# IVL L6 Cohort Study

Intravascular Lithotripsy as the primary treatment strategy for calcified iliac/aorto-iliac/femoral arteries IVL L6 Cohort Study

**PROTOCOL VERSION NUMBER AND DATE**

Version 2.0
Date 11 August 2026

| | |
|---|---|
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| **Study registration number** | ISRCTN 54437647 |

***This protocol has regard for the Health Research Authority (HRA) guidance and the University of Leicester Sponsor Standard Operating Procedures (SOPs)***

## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirement.

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 study without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given. Any discrepancies and serious breaches of Good Clinical Practice (GCP) from the study as planned in this protocol will be explained.

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| NIHR Portfolio adopted | East Midlands RDN (Research Delivery Network), CPMS ID: 65196 |

## ROLE OF THE STUDY SPONSOR

The Sponsor for this research project is the University of Leicester.
The University of Leicester is responsible for the design, management and output of the research. Participating locations are responsible for the conduct of the study within their organisation.

The Research Governance Office review and approve all iterations of the protocol as part of their initial Sponsor review and amendment review process. Further information is available from our Sponsor Standard Operating Procedures webpage.

## ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

### Trial Management Group (TMG)

The TMG will oversee the running of the study and will meet according to the demands of the study, with meetings taking place online. This group will include the Chief Investigator (CI), Study Coordinator, Senior Clinical Research Manager and the named collaborators.

These operational meetings will enable continuous monitoring of key milestones to ensure that the study is being delivered to target and provide a vehicle to highlight issues, discuss, and agree resolutions. The TMG will provide input to the protocol and protocol modification(s) recommend protocol modification(s) where applicable, ensure the protocol is adhered to, and act as necessary to remedy any difficulties.

In addition to these meetings, a core TMG group based at Leicester, and comprising the CI, Study Coordinator and the Senior Clinical Research Manager will meet regularly to discuss the day-to-day running of the study.

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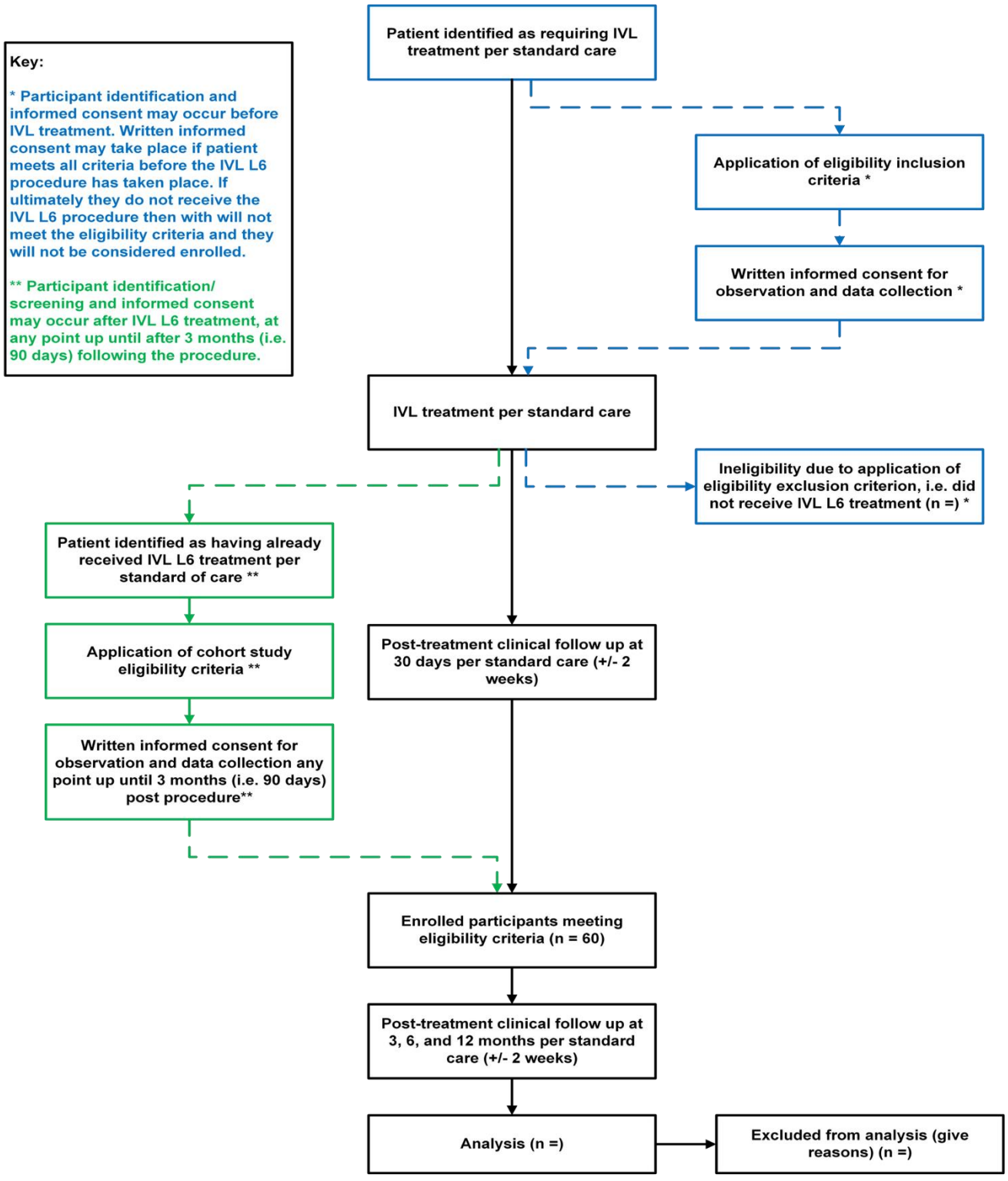
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## STUDY SUMMARY

