CLARITY PAD

CLopidogrel, Aspirin and RIvaroxaban after revascularisation with angioplasTY for limb-threatening Peripheral Arterial Disease

CLOPIDOGREL, ASPIRIN AND RIVAROXABAN AFTER REVASCULARISATION WITH ANGIOPLASTY FOR LIMB-THREATENING PERIPHERAL ARTERIAL DISEASE (CLARITY PAD)

A Phase IV, pragmatic, adaptive multicentre open-label randomised trial examining the clinical and cost-effectiveness of three antithrombotic regimens following endovascular lower-limb revascularisation for chronic limb-threatening ischaemia.

CLINICAL TRIAL PROTOCOL
VERSION 1.0
DATE: 19.06.2024

Sponsor:	North Bristol NHS Trust Level 3, Learning & Research building, Southmead Hospital Westbury on Trym Bristol BS10 5NB
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:

Name	Position	Signature	Date
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Director:

Name	Signature	Date
Dr David Gillespie	Approved by email	19/06/2024

Chief Investigator:

Name	Signature	Date
Mr Christopher Twine	Approved by email	19/06/2024

General Information This protocol describes the CLARITY clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

Contact details – Chief Investigator & Co-Investigators

If this trial is opening under EU Clinical Trial Regulation 536/2014 then no names are to be included and functional contact points such as trial mailboxes should be used.

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Trial Co-ordination:
The CLARITY trial is being coordinated by the Centre for Trials Research (CTR) at Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the CLARITY Trial Management Group (TMG).

For **all queries** please contact the CLARITY team through the main trial email address. Any clinical queries will be directed through the Trial Manager (TM) to either the Chief Investigator (CI) or a Co-Investigator.

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Randomisations:

Randomisation

To randomise a participant, visit the CLARITY trial database https://clarity.ctr.cardiff.ac.uk or call +44(0)29 20687 457 from Monday to Friday between 9am to 5pm

(See section 9.5 for more details).

Clinical queries:

Clinical queries

Clarity-Trial@cardiff.ac.uk

All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to Centre for Trials Research Safety Team within 24 hours of becoming aware of the event (See section 13 for more details).

Contact details: CTR-Safety@Cardiff.ac.uk

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Glossary of abbreviations

AE	Adverse Event
API	Associate PI
AR	Adverse Reaction
BARC	Bleeding Academic Research Consortium
C&C	Capacity and Capability
CA	Competent Authority
CI	Chief Investigator
CLTI	Chronic Limb Threatening Ischaemia
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
DH	Department of Health
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
DSUR	Development Safety Update Report
eMC	Electronic Medicines Compendium
ESC	European Society of Cardiology
EudraCT	European Clinical Trials Database
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
HRA	Health Research Authority
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISR	Investigator safety report
ISRCTN	International Standard Randomised Controlled Trial Number

ISTH	International Society for Thrombosis and Haemostasis
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LAM	lactational amenorrhoea method
LT	Life-Threatening
MACE	Major Adverse Cardiovascular Events
MALE	Major Adverse Limb Events
MHRA	Medicine and Healthcare products Regulatory Agency
MI	Multiple Imputation
MRC	Medical Research Council
NCA	National Competent Authority
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Health Research
PAD	Peripheral arterial disease
PI	Principal Investigator
PID	Participant Identification number
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROMs	Patient-reported Outcome Measures
QALY	Quality-adjusted Life Year
QAP	Qualitative Analysis Plan
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCARs	Severe Cutaneous Adverse Reaction
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWAT	Study Within a Trial
TIA	Transient Ischemic Attack

TIMI	Thrombolysis In Myocardial Infarction
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	United Kingdom Clinical Research Collaboration
USM	Urgent Safety Measure
UTI	Urinary Tract Infection

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A	1.0		First version

2 Synopsis

Short title	Clopidogrel, Aspirin and Rivaroxaban after revascularisation with angioplasty for limb-threatening Peripheral Arterial Disease
Acronym	CLARITY PAD
Internal ref. no.	UID 948
Clinical phase	Phase IV
Funder and ref.	NIHR HTA 154252
Trial design	Pragmatic, adaptive multicentre open-label three-arm individually randomised controlled trial (RCT)
Trial participants	Adults undergoing percutaneous or hybrid endovascular intervention for Chronic Limb Threatening Ischemia (CLTI)
Planned sample size	1,239
Planned number of sites	Around 20
Inclusion criteria	• Adults (aged 18 years and over) undergoing percutaneous or hybrid endovascular intervention for CLTI of the lower limbs • Atherosclerosis as the cause of CLTI • Target arteries: infrainguinal (common femoral to pedal) if percutaneous, or iliac to pedal if performed as part of hybrid revascularisation with common femoral endarterectomy • Clinicians would use trial antithrombotic combinations in normal clinical practice • Able to provide informed consent • First time in the CLARITY trial
Exclusion criteria	• Open bypass as part of hybrid procedure • Intervention for asymptomatic restenosis of a bypass graft • Pre-existing indication for dual antiplatelet therapy or anticoagulant e.g. atrial fibrillation • Active malignancy or any other non-vascular condition associated with a life expectancy of less than 36 months • Embolic arterial disease • Renal failure with creatinine clearance <15ml/minute • Thrombophilia or any other inherited or acquired bleeding disorder • Persons of childbearing potential who have a positive pregnancy test, are breastfeeding or attempting pregnancy
Treatment duration	12-36 months
Follow-up duration	Up to 36 months
Planned trial period	01 January 2024 – 01 January 2029
Primary objective	To compare the clinical effectiveness of three commonly used antithrombotic regimens (clopidogrel; aspirin plus clopidogrel; aspirin plus low-dose rivaroxaban) following endovascular intervention for CLTI
Secondary objectives	• To evaluate the clinical and cost-effectiveness of clopidogrel; aspirin plus clopidogrel; aspirin plus low-dose rivaroxaban following endovascular intervention • To evaluate the delivery of the CLARITY trial and trial interventions

Tertiary/Exploratory objectives	To explore how the trial interventions work in the real healthcare system
Primary outcomes	Primary effectiveness outcome: A composite event-free survival time of: • Acute limb ischaemia • Major lower limb amputation • Myocardial infarction • Ischaemic stroke • All-cause mortality Primary safety outcome: The International Society for Thrombosis and Haemostasis (ISTH) defined major- or clinically relevant non-major bleeding
Secondary outcomes	• Major adverse limb events (MALE) (defined as amputation or major reintervention of the trial limb) • Major adverse cardiovascular events (MACE) (defined as recurrent CLTI, amputation affecting contralateral limb, acute coronary syndrome, ischaemic stroke) • Bleeding Academic Research Consortium (BARC 2, 3 or 5) and Thrombolysis In Myocardial Infarction (TIMI) defined major bleeding • Minor bleeding • Primary and secondary patency of artery • Reintervention • Healing of tissue loss • Health-related quality of life (VascuQoL-6 and EQ-5D-5L) • Cost-effectiveness • Qualitative process evaluation
Tertiary/Exploratory outcomes	• MALE using other major definitions (composite outcome using trial variables) • MACE using other major definitions (composite outcome using trial variables) • Complications from trial medications • Qualitative exploration of trial intervention implementation, feasibility and acceptability
Investigational medicinal products	• Clopidogrel • Aspirin plus Clopidogrel • Aspirin plus Rivaroxaban
Form	Tablet
Dose	Clopidogrel 75mg (once/day) Aspirin 75mg (once/day) plus clopidogrel 75mg (once/day) Aspirin 75mg (once/day) plus rivaroxaban 2.5mg (twice/day)
Route	Oral

3. Trial summary & schema

3.1 Trial schema and Participant flow

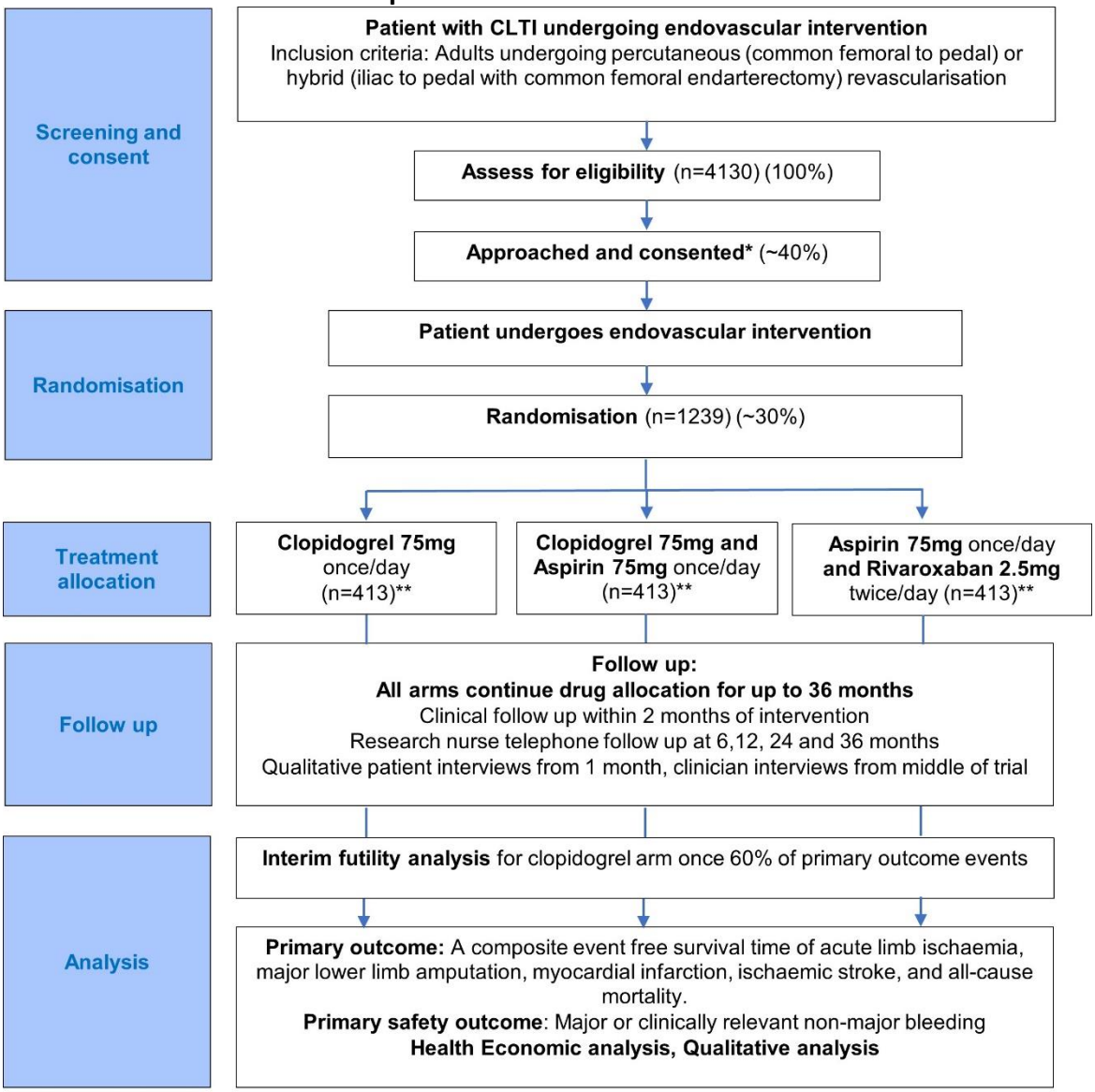

Figure 1. Trial Schema and participant flow

3.2 Trial lay summary

THE PROBLEM:
Blocked leg arteries are very common and are often caused by diabetes or smoking. Blocked leg arteries are becoming more common as diabetes becomes more common and can lead to amputation, or even death if left untreated. Each year in the UK, between 16,500 and 30,000 people die and 3500 legs are amputated because of heavily blocked leg arteries. The most common way to reduce these risks is to open the blocked arteries with a balloon or stent, a procedure called an angioplasty.

Over 4000 angioplasties to increase blood flow in the leg are performed each year in the UK. Patients are given blood-thinning tablets after this treatment to reduce the risk of artery-blocking again and reduce the risk of amputation. These tablets also reduce the risk of other arteries in the body blocking, preventing heart attack, stroke or death. There are several different tablets and combinations available.

RESEARCH IMPORTANCE:
Sometimes two blood thinners are given together. If two blood thinners work better than one, we may be able to save up to 1600 lives and prevent 800 amputations each year in the UK by using them routinely. The problem with two blood thinners is that they cause more life-threatening bleeding than one. This might be up to 700 more bleeds per year in people having an angioplasty.

AIMS:
Our trial will compare three different combinations of tablets for thinning the blood after angioplasty:
1) Clopidogrel,
2) Aspirin and Clopidogrel,
3) Aspirin and Rivaroxaban.
The aim is to see which tablet(s) are best at preventing complications of blocked arteries after angioplasty and to make sure any combination does not cause too much bleeding.

WHAT WE HAVE ALREADY DONE:
No-one knows which blood-thinning tablet or tablets, are best. When we surveyed vascular surgeons in the UK, they mainly used the three combinations of tablets we are testing. 90% felt that there was not enough evidence and 94% supported this trial. This trial fits with the number one research priority in vascular surgery from the James Lind research priority-setting exercise.

WHAT WE ARE PLANNING:
We will randomly assign 1239 participants to be prescribed one of the three tablet combinations after an angioplasty. Participants will take the tablets for up to three years. We will follow them up to see how many patients have further blockage of their leg arteries, lose their leg, have a heart attack or stroke, die or have a major bleed. We will also measure their quality of life and assess how cost-effective the tablets are to the National Health Service (NHS).

