Full Study Title: SHOCkwave lithotripsy for Calcified plaques in patients with peripheral arterial disease: a pragmatic registry with in-depth automated plaque analysis – the SHOCC study.

Short Title: The SHOCC study.

Sponsor Reference No: 0831

Ethics (NHS REC) Reference: PENDING

IRAS number: 299307

Date and Version No: version 1.0; 14th September 2021

Chief Investigator:	Mr Athanasios Saratzis
Investigators:	Mr Patrick Coughlin Mr Daniel Carradice Mr Hany Zayed Mr Said Abisi Dr Narayanan Thulasidasan Dr Neghal Kandiyil Dr Raghu Lakshminarayan Mr Robert SM Davies Professor Robert D Sayers Mr Soroush Sorabi
Sponsor:	University of Leicester
Funder:	Shockwave Medical
Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and the Sponsor (University of Leicester).

Authors

Authors and **Collaborators** who have assisted with writing the protocol (they all approved the current version of the protocol):

- **Mr Athanasios Saratzis**, Associate Professor of Vascular Surgery, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK.
- **Mr Patrick Coughlin**, Consultant Vascular and Endovascular Surgeon, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
- **Mr Robert SM Davies**, Consultant Vascular and Endovascular Surgeon, University Hospitals of Leicester NHS Trust, Leicester, UK.
- **Mr Daniel Carradice**, Senior Lecturer in Vascular Surgery, Academic Vascular Surgical Unit Hull York Medical School & Hull University Teaching Hospitals NHS Trust, Hull, UK.
- **Professor Robert D Sayers**, Professor of Vascular Surgery, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK & Lead of the George Davies Peripheral Arterial Disease Research Group.
- **Mr Hany Zayed**, Consultant Vascular and Endovascular Surgeon, Guys' and St Thomas' NHS Foundation Trust, London, UK.
- **Mr Said Abisi**, Consultant Vascular and Endovascular Surgeon, Guys' and St Thomas' NHS Foundation Trust, London, UK.
- **Dr Narayanan Thulasidasan,** Consultant Vascular Radiologist, Guys' and St Thomas' NHS Foundation Trust, London, UK.
- **Dr Neghal Kandiyil**, Consultant Vascular Radiologist, University Hospitals of Leicester NHS Trust, Leicester, UK.
- **Dr Raghu Lakshminarayan**, Consultant Vascular Radiologist, Hull University Teaching Hospitals NHS Trust, Hull, UK.

- Signature Page

Chief Investigator Name: **Mr Athanasios Saratzis**

Chief Investigator signature: _____

Date: _____

Sponsor Representative Name: _____

Sponsor Representative signature: _____

Date: _____

Principal Investigator Name: _____

Principal Investigator signature: _____

Date: _____

(This page must be replicated for each site)

TABLE OF CONTENTS

To update table of contents (TOC), hover cursor over the top left hand corner until the whole TOC highlights. Press the 'F9' button. Choose 'update entire table'.

1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	SHOCkwave lithotripsy for Calcified plaques in patients with peripheral arterial disease: a pragmatic registry with in-depth automated plaque analysis – the SHOCC study.
Study Design	Prospective multicentre cohort study
Participants	• Adult patients with Peripheral Arterial Disease (PAD) and Chronic Limb Threating Ischaemia (CLTI) referred to secondary care, who undergo Intravascular Lithotripsy (IVL) as part of their standard NHS care. • Clinicians performing the intravascular lithotripsy procedure on study participants
Planned Sample Size	Main study: 60 patients. Sub study participants: 20. Clinicians: 10.
Follow-up duration	Six (6) months.
Planned Study Period	Start date: 01/10/2021 Study end date: Twenty one (21) months after start date. • 3 months for NHS sites' set up and regulatory approvals • 9 months for recruitment and imaging analyses • 6 months for follow-up • 3 months for analyses and dissemination Overall duration of the study: Twenty one (21) calendar months.
Primary Aim and Primary Objective	Primary objective: Investigate the effect of intravascular lithotripsy on the patency of a lower limb atherosclerotic lesion in patients with symptomatic PAD treated in the NHS, six months after the procedure.
Secondary Aim(s) and Secondary Objective(s)	Secondary objectives: 1. To investigate whether patients require further angioplasty or other procedures in the six months post intravascular lithotripsy. 2. To investigate whether patients suffer any of the following complications; stroke, transient ischaemic attack, myocardial infarction, or lower limb amputation in the six months post intravascular lithotripsy. 3. To investigate whether patients are readmitted to hospital for PAD related treatment in the six months post intravascular lithotripsy. 4. To investigate whether changes in atherosclerotic plaque consistency are observed within three days post intravascular lithotripsy 5. To gather information about how and why clinicians decided upon this choice of treatment over alternative methods available in the NHS.