| | | |
|---|---|---|
| Short Study Title or Acronym | IVL L6 Cohort Study | |
| Study Design | Multicentre observational cohort study with prospective follow-up and a combination of prospective and retrospective recruitment with a single arm. | |
| Study Participants | Adult patients with symptomatic Peripheral Arterial Disease (PAD) who undergo primary treatment with Shockwave Intravascular Lithotripsy (IVL) for calcified lesions in the iliac/aorto-iliac/femoral arteries. | |
| Sample Size | Minimum of n = 60 participants internationally. | |
| Follow up duration | 12 months | |
| Planned Study Period | Study start date (funding period): 1st March 2026<br>Estimated study end date (funding period):<br>1st December 2028<br>(1 year for enrolment, 1 year for follow up, 9 months for analysis, dissemination, closedown and archiving) | |
| | **Objectives** | **End Points / Outcome Measures** |
| Primary | • Assess the safety and short and longer-term (30 days to 1 year) efficacy of intravascular lithotripsy (IVL) as the primary treatment of calcified lesions in the iliac/aorto-iliac/femoral arteries in patients with symptomatic peripheral arterial disease (PAD) who have been selected to undergo treatment with IVL. | • Procedural success defined as patent target lesion on completion of the procedure with or without adjuncts<br>• Need for clinically driven arterial re-intervention at 30 days to 1 year<br>• Primary and secondary vessel patency within 12 months post treatment |
| Secondary | • To investigate whether patients require, or are readmitted to hospital for, any other PAD related treatment including Major Adverse Limb Events (MALE) within the 12 months post IVL treatment. | • Re-admissions (all and disease-specific), Major Adverse Limb Events (MALE), need for any revascularisation,<br>• Adverse events (as per table in section 7) including |

| | | |
|---|---|---|
| | • To investigate whether patients are admitted to hospital for any other health conditions in the 12 months post IVL treatment.<br>• To investigate whether patients suffer any other adverse events including cardiovascular events in the 12 months post IVL treatment. | cardiovascular events (as per American Heart Association definition[1]), and mortality (all-cause) within 12 months post IVL treatment. |