PATIENT AND PUBLIC INVOLVEMENT (PPI):
We had two members of the public on the trial development group. One takes blood-thinning tablets for blocked leg arteries and one has parents who died of blocked leg arteries. Ten people who had taken blood thinners confirmed their acceptance of being involved in a trial of blood thinners to prevent amputation. Subsequently, six people who had taken blood thinners helped develop the trial and what it would measure. For example, they had a clear preference for preventing amputation resulting from blocked arteries and their feedback reduced the number of questionnaires.

DISSEMINATION:
We will publish the trial findings in medical journals and present them at conferences. International guidelines will be updated. Participants will be informed of the trial results by a card or letter. A stakeholder meeting will be held at the end of the trial.

4 Background

4.1 Background:

CLTI is the most devastating consequence of peripheral arterial disease (PAD), leading to leg amputation and death when untreated (1). CLTI causes between 16,500-33,000 deaths and over 3500 amputations per year in the UK (2,3). Improving the blood supply of the affected limb significantly reduces these risks. The commonest way to do this is by minimally-invasive endovascular lower limb intervention ('endovascular intervention') such as angioplasty; over 6,500 are performed in the UK each year (2).

Antithrombotic (antiplatelet and/or anticoagulant) medication is given to all patients after endovascular intervention for CLTI. It improves outcomes by reducing the risk of ischaemic events such as amputation by maintaining the blood supply to the limb (4). Antithrombotic therapy also reduces the risk of secondary cardiovascular events such as myocardial infarction, stroke and related death (5). There is a historical lack of randomised controlled trial (RCT) evidence for the clinical and cost-effectiveness of the major antithrombotic regimens used in routine clinical practice in the UK. This is a major barrier to providing the best evidence-based treatment to patients.

As there is no specific Cochrane review, we performed and published a systematic review and meta-analysis (umbrella review) of RCTs for antithrombotics for PAD. Our systematic review and meta-analysis showed a stark evidence gap for antithrombotic therapy after endovascular intervention (5). We found no adequately powered RCTs but found a higher rate of major bleeding with dual antiplatelet therapy (aspirin plus clopidogrel) compared to single antiplatelet therapy for other indications in PAD. The only RCT before 2020 examining antithrombotics following endovascular intervention was a non-powered pilot trial (50 patients in each arm), which showed a signal towards a reduced amputation rate using dual antiplatelet therapy over aspirin alone (6). Another Cochrane review showed dual antiplatelet therapy prevented more ischaemic events than aspirin alone at the cost of more bleeding events in a mixed patient group including a minority with PAD (7). This review did not include as many PAD RCTs as our meta-analysis since it ostensibly examined a different patient group.

Since our systematic review, the VOYAGER PAD RCT was published in 2020. VOYAGER compared aspirin alone with aspirin plus low-dose rivaroxaban following endovascular or open intervention for PAD. VOYAGER found aspirin plus rivaroxaban significantly decreased the primary composite endpoint over aspirin alone at a cost of more major bleeding events (4). VOYAGER was sponsored by the manufacturer of rivaroxaban. Only 30% of the included patients had CLTI: the rest had less severe PAD (claudication) so were at lower risk of ischaemic events. The control arm chosen was aspirin, which was shown to be inferior to clopidogrel for treating patients with PAD 25 years ago in the CAPRIE RCT (8). Aspirin is used infrequently in clinical practice as a result (9). Rivaroxaban is expensive, on-patent (expires in 2026) and may not be cost-effective compared to dual antiplatelet therapy or clopidogrel alone, which are used more frequently in everyday clinical practice.

Observational study evidence:

Four low-quality observational studies have shown a reduction in amputation and/or death using dual antiplatelet therapy compared to aspirin alone after lower limb endovascular intervention (10–13). We conducted our retrospective study of local data using a sample size calculation, strict inclusion/exclusion criteria and clear follow-up definitions (14). We found no difference in amputation or death for the short-course (3 months) dual antiplatelet therapy compared with single therapy. Other studies used at least six months of dual antiplatelet therapy, which is known to be superior in patients who have had a myocardial infarction or undergone coronary artery stenting. The risk of major bleeding with dual antiplatelet therapy was low. The conflict between these studies and the risk/benefit balance further highlights the need for an RCT.

Questionnaire studies of UK practice and equipoise:
We published a survey of 162 UK consultants in 2019 which showed equipoise between dual antiplatelet therapy (aspirin plus clopidogrel 50%) and single antiplatelet therapy (clopidogrel or aspirin, 37%) following endovascular intervention (9). We repeated the survey in 2022 with 52 responses covering most UK vascular units. The majority of practice was clopidogrel alone (46%), dual antiplatelet therapy with aspirin plus clopidogrel (27%) and aspirin plus low-dose rivaroxaban (6%). These are also the drug choices with weak guideline recommendations (15,16) and therefore constitute our trial arms. Aspirin plus low-dose rivaroxaban will likely become more widely adopted with time after the publication of VOYAGER in 2020. To what extent this will happen is unclear as, despite a large marketing push from the company, clinical use has been limited as shown by our questionnaires. 90% of vascular surgeons still thought there was insufficient evidence to guide practice and 94% said they were willing to randomise patients in an RCT. A further survey was performed in December 2022 as part of reassuring the National Institute of Health Research (NIHR) funding panel on feasibility. Sixty-seven responses from vascular consultants in 47 UK vascular centres were received, with the same results as the previous questionnaire.

Combining the results of the literature review, questionnaire and patient and public involvement (PPI) work (outlined in subsequent sections) led to the 3-arm design and choice of antithrombotics.

Current guideline recommendations:
There is no formal National Institute for Health and Clinical Excellence (NICE) guidance in this area, only technology appraisal guidance for rivaroxaban (17) and clopidogrel (18). This is in stark contrast to cardiology (endovascular coronary intervention which is similar to endovascular lower limb intervention) where there are multiple large RCTs and detailed NICE guidance as a result (19). Other PAD guidelines can only make weak recommendations for antithrombotics after endovascular intervention due to the lack of data (15,16). Rivaroxaban 2.5mg is still on patent and is significantly more expensive than clopidogrel (rivaroxaban 2.5mg NHS tariff £1.80/day, clopidogrel £0.05/day).

4.2 Rationale for current trial/Justification of treatment options

Over 6,500 lower limb endovascular interventions are performed in the UK every year, of which 4,400 are for CLTI (2). This will rise in line with the global diabetes epidemic, as diabetes is a major risk factor for developing PAD (20,21).

CLARITY addresses six of the top ten James Lind research priorities for PAD research from the UK vascular surgery priority setting process, including the number one priority: ‘What can be done to improve outcomes in CLTI?’. This is also the number one research priority from the overall exercise encompassing all vascular conditions. CLARITY also addresses ‘How can we reduce progression of arterial disease?’, ‘Can we develop a CLTI care pathway to ensure optimal management?’, ‘What is

the best medical therapy for PAD?', 'How can we reduce the cardiovascular risk for PAD patients?' and 'What is the optimal antiplatelet therapy following lower limb revascularisation?'.

The trial drug combinations are all currently used in UK clinical practice (clopidogrel alone 46%, dual antiplatelet therapy with aspirin plus clopidogrel 27% and aspirin plus low-dose rivaroxaban 6%) following endovascular intervention for CLTI although there is no current NICE recommendation. The selection of drugs for the three arms was collaboratively determined with input from PPI and UK-based clinician users. The clopidogrel-alone and aspirin-plus-clopidogrel arms were co-produced by three studies in 2019, including a questionnaire with responses from 162 consultant-level vascular surgeons and interventional radiologists (9), qualitative discussions with 10 vascular surgeons and interventional radiologists, and a PPI group meeting with 8 patients. In 2022, two questionnaires with responses from UK consultant vascular surgeons and interventional radiologists reaffirmed practices, confirmed equipoise, and assessed feasibility. A second PPI group meeting involving 6 patients discussed the results of the first PPI group and the second questionnaire, confirming acceptability and leading to the addition of an aspirin-plus-rivaroxaban arm, and prompting the inclusion of a futility analysis.

CLARITY will further address (i) the first research priority from the international CLTI guideline from the European and American societies for vascular surgery: 'Define the optimal antithrombotic regimen (safety and efficacy) in patients with CLTI to reduce cardiovascular and limb specific events' (1), and (ii) the number one intervention research priority from the European Society for Vascular Surgery antithrombotic guideline, 'RCTs comparing single antiplatelet, dual antiplatelets and antiplatelet plus low dose anticoagulants post endovascular intervention. Focus on high-risk groups' (15).

The target population fits within multiple groups identified as under-served by clinical research in the INCLUDE project (22) and National Confidential Enquiry into Patient Outcome and Death 2022 healthcare inequalities review (23).

5 Trial objectives/endpoints and outcome measures

CLARITY aims to provide the definitive clinical and cost-effectiveness evidence for antithrombotic therapy following endovascular intervention for patients with CLTI so that policy makers will be able to make clear recommendations.

5.1 Primary objective

The primary objective of CLARITY is to evaluate the clinical effectiveness (using the outcomes listed in 5.3) of three antithrombotic regimens following endovascular intervention for CLTI: clopidogrel alone; aspirin plus clopidogrel; aspirin plus low-dose rivaroxaban.

5.2 Secondary objectives

The secondary objectives are to evaluate the clinical and cost-effectiveness outcomes listed in 5.4, and to evaluate the delivery of the CLARITY trial and trial interventions through the qualitative process evaluation.

5.3 Primary outcomes measures

The primary clinical effectiveness endpoint is a composite event-free survival time examined over the trial duration (36 months) comprising:

- Acute limb ischaemia
- Major lower limb amputation
- Myocardial infarction

- Ischaemic stroke
- All-cause mortality

The primary safety outcome is the International Society for Thrombosis and Haemostasis (ISTH) defined major- or clinically relevant non-major bleeding*.

*Clinically relevant non-major bleeding is bleeding that results in hospitalisation, medical or surgical intervention for bleeding, an unscheduled clinical visit, or a change in antithrombotic therapy (24).

5.4 Secondary outcomes measures

Secondary outcome measures include:

- Major adverse limb events (MALE) (defined as amputation or any major reintervention of the trial limb*)
- Major adverse cardiovascular events (MACE) (defined as recurrent CLTI, amputation affecting contralateral limb, acute coronary syndrome, ischaemic stroke)
- Bleeding Academic Research Consortium (BARC 2, 3 or 5) and Thrombolysis In Myocardial Infarction (TIMI) defined major bleeding
- Minor bleeding
- Primary and secondary patency of artery
- Reintervention
- Healing of tissue loss
- Health-related quality of life (VascuQoL-6 and EQ-5D-5L)
- Resource use, costs and cost-effectiveness
- Qualitative process evaluation, evaluating trial and intervention delivery through exploring trial conduct, trial acceptability (including barriers and facilitators to recruitment and retention), intervention adherence and contextual factors affecting trial delivery.

* The term "trial limb" refers to the specific limb that will undergo the endovascular intervention for CLTI.

5.5 Separate exploratory/translational objectives and endpoints

Tertiary/exploratory outcomes include:

- MALE using other major definitions
- MACE using other major definitions
- Complications from trial medications
- Qualitative exploration of trial intervention implementation, feasibility and acceptability

6 Trial design and setting

6.1 Design

We will conduct a pragmatic, adaptive, multicentre, open-label, three-arm RCT, with internal pilot and adaptive interim analysis to examine the futility of the arm with the lowest predicted clinical effectiveness. The trial will evaluate the clinical and cost-effectiveness of three commonly used antithrombotic regimens following endovascular intervention for CLTI: once daily 75mg clopidogrel alone; once daily 75mg aspirin plus once daily 75mg clopidogrel; and once daily 75mg aspirin plus twice daily 2.5mg low-dose rivaroxaban. We plan to enrol 1,239 participants. This is a Type A Clinical Trial of Investigational Medicinal Product (CTIMP) as all 3 arms include only medicinal products within the licensed range of indications, dosage and form, and which are already given in routine clinical practice. We expect to reach the enrolment target within 36 months of starting recruitment. The study

will end 6 months after the date of the last data capture. Data collection will involve recording health outcomes, patient-reported outcome measures (PROMs) and serious adverse events in the electronic case report form (CRF) as well as questionnaires administered via telephone, videocall, email and post.

6.1.1 Setting

The trial will take place in inpatient settings in NHS hospitals at vascular units performing endovascular intervention for patients with CLTI in the United Kingdom (n=~20 sites). Eight lead centres (Bristol, Imperial, Guy's and St Thomas', St George's, Leeds, Newport/Cardiff and Vale, Hull, and Sheffield) will take part in the internal pilot. Further additional sites will be opened as required. If further sites are needed, those who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

6.2 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the Medical Research Council/Department of Health/Medicine and Healthcare products Regulatory Agency (MRC/DH/MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a Type A, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 23.1).

This clinical trial is to be conducted in compliance with the protocol, the EU Clinical Trial Regulation 536/2014 and Good Clinical Practice (GCP).

7 Site and Investigator selection

This trial will be carried out at participating sites (n~20) within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial. Before any site can begin recruitment, a Principal Investigator (PI) at each site must be identified. Each site will have a co-investigator model consisting of a vascular surgeon and an interventional radiologist. Either of them may be the Principal Investigator. The following documents must be in place and copies sent to the CLARITY Trial email account (see contact details on page 3):

- Confirmation of Capacity and Capability (C&C) from the Research and Development (R&D) department following the sharing of local information pack
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the PI
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet (PIS) and Consent Form(s) on host care organisation headed paper

- A copy of the most recent approved General Practitioner (GP) letter on host care organisation headed paper
- A copy of the most recent Pregnancy Information Sheet(s) and Consent Form(s) on host care organisation headed paper

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the PI/lead Research Nurse detailing that the site is now ready to recruit participants for the trial. This letter/email must be filed in each site's Investigator Site File (ISF). Along with the written confirmation, the site should receive a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

The Trial Management Group (TMG) will apply for the trial to be registered with the Associate PI (API) scheme run by NIHR and will encourage the PI at each site to recruit a healthcare professional early in their research career to consider registering with the scheme.