Primary Endpoint/Outcome Measure	Primary outcome measure: patency of the treated arterial atherosclerotic lesion based on duplex ultrasound measurement at six months after the procedure has taken place (recorded as a binary outcome i.e. yes or no).
Secondary Endpoints/Outcome Measures	**During the inpatient stay:** Additional treatments during the index procedure, including other endovascular treatments (e.g. application of stent or drug coated balloon therapy or any other intervention deemed necessary by each operator) All complications during the in-hospital stay Duration of in-hospital stay. **Thirty days after the procedure and at six months (final follow-up):** Re-intervention (open or endovascular - including re-intervention for other indications, which will be reported separately) Lower limb amputation Change in the treated atherosclerotic plaque consistency for patients requiring re-intervention or having additional imaging due to re-stenosis (secondary outcomes) Patients' quality-of-life.

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CLTI	Chronic Limb Threatening Ischaemia
CRF	Case Report Form
EC	Ethics Committee (see REC and / or NHS REC)
GCP	Good Clinical Practice
GP	General Practitioner
IC	Intermittent Claudication
ICF	Informed Consent Form
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
IVL	Intravascular Lithotripsy
PAD	Peripheral Arterial Disease or Peripheral Artery Disease
PI	Principal Investigator
PPI	Patient and Public Involvement
PIL/S	Participant/ Patient Information Leaflet/Sheet
R&D	NHS Trust R&D Department
SC	Study Co-ordinator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
SMF	Study Master File
SSC	Study Steering Committee
UK	United Kingdom

4. BACKGROUND AND RATIONALE

Peripheral Arterial Disease (PAD) affects a fifth of people over the age of 60 in the United Kingdom (UK)(1-3). It is the commonest cause of lower limb amputation(4). Patients with PAD who develop symptoms present either with pain when walking, called intermittent claudication, or chronic limb threatening ischaemia, a condition characterised by constant pain in the leg and/or gangrene. More than half of patients who have chronic limb threatening ischaemia or intermittent claudication are expected to die, have an amputation or a major cardiovascular event i.e. heart attacks or strokes, within five years (2, 5-8). The number of people with PAD is expected to rise in the next few years, due to a sedentary life-style, poor dietary choices, rising prevalence of diabetes and longer life-expectancy(3, 9, 10).

Approximately 5% of individuals between the age of 55 and 74 have intermittent claudication or chronic limb threatening ischaemia in the UK (1, 2, 6-8, 10). In patients with chronic limb threatening ischaemia the one-year risk of limb amputation is 30% and five-year all-cause mortality is 50%, similar to various advanced forms of cancer (1, 2, 5-8, 11). Patients with chronic limb threatening ischaemia require urgent revascularisation (restoration of blood flow) in order to save their leg (prevent amputation). Overall, 27,465 leg amputations took place in patients with PAD between 2015 and 2018 in the UK(12). A timely and successful lower limb revascularisation is required to prevent these amputations and subsequent impact on patients' autonomy, quality-of-life and future health problems(3, 5, 16, 17).

An angioplasty is a procedure where an artery is opened using wires and balloons. It is the most common procedure offered to patients with PAD, especially those with limb threatening ischaemia, and it is recommended by international guidelines(18). Many factors can affect how long the arteries treated with angioplasty can remain open for(19). Calcium in the artery is one of the main factors which might cause a new blockage in an artery treated with angioplasty(20). Our research group has previously reported that the percentage of calcified plaque independently predicts restenosis at one year after angioplasty and the absolute volume of calcium was associated more amputation(23).

Intravascular lithotripsy has been developed as an adjunct to plain balloon angioplasty and stenting for severely calcified arterial plaques in patients with PAD. This device (produced by Shockwave Medical) shatters the calcium within the atherosclerotic plaque into tiny particles using ultrasound (energy) via a standard angioplasty balloon. The assumption is that applying intravascular lithotripsy makes the plaque more compliant and hence the plaque responds better to angioplasty. It has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and is used routinely for coronary artery procedures. It is licensed for treatment of lower limb vessels in the UK and Europe. A recently completed randomised controlled trial involved 306 lesions (stenoses or occlusions of femoral or popliteal arteries or both) treated with either intravascular lithotripsy and angioplasty or conventional means (full data under publication) showed a 79% reduction in dissection(s) of the artery (which would have required a stent to treat), and a 69% reduction in using further angioplasty (i.e. more balloons) to treat the disease. This study only presented information up to 30 days after surgery, which is not sufficient to draw conclusions about longer-term performance of this technology. There is also no high-quality multicentre clinical data, from a study conducted within the NHS regarding the use of this technology in patients with PAD, especially those with chronic limb threatening ischaemia.