## STUDY FLOW


Key:
* Participant identification and informed consent may occur before IVL treatment. Written informed consent may take place if patient meets all criteria before the IVL L6 procedure has taken place. If ultimately they do not receive the IVL L6 procedure then with will not meet the eligibility criteria and they will not be considered enrolled.
** Participant identification/ screening and informed consent may occur after IVL L6 treatment, at any point up until after 3 months (i.e. 90 days) following the procedure.
Patient identified as requiring IVL treatment per standard care
Application of eligibility inclusion criteria *
Written informed consent for observation and data collection *
IVL treatment per standard care
Ineligibility due to application of eligibility exclusion criterion, i.e. did not receive IVL L6 treatment (n =) *
Patient identified as having already received IVL L6 treatment per standard of care **
Application of cohort study eligibility criteria **
Written informed consent for observation and data collection any point up until 3 months (i.e. 90 days) post procedure**
Post-treatment clinical follow up at 30 days per standard care (+/- 2 weeks)
Enrolled participants meeting eligibility criteria (n = 60)
Post-treatment clinical follow up at 3, 6, and 12 months per standard care (+/- 2 weeks)
Analysis (n =)
Excluded from analysis (give reasons) (n =)

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| BHF | British Heart Foundation |
| CI | Chief Investigator |
| CLTI | Chronic limb-threatening ischaemia |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DHSC | the Department of Health and Social Care |
| DoA | Delegation of Authority |
| DPIA | Data Protection Impact Assessment |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ICH | International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journals Editors |
| IQR | Interquartile Range |
| IRAS | Integrated Research Application System |
| ISF | Investigator Site File |
| IVL | Intravascular Lithotripsy |
| MALE | Major Adverse Limb Events |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| PAD | Peripheral Arterial Disease |
| PI | Principal Investigator |

| | |
|---|---|
| PIS | Participant Information Sheet |
| PMS | Post-Market Surveillance |
| PPI | Patient and public involvement |
| RDN | Research Delivery Network |
| REC | Research Ethics Committee |
| REDCap | Research Electronic Data Capture |
| RFS | Research File Store |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| TLR | Target Lesion Revascularisation |
| TMF | Trial Master File |
| TMG | Trial Management Group |

**KEY WORDS**

Intravascular lithotripsy, Peripheral Arterial Disease, Vascular calcification, Endovascular treatment.

## PROTOCOL MODIFICATION HISTORY

| Modification Reference | Protocol version no. | Protocol Date | Author(s) of changes | Summary of changes made |
|---|---|---|---|---|
| Substantial Modification 01 | 2.0 | 07 August 2026 | Anieka Pancholi, Deepthi Krovi, Dr Sian Elizabeth Baldock | • Addition of calcified iliac/aorto-iliac/femoral arteries wording in the title<br>• The addition of Femoral artery wording to objectives.<br>• Correction of PACSS in Abbreviations and Study assessments<br>• Change of word(s) from amendment(s) to modification(s)<br>• Change of word(s) from site(s) to location(s)<br>• Addition of Exclusion criteria<br>• Change to Study Start date and end date as per study ODI<br>• The removal of ABPI data collection<br>• Removal of PACSS Data collection<br>• Clarification of 6-month initial visit 'window' to be a window for initial data collection not a window for consent.<br>• The addition of telephone consenting<br>• Added clarity about retrospective consent and recruitment<br>• Added different possible consent methods and independent witness<br>• Schedule of events – Removal of ABPI, Removal of Adverse event data collection at pre-op time point, Clarification that Rutherford staging should always be collected at follow-up.<br>• The alignment of wording of the participant/screening/enrollment log to match |

| | | | | |
|---|---|---|---|---|
| | | | | provided documentation.<br>• Screening number of patients mentioned.<br>• Added clarity about lost to Follow Up<br>• Added more clarity about the withdrawal and different types of withdrawal<br>• Changes to Study Flow Chart include the key which has been edited to clarify eligibility criteria and timelines so that it is consistent across the protocol.<br>• Small change to the wording in Study Design to clarify prospective and retrospective recruitment. |