Site initiation will be in person or by teleconference.

8 Participant selection

Patients undergoing percutaneous endovascular or hybrid intervention for CLTI of the lower limb may be assessed for eligibility.

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration using the CLARITY email address.

8.1 Inclusion criteria

- Adults (aged 18 years and over) undergoing percutaneous or hybrid endovascular intervention for CLTI of the lower limbs
- Atherosclerosis as the cause of CLTI
- Target arteries: infrainguinal (common femoral to pedal) if percutaneous, or iliac to pedal if performed as part of hybrid revascularisation with common femoral endarterectomy
- Clinicians would use trial antithrombotic combinations in normal clinical practice
- Able to provide informed consent
- First time in the CLARITY trial

8.2 Exclusion criteria

- Open lower-limb bypass as part of hybrid procedure
- Pre-existing clinical indication for dual antiplatelet therapy or anticoagulant e.g. atrial fibrillation
- Active malignancy or any other non-vascular condition associated with a life expectancy of less than 36 months
- Patients undergoing intervention to treat asymptomatic restenosis of a lower-limb bypass graft
- Embolic arterial disease
- Renal failure with creatinine clearance <15ml/minute

- Thrombophilia or any other inherited or acquired bleeding disorders
- Persons of childbearing potential* who have a positive pregnancy test, are breastfeeding or attempting pregnancy

*A person is considered to be of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
- Permanent sterilisation includes hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
In line with NICE guidelines on routine preoperative tests for elective surgery, including angioplasty, it is recommended to conduct pregnancy assessments for individuals of childbearing potential. Healthcare providers must sensitively enquire about the possibility of pregnancy on the day of surgery for all people of childbearing potential, ensuring they understand the risks to the foetus posed by anaesthesia and the procedure. In instances of uncertainty regarding pregnancy status, obtaining consent for a pregnancy test is advisable.

CLARITY has a pragmatic design which encourages all patient groups to be included. There is no inclusion or exclusion by protected group characteristics (other than pregnancy) and the design encourages inclusion of under-served patient groups who will benefit most from the treatment.

9 Recruitment, screening and registration

9.1 Internal pilot

An internal pilot is planned in the eight lead sites (including those where the CI/PI co-applicants are based). It will assess participant recruitment rates and the proportion of participants providing primary outcome data.

9.1.1 Recruitment rates

To confirm the recruitment rate, a retrospective audit of the CI's unit (1.2 million population for CLTI; most UK vascular centres are now over 1 million) over 6 months in 2021 showed 103 patients treated endovascularly for CLTI in the trial arterial segments. A total of 41% would be excluded by our criteria (some in multiple categories: 20 (19%) for a pre-existing antithrombotic regimen, 15 (15%) for bleeding risk, 4 (4%) for renal failure, 5 (5%) for malignancy). This is higher than a published 30.7% exclusion estimate for the VOYAGER PAD trial from the Danish Vascular Registry (25). Assuming a pessimistic 30% enrolment rate, our centre would enrol 3 patients per month (26). Our sample size assumptions use a recruitment rate of 2 patients per site per month.

Pooled data from NIHR-funded studies show internal pilots typically recruit 15% of their participants within 33% of the total recruiting period (27). These figures have been used to calculate the number of participants expected to be recruited (n=186; 15% of 1239) by 9 months (24% of the total 36-month recruitment window).

A nine-month internal pilot (to take into account slower recruitment as sites first open) will start when the first centre is open to recruitment. The average recruitment rate would need to be 2.8 participants/site/month. The remaining recruitment time after the internal pilot is completed (27 months) would need to average 2.1 participants/site/month with 20 sites open. This takes into account smaller non-lead sites that will not see as many eligible patients and will recruit fewer

participants than the bigger lead sites. Also included in the progression criteria is the proportion of participants providing primary outcome data. The pilot has a challenging recruitment rate which is higher than the rest of the trial as we are opening a high number of sites early.

Table 1. Proposed internal pilot phase 9 months

Progression criteria	Red	Amber	Green
% Threshold for recruitment	<60%	60-99.9%	100%
Total number of participants recruited	<112	112-185	186
Recruitment rate/site/month	<1.59	1.59-2.64	>2.64
Number of sites open	<4	4-7	8
Participants providing primary composite and bleeding outcomes at 2 months	<70%	70-90%	>90%

If issues are identified regarding site opening or recruitment during the pilot phase, the trial qualitative researcher may attend a Vascular Surgery conference to discuss this with PIs. Additional data collection to explore reasons for low recruitment may also be conducted if necessary, which could include mapping the patient recruitment pathway, recording/observing recruitment discussions (with the permission of the patient and clinician), or analysis of documents such as trial meeting minutes.

There will be a planned review of the internal pilot at the 9-month time point. The results of this review will be discussed with the Trial Steering Committee (TSC) and fed back to the NIHR Health Technology Assessment (HTA) Programme.

9.2 Participant identification

Patients listed for, or who are within 10 days of treatment of CLTI of the lower limb will be screened by members of the clinical care team against the above inclusion/exclusion criteria. Those who are considered potentially suitable for inclusion will be approached and provided with a PIS. The site PI, or suitably qualified medical practitioner who has been delegated the role, will confirm eligibility prior to consent.

For those who struggle to read, the PIS will be read to them. An opportunity will be given to them to ask questions. A trial infographic video/animation will also be developed.

Non-English language translation of participant-facing documentation (e.g., PIS and consent form(s), questionnaires), subtitles to the infographic videos/animations, and interpretation services such as 'Language Line' will be used where available, to ensure language is not a barrier to being considered for the trial.

Patients will ideally be approached before the endovascular procedure and then be randomised afterwards to start the trial medication as soon as clinically possible. It is acceptable to approach and randomise the patient following the procedure as long as the trial medication is started within 10 days of the procedure.

9.3 Screening logs

A screening log of all ineligible and eligible but not consented/not approached patients will be kept at each site so that any biases from differential recruitment will be detected. The screening log will be

integrated into the trial database for each site. When at the site, logs may contain identifiable information but this **must** be redacted before being sent to the CTR. The screening log should completed directly on the trial database or a copy of the paper version (if used) sent to CLARITY-Trial@cardiff.ac.uk every month (see section 23 for further details on data monitoring/quality assurance).

Once screened, participants not selected for recruitment due to polyvascular disease will be eligible to participate in the study within a trial (SWAT). A review of trial screening logs would identify patients with polyvascular disease and these will be approached by the research team for inclusion in the SWAT. Written informed consent will be received for the SWAT (consent for the SWAT will be distinct and separate from that of the main trial). The SWAT is detailed in section 17.

9.4 Informed consent

Patients undergoing percutaneous or hybrid endovascular intervention for CLTI of the lower limbs will be approached. Before being enrolled on the trial, the participant's written informed consent must be obtained using the CLARITY Consent Form, which follows the PIS. The patient should be given sufficient time after the initial invitation to participate before being asked to sign the Consent Form.

Patients should be given as much time as they require after being given the trial PIS to consider and discuss participation in the trial with friends and family (including their personal legal representative - a person who, by virtue of their relationship, is suitable to act as their legal representative and is available and willing to act, see section 9.4.1). A contact number for someone at the site should be given to the patient should they wish to discuss any aspect of the trial. Following this, the investigator should determine that the patient is fully informed of the trial and their participation, in accordance with the principles of GCP. Patients should always be asked to sign a consent form. One copy should be given to the participant but the original copy should be kept in the ISF and a further copy should be kept with the participant's hospital notes.

Capacity will be assessed by a suitably qualified person at the site before informed consent is received. Informed consent must be obtained prior to the participant being given any medication specifically for the purposes of the trial. Please note, only when written informed consent has been obtained from the patient and they have been registered into the trial can they be considered a trial participant.

The patient's consent to participate in the trial should be taken by those delegated to do so (usually the PI or a medically qualified member of staff who has been delegated this role on the CLARITY delegation log) after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. All patients must be informed of the aims of the trial, the possible adverse events, the procedures and the possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

Participants' consent will be requested to collect: NHS number and postcode to utilise NHS data for future research, and they will be asked to consent to data-linked longer-term follow-up.

Patients participating in the trial may also opt to consent to participate in qualitative interviews (see Section 12.3). This is optional. If trial participants provide their written consent on the CLARITY consent form to indicate their interest in participating in an interview, the local site Research Nurse should go through the separate information sheet with them describing the full details of the qualitative study.

Patients who are eligible for trial participation but decline to participate may opt to consent to participate in qualitative interviews. Patients excluded from trial participation due to polyvascular disease may consent to participate in the qualitative SWAT (see Sections 9.3 and 17). Health professionals involved in the CLARITY trial may consent to participate in qualitative interviews.

Potential interview participants will be identified by the local site PI or Research Nurse, who will provide them with a PIS with details of the qualitative study. Once they have had time to consider the study information, potential interview participants will be asked by the local site PI or Research Nurse to complete a consent to contact form and consent form, which will be securely electronically transferred from the site to the research team. The qualitative researcher may then contact them directly to arrange a suitable time for an interview. If a completed consent form is not received, consent will be taken over the telephone/ videocall and recorded prior to the start of the interview.

Sites are required to send consent forms to the CLARITY Trial Team at the CTR by secure file transfer or encrypted email within 24 hours (or the next working day) of consent being taken. Patient consent will be obtained for this. In instances where the original copy of the consent form cannot be obtained straight away, for example, due to restrictions on paperwork leaving the bed space because of confirmed or suspected COVID-19, the consent form may be sent to the research delivery staff later when able to leave the bed space.

At all follow-up points, research staff will confirm that the patient is happy (continued consent) and still has capacity for ongoing trial participation. The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment (see Section 10 for further details).

9.4.1 Loss of Capacity during the trial

The site PI, or suitably qualified medical practitioner who has been delegated the role, will confirm suspected loss of capacity.

In the event that a participant gives informed consent and subsequently loses capacity, the participant's initial consent to participate in the trial, given while capable, remains legally valid according to the Medicines for Human Use (Clinical Trials) Regulations, 2004. The participant will remain in the trial unless it becomes apparent that continued participation is not in the best interests of the participant (for medical or other reasons) or if there is any indication that the participant would object to continued participation (based on previous known wishes or any expression of distress or objection), as outlined in the Mental Capacity Act, 2005. Information about options after loss of capacity will be discussed at the time of consent and included in the PIS and consent form.

In cases where a participant's loss of capacity is anticipated to be very short-term or fluctuating, non-safety related activities directly involving the participant (e.g., patient-reported questionnaires) can be temporarily paused. Collection of safety data and clinical data from medical notes may continue When capacity is regained, the participant's willingness to continue in the trial should be confirmed when appropriate (at the next follow up timepoint if not earlier).

If the participant's loss of capacity is anticipated to be for an extended period or capacity is unlikely to be regained (e.g., lost capacity because of dementia), the participant should be withdrawn from the patient-reported questionnaires, and collection of safety data and clinical data from medical notes may continue. If their personal legal representative declines, the participant should be fully withdrawn from the trial. However, if there is a possibility of capacity being regained, the participant should remain in the trial and contacted at the next follow up timepoint.

A participant's personal legal representative should be asked to give informed consent representing the participant's presumed will to continue participating in the trial if:

- There are major protocol changes during the trial
- Or additional consent is required from participants during the trial.

Any request made by a personal legal representative to withdraw a participant from the trial, even if outside of the above conditions, should be considered. If the participant themselves raises any objections, their withdrawal will be processed. An Information Sheet and Consent Form for Legal Representative will be provided.

If the participant does not consent to consulting their legal representative upon losing capacity, or it is not possible to contact their personal legal representative, the participant should be fully withdrawn if the protocol is changed or additional consent is required from participants.

9.5 Registration and randomisation

9.5.1 Registration

Eligible participants with CLTI undergoing percutaneous or hybrid endovascular intervention who have consented to take part in the trial will be registered in the trial before or within 10 days after the procedure. Registration before the procedure will be encouraged. Key information will be collected, including past medical, surgical and drug history. The database will generate a unique trial number which will be the primary identifier for all participants in the trial.

9.5.2 Randomisation

Participants will be randomised within 10 days of the endovascular procedure being performed.

Randomisation will be in a 1:1:1 ratio to receive: (1) clopidogrel alone, (2) aspirin plus clopidogrel or (3) aspirin plus low-dose rivaroxaban for up to 36 months. To reduce the risk of imbalance of key covariates, covariate-adaptive randomisation with a random element will be used for the target artery, antiplatelet loading at the time of procedure and trial site (see Section 14.1). If one arm is dropped due to futility after the interim analysis (see Section 15.1.1), the randomisation ratio will be adjusted to 1:1 between the two remaining arms. This will be detailed in the randomisation plan.

Computerised web-based remote randomisation (available 24 hours a day) will be used. The Trial Manager will also be notified that a participant has been randomised via an automated e-mail alert mechanism to the CLARITY email inbox.
In the event the online randomisation system is unavailable at site or the site has problems accessing the online website, then the local investigator may contact the CTR (during office hours). Randomisation may be performed by CTR staff on request of the local investigator.

If the online system does not work, a telephone back-up managed by the CTR Trial team will be available for use during office hours Monday to Friday:

For online randomisation: A randomisation form must be completed on the trial database to randomise the participant.