Intravascular lithotripsy has the potential to greatly improve the treatment of patients with calcified atherosclerotic plaques and severe PAD, since it might decrease the need for

stenting (associated with increased costs and the complications listed above), decrease the duration of the procedure, limit the need for re-intervention, reduce the possibility of peripheral embolisation, and overall improve long-term clinical results i.e. reduce the chance of amputation.

Before, proceeding to a large-scale randomised study across the whole of the NHS, this current study will provide us with valuable information in order to plan such future studies, including: clinical performance of this technology in patients with severe PAD and chronic limb threatening ischaemia (a group of patients who have very calcified arterial disease), mechanistic information as to how the plaque responds to intravascular lithotripsy, information about clinicians' equipoise and feasibility of performing a randomised study and the number of eligible patients seen at NHS centres treating patients with PAD. Further, this prospective multi-centre cohort study will provide important clinical information for patients treated with intravascular lithotripsy in the NHS, including: patency after treatment with this technology, additional treatments used with the intravascular lithotripsy, amputation free survival, duration of hospital stay, and number of re-interventions. This is vital information in order to be able to plan a future high-quality randomised assessment of clinical effectiveness in the NHS. As far as the mechanistic elements of intravascular lithotripsy are concerned, we have pioneered and validated a detailed analysis of atherosclerotic plaque composition using 3 dimensional plaque analysis, based on computed tomographic imaging. This allows us to calculate with extreme precision the volume and proportion of calcium, fibrotic tissue, fat and other extracellular constituents within any atherosclerotic plaque. Using this technique in the SHOCC study, we will be able to quantify what exactly happens to the atherosclerotic plaque after applying intravascular lithotripsy and therefore provide mechanistic evidence for this technology, which is currently non-existent. Again, this is vital information before proceeding to further randomised clinical assessments of the technology. Finally, even though intravascular lithotripsy is now commercially available in the NHS, we still do not know how clinicians (surgeons and radiologists) decide who to treat with this technology. We will attempt to answer that question using information collected during the SHOCC study.

5. OBJECTIVES

Primary objective:

Investigate the effect of intravascular lithotripsy on the patency of a lower limb atherosclerotic lesion in patients with symptomatic PAD treated in the NHS, six months after the procedure.

Secondary objectives:

1. To investigate whether patients require further angioplasty or other procedures in the six months post intravascular lithotripsy.
2. To investigate whether patients suffer any of the following complications; stroke, transient ischaemic attack, myocardial infarction, or lower limb amputation in the six months post intravascular lithotripsy.
3. To investigate whether patients are readmitted to hospital for PAD related treatment in the six months post intravascular lithotripsy.
4. To investigate whether changes in atherosclerotic plaque consistency are observed within three days post intravascular lithotripsy
5. To gather information about how and why clinicians decided upon this choice of treatment over alternative methods available in the NHS.

6. STUDY DESIGN

6.1 Summary of Study Design

Patients: Patients with chronic limb threatening ischaemia or severe claudication and femoro-popliteal or below-the knee arterial occlusion or stenosis, amenable to treatment with endovascular means and intravascular lithotripsy.

Intervention: Intravascular lithotripsy of an atherosclerotic plaque; this is part of the patients' standard NHS care. This study is observational in nature (i.e. no additional intervention is offered to these patients). The indication(s) for use of intravascular lithotripsy will have been discussed in the Departments' Multidisciplinary Team Meeting(s) and patients will have been consented for the procedure(s) accordingly.

Outcomes: all complications during the in-hospital stay, at thirty days and six months will be documented, including: patency of the treated arterial lesion (primary outcome of interest), re-intervention, lower limb amputation; change in the treated atherosclerotic plaque consistency for patients requiring re-intervention or having additional imaging due to re-stenosis (secondary outcomes). Further, all intra-operative details, including additional treatments, will be recorded.

Study design: multicentre prospective cohort study. Non-randomised research. Standard NHS care will be provided to patients as per current National Institute for Health and Care Excellence for PAD. A sub-study is included which requires a small number of patients (maximum of 20 patients) to undergo a second CT scan soon after their procedure. Further, a total of 10 healthcare professionals (vascular surgeons and radiologists) will be asked to fill in an online survey, to document why they chose to use intravascular lithotripsy for these patients.

Duration of participant participation: Six months (i.e. until end of follow-up).

6.2 Primary and Secondary Endpoints/Outcome Measures

Primary outcome measure: patency of the treated arterial atherosclerotic lesion based on duplex ultrasound measurement at six months after the procedure has taken place (recorded as a binary outcome i.e. yes or no).

Secondary outcome measures:

During the inpatient stay:

Additional treatments during the index procedure, including other endovascular treatments (e.g. application of stent or drug coated balloon therapy or any other intervention deemed necessary by each operator)

All complications during the in-hospital stay:

Duration of in-hospital stay.