## 1 Background and Rationale

Peripheral arterial disease (PAD) represents a major health problem worldwide and affects one-fifth of people over the age of 60 in most societies (2–4). In PAD, fatty substances (or plaques) build-up within artery walls, reducing blood flow to limbs, especially peripheral areas. For this reason, PAD is the most common cause of lower limb amputation (5). Though not all patients with PAD develop symptoms, those who are symptomatic present either with pain when walking, called intermittent claudication, or chronic limb threatening ischaemia (CLTI), a condition characterised by constant pain in the leg and/or gangrene. More than half of patients who have CLTI or intermittent claudication are expected to die, have an amputation, or a major cardiovascular event i.e. heart attack or stroke, within five years (3, 6-9). 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 (4, 10, 11).

Approximately 5% of individuals between the age of 55 and 74 have intermittent claudication or CLTI in modern societies e.g. Europe and the United Kingdom (2, 3, 7-9, 11). In patients with CLTI the one-year risk of limb amputation is 30% and five-year all-cause mortality is 50%, similar to various advanced forms of cancer (2, 3, 6-9, 12). Patients with CLTI 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 (13). A timely and successful lower limb revascularisation is required to prevent these amputations and subsequent impacts on patients' autonomy, quality-of-life and future health problems (4, 6, 14, 15).

An angioplasty with or without a stent 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 CLTI, and it is recommended by international guidelines for arterial steno-occlusive disease (16). Many factors can affect how long the arteries treated with angioplasty can remain open for (17). Calcium in the artery is one of the main factors which might cause a new blockage in an artery treated with angioplasty (18). Our research group has previously reported that the percentage of calcified plaque independently predicts restenosis at one year after angioplasty and greater absolute volumes of calcium were associated with more amputations (19).

Intravascular Lithotripsy (IVL) has been developed as an adjunct to plain balloon angioplasty and stenting for severely calcified arterial plaques in patients with PAD, including in the iliac arteries (often affected by PAD) and the aorta. 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 IVL 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 recent randomised controlled trial involving 306 lesions (stenoses or occlusions of femoral or popliteal arteries or both) treated with either IVL and angioplasty or conventional means showed a 79% reduction in dissection(s) of the

occlusions of femoral or popliteal arteries or both) treated with either IVL and angioplasty or conventional means 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 (20). More recently, our research group led a prospective multicentre cohort study across 8 NHS hospitals in the UK. 91 patients with PAD and CLTI were followed for up to 6 months after treatment with IVL. The study concluded that IVL was a safe and efficacious option for vessel preparation with high procedural success rates, and acceptable rates of medium-term complications and re-interventions (21).

Overall, IVL 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.

In 2024, new catheters (M5+ and L6) with wider/larger diameters were introduced in clinical care (UK and Europe), allowing for the treatment of bigger arteries with IVL.

However, there is limited data for M5+ and L6 in the iliac vasculature though this is frequently done in many centres in the UK and Europe where other treatments such as open surgery are considered unsuitable for some patients. Moreover, there is limited clinical and health economic data to support the use of IVL as the primary treatment strategy, with the avoidance of stenting in this territory.

We propose a multicentre prospective registry including vascular locations in Italy, the UK and Switzerland performing IVL routinely in their hospital centres to assess the outcomes of the Shockwave L6 catheter as the primary treatment strategy in the common, external iliac and femoral arteries (including also extension of the disease to the aorta i.e. aortoiliac lesions). Basic health economic data will also be gathered. A minimum of 60 patients with symptomatic PAD undergoing IVL as the primary treatment for calcified lesions in the iliac/aorto-iliac/femoral arteries will be followed for up to 12 months.

We do not know exactly how many catheters are used per case in the real world or what other adjuncts might be required, especially regarding the aorta and/or iliac arteries and/or femoral arteries (i.e. large diameter arteries), which is why this study will also collect information regarding the use of catheters and their cost per lesion/patient.