For telephone randomisation: A randomisation form must be completed before telephoning the randomisation line.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants' care will not be affected at any time as a result of declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, a clear distinction must be made as to what aspect of the trial the participant is withdrawing from, unless it is not appropriate to contact the participant for this information. These aspects could be:

1. Withdrawal from randomisation to receive trial medication
2. Withdrawal from trial medication
3. Withdrawal from using routinely collected clinical data for the trial (no permission for the research team to look in medical notes to collect health and medication information)
4. Withdrawal from follow-up questionnaires (no permission to be contacted by a member of the research team to ask questions about health at 2, 6, 12, 24 and 36 months)
5. Withdrawal from contacting alternative contact for completing questionnaires (no permission to be contacted by a member of the research team to ask questions about health at 2, 6, 12, 24 and 36 months)
6. (If applicable) Withdrawal from the optional qualitative interview (interview about the trial process)
7. Withdrawal of use of participant contact data (personal identifying data collected for the purposes of contacting participants).
8. Withdrawal from future data linkage
9. Withdrawal from contact regarding eligibility for potential future study
10. Withdrawal of consent to all of the above

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal.

If a participant withdraws form the trial, all endpoint data collected up to the point of withdrawal will be retained and used in analysis as per the GDPR guidelines and the PeRSEVERE principle on retaining data (28). Participants will be informed of this before they join the trial as outlined in the PIS.
All data collected prior to participant withdrawal will be kept with the other trial data and archived after the trial analysis (see section 20 for archiving details).

Furthermore, it is important to collect ongoing safety data at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet, but briefly: if a participant wishes to stop taking part in the trial completely, they may need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, information about them will continue to be collected for as long as the reaction lasts.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Serious toxicity
- Withdrawal of consent for treatment by the participant
- Any alteration in the participant's condition which justifies the discontinuation of the treatment in the Investigator's opinion
- Non-compliance

Participants who consent and subsequently withdraw may complete a withdrawal of consent form if they withdraw in person. However this is not mandatory if deemed not appropriate or burdensome to the participant. In all instances, the withdrawal CRF should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal CRF should be sent to the CLARITY TM. Any queries relating to the potential withdrawal of a participant should be forwarded to the CLARITY TM.

10.2 Lost to follow-up

Participants will be identified as lost to follow-up if it is not possible to contact them directly or the designated additional contact person for follow-up. At enrolment, participants will be asked to provide details of an alternative contact person (e.g. close friend, relative or carer) whom they are happy for members of the research team to contact for follow-up if the participant themselves cannot be contacted. Participants will also be asked to consent to the research team communicating with their GP if required.

11 Trial intervention

Participants will be randomised in a 1:1:1 ratio to receive an oral course (up to 36 months) consisting of one of the following treatments:

1) A 75mg clopidogrel tablet taken once daily
2) Dual antiplatelet therapy with a 75mg aspirin tablet and 75mg clopidogrel tablet, both taken once daily
3) Dual antiplatelet therapy with a 75mg aspirin tablet taken once daily and a 2.5mg rivaroxaban tablet taken twice daily

Sites are encouraged to prescribe 'best care' concomitant risk factor reduction medication as per NICE guidelines. If indicated, this includes high-dose statin therapy, blood pressure and diabetes control, and smoking cessation help.

11.1 Treatments

All 3 Investigational Medicinal Products (IMPs) are commonly prescribed in primary and secondary care and will be as outlined in section 11.3. The use of generic brands is permitted and trial risk for this is assessed in the CLARITY risk assessment form.

- The Summary Product Characteristics (SmPC) for clopidogrel (dated 08-Jan-2024 as updated by electronic medicines compendium (eMC)) made by Aspire Pharma Ltd will be used as the RSI.

- The SmPC for aspirin (dated 26-Aug-2021 as updated by eMC) made by Dexcel Pharma Ltd will be used as the RSI.
- The SmPC for rivaroxaban (dated 04-Aug-2023 as updated by eMC) made by Bayer plc will be used as the RSI.

Updated versions of the RSI will be circulated to sites by email as required by the central trial team at CTR.

11.2 Treatment supply and storage

The IMPs will be sourced from local NHS hospital stock at participating sites and are typically available and stored in the Pharmacy department. These medicinal products do not require any special storage conditions and are stored in clearly labelled containers at room temperature/below 25°C, the conditions specified in the SmPCs. They are stable with a long shelf life under standard conditions (room temperature/below 25°C) therefore, IMP storage temperature will not be monitored in this trial consistent with Type A clinical trials.

11.3 Treatment prescribing and dispensing

Local routine prescribing procedures will be followed for each IMP, for example, the IMP will be prescribed by the participant's treating clinician according to the trial arm allocation and either dispensed by the hospital pharmacy department or a community pharmacy.
Treatment will commence within 10 days post-endovascular intervention.

For inpatient cases, the medication will be administered by ward nurses or other appropriate health care providers in accordance with the relevant SmPC, manufacturer's recommendations and instructions of use. Before discharge, patients will be given clear instructions for use. Once discharged from the hospital, participants will self-administer the allocated IMP.

For day patients/outpatient procedures, participants will be supplied with the IMP as part of routine discharge after the endovascular procedure and treatment will commence at home. If the patient is already in the community after the procedure and at the point of randomisation, primary or secondary care prescribers will be used and stock dispensed from either hospital or community pharmacies depending on local arrangements.

Each dispensed drug supply will vary depending on local arrangements. The post-procedural antithrombotic medication may be prescribed by either vascular surgery or interventional radiology teams. Participants will obtain an additional supply of their prescribed medication from a community pharmacy or secondary care pharmacy depending on the local set-up.
The participant will take the trial medication during the trial duration (up to 36 months). The treating clinician will be responsible for the care of the participant once the participant is no longer in the trial or withdraws from taking the trial medication for any reason.

Participants may continue on the medication after completion of the trial as part of their standard care. Prescribing and dispensing arrangements will not change after the trial has ended.

11.4 Dosing schedule

Standard care peri-procedural antithrombotic medication should be used as per unit preference. The IMP may be started at any time post-procedure at the discretion of the clinician up to 10 days post-procedure. Sites will be encouraged to start the IMP as soon a clinically possible.

Participants will only be permitted to have a single type of antithrombotic regimen for the duration of the trial. Clinically mandated changes to the patient's antithrombotic regimen would usually be secondary to one of the events we are capturing which would truncate the patient in the trial as part of the statistical plan. If there were another reason for a clinically mandated change in antithrombotic medication, for example, a new diagnosis of atrial fibrillation, the patient would be censored the day they start the new medication.

Supply chain issues are not expected for any of the drugs. Changes to trial drugs and reason will be followed-up in the trial (see section 12.2).

Each IMP will be administered orally in tablet form throughout the trial to the following dosing schedule:

Clopidogrel

- Dose: 75mg
- Dosage Form: Tablet
- Strength of Unit Dose: 75mg/tablet
- Frequency and Timing: Once daily for up to 36 months

Aspirin

- Dose: 75mg
- Dosage Form: Tablet
- Strength of Unit Dose: 75mg/tablet
- Frequency and Timing: Once daily for up to 36 months

Rivaroxaban

- Dose: 2.5mg
- Dosage Form: Tablet
- Strength of Unit Dose: 2.5mg/tablet
- Frequency and Timing: Twice daily for up to 36 months

Concomitant therapies

All patients should be treated with 'best care' concomitant risk factor reduction medication as per NICE guidelines (29). This includes high-dose statin therapy, blood pressure and diabetic control, and smoking cessation help (30). Patients taking other doses of anticoagulant or antiplatelet medication are excluded by the inclusion/exclusion criteria. Patients being admitted to the hospital during the trial should have thromboprophylaxis (usually with low molecular weight heparin) as per local protocol (see 11.4.1).

11.4.1 Recommendations for patients undergoing subsequent interventional procedures

Patients can temporarily stop trial medication to undergo interventional procedures where standard clinical practice would be to stop trial IMPs. Sites are encouraged to recommence trial medication as soon as clinically possible.

11.5 Dose modification for toxicity

There will be no dose modifications in this trial.

11.6 Management of toxicity and hypersensitivity reactions

Clopidogrel, aspirin and rivaroxaban are licensed medications with rare, very rare/unknown reports of hypersensitivity reactions.

Patients should be evaluated for history or risk of hypersensitivity to the IMPs and monitored for signs of hypersensitivity and toxicity as per routine practice. Investigators should refer to the IMP SmPC for further information.

If hypersensitivity or systemic toxicity is suspected, the trial medication should be stopped immediately and the participant switched to another medication as deemed appropriate by the treating clinician. Intolerances of the IMP will be managed and reported through the treating clinician according to standard procedures.

Severe antiplatelet or anticoagulant toxicity would be considered a SAR and would be reported within 24 hours (see Section 13 on Pharmacovigilance). Participants will be given a card with details of who to contact at the local recruiting site should they experience any serious adverse reactions due to medication toxicity.

11.7 Management of overdose

If a toxic dose of IMP has been ingested, the management and treatment of the overdose should be conducted in accordance with the IMP's SmPC and the usual clinical pathway (section 4.9 Overdose).

An overdose is not an AE and may not result in any noticeable effect on the participant. However, if the participant experiences a serious adverse event (SAE) that the PI considers may be causally related to an overdose, then this must be clearly stated on the SAE form. Any resulting SAE will be reported following standard reporting procedures for SAEs (see section 14 for SAE reporting procedures).

11.8 Pre-medication

The individual unit standard of care antithrombotic, antibiotic and secondary cardiovascular prevention drugs should be used as normal peri-procedurally.

11.9 Prohibited medications and interaction with other drugs

Clopidogrel, aspirin and rivaroxaban have interactions with other medicinal products. For medications known to be contraindicated with the IMPs, concomitant treatment should adhere to precautions outlined in the SmPCs.

NICE recommends the co-prescription of a proton pump inhibitor for patients at high risk of gastrointestinal bleeding being prescribed dual antiplatelet therapy following coronary artery endovascular intervention to reduce this risk (31).

Omeprazole, a widely prescribed proton pump inhibitor, interacts with clopidogrel and may reduce effectiveness. As a result, we recommend that trial patients have a proton pump inhibitor considered with any history or concern about gastrointestinal bleeding. Patients already taking omeprazole or esomeprazole should be switched to lansoprazole or pantoprazole, which are both available in generic form.

Inhibitors of cytochrome P450 co-prescribed with trial medication (clopidogrel or rivaroxaban) should be managed as per local protocol.

Investigators should refer to section 4.5 of the respective drug SmPC for details of interactions with other drugs.

11.10 Permitted concomitant medications

All concomitant medications clinically indicated are permitted.

11.10.1 Trial Restrictions

As per routine practice, people of childbearing age will be advised not to attempt pregnancy whilst taking a Direct Oral Anticoagulant (DOAC) like rivaroxaban. This will be described in the participant information sheet. If they do become pregnant, they will be advised to contact the local team at the recruiting site and this will be managed according to normal clinical practice.

11.11 Accountability procedures

The accountability requirement for this trial is "low – 1" and the trial will follow local NHS procedures for the management, dispensing and accountability of the IMPs, with no requirement for CTR accountability, recall and disposal procedures as described in the CLARITY IMP Management Plan.

11.12 Compliance

Compliance/ adherence to the medication will be self-reported by participants through questionnaires at the follow-ups. As this is a real-world, pragmatic trial there are no formal compliance checks such as tablet counting.

11.12.1 Treatment fidelity and adherence:

A combination of methods will be used to effectively assess treatment fidelity. The current medications CRF will be used to document changes and adherence to trial medication.
Fidelity will be assessed by:

- Documenting that the correct/allocated IMP is commenced and the timing of IMP initiation post-procedure to ensure it is within the 10 days (see section 11.3).
- Evaluating continuity in treatment for the duration of the trial by examining reports of changes in trial medication and monitoring adverse events or circumstances necessitating a stop to trial medication such as hypersensitivity reactions or pregnancy (see sections 11.6 and 12.1.1).
- For patients who temporarily stop trial medication to undergo interventional procedures, the time to recommence trial medication will also be recorded (see section 11.4.1).

The impact of deviations from the treatment regimen will be analysed as part of the main statistical analysis (see section 15.1, page 53).

- Treatment adherence will be assessed via participant-reported adherence data collected through questionnaires at follow-ups to identify trends or patterns in adherence behaviour, allowing for timely interventions if needed (see section 11.12).
- Intervention adherence and consistency in treatment administration will also be assessed through qualitative process evaluation (see section 12.3), obtaining feedback from participants about their experiences with the medication, including any challenges they face in adhering to the treatment regimen.

Regular monitoring and review of adherence data will be detailed in the CLARITY monitoring plan.

12 Trial procedures

Participants will be recruited over 36 months, and the follow-up period will be variable, with a minimum of 12 months for those recruited at the very end of the recruitment period, and up to 36 months for those recruited early. This is in line with the NICE and European Society of Cardiology (ESC) guidance on dual antiplatelet therapy following acute coronary syndromes in high-risk groups (31,32). All other trial procedures are outlined below.

12.1 Assessments

Outcomes will be assessed at baseline, within 2 months of the endovascular procedure, 6 months and every 12 months post-randomisation (up to 36 months). Data will be collected by the research nurses either in person or via telephone, videocall, email or review of patient records, and entered in electronic format.

The baseline assessments will take place before or within 10 days of the endovascular procedure.

12.1.1 Baseline

The baseline assessment consists of collecting the following information:

- Confirmation of eligibility (by medically qualified doctor)
- Registration
- Medical history
- Endovascular procedure details
- Demographic details including sex at birth, ethnicity
- Presence of rest pain
- Presence of tissue loss
- Participant-reported health-related quality of life (QoL) assessed using EQ-5D-5L and VascuQoL-6

At baseline, participants will be given a contact card providing them with contact details of their local research team. They will be asked to contact the team if there is a change in their medication regimen, specifically when the trial medication is discontinued and replaced with a different medication; they become pregnant; or they experience a major bleeding event, any primary outcomes or an SAE. The contact card will also detail their follow-up appointment schedule.