Thirty days after the procedure and at six months (final follow-up):

Re-intervention (open or endovascular - including re-intervention for other indications, which will be reported separately)

Lower limb amputation

Change in the treated atherosclerotic plaque consistency for patients requiring re-intervention or having additional imaging due to re-stenosis (secondary outcomes)

Patients' quality-of-life.

7. STUDY PARTICIPANTS

7.1 Overall Description of Study Participants

Male and female patients aged >18 years old who have been diagnosed with chronic limb threatening ischaemia or severe intermittent claudication that are referred to secondary care to undergo lower limb revascularisation using intravascular lithotripsy.

Clinicians performing the intravascular lithotripsy procedure on study participants

7.2 Inclusion Criteria

Patient participants:

1. Adults (>18 years of age)
2. Diagnosed with symptomatic PAD (severe incapacitating intermittent claudication or chronic limb threatening ischaemia -Rutherford stages 4–6)
3. Referred to secondary care to undergo lower limb revascularisation using intravascular lithotripsy
4. Able to understand written and spoken English
5. Is willing and able to give written informed consent for participation in the study

Healthcare professionals:

The clinicians who have performed the intravascular lithotripsy procedure on participants included in this research study.

7.3 Exclusion Criteria

Patient participants:

The participant may not enter the study if ANY of the following apply:

1. Female participants who are pregnant, lactating or planning pregnancy during the course of the study.
2. Patients who do not have capacity to consent for themselves.
3. Patients with life limiting condition whereby conservative management is most appropriate.
4. Patients with asymptomatic PAD.
5. Patients with acute lower limb threatening lower limb ischaemia.
6. Patients not being referred for lower limb revascularisation using intravascular lithotripsy.

8. STUDY PROCEDURES

8.1 Screening and recruitment

Participants attending vascular clinics or vascular wards at the participating NHS sites who have been referred for an intravascular lithotripsy procedure will be identified and approached by GCP trained study investigators and collaborators who will be their usual clinicians. Investigators will be listed on the Delegation of Authority and Signature Log. The clinician responsible for the patients care will provide a brief explanation of the study and supply the patient with a patient information sheet. The participant will be allowed at least 24 hours to consider the information, and will be given the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. To allow sufficient time for potential participants to review the PIS and study information, we will contact the potential participants at least 24 hours before the intravascular lithotripsy.

8.2 Consent

Patients

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

If the participant agrees to take part in the study, written informed consent will be obtained by a participant signed and dated version of the latest approved consent form before any study specific procedures are performed. We expect participants to provide written informed consent on the day they are being consented for the intravascular lithotripsy. The person who obtained the consent will be suitably qualified and experienced, and will have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF) as per standard NHS principles (at each of the NHS sites taking part in this study). A copy of the signed Informed Consent Form will be given to participants and a copy retained in the participant medical notes. A fourth copy will be sent to the patients GP to inform them of their participation in the study.

Healthcare professionals

The clinicians performing the intravascular lithotripsy will be given a participant information sheet and they will be asked to sign a written informed consent form. The person who obtained the consent will be suitably qualified and experienced, and will have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF) as per standard NHS principles (at each of the NHS sites taking part in this study). A copy of the signed Informed Consent Form will be given to participants.

8.3 Data collection

8.3.1 Main study

This study wishes to obtain the following routinely collected data from the patients' medical records and conduct further analyses* on routinely performed scans at various time points during patients' routine PAD care.

Baseline (pre intravascular lithotripsy) data collection:

1. Demographic information (age at time of recruitment, sex).
2. Weight/height, resting BP (anthropometric measurements).
3. Rutherford stage relating to PAD presentation.
4. Ankle brachial pressure index.
5. Baseline full blood count results and routine biochemistry, including total cholesterol levels, and lipid profile.
6. Baseline serum creatinine and estimated glomerular filtration rate.
7. Chronic kidney disease status.
8. Diabetes status, duration of diabetes history, and current diabetes medication(s).
9. History of previous major cardiovascular events.
10. Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography*
11. Smoking status.
12. WiFi score.
13. Previous operations, including a full surgical and vascular history.
14. All concomitant medications as reported by patients.
15. Anonymised minutes from multi-disciplinary team meetings relating to the patients care.

Day of procedure (Post intravascular lithotripsy) data collection:

The data collected here will relate to information obtained during the intravascular lithotripsy

1. Exact location of the lesion treated,
2. Number and size(s) of intravascular lithotripsy catheters used
3. Duration of intravascular lithotripsy application per arterial site in seconds
4. Exact anatomy (number of occlusions or stenoses) of the arterial lesions present on intra-operative angiography
5. Nature of the additional surgical or endovascular treatments taking place
6. Duration of the whole procedure
7. Immediate complications during the procedure and steps taken to address them (e.g. thrombectomy)
8. Patency of the treated lesions
9. Level of operators performing the procedures
10. Volume of contrast used during the procedure.

