
Herries Road  
Sheffield  
United Kingdom  
S5 7AU

**Study participating centre**  
**Royal Sussex County Hospital**  
Eastern Road  
Brighton  
United Kingdom  
BN2 5BE

**Study participating centre**  
**St Georges Hospital**  
Blackshaw Road  
London  
United Kingdom  
SW17 0QT

**Study participating centre**

**Freeman Hospital**  
Freeman Road  
High Heaton  
Newcastle upon Tyne  
United Kingdom  
NE7 7DN

**Study participating centre**  
**Norfolk and Norwich University Hospital**  
Colney Lane  
Colney  
Norwich  
United Kingdom  
NR4 7UY

**Study participating centre**  
**Kent and Canterbury Hospital**  
Ethelbert Road  
Canterbury  
United Kingdom  
CT1 3NG

**Study participating centre**  
**Manchester Royal Infirmary**  
Cobbett House  
Oxford Road  
Manchester  
United Kingdom  
M13 9WL

**Study participating centre**  
**Royal Gwent Hospital**  
Cardiff Road  
Newport  
United Kingdom  
NP20 2UB

**Study participating centre**  
**St Thomas' Hospital**  
Westminster Bridge Road  
London

United Kingdom  
SE1 7EH

**Study participating centre**

**Derriford Hospital**

Derriford Road  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre**

**University Hospital (coventry)**

Clifford Bridge Road  
Coventry  
United Kingdom  
CV2 2DX

**Study participating centre**

**Hull Royal Infirmary**

Anlaby Road  
Hull  
United Kingdom  
HU3 2JZ

**Study participating centre**

**Pinderfields Hospital**

Aberford Road  
Wakefield  
United Kingdom  
WF1 4DG

**Study participating centre**

**Gloucestershire Royal Hospital**

Great Western Road  
Gloucester  
United Kingdom  
GL1 3NN

**Study participating centre**

**York Hospital**  
Wigginton Road  
York  
United Kingdom  
YO31 8HE

## Sponsor information

### Organisation

University of Bristol

### Sponsor details

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### Sponsor type

University/education

### Website

<https://bristol.ac.uk/>

### ROR

<https://ror.org/0524sp257>

### Organisation

Hamilton Health Sciences

### Sponsor details

Population Health Research Institute, David Braley Cardiac, Vascular and Stroke Research  
Institute, Hamilton General Hospital, 237 Barton Street East  
Hamilton  
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+1 905-521-2100  
[leaderpad@phri.ca](mailto:leaderpad@phri.ca)

### Sponsor type

Hospital/treatment centre

# Funder(s)

## Funder type

Charity

## Funder Name

British Heart Foundation

## Alternative Name(s)

the\_bhf, The British Heart Foundation, BHF

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Trusts, charities, foundations (both public and private)

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

The results will be published in peer-reviewed scientific journals, presented at conferences and published on the study website.

## Intention to publish date

31/10/2029

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository.

12 months after the main LEADER-PAD trial publications, UK anonymised trial data will be made available for sharing with academic researchers subject to the secondary research protocol being approved by a UK REC or other similar, approved ethics review body. Requests for sharing can be made by emailing the UK Chief Investigator Professor Robert Hinchliffe, robert.hinchliffe@bristol.ac.uk.

## IPD sharing plan summary

Stored in non-publicly available repository, Available on request