A letter will be sent to the participant's GP to notify them about the participant's involvement in the trial, the allocated IMP after randomisation, the requirement for repeat prescriptions, and to request the GP promptly inform the local site team of any major bleeding or primary outcome events, SAEs, or interruptions to medication that come to their attention.

Table 2. Schedule of enrolment, interventions and assessments[1]

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
1.	Informed Consent	Consent form, documented in medical notes	-	X									Clinician with delegated responsibility	Consent
2.	Eligibility Assessment	CRF, documented in medical notes	Inclusion/Exclusion criteria	X									Clinician with delegated responsibility	Eligibility
3.	(For participants of child-bearing potential) Review of pre-operative pregnancy test result	CRF and documented in medical notes – eligibility assessment	Confirmation of negative pregnancy result	X	-								Site Research team	Eligibility

[1] Taken from the HRA CTIMP protocol template (2016).

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
4.	Randomisation	CRF	Randomised medication regimen: Dose, Frequency			X							Site Research team	Randomisation
5.	Post-surgery form	CRF/Medical notes	Revascularisation details: - Treated arteries - Common femoral endarterectomy - Type of endovascular treatment - Antiplatelet loading at the time of procedure - Adjuvants during procedure			X							Site Research team	Randomisation and all outcomes
6.	Registration	CRF	- Contact details (inc. Postcode) - Alternative Contact details - GP Contact details		X								Site research team	Study Management
7.	Demographics	CRF	- Age - Sex - Gender - Ethnicity		X								Site research team	Baseline
8.	Medical history	Medical notes and CRF	- Smoking status - Weight - Alcohol use - Co-occurring conditions		X								Participant Reported/ Site research team	Baseline

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
			- Past surgery											
9.	Current Medications	Medical Notes/CRF	- Current medications - Trial medication		X		X	X	X	X	X			Baseline and Secondary Outcome/ Fidelity of interventions
10.	Details of CLTI	CRF/Medical Notes	- Rest Pain (yes/no) - Tissue loss (yes/no)		X								Site research team	Baseline
11.	Health-related Quality of Life	Questionnaire	- EQ-5D-5L - VascuQoL-6		X		X	X	X	X	X	X	Participant reported	Secondary Outcomes
12.	Composite event-free survival time	CRF/Medical notes	- Acute limb ischaemia - Major lower limb amputation - Myocardial infarction - Ischaemic stroke - All-cause mortality				X	X	X	X	X			Primary outcome
13.	Bleeding events	CRF/Medical notes	ISTH defined major bleeding: - Fatal bleeding - Symptomatic bleeding in a critical area - Bleeding causing a fall in hemoglobin levels (2g/dL or above)				X	X	X	X	X			Primary safety outcomes

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
			- Leading to a transfusion of 2 U or more of whole blood or red cells											
14.	Bleeding events	CRF/Medical notes	ISTH defined clinically relevant minor bleeding resulting in: - Hospitalisation; - Medical or surgical intervention; - Unscheduled clinical visit/evaluation e.g. telephone/videocall by clinician; - A change in antithrombotic therapy				X	X	X	X	X			Primary safety outcomes
15.	Bleeding events	CRF/Medical notes	BARC and TIMI-defined major bleeding including: - Overt bleeding less than type 3 criteria that led to hospitalisation; increased level of care; nonsurgical medical intervention; unscheduled clinical evaluation e.g. telephone/ videocall by clinician				X	X	X	X	X			Secondary Outcomes

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
			- Required surgical intervention or intravenous vasoactive agents - Cardiac tamponade - Hemoglobin drop related to bleed - Hemoglobin drop amount 3 g/dL and more - Symptomatic bleeding in a critical area - Leading to any transfusion - Probable fatal bleeding - Definite fatal bleeding											
16.	Bleeding events	CRF/Medical notes	Minor bleeding: Not meeting major bleeding criteria				X	X	X	X	X			Secondary Outcomes
17.	Post-Operative	CRF/Medical notes	Protocol-specified MALE and MACE events including: - Major or minor amputation (trial limb) - Reintervention (trial limb) - Venous thromboembolism - Major amputation (contralateral limb) - Acute coronary syndrome - Ischaemic stroke				X	X	X	X	X			Secondary Outcomes

Assessment		Source Data	Data type/Measure	Screening	Baseline assessment	Randomisation	Clinical Assessment: 2 months	6 month Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up	AD HOC	Responsible for Data Collection	Justification
			- Recurrent CLTI											
18.	Healing of tissue loss		Healing tissue loss defined as full epithelialisation (yes/no)				X	X	X	X	X			Secondary Outcomes
19.	Patency following revascularisation	CRF/Medical Notes	- Primary patency of artery (yes/no) - Secondary patency of artery (yes/no)				X	X	X	X	X			Secondary Outcomes
20.	Reintervention rates	CRF/Medical notes					X	X	X	X	X			Secondary Outcomes
21.	Resource Use	Questionnaire / CRF	Client Service Receipt Inventory (CSRI)					X	X	X	X	X	Participant reported / Site Research team	Secondary outcome
22.	Qualitative Interviews	Audio recordings										X		Qualitative/SWAT
23.	SAEs / SARs	Medical notes /CRF										X	Site Research team	Pharmacovigilance
24.	Withdrawal	CRF										X	Site Research team	Withdrawal

12.2 Follow-up

Follow-up assessments will occur at specific intervals: within 2 months of the endovascular procedure (+ 1-month window), at 6 months (+/- 2-month window) and 12 months (+/- 2-month window) after randomisation. These assessments can be conducted in person (at a 2-month routine clinical appointment) or by telephone/video call/email communication. Early recruits will have additional follow-ups at 24 months (+/- 2-month window) and 36 months (+/- 2-month window) after revascularisation, if they reach those timepoints. The duration of follow-up will depend on the timing of entry into the trial, with follow-up ending either at 36, 24 or 12 months after revascularisation. The follow-up period will end 12 months (+/- 2-month window) after the last recruited participant has been randomised and initiates medication (at completion of their 12 follow-up assessments).

Participants will be sent two reminders by either the central research team or the research nurse via their chosen method of contact (text, email, post) to maximise follow-up.

Around 3 attempts will be made to contact the participant at each follow-up according to their preferred method of contact. If it is not possible to contact participants, a relative/carer may be contacted as an alternative. If all contact attempts are unsuccessful, a questionnaire booklet may be posted to the participants for them to complete and return. If a routine in-person outpatient visit is scheduled for clinical reasons within the follow-up visit windows, the follow-up questionnaires may be completed in-person, and/or clinical information collected at this visit may be used for follow-up assessments. Site staff will ensure, to the best of their knowledge, that participants are still alive before any contact attempts are made, by checking all local patient management systems available to them e.g. Spine data (England), Welsh Clinical Portal (Wales).

12.2.1 Month 2 – Clinical follow-up

Within two months of the revascularisation, data from the routine clinical follow-up appointment, attended by the patients and conducted by their clinicians, will be collected by research staff. Current medications, all primary composite and bleeding outcomes, and all secondary and tertiary outcomes other than health economic data will be assessed, including:

- **Primary composite and bleeding outcomes**

1. A composite event-free survival time of:
    i. acute limb ischaemia
    ii. major lower limb amputation
    iii. myocardial infarction
    iv. ischaemic stroke
    v. all-cause mortality
2. Major bleeding

- **Secondary outcomes**

1. Major adverse limb events (MALE) defined as amputation or any major reintervention;
2. Major adverse cardiovascular events (MACE) defined as recurrent CLTI, amputation affecting the contralateral limb, acute coronary syndrome or stroke;
3. BARC and TIMI major bleeding;
4. Minor bleeding;
5. Primary and secondary patency of artery;
6. Reintervention rates;
7. Healing of tissue loss;
8. Participant-reported health-related QoL (VascuQoL-6 and EQ-5D-5L);

- **Current medications** (including changes to trial drugs and reasons)

- **Tertiary outcomes**

1. MALE using other major definitions
2. MACE using other major definitions
3. Complications from trial medications

12.2.2 Month 6 and Month 12 (and Months 24 and 36 if applicable) – follow-up

All outcomes measured at 2 months will be assessed at the 6- and 12-months follow-up time points for all participants, and also at 24 and 36 months for those recruited earlier.

A healthcare resource use CRF/Questionnaire (adapted CSRI) will additionally collect:

- Hospital admissions, emergency department attendance and outpatient attendance via medical notes.
- Community-based resource use via patient-reported questionnaire supported by a patient diary as an *aide mémoire.*

12.2.3 Longer-term follow-up

Participants will be asked to consent to data-linked longer-term follow-up. Should our results indicate longer-term follow-up is desirable (for example, to further explore the impact of the trial medications on the primary effectiveness or safety outcome events), we will apply for further funding.

12.3 Qualitative Process Evaluation

12.3.1 Objectives

The objectives of the qualitative study are:

- To conduct a process evaluation of the CLARITY trial: Evaluate the delivery of the CLARITY trial and trial interventions through exploring trial conduct, trial acceptability (including barriers and facilitators to recruitment and retention), intervention adherence and contextual factors affecting trial delivery.
- To explore how the trial interventions work in the real healthcare setting: Explore feasibility, participant responses, acceptability to health professionals and patients, implementation, practicality and contextual factors that shape how the interventions work.

12.3.2 Semi-structured interviews

Semi-structured interviews will be conducted with a sample of CLARITY trial participants, patients who are eligible for the trial but decline to participate and health professionals involved in trial delivery. This method has been chosen to encourage participants to initiate and elaborate on topics most important to them which may not have been pre-empted if using survey-type closed questions.

Interview topic guides will be developed by the qualitative researchers in consultation with the CLARITY trial team and PPI representatives. Interview questions will then be developed iteratively in response to evolving study findings. The first five interviews with patients and the first five interviews with health professionals will be used as a pilot and interview questions reviewed after the pilot interviews have been carried out. Data from these interviews will be included in the analysis. Field notes will be made where applicable.

Interviews will explore contextual factors that shape how the trial interventions work in practice, patient responses to the interventions (e.g. acceptability and adherence), trial conduct, barriers and facilitators to trial recruitment and retention (including reasons for declining trial participation, where applicable), and patients' understanding of the trial, consent and randomisation process. Interviews will also explore patients' and clinicians' views on the balance of bleeding risk vs. gain (ischaemic events prevented), to better understand views on the 'net benefit' of antithrombotic therapy.

Through the qualitative interviews, the researcher will gain an impression of participants' understanding of the trial, consent and randomisation process. Any actionable points from the interviews will be reported to the TMG promptly so that if understanding remains poor, the TMG can propose solutions, review these with the PPI representatives, and present them to the TSC rapidly.

Depending on location and participant preference, interviews may be conducted via telephone/videocall or face-to-face. Face-to-face interviews with health professionals will be conducted at the participant's workplace. Face-to-face interviews with patients may take place in a private room in the hospital or at the patient's home. Lone working procedures will be followed where applicable. Patients will be invited to include a relative or friend in the interview if they wish. Interviews may bring back memories of a difficult and distressing time for participants – if participants become upset the interview can be stopped at any time, and the qualitative researcher will direct the participant to more support if required.

A password-protected Cardiff University laptop will be used to conduct telephone/videocall interviews. Interviews will be recorded using a password-protected digital voice recorder or a password-protected Cardiff University laptop.

12.3.3 Recruitment and sampling

We will aim to carry out patient interviews at around 1-3 months following trial enrolment (or following their invitation to participate in the trial), aiming to ensure patients have had sufficient time to recover from their endovascular intervention procedure and to be able to reflect on their experiences of the trial intervention if applicable. We will aim to carry out health professional interviews from the middle of the site's involvement in the trial so that health professionals can comment on any initial issues while having sufficient experience running the trial.

Potential interview participants (patients and clinicians) will be given a PIS about the qualitative interview study by the Research Nurse or local site PI. Once they have had time to consider the study information, potential interview participants will be asked by the local site PI or Research Nurse to complete a consent to contact form and consent form, which will be securely electronically transferred from the site to the research team. The qualitative researcher may then contact them directly to arrange a suitable time for an interview. If a completed consent form is not received, consent will be taken over the telephone/ videocall and recorded before the start of the interview.

Patient participants will be reimbursed for their time with a £20 gift voucher for taking part in the qualitative interviews. No other financial incentives will be provided for participants enrolled on the study.

Interview participants will be sampled purposively to maximise diversity. The sampling strategy for patients will be developed to include participants from each of the three treatment allocation arms (if applicable) and different trial sites, aiming for a range in terms of age, gender and ethnicity. The sample strategy for health professionals will be developed to include representation from around 4-6

different trial sites and variations in HCP roles (e.g. Research Nurse, Vascular Surgeon, Interventional Radiologist). We anticipate that interviews with around 10-20 health professionals and 20-30 patients (including up to 10 patients who have declined to participate in the trial) will be sufficient to encompass a breadth of views. The qualitative researchers will make pragmatic decisions in consultation with the trial team regarding when enough is known about certain themes (i.e. data saturation has occurred) and no further sampling is necessary.

13 Pharmacovigilance

The PI at each site is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All serious adverse events (SAEs) must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 13.2). This includes SAEs related to IMPs.

The trial population comprises mainly elderly, unwell participants. Acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke, major bleeding and death are common. As these are composite primary outcomes of the trial, they will be recorded on the Primary Composite and Bleeding Outcomes CRF as part of data collection within 24 hours of knowledge of the event, and therefore not subject to expedited reporting on an SAE form. See the Adverse event reporting procedures flow diagram (Figure 2 on page 44).