Day of discharge data collection:

Where available, the data collected here will relate to the period between the completion of the intravascular lithotripsy procedure and the day of discharge

1. Re- interventions of any nature
2. Amputations of any nature
3. Ankle brachial pressure index.
4. Full blood count results and routine biochemistry.
5. Major cardiovascular events during inpatient stay.
6. Duration of inpatient stay (ward and intensive care where applicable).
7. Reason(s) for admission to intensive care if relevant.
8. Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography (all of these are routine care).
9. WiFi score.
10. All concomitant medications.

30 day post discharge data collection:

The data collected here will relate to the time period between the procedure 30 days post discharge.

1. Re-intervention(s) - nature and reasons why this occurred.
2. Amputation(s) - nature and reasons why this occurred.
3. Ankle brachial pressure index.
4. Major cardiovascular events.
5. Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography
6. WiFi score.
7. All concomitant medications.
8. Arterial duplex scan of the affected lower limb (standard of care for patients with severe limb threatening ischaemia).

Six months post discharge data collection (final follow-up):

The data collected here will relate to the time period between the procedure 6 months post discharge.

1. Weight/height, resting BP (anthropometric measurements).
2. Rutherford stage.
3. Ankle brachial pressure index.
4. Baseline full blood count results and routine biochemistry, including total cholesterol levels, and lipid profile.
5. Baseline serum creatinine and estimated glomerular filtration rate.
6. Chronic kidney disease status.
7. Diabetes status, duration of diabetes history, and current diabetes medication(s).
8. History of previous major cardiovascular events.
9. Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography (all of these are routine care).
10. Smoking status.
11. Previous operations, including a full surgical and vascular history.
12. Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography*
13. WiFi score.
14. Quality of life using the EuroQol-5D (EQ-5D) questionnaire.
15. Recording of all concomitant medications as reported by patients.

*Plaque analysis will be performed on the routine CT scans obtained at baseline. Additional plaque analysis will be undertaken on any additional CT angiograms which have been undertaken on any patient, for any reason during the six month follow-up period. We will use the scans in order to assess plaque volume (at any arterial segment treated with intravascular lithotripsy) and detailed plaque composition using a technique which our group pioneered and validated, described in detail before(23, 24). All PIs will be trained by the CI and Mr Hany Zayed in this technique prior to commencing the study, using software which is already available at each clinical site (Aquarius TeraRecon). The scans will be analysed locally within seven days and we will report the following for each atherosclerotic plaque (i.e. target of intravascular lithotripsy treatment): volume of plaque which is calcified / fibro-calcific / fibrotic, lumen volume, plaque volume, plaque length. We will also report which vessels are patent and/or stenosed and/or occluded below the origin of the ipsilateral common iliac artery as well as the length (in mm) of each occluded segment. Inter- and intra-operator variability will be calculated and reported for the first five scans at each site (the CI and Mr Hany Zayed will report the first five scans performed at each site together with the local PIs). Further, for each patient taking part we will report and record the Peripheral Arterial Calcium Scoring System (PACSS), a validated method to report degree of calcification, both before and after treatment(25).

The only study related data that is not collected as part of routine care is the completion of the EuroQol-5D (EQ-5D) questionnaire in relation to quality of life. The completion of a quality of life

survey will be requested from all participating patients at baseline (pre-op) and at 6 months post discharge during their routine appointments.

Considerations due to COVID-19

We expect that COVID-19 will not have a major impact on inpatient and/or outpatient pathways for chronic limb threatening ischaemic and severe symptomatic PAD (our target population), given that these vascular pathologies are limb and/or life threatening. This has already been documented in our international study of vascular care during the COVID-19 pandemic (see: https://vascular-research.net/projects/cover-study-covid-19-vascular-service-study/)

Patient involvement in this study falls alongside routine care and there is therefore no further risk of exposure to COVID-19 due to additional hospital visits as a result of taking part in this study.

Patients and staff will follow local trust COVID guidelines on the use of face masks and social distancing when they attend their routine hospital appointments.

8.3.2 Qualitative survey of the operators immediately after the procedure

All operators will be asked to fill in a survey relating to the procedure (intravascular lithotripsy) on the day that the procedure has taken place (online survey) using REDCap software. They will be questioned using multiple choice closed questions and open questions on the ease of the procedure, immediate peri-operative complications, and why they chose to use the devices that were used during the procedure, including the opinion/verdict of their multi-disciplinary meeting.