13.1 Definitions

Table 3. Definitions of Adverse and Serious Adverse Events and Reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which is not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued use of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.
**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.
***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements defined in Table 3, for the purposes of this trial, the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Toxicity reactions of CTCAE grades 3 and above to trial IMPs (see Section 11.6)

These events should also be completed in the participant's medical notes.

The following adverse events are reasonably anticipated to occur in this population during routine care and treatment and as such, for the purposes of this trial, the following events will **not** require immediate reporting as SAEs:

- AEs as a result of IMP of Common Terminology Criteria for Adverse Events (CTCAE) grades 1 and 2.
- Loss of patency of the artery in the trial leg of CTCAE grades 1 and 2.

As stated above, acute limb ischaemia, major lower limb amputation, myocardial infarction, ischaemic stroke, major bleeding and death (all-cause mortality) are composite primary outcomes of the trial and are recorded the CRF as part of data collection, therefore they are not subject to expedited reporting at any grade on an SAE form.
These should be recorded on the Primary Composite and Bleeding Outcomes CRFs within 24 hours of knowledge of the event.

All anticipated events should also be completed in the participant's medical notes (see Figure 2).

Pre-existing conditions should only be reported if they meet the definitions for an SAE and if the condition worsens by at least one CTCAE grade.

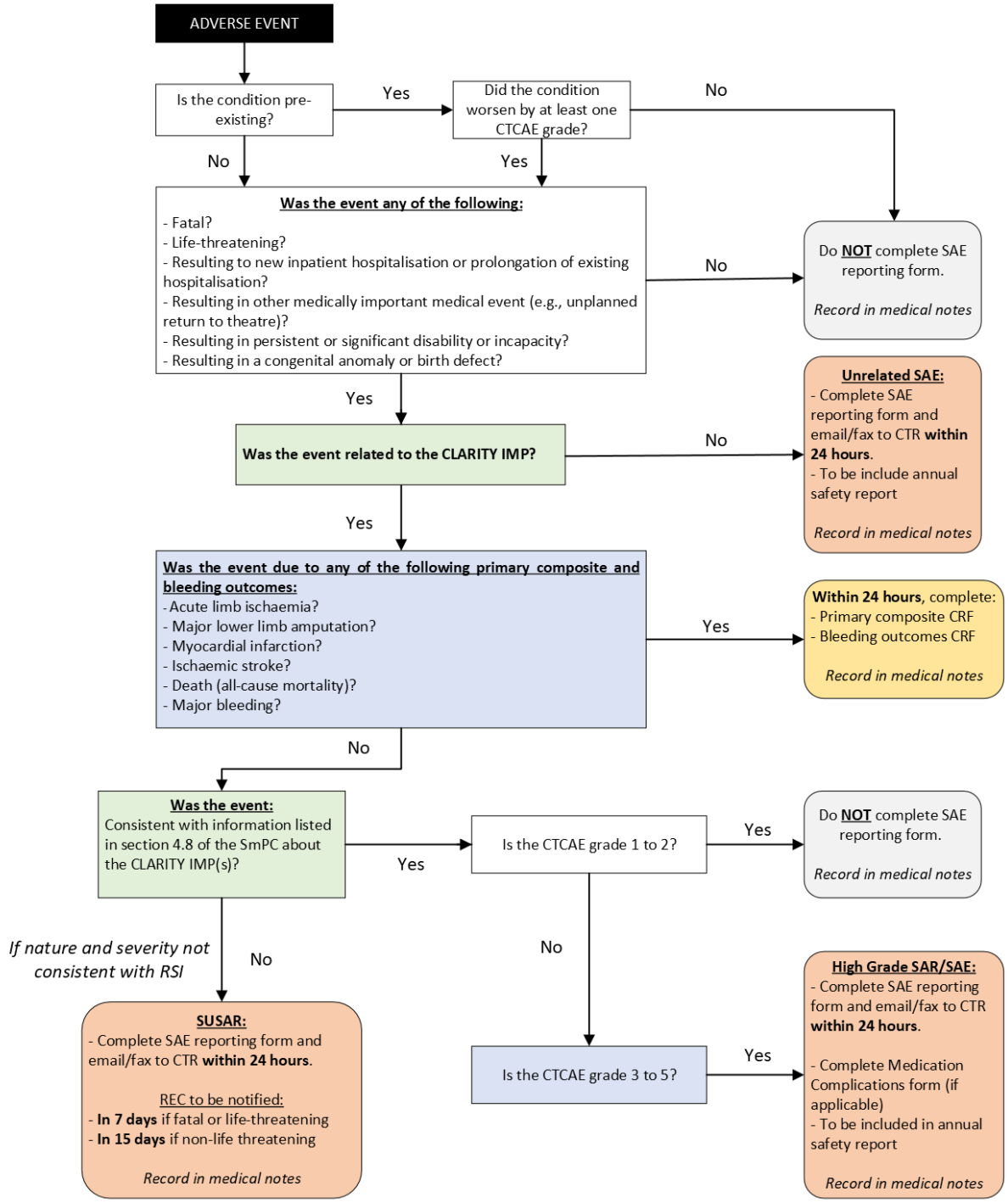

Figure 2. Adverse event reporting procedures flow diagram.
Serious events should be reported on specified forms within 24 hours of knowledge of the event.

13.3 Causality

Causal relationship of serious adverse events and serious adverse drug reactions in this trial will be assessed for the following:

Table 4. Causal relationship assessment of adverse events

IMPs: Clopidogrel, Aspirin and Rivaroxaban **nIMPs:** N/A **Procedures:** Endovascular procedure

The PI (or another delegated medically qualified doctor from the trial team) and CI (or another medically qualified doctor from the TMG) will assess each SAE to determine the causal relationship according to the following categories:

Table 5. Definition of causal relationship with IMP

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, and other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the PI (or delegate) cannot be downgraded by the CI (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The CI (or another delegated appropriately qualified individual) will assess each SAR to assess expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

SARs which add significant information on the specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Any AEs causally related to the endovascular procedure are likely to occur during and immediately after the procedure before the patient starts the trial medication. However, loss of patency of the trial leg is an expected AE related to the endovascular procedure and a secondary outcome measure.

Anticipated treatment-related AEs of grade ≤2 are not subject to expedited reporting. These should be completed in the participant's notes and submitted to the CTR in the normal timeframes for CRFs.

Any AEs that are solely causally related to the endovascular procedure are not subject to expedited reporting. These should be completed in the participant's notes.

The table below lists the RSIs that should be referenced:

Table 6. Reference Safety Information

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Clopidogrel	SmPC for Clopidogrel 75mg tablet to be used as RSI	Section 4.8 of SmPC
Aspirin	SmPC for Aspirin 75mg tablet to be used as RSI	Section 4.8 of SmPC
Rivaroxaban	SmPC for Rivaroxaban 2.5mg tablet to be used as RSI	Section 4.8 of SmPC

RSI on any CTR trial will be reviewed regularly according to CTR procedures.

13.5 Reporting procedures

13.5.1 Participating site responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that they have performed the seriousness and causality assessments. Investigators should also report SAEs to their health boards or trust in accordance with local practice.
A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, month or year of birth and initials. The participant's name (or any other personal identifier) should not be used in any correspondence.
It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

SAEs should be reported from the time of signature of informed consent, throughout the treatment period up to, and including the participant's final follow-up visit (12, 24 or 36-months) or 30 days after withdrawal from trial treatment (whichever is soonest). SARs (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow-up as defined in the protocol (page 44).

SAEs should be graded using the National Cancer Institute (NCI) CTCAE Version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event / Adverse Reaction
- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

AEs will **not** be recorded in this trial. All such non-serious events, whether expected or not, should be recorded in the patient medical notes as per routine procedures.

13.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow-up information must be provided on a new SAE form.
Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the CI (or their delegate) for an assessment of expectedness.
Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA and Main Ethics.

13.6 SUSAR reporting

North Bristol NHS Trust is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (National Competent Authorities (NCAs) and relevant ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.
- SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.
- If the report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life-threatening.

Any additional, relevant information must be reported within a further 15 days.

13.7 Unblinding for the purposes of SUSAR reporting

Not applicable as the drug allocations are not blinded.

13.8 Safety reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA REC and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.
The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

13.9 Contraception and pregnancy

13.9.1 Contraception

While clinical studies suggest that aspirin doses up to 100 mg/day appear safe for restricted obstetrical use under specialised monitoring, there is no clinical data on clopidogrel exposure during pregnancy, making its use inadvisable. Similarly, the safety and efficacy of rivaroxaban in pregnant women are unestablished, and animal studies have shown reproductive toxicity.

People of childbearing potential entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least 7 days after the last dose of clopidogrel, aspirin and clopidogrel, or aspirin and rivaroxaban (based on section 4.4 of the drug SmPCs and the NICE Clinical Knowledge Summary guidance on the discontinuation of clopidogrel and rivaroxaban before surgery for people with a high risk of bleeding (33,34). A highly effective method of contraception is considered as having a failure rate of less than 1% per. Some acceptable contraception methods are listed below;

- combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*
- sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.
**These contraception methods are considered to be low user dependency.*

13.9.2 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol (for example, some trial protocols may state that SAEs should be reported during the trial treatment period and up to 30 days after the last date of treatment, this timeline would also apply to the reporting of pregnancies). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

13.10 Urgent Safety Measures (USMs)

An urgent safety measure (USM) is an action that the Sponsor, CI or PI may carry out to protect the subjects of a trial against any immediate hazard to their health or safety. Any USM relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Randomisation

Within 10 days of the endovascular procedure being performed, participants will be individually allocated in a 1:1:1 ratio to one of the initial three trial arms: (1) clopidogrel alone, (2) aspirin plus clopidogrel or (3) aspirin plus low-dose rivaroxaban for up to 36 months. Covariate-adaptive randomisation will be used to minimise the imbalance of key covariates with a random element apply to reduce the risk of subversion. These key covariates are:

- target artery (including iliac plus common femoral endarterectomy, iliac plus femoropopliteal, femoropopliteal, femoropoplital plus tibial, tibial, Iliac and tibial, hybrid with common femoral endarterectomy)
- trial site
- antiplatelet loading at the time of procedure (yes/no)

If one arm is dropped due to futility after the interim analysis (see Section 15.1.1.), the randomisation ratio will be adjusted to 1:1 between the two remaining arms.

The randomisation procedure will be implemented via a web-based remote system (available 24 hours a day) with telephone back-up as described in Section 9.5.2. Full details will be provided in a separate randomisation protocol.

14.2 Blinding

The CLARITY trial does not use blinding of patients or clinicians. The statistician will perform the primary analysis blind to allocation.

14.3 Sample size

We aim to recruit 1239 participants over 36 months and follow them up for a maximum of 36 months if recruited earlier in the trial, or a minimum of 12 months if recruited later. Assuming a 12-month event-free survival rate of 65.0% in the clopidogrel alone arm; an increase to 75.6% in at least one of the intervention arms, corresponding to a hazard ratio of 0.65 (10,11,14,35), a dropout/loss to follow-up rate of 8%/year (unpublished BASIL 3 data); a two-group log-rank test of equal exponential survival with a two-sided alpha of 2.5% (accounting for the three-arm design) and 90% power requires 387 primary outcome events (157 expected in the clopidogrel alone arm, 115 in each of the combination arms) to be observed (BASIL 3 data provided by Chief Investigator). Given the 36-month recruitment period (assuming 25%, 35% and 40% recruitment in the first, second and third year, respectively) and a maximum follow-up period of 36 months, this translates into 413 participants per arm, or 1239 in total (calculated with ART version 1.1.0 using Stata version 17.0) (36,37).

14.4 Missing, unused & spurious data

Participants with incomplete follow-up will enter the primary time-to-event analysis as right-censored observations. Further detail will be provided in the Statistical Analysis Plan (SAP).

14.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the trial

Progression criteria for the internal pilot phase are described in Section 9.12. There is the potential for the trial to terminate early if our funder assesses the trial as not being feasible following the assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

14.7 Inclusion in analysis

All randomised participants with non-zero follow-up time will be included in the primary intention-to-treat analysis. As part of sensitivity analyses, ineligible participants will be excluded from the analysis, and alternative analysis populations (as described in Section 15.1) will be used.

15 Analysis

15.1 Main analysis

The final analysis will be performed after the end of the trial follow-up period, which is 48 months after the start of recruitment. Baseline demographic and clinical characteristics will be summarised descriptively by arm.

The primary analysis will be an intention to treat (ITT), including all randomised participants with non-zero follow-up time.

For the composite primary outcome (time from randomisation to the first occurrence of any element of the composite), a two-level Cox proportional hazards regression model will be fitted to estimate hazard ratios, including fixed effects for allocation and random effects to model heterogeneity between sites. Participants are censored at the end of the planned follow-up period (36 months), at

the end of the trial follow-up period, or (in case of dropout) at the time of their last follow-up, whichever occurs first. Regression analysis results will be presented as point estimates with confidence intervals and p-values from a log-rank test, and Kaplan-Meier curves of cumulative event rates at 36 months (31,32) will be generated to compare arms over time.

Primary estimand

Primary outcome question: In patients following endovascular intervention for CLTI, what is the event-free survival time of the three commonly used antithrombotic regimens (clopidogrel; aspirin plus clopidogrel; aspirin plus low-dose rivaroxaban), for those with a non-zero follow-up time?

The primary estimand is described by the following attributes:

- **Population**: Adults who are first time in CLARITY trial undergoing percutaneous or hybrid endovascular intervention for CLTI of the lower limbs, with atherosclerosis as the cause of CLTI, and with non-zero follow-up time.
- **Endpoint**: The clinical effectiveness endpoint is a composite event-free survival time examined over the trial duration. These events included acute limb ischaemia, major lower limb amputation, myocardial infarction, ischaemic stroke, and all-cause mortality. Participants are censored at the end of the planned follow-up period (36 months), at the end of the trial follow-up period, or (in case of dropout) at the time of their last follow-up, whichever occurs first.
- **Treatment condition**: Clopidogrel, aspirin plus clopidogrel, and aspirin plus low-dose rivaroxaban, regardless of discontinuation or initiation of the antithrombotic regimens.
- **Remaining intercurrent events**: Death is incorporated into the clinical effectiveness primary outcome. Treatment discontinuation is covered by the previous attribute.
- **Population-level summary**: Hazard ratios, including fixed effects for allocation and random effects to model heterogeneity between sites. Regression analysis results will be presented as point estimates with confidence intervals and p-values from a log-rank test, and Kaplan-Meier curves of cumulative event rates at 36 months (31,32) will be generated to compare arms over time.

The primary safety outcome analysis will also use a two-level Cox regression as described above but include only those participants who received at least one dose of their allocated medication ('on-treatment' population). This analysis will include safety events that occurred after receiving the first dose of the trial medication and within 5 days after receiving the last dose.

Secondary outcomes will also be analysed based on ITT (for effectiveness outcomes) or 'on- treatment' populations (for safety outcomes) and using appropriate two-level regression models depending on the type of outcome: Cox regression for time-to-event outcomes, linear regression for continuous outcomes such as QoL measures (allowing for repeated measures where appropriate), and logistic regression for binary outcomes such as reintervention rates.

Table 7. Planned outcome analysis

Outcome	Measure	Analysis	Time frame
Composite primary outcome - Composite event-free survival time of the following:	Acute limb ischaemia	Two-level Cox regression	2m, 6m, 12m, 24m and 36m
	Major lower limb amputation	Two-level Cox regression	
	Myocardial infarction	Two-level Cox regression	
	Ischaemic stroke	Two-level Cox regression	

Outcome	Measure	Analysis	Time frame
	All-cause mortality	Two-level Cox regression	
Primary safety outcome	Major bleeding (ISTH definition)	Two-level Cox regression	2m, 6m, 12m, 24m and 36m
Secondary outcomes	MALE (defined as amputation or any major reintervention)	Two-level Cox regression	2m, 6m, 12m, 24m and 36m
	MACE (defined as recurrent CLTI, amputation affecting contralateral limb, acute coronary syndrome, ischaemic stroke)	Two-level Cox regression	
	Major bleeding (BARC definition)	Two-level Cox regression	
	Major bleeding (TIMI definition)	Two-level Cox regression	
	Minor bleeding	Two-level Cox regression	
	Primary patency of artery	Two-level logistic regression	
	Secondary patency of artery	Two-level logistic regression	
	Reintervention	Two-level logistic regression	
	Healing of tissue loss	Two-level logistic regression	
	VascuQoL-6	Two-level linear regression	Baseline, 2m, 6m, 12m, 24m and 36m
	EQ-5D-5L	Two-level linear regression	
Tertiary outcomes	MALE using other major definitions	Two-level Cox regression	2m, 6m, 12m, 24m and 36m
	MACE using other major definitions	Two-level Cox regression	
	Complications from trial medications	Two-level logistic regression	Baseline, 2m, 6m, 12m, 24m and 36m

The components of the composite primary outcome will also be analysed individually; for this, we will use competing risk models with all-cause mortality being a competing risk for other non-fatal outcomes. We will also explore the use of recurrent event models to reflect that patients may experience more than one outcome event and/or the same event multiple times (38,39). The distribution of different types of events over time will be visualised using e.g. swimmer plots.

In additional secondary analyses, we will calculate win statistics such as the win ratio or win odds to more directly express the probability of one treatment being better than the other, or being the best (40,41). We will also estimate and compare proportions of primary outcome events (as a composite and also each component individually) at 12 and 24 months, respectively.

We will consider the impact of different types of intercurrent events such as the timing of starting trial medication, discontinuing the prescribed medication, crossing over between arms, or using non-trial medication. To this end, sensitivity analyses will be performed using the 'on-treatment' population (for effectiveness outcomes) as well as other meaningful analysis populations e.g., based on the medication actually received ('as-treated') or including only those who fully adhered to their allocated

regimen ('per-protocol'). These will be specified in detail in the SAP using the estimands framework (40). Additional adjusted analysis incorporating important covariates, as well as potential subgroup analyses, will be specified in the SAP with stakeholder and PPI input (41). Variables likely to be considered include arterial territory (such as femoropopliteal or tibial), devices used during the intervention such as drug-eluting technology and diabetes.

If key assumptions such as proportional hazards do not hold, we will try alternatives such as accelerated failure time models or adding a stratification variable or time-varying covariate. To assess potentially informative censoring and non-compliance, an inverse probability-of-censoring weighted analysis will be undertaken.

A comprehensive SAP will be finalised by the trial statistician, with support from the TMG, agreed by the TSC, and signed off prior to any analysis being conducted. Results will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement and its extensions to multi-arm (42) and adaptive designs (43).

15.1.1 Sub-group & interim analysis

A planned interim analysis of the co-primary outcomes will be conducted when 60% of the planned maximum number of primary outcome events have been observed. The interim analysis will compare each of the combination arms against the clopidogrel-only arm (which has the lowest predicted clinical effectiveness) using futility-stopping criteria based on conditional or predictive power which leads to minimal overall power loss. These criteria will be finalised during the trial set-up phase and fully specified in the SAP.

If the futility of the clopidogrel-only arm is shown in at least one of the two comparisons, the trial will continue with the two combination arms only. Participants in the futile arm will continue with the allocated drug and will be followed up until the end of the trial. If all three arms continue through to the final analysis, each of the combination arms will be compared to clopidogrel only, each at 2.5% alpha. If only one is significantly better, it will be declared the most effective. If both combination therapy arms are significantly better, they will then be compared against each other using the full 5% alpha, thus ensuring strong control of the familywise type I error rate.

15.2 Qualitative analysis

Interviews will be recorded with the consent of participants and transcribed verbatim and anonymised by a professional transcription company. Interview transcripts will be quality-checked and uploaded to NVivo 12 for analysis. Thematic analysis will be used to identify key patterns in the interview data. This will consist of a series of steps: familiarisation with data, generating initial codes, and searching, reviewing and defining themes. Themes that relate to the objectives of the research will be identified, but analysis will also allow new themes generated by interviewees to be identified. A proportion of the transcripts will be double-coded, and the thematic framework will be discussed and refined by the trial qualitative researchers. Full details of the analysis will be included in the qualitative analysis plan (QAP).

15.3 Cost-effectiveness analysis

A health economic evaluation will provide evidence of the relative costs and outcomes of these common antithrombotic strategies to inform future decision-making. The evaluation will be designed, conducted and reported following best-practice guidelines conforming to the Consolidated Health Economic Evaluation Reporting Standards (44).

A UK NHS/Personal Social Services Perspective will be taken for the base case. Acknowledging the wider economic impact of CLTI and its treatments, a restricted societal perspective will report the additional costs to patients and carers (e.g. out-of-pocket expenses for travel) alongside capture of time away from usual activities (such as work) as part of a supplementary analysis.

Resource use and costs:
We will collect information from trial records and patient-reported outcome measures to assess resource use as part of the CLARITY data collection schedule (see Table 2). We will use an adapted CSRI to capture resource use. We will work with the CLARITY PPI group and research team to develop this during the trial set-up to ensure we capture the key drivers of resource use associated with the use of the different antithrombotic strategies (e.g. hospital re-admission related to an adverse event), balanced with the need for a proportionate measure to minimise patient and researcher burden in the collection of resource use.

We will use published UK unit costs to value resource use in £ sterling to the most relevant price year available at the time of final analysis. We will present the total and per-participant costs associated to produce a comprehensive summary of resource use and associated costs associated with the intervention and comparator groups.

Health outcomes:
The EQ-5D-5L will be used in the economic analysis, with the schedule for data collection and approach summarised in Table 2. This has been chosen as it is the preferred measure for capturing HRQOL in adults by NICE. We will use the most appropriate method recommended at the time of analysis to derive utilities for a UK population (e.g. pending completion of the new UK 5L valuation set or using a 5L-3L cross-mapping function) (45). With the use of the VascuQoL-6 as a condition-specific measure of HRQOL within CLARITY, we will use this measure to present a secondary cost-effectiveness analysis.

Primary analysis:
A cost-utility analysis will be conducted based on the follow-up of 36 months of the ITT population alongside a secondary analysis at 12 months to assess the short and longer-term cost-effectiveness of the antithrombotic strategies. Discounting at 3.5% will be applied to costs and outcomes beyond 12 months. A within-trial analysis will be conducted.

We will consider the feasibility of undertaking an economic model to extrapolate costs and outcomes beyond the three-year time horizon based on the trial findings and the plausibility of making longer-term estimations from robust literature input available (e.g. systematic reviews) and/or clinical expert opinion. We will undertake a rapid review of relevant literature (including UK HTA reports from NICE) to identify potential models and decide on a suitable model structure. Whilst we expect this to be a relatively simple model (e.g. decision tree and/or Markov), we will make the final decision (e.g. whether a more complex simulation model is necessary) as part of developing our health economic analysis plan Our analysis plan will be prepared in collaboration with the CLARITY research team alongside the development of the SAP. As required, the final economic analysis plan will follow the decisions made following the adaptive interim analysis proposed in CLARITY. We will use consistent methods to produce the within-trial analysis and, if applicable, inform the model e.g. cost and outcome inputs.

An adjusted analysis using suitable regression models will be performed to calculate incremental costs and quality-adjusted life years (QALYs). The pattern of missing data (e.g. missing at random) will be examined and accounted for by suitable methods such as multiple imputation (MI) for missing

observations of cost and EQ-5D 5L measure. Imputed data based on the ITT population will be used for the base-case analysis for both analyses. An incremental cost per QALY gain at 12 and 36 months for each antithrombotic strategy included in the final analysis will be calculated, with the presentation of incremental net monetary benefit. We will use appropriate decisions such as identifying dominant strategies (if all strategies remain in the final analysis) in reporting our findings. Consistent with the statistical analysis, alternative analysis populations will be used. Any modelling of costs and outcomes beyond the trial time horizon will be exploratory analysis.

Deterministic and probabilistic sensitivity analyses will be conducted to explore the uncertainty in our findings from our cost-utility analysis. Cost-effectiveness acceptability curves will be presented to consider which optimal antithrombotic strategy represents value for money, based on a societal threshold of £20,000-£30,000 per QALY gain. A secondary cost-effectiveness analysis will be undertaken to assess the incremental cost-per-point improvement in VascuQoL-6 score.

16 Data Management

Source data is defined as *"All information in original records and certified copies of original records of 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."*

There is only one set of source data at any time for any data element, as defined in the site source data agreement. The source data for CLARITY will be from a variety of sources as described in Table 2.

16.1 Data collection

Data will be collected using an electronic CRF system with paper CRF backup for PROMs. Training for completion of trial CRFs will be provided to the appropriate trial staff before trial commencement at site initiation.
Data collection data will be captured by sites in real-time as events arise as well as at fixed points by request of the trial team.

16.2 Completion of Case Report Forms (CRFs)

All data collection will be completed using web-based CRFs, held on a secure encrypted system hosted by Cardiff University. It is accessed by username and password and complies with the General Data Protection Regulation 2016. If the web-based system is not accessible, the data will be inputted by local site staff once it is accessible. A full Data Management Plan (DMP) for the CLARITY trial will accompany this protocol and will be stored in the TMF.

The trial's DMP provides an overview of the data management process to be applied to the trial to assure data quality. The DMP will:
- Define the different types of data collection documents used
- Define the procedures by which data will be collected, entered, verified and cleaned
- Define the procedures to securely manage and store the data
- Define requirements for the retention of trial data
- Describe the processes and data security measures involved in data linkage with NHS England (formerly NHS Digital) datasets

16.2.1 Electronic CRFs

The system can be accessed on:

https://clarity.ctr.cardiff.ac.uk

A user password will be supplied to investigators upon completion of all processes required prior to opening. Site staff will only have access to their participants and not see other sites' participants. Web-based data collection forms should be completed as described in the CLARITY Site Manual.

Electronic tablets will be made available to recruiting sites to facilitate direct data entry into the trial database.

16.2.2 Paper CRFs

Paper CRFs will be used for PROs if the electronic database is not available, or if participants prefer follow-up via post. Data will then be entered into the database by site staff at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.
CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.
If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form pages should not be altered.
All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participants' CRFs.
The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in a timely manner. Further details of data management procedures can be found in the CLARITY DMP.

16.3 Qualitative Data Management

Recordings of qualitative interviews will be captured on a password-protected and encrypted recording device. Demographic data about participants will be captured on a password-protected Cardiff University laptop and/or on completed paper consent to contact forms. All files containing personal data will be password-protected and stored in a folder on the Research drive of the secure Cardiff University server with restricted access. A trial identification number will be used for filenames, which will not include any personal details such as participants' names. Hard copies will be stored securely at the site in a locked cupboard.

Completed consent forms and consent to contact forms will be securely electronically transferred by the research nurse at the site to the research team at Cardiff University via FastFile or a Trust-approved file transfer system, and uploaded to the Research drive of the secure Cardiff University server. Interview recordings will be transferred from portable devices to the Research drive of the secure Cardiff University server as soon as practicably possible and permanently deleted from the portable device. Paper field notes will be typed up and saved on the Research drive of the secure Cardiff University server as soon as practicably possible, and hard copy notes shredded.