8.3.3 Optional Sub-study

A total of 20 consecutive patients will be invited to take part in sub-group analysis to document the impact of the intravascular lithotripsy on the calcified component of the atherosclerotic plaque. These patients will be recruited from the main site, University Hospitals of Leicester. We will stop recruiting in this sub-analysis once 20 patients have been recruited and have had their second CT scan three days after their intravascular lithotripsy procedure.

8.6 Randomisation and Codebreaking

This is a non-randomised study. Participants will be allocated a unique study identification number which will be site-specific, upon recruitment. This will be used in all CRFs.

8.7 Definition of End of Study

The end of study is the date of the last visit/ telephone follow up/ home visit of the last participant i.e. six months after the date the last patient has been recruited.

8.8 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)

- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

The reason for withdrawal will be recorded in the CRF.
If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.
It is unlikely that adverse events will occur as this study follows national and international clinical guidance and standard NHS care pathways.

8.9 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, computed tomographic or ultrasound scans, and correspondence with primary or secondary care. CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name. All research team members taking part in either the qualitative or quantitative parts of the study will have received Good Clinical Practice (GCP) training; the PI at each site is responsible for delivering the required training and ensuring everyone is up to date with regulatory requirements as per GCP.

9. TREATMENT OF STUDY PARTICIPANTS

9.1 Description of Study Treatment

Patients will not receive any additional treatment as a result of taking part in this research. All patients taking part in this research will already have been offered treatment with intravascular lithotripsy (Shockwave) as part of their standard NHS care.

9.2 Storage of Study Equipment or Related apparatus

The intravascular lithotripsy (Shockwave) catheters will be stored as per standard NHS principles and guidance at each NHS site.

10. SAFETY REPORTING

10.1 Definitions

10.1.1 **Adverse Event (AE)**

An AE or adverse experience is:
Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the the study, whether or not considered related to the study.

10.1.2 **Adverse Reaction (AR)**

All untoward and unintended responses related to the study.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

10.1.3 **Severe Adverse Events**

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 **Serious Adverse Event or Serious Adverse Reaction**

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 **Expected Serious Adverse Events/Reactions**

This study follow established international guidance (including NHS and NICE guidance) as to what constitutes best medical therapy for PAD, and we therefore do not expect major issues with serious adverse events or reactions. Standard care NHS pathways will be followed. Minor bleeding such as bruising is expected in patients who are on therapy with an antiplatelet agent such as clopidogrel.

Further, myalgia might be associated with high-dose statin therapy. These are the two most common adverse reactions which we might expect in this patient group.

10.1.6 **Suspected Unexpected Serious Adverse Reactions**

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study, will be recorded on the CRF.
The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.
AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.
It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 7.7). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.
The relationship of AEs to the study will be assessed by a medically qualified investigator.

10.3 Reporting Procedures for Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

SAEs, with the exception of expected SAEs and SARs, must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.
The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.
In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

11. STATISTICS

11.1 Description of Statistical Methods

This is a non-randomised prospective observational multicentre cohort study.
We will report descriptive statistics for all parameters of interest, including mean and standard deviation with 95% confidence interval (CI) for normally distributed variables and median values with interquartile range(s) for non-normally distributed variable.
Standard tests will be used to assess differences between categorical and non-categorical variables of interest.
The analyses will be overseen by the CI and the Bioinformatics Hubs within the Department of Cardiovascular Sciences, University of Leicester.
Results will be presented in tabular format where possible.

11.2 The Number of Participants

We will record clinical characteristics for 60 patients treated with intravascular lithotripsy in the participating NHS centres over the period of one year. We will follow-up patients for six months. We expect a total of 60 patients to complete follow-up during this period of time, providing full clinical and imaging data, based on our national audits and UK PAD data for 2019-2021 based on the National Vascular Registry and the Vascular and Endovascular Research Network.
For the imaging sub-study (which is only taking part in Leicester i.e. the main study site), we have used a total of 182 patients' data (with femoro-popliteal disease) to estimate the sample size required, based on a study which is ongoing (using this type of plaque analysis for femoro-popliteal plaques). These 182 patients had their plaques analysed using the same technique that we are planning to use in this instance, prior to plain balloon angioplasty. Based on that data, we estimate a mean volume of 1.22mm3 for the calcified part of the femoro-popliteal plaque (based on Hounsfield units) and a standard deviation of 0.4 units; with the assumption we will document a reduction of the calcified component to 0.61 mm3 and to document this within a standard deviation of 0.4 units with a power of 90% and an alpha set at 0.05, we will require 20 patients to take part in this imaging sub-analysis.

11.3 The Level of Statistical Significance

A p value of <0.05 will be regarded as statistically significant.

11.4 Criteria for the Termination of the Study.

Given that this is an observational study which is recruiting patients who undergo a treatment that is already available in the NHS, we do not have specific stoppage criteria at this point in time. A Data Safety Monitoring Committee (DSMC) will convene at regular intervals, chaired by an independent specialist.