Interview recordings will be securely sent to be transcribed and anonymised by an approved transcription company. A data processing agreement will be in place between Cardiff University and the transcription company. Returned transcripts will be saved on the Research drive of the secure

Cardiff University server and checked for any errors in transcription or anonymisation. Interview transcripts will be uploaded to NVivo 12 for analysis.

Participants will not be personally identified in any report or publication of findings. Written quotes of what the participant has said in the interview may be used word for word, but quotes will be anonymised. Participant names will not appear in any publications. All trial-related records will be stored for a minimum of 15 years. Full details of qualitative data management are specified in the CLARITY Qualitative Data Management Plan.

16.4 Data sharing integrity, security and integrity

The personal data (including name, address, email address and telephone number) of participants will be stored on a dedicated trial database. The data will be entered into a password-protected main database on secure Cardiff University-maintained servers. Clinical data will be exported for statistical analysis. Patients' identifiable data will be encrypted and not exported from the trial database. Participants will consent to clinical members of the research team viewing their records to gain baseline data and healthcare resource usage data during the follow-up period. If participants consent to be contacted about the results of the trial, their contact details will be stored in encrypted files and will only be accessible by delegated members of the trial team for purposes specified in the PIL. Participants will be asked to express their preferred method of contact (e.g. email or postal address) for this purpose and this question will be asked explicitly on the consent form.

A unique participant identification number (PID) will be assigned sequentially by site to each participant as they are allocated to a treatment arm. The PID will be used for participant identification and data collection throughout the trial.

Clinically trained members of the research team (research doctors and/or nurses) will have access to hospital and GP records for the collection of resource usage data. This is described in the PIS and informed consent form (ICF). Members of the research team will also have access to trial-specific data, and consent for this will be sought. Qualified Quantitative researchers, Trial Statisticians (TS) and Data Managers (DM) at the Centre for Trials Research, Cardiff University will be responsible for data analysis.

Personal data collected for the purposes of contacting participants will be stored or accessed for 3 to 6 months after the trial activities have concluded (activities include sending questionnaires/vouchers, dissemination of results and potential communications about safety) and will not be archived.

Electronic files will be stored securely on a Cardiff University research drive with restricted access. Paper files will be stored in a locked cupboard for up to 5 years after the database lock and then archived onsite for 10 years.

17 Study within a trial (SWAT)

Our SWAT proposes to gain an understanding of how to improve the recruitment of high-risk groups to antithrombotic trials.

Knowledge gap: Some patients have the presence of previously symptomatic atherosclerosis in more than one arterial bed (coronary arteries, peripheral arteries, and cerebrovascular arteries) defined as polyvascular disease, and are known to be at higher risk of both ischaemic and bleeding events. A history of at least 2 of the following is indicative of polyvascular disease: Ischaemic heart disease,

carotid artery disease, peripheral arterial disease. Patients with polyvascular disease potentially derive a greater benefit from escalated antithrombotic regimens such as aspirin plus clopidogrel or aspirin plus rivaroxaban. Unfortunately, this group is also known to have a higher risk of bleeding and is often excluded from RCTs as a result (46).

Context warranting multiple long-term conditions SWAT: The bleeding risk of some patients with polyvascular disease will exclude them from CLARITY, as they have been excluded from other major RCTs of antithrombotics for coronary artery disease, peripheral arterial disease and deep vein thrombosis. The excluded group fit into even more underserved populations than the main trial population due to extreme multimorbidity.

Generalisability of learning from the SWAT: All antithrombotic trials, in cardiology, vascular surgery and deep vein thrombosis/pulmonary embolus will exclude higher-risk patients to some degree. Learning will apply to all future trials examining antiplatelet and/or anticoagulant medication across any field.

Methods: A mixed methods study will be performed. Initially, a quantitative review of trial screening logs will identify patients with polyvascular disease who have been excluded from the trial and explore clinical characteristics leading to exclusion. A patient is eligible for the SWAT if they have been excluded from the main trial for any reason and have polyvascular Disease.

A qualitative study of excluded patients (n=10-20) and participating clinicians (n=10-20) will then be performed to understand how to better recruit this population for future research. Patient and stakeholder clinicians' views and beliefs on the balance of bleeding risk vs. gain will also be explored, to better understand the patient's view on the 'net benefit' of antithrombotic therapy in terms of ischemic events prevented vs. bleeding events caused. This 'net benefit' is sometimes discussed in the literature but there has never been a process to examine the patient or clinician perspective (47). Our group has pre-existing experience in mixed methods research to understand clinician and patient views within complex shared decision-making. Patient participants will be reimbursed for their time with a £20 gift voucher for taking part in an interview as part of the SWAT.

How this SWAT builds on existing knowledge: Patients are currently excluded from trials on theoretical grounds despite the patient and clinician perspective being unknown. Understanding the clinician and patient perspective should allow more patients with polyvascular disease to be recruited into antithrombotic RCTs in the future. The Northern Ireland Trials MRC Hub for Methodology Research SWAT registry has no entries for this type of study.

18 Protocol/GCP non-compliance

The PI should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their Standard Operating Procedure (SOP).

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g., consent process or administration of trial intervention) or GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a non-compliance form and filed in the CLARITY trial master file (TMF).

A CTR SOP is in place describing the procedure for identifying non-compliances, escalation to the central safety team and assessment of whether a non-compliance/deviation may be a potential Serious Breach.

19 End of Trial definition

The end of the trial is defined as the date of final data capture (i.e., the act of entering the final data into the trial database) of the last participant to meet the trial endpoints.

Database lock, defined as the final lock of the database when no further locks are required, will be requested when all cleaning and validation of the data in the database is complete (within 6 months of the end of the trial).

The sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or 15 days if the trial is terminated early.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 10 years in line with the North Bristol NHS Trust Sponsor and Cardiff University archiving process for clinical research. All essential documents generated by the trial will be kept in the TMF. The CTR will archive the TMF and TSFs on behalf of the Sponsor. This data will be stored confidentially on password-protected servers maintained on the Cardiff University Network. Files will only be accessible to researchers responsible for the running of the trial and the CI.

In line with the International Conference on Harmonization (ICH) GCP requirement, electronic clinical trial data will be shared with the investigators at the site at the end of the trial. The processes for supplying a copy of the clinical trial data is documented in the Returning Data to Trial Sites SOP (as detailed in the data management plan). The PI is responsible for the archival of the ISF at the site on approval from the Sponsor.

Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

All procedures for data storage, processing and management will comply with the General Data Protection Regulations (GDPR) 2018. All paper records will be stored in a locked filing cabinet, with keys available only to researchers and the CI.

21 Regulatory Considerations

21.1 CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority (CA): MHRA.

Classification of whether any changes to the protocol are defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and if necessary, the sponsor representative, for approval before being submitted, via IRAS and email, to REC, HRA, and if necessary, the MHRA. The central trial team will alert all site trial teams and R&D departments once approval has been received for the amendment. The amendment history will be listed in the protocol and in the amendment log which is filed in the CLARITY TMF.

21.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.
This trial protocol will be submitted through the relevant permission system for global governance review depending on the location of the lead site i.e., Health Research Authority (HRA) for England-led trials.

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1996, and later revisions.

Approval will be obtained from the host care organisation which will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before the recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the trial, in addition to approval by NHS R&D. Minor amendments will not require prior approval by the REC.

If the trial is stopped due to serious adverse events or an urgent safety measure, it will not be recommenced without reference to the REC responsible for the trial. A summary of the results will be submitted to the REC responsible for the trial within one year of completion of trial closure.

21.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored securely and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian for this trial is the CI at North Bristol NHS Trust (Sponsor). This includes the collection of NHS number (or equivalent – e.g. CHI number in Scotland), name, date of birth, gender and postcode to register and trace participants with the Health and Social Care Information Centre (HSCIC), and the collection of NHS number (or equivalent) to utilise NHS data for future research through NHS England (formerly NHS Digital).

21.4 Indemnity

- Non-negligent harm: CLARITY is an academic, investigator-led and designed trial sponsored by North Bristol NHS Trust and coordinated by the CTR at Cardiff University. The Sponsor, CI, local PIs and CTR do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and therefore cannot offer any non-negligent harm indemnity (i.e. harm that has been caused through no fault of those conducting research). The Association of the British Pharmaceutical Industry guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

All participants will be recruited at NHS sites and therefore the NHS Clinical Negligence Scheme will apply and provide unlimited cover for NHS staff, medical academic staff with honorary contracts and those conducting research against negligent harm.

North Bristol NHS Trust does not accept liability for any breach in the other NHS Organisations' duty of care, or any negligence on the part of employees of these NHS Organisations.

Human Research Authority statement (https://www.hra.nhs.uk/about-us/news-updates/indemnity-cover-nhs-staff-delivering-research/): Research is a core NHS activity. NHS staff (including honorary contract holders) undertaking research as part of their job role are covered by NHS Resolution indemnity schemes if working for a member of those schemes, subject to the usual scheme terms and conditions. The Clinical Negligence Scheme for Trusts (CNST) and Clinical Negligence Scheme for General Practice (CNSGP) provide cover against harm to patients arising from clinical negligence in the conduct of research. The Liabilities to Third Parties Scheme (LTPS) provides cover for Employer Liabilities in the conduct of research. These schemes provide cover for NHS staff conducting research, whether that activity is taking place within NHS premises, patients' homes, care homes, hospices or other spaces in which NHS researchers undertake NHS research. NHS research in England is research that has HRA and HCRW Approval.

21.5 Trial sponsorship

The trial is being sponsored by North Bristol NHS Trust with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2018.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol, the EU regulation and Good Clinical Practice as required by the regulations.

Delegated responsibilities will be assigned to the sites taking part in this trial. The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

21.6 Funding

This trial is funded by the NIHR HTA Programme (NIHR 154252).

22 Trial management

22.1 Project Team

The project team will meet at least fortnightly and will include the CI, trial lead (TL), TM, DMs, TS, trial administrator (TA), and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the TMG.

22.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS, and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). Recruitment will be carefully monitored and communicated amongst the team. They will also advise on the promotion and running of the trial and deal with any issues that arise.

The TMG will meet monthly by teleconference throughout the trial and annually face-to-face. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter which will be filed in the TMF.

22.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) comprising an independent chair, and two or three other independent members including a research partner/lay representative will meet twice a year. The TSC will meet prior to the trial launch to review the protocol, roles and responsibilities, timelines for subsequent meetings (particularly for the internal pilot and adaptive interim analysis) and agree on roles and responsibilities. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter which will be filed in the TMF.

22.4 Independent Data Monitoring Committee (IDMC)

To monitor accumulating data on safety and any trial intervention benefit, an Independent Data Monitoring Committee (IDMC) will be established. Like the TSC, the Committee will consist of an independent chair and two/three other independent members including a research partner, at least one clinician and a statistician. The first meeting will take place before the trial commences to review the Protocol. The main role of the IDMC is to review the data periodically (bi-annually) and also review the results of the planned interim analysis and make recommendations to the TSC. The IDMC will meet at least twice a year.

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the CLARITY trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial-related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. All consent forms will be monitored centrally.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

23.2 Audits & inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be a participant to inspection and audit by North Bristol NHS Trust under their remit as Sponsor.
The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/IRB review, and regulatory inspection(s), providing direct access to source data/documents.
The site must inform the CTR of any MHRA inspections.

24 Public Involvement and Engagement

Full details of the public involvement and engagement for the trial are summarised below and detailed in the CLARITY PI&E plan.

The CLARITY trial will have PPI representation on the TMG and TSC.

PPI representatives will review patient-facing materials to ensure they are presented suitably and will provide feedback throughout the trial to refine the methodology and to support the dissemination of activities and results.
A Patient Advisory Group of around 6-8 members with experience in CLTI will be set up and meet 3-4 times to discuss and provide feedback on various aspects of the trial, which may include reviewing patient-facing materials and data collection materials, discussing any recruitment issues, and inputting into interview analysis and dissemination.
PPI activities will be overseen by the PPI lead with support from the CI and Trial Manager.

A PPI impact log will detail the impact the PPI representatives have on trial design and management. Feedback questionnaires based on the 'cube framework' for assessing PPI impact in health research (48) will be used to review the process and quality of PPI representation in CLARITY, with results shared with the TSC, TMG and NIHR.

25 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group, as per the publication policy.

In addition to the requirements of the NIHR HTA Programme publication model, we will publish the main trial results in international, high-impact, peer-reviewed journals and present at vascular surgery research conferences. With the assistance of our collaborators and lay representatives, we will disseminate the trial findings to a wide NHS and general audience and vigorously promote the uptake of the trial results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups.

At a local level, we will interact with and promote research findings through wider NHS Trusts and the NIHR Clinical Research Networks. Nationally, we will engage with NICE, the Vascular Society of Great Britain and Ireland, the British Society of Interventional Radiology, the British Society for Endovascular Therapy, the Vascular Anaesthesia Society of Great Britain and Ireland, and the Vascular and Endovascular Research Network, as well as relevant charities such as the Douglas Bader Foundation. We anticipate the results directly impacting clinical antithrombotic guidelines, which to date do not

include recommendations regarding optimal antiplatelet/anticoagulant usage post-endovascular intervention.

26 Milestones

The CLARITY trial is a five-year trial with the following project timetable:

- Month 1-8: Trial and site set-up, contracts, regulatory approvals.
- Month 9-17: Internal pilot (assessed by progression criteria) and recruitment. Assess the acceptability of intervention and trial processes.
- Month 18-54: Continuation of RCT recruitment, follow-up and data collection, and interim analysis (when 60% of primary outcome events have been observed).
- Month 55-60: Data cleaning, statistical analysis, preparing HTA report, draft papers, and dissemination activities.

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