11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

The PI will be contacted at each site in case of missing or spurious data to ensure that the information collected is precise.

11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the original plan will be discussed in the regular research team meetings and reported to the Sponsor and Funder and justified in the final report.

11.7 Inclusion in Analysis

All participants will be included in the final analysis as this is a pragmatic cohort study.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit study-related monitoring, audits and inspections.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.
The University of Leicester operate a risk based audit programme to which this study will be subject.
The study research team (including the authors of this protocol and all local PIs) will meet online in two monthly intervals to ensure appropriate conduct of the study.
Data completion and quality will be reviewed once monthly by the CI and the study co-ordinator.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Ethics

This study is subject to NHS REC and HRA approvals before any patient can be recruited.

14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet, and any study material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), and host institution(s) for written approval.

Once Sponsor authorisation has been confirmed, the Investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.6 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.7 Other Ethical Considerations

Some patients will be asked to participate in a sub-group analysis where post-operative computed tomographic angiograms will be performed. This involved additional radiation. At the same time, these will be limited computed tomographic angiograms which will only scan the affected area of the body, usually over a length of 30cm. This means that the radiation is minimised. Patients will be counselled with regards to this and will provide written informed consent. They will be given the chance to not participate in this part of the study should they wish, without having to offer any form of explanation.

15. DATA HANDLING AND RECORD KEEPING

All study data will be entered on a REDCap based data collection form, created specifically for the study by the National Institute for Health Research Leicester Biomedical Research Centre Bioinformatics Hub staff. As per ICH GCP (Section 5.5), all electronic data entry systems are validated and Standard Operating Procedures are maintained by the National Institute for Health Research Leicester Leicester Biomedical Research Centre.

The participants will be identified by a study specific participant number and/or code in any database. The patient's name and any other identifying detail will NOT be included in any study data electronic file. No identifiable information will be shared between study sites at any point. Consent forms (signed) will be kept in study-specific site files at the NHS institutions taking part in this research in a locked safe NHS office as per standard Good Clinical Practice guidance and NHS policies.

Cross sectional imaging including duplex scans and computed tomographic angiograms will be analysed and reported locally at each NHS site by expert radiology doctors and the reports (fully anonymised) will be uploaded on the REDCap CRFs remotely. Further, the plaque analyses will be performed locally using computed tomographic angiograms as per the agreed study protocol and the relevant results will be reported (fully anonymised) on the CRFs for each patient. Non-anonymised scans will not be shared between sites at any point.

16. STUDY GOVERNANCE

16.1 Study Steering Committee (SSC)

The SSC will convene at least once every two months and will consist of:

- Mr Athanasios Saratzis (CI) - chair
- All PIs at each clinical site
- Professor Robert D Sayers

16.2 Data Safety Monitoring Committee (DSMC)

The DSMC will convene once every three months; a data report will be prepared two weeks before each meeting by the National Institute of Health Research Leicester Biomedical Research Centre Bioinformatics Hub.

The DSMC will consist of:

- An independent specialist chair (vascular surgeon or interventional radiologist)
- Mr Athanasios Saratzis (CI)
- A representative of the National Institute of Health Research Leicester Biomedical Research Centre Bioinformatics Hub
- A lay participant.

The findings of the DSMC will be fed back to the SSC which will convene after the DSMC meeting (after two weeks). A final data report will be made available to both the SSC and DSMC.

17. FINANCING AND INSURANCE

This study is funded by Shockwave Medical (Funder) and sponsored by the University of Leicester (Sponsor).

18. PUBLICATION & DISSEMINATION POLICY

Final analysis of data will be overseen by the CI and the National Institute of Health Research Leicester Biomedical Research Centre Bioinformatics Hub, who will independently report findings. Results will be submitted for publication to a peer-reviewed medical journal with broad cross-disciplinary readership in English language. The manuscript will be prepared and approved by all study investigators prior to submission for publication. Authorship will be based on the latest version of the criteria published by the International Committee of Medical Journals Editors: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. We aim to publish study outputs using a collaborative authorship model, including all clinicians who uploaded at least 80% of data points for at least 5 patients at 6 months i.e. completion of follow-up. The group will be named “The SHOCC study collaborators”.

Prior to publication the manuscript and a blinded report of the data analysis will be submitted to the funder. The Funder will have no role in preparing the publication and will not be involved in data analysis in any way. Clinical data and relevant outputs will be owned (copyright) by the Sponsor of this study. At no point will any form of identifiable data or reports be shared with the Funder (Shockwave Medical).

Wherever possible, data will be published in open-access format. Anonymised open data will be shared on appropriate platforms (ClinicalStudyDataRequest and “Supporting Open-Access for Researchers” initiative).

Finally, results of this study will be disseminated to vascular surgery and interventional radiology societies internationally and to the National Institute of Heath and Care Excellence. A lay summary will be prepared with the help of patients in existing patient and public involvement groups in the National Institute of Health Research Leicester Biomedical Research Centre (led by the CI) and they will be made widely available on social media and the Vascular Society of Great Britain and Ireland website.

19. REFERENCES

1. Cea-Soriano L, Fowkes FGR, Johansson S, Allum AM, Garcia Rodriguez LA. Time trends in peripheral artery disease incidence, prevalence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. BMJ Open. 2018;8(1):e018184.

2. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. 2018;360:j5842.

3. NICE. Peripheral Arterial Disease Guidance National Institute of Health and Care Excellence NICE; 2013 [Available from: https://www.nice.org.uk/guidance/cg147.

4. Diabetes-UK. Facts and Figures 2019 Diabetes UK: Diabetes UK; 2019 [Available from: https://www.diabetes.org.uk/resources-s3/2019-02/1362B_Facts%20and%20stats%20Update%20Jan%202019_LOW%20RES_EXTERNAL.pdf.

5. Parvar SL, Fitridge R, Dawson J, Nicholls SJ. Medical and lifestyle management of peripheral arterial disease. J Vasc Surg. 2018;68(5):1595-606.

6. Dhaliwal G, Mukherjee D. Peripheral arterial disease: Epidemiology, natural history, diagnosis and treatment. Int J Angiol. 2007;16(2):36-44.

7. Dua A, Lee CJ. Epidemiology of Peripheral Arterial Disease and Critical Limb Ischemia. Tech Vasc Interv Radiol. 2016;19(2):91-5.

8. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg. 2014;60(3):686-95 e2.

9. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.

10. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. Circ Res. 2016;118(4):535-46.

11. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326(6):381-6.

12. GOVUK. Amputations in England: GOVUK; 2019 [Available from: https://www.gov.uk/government/news/preventing-amputations-major-concern-as-diabetes-numbers-rise.

13. Harwood AE, Totty JP, Broadbent E, Smith GE, Chetter IC. Quality of life in patients with intermittent claudication. Gefasschirurgie. 2017;22(3):159-64.

14. Gardner AW, Montgomery PS, Killewich LA. Natural history of physical function in older men with intermittent claudication. J Vasc Surg. 2004;40(1):73-8.

15. Nehler MR, McDermott MM, Treat-Jacobson D, Chetter I, Regensteiner JG. Functional outcomes and quality of life in peripheral arterial disease: current status. Vasc Med. 2003;8(2):115-26.

16. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, et al. Association of Statin Dose With Amputation and Survival in Patients With Peripheral Artery Disease. Circulation. 2018;137(14):1435-46.

17. Coughlin PA, Rudd JHF. Optimizing medical management in peripheral artery disease. Br J Surg. 2018;105(9):1079-81.

18. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in

collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(3):305-68.

19. Katsanos K, Tepe G, Tsetis D, Fanelli F. Standards of practice for superficial femoral and popliteal artery angioplasty and stenting. Cardiovasc Intervent Radiol. 2014;37(3):592-603.

20. Cassese S, Byrne RA. Endovascular stenting in femoropopliteal arteries. Lancet. 2018;392(10157):1491-3.

21. Yang X, Lu X, Li W, Huang Y, Huang X, Lu M, et al. Endovascular treatment for symptomatic stent failures in long-segment chronic total occlusion of femoropopliteal arteries. J Vasc Surg. 2014;60(2):362-8.

22. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2018;7(24):e011245.

23. Patel SD, Zymvragoudakis V, Sheehan L, Lea T, Modarai B, Katsanos K, et al. Atherosclerotic Plaque Analysis: A Pilot Study to Assess a Novel Tool to Predict Outcome Following Lower Limb Endovascular Intervention. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2015;50(4):487-93.

24. Saratzis A, Rudarakanchana N, Patel S, Diamantopoulos A, Lea T, Corbo B, et al. Interwoven Nitinol Stents versus Drug Eluting Stents in the Femoro-Popliteal Segment: A Propensity Matched Analysis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2019;58(5):719-27.

25. Zettervall SL, Marshall AP, Fleser P, Guzman RJ. Association of arterial calcification with chronic limb ischemia in patients with peripheral artery disease. Journal of vascular surgery. 2018;67(2):507-13.

20. APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Visits					
	Screening	**Baseline (pre operative)**	**Day of procedure (post intravascular lithotripsy)**	**Discharge date**	**30 days**	**6 months**
Eligibility assessment	**x**					
Informed consent		**x**				
Quality of Life questionnaire		**x**				**x**
Computed tomographic imaging for the sub-groups analysis				**x (for those in the sub-analysis)**		
Review of medical records	**x**	**x**	**x**	**x**	**x**	**x**