## 2 Objectives and Outcome Measures/Endpoints

| Objectives | Outcome Measures/Endpoints | Timepoint(s) of evaluation of this outcome measure |
|---|---|---|
| Primary Objective, Outcome, Timepoint(s) | | |
| • Assess the safety and short and longer-term (30 days to 1 year) efficacy of intravascular lithotripsy (IVL) as the primary treatment of calcified lesions in the iliac/aorto-iliac/femoral arteries in patients with symptomatic peripheral arterial disease (PAD) who have been selected to undergo treatment with IVL. | • Procedural success defined as patent target lesion on completion of the procedure with or without adjuncts.<br>• Need for clinically driven arterial re-intervention at 30 days to 1 year.<br>• Primary and secondary vessel patency within 12 months post treatment | Data to be collected at 0 days (baseline)<br>• Data to be collected at 30 days and at 3, 6 and 12 months post IVL treatment<br>• Data to be collected within 12 months from treatment, when available as per local standard of care |
| Secondary Objective(s), Outcome(s), Timepoint(s) | | |
| • To investigate whether patients require, or are readmitted to hospital for, any other PAD related treatment including Major Adverse Limb Events (MALE) within the 12 months post IVL treatment.<br>• To investigate whether patients are admitted to hospital for any other health conditions in the 12 months post IVL treatment.<br>• To investigate whether patients suffer any other adverse events including cardiovascular events in the 12 months post IVL treatment | • Re-admissions (all and disease-specific), Major Adverse Limb Events (MALE), need for any revascularisation,<br>• Adverse events (as per table in section 7) including cardiovascular events (as per American Heart Association definition[1]), and mortality (all-cause) within 12 months post IVL treatment. | • Data to be collected at 30 days, and at 3, 6, and 12 months post IVL treatment |

## 3 Study Design

The study is an investigator-initiated, Post-Market Surveillance (PMS), non-interventional, observational, single arm, multicentre cohort study, with prospective follow up. Participants may be recruited either prospectively before treatment or retrospectively following treatment (within three months of the index IVL L6 procedure) It will be non-randomised and include vascular locations in Italy, the UK and Switzerland already performing IVL treatment as a primary treatment, with all locations performing the same activities as per local established protocol(s), which are identical at all participating locations (including international locations).

## 4 Participant Eligibility Criteria

To be eligible patients must be aged 18 years old and above and attending vascular clinics or wards at the study locations. Patients will have been diagnosed with symptomatic PAD and already selected to undergo iliac/aorto-iliac/femoral arteries treatment with IVL using the L6 catheter by the treating clinicians. This study will not impact on the type of endovascular PAD treatment offered and/or adjuncts at any point.

### 4.1 Inclusion criteria

- People aged 18 years and above
- Diagnosed with symptomatic PAD (Rutherford classification 3-5)
- Calcified lesions confirmed via cross-sectional imaging, potentially requiring use of IVL as part of endovascular PAD treatment
- Referred for revascularisation via IVL L6 as chosen by the local treating clinicians, or have received revascularisation via IVL L6 within the previous 3 months (i.e. 90 days)
- Willing and able to provide written informed consent for participation in the study

### 4.2 Exclusion criteria

- Patients who do not receive IVL L6 as the primary treatment strategy for the target iliac/aorto-iliac/femoral arteries.

# 5 Study Schedule

## 5.1 Schedule of procedures

| Procedures | Visits (all at study site – vascular clinic/ward, except phonecall follow-up) | | | | | |
|---|---|---|---|---|---|---|
| | **Screening** (May occur from pre-op w6 months pre-treatment andup until 3 months (i.e. 90 days) post treatment. See note: ⊗ for further clarification) | | | | | |
| | **Pre-op** | **Baseline (day 0/ IVL treatment)** | **30 days post IVL** | **3 months post IVL (90 days)** | **6 months post IVL** | **12 months post IVL** |
| Visit window (for data collection) | | | ± 14 days (2 weeks) | ± 14 days (2 weeks) | ± 14 days (2 weeks) | ± 14 days (2 weeks) |
| Clinical follow-up | → | → | → | → | → | → |
| Identify and approach potential participants | X | → | → | → Δ | | |
| Informed consent | X | → | → | → Δ | | |
| Rutherford classification | X | X * | X | X | X | X |
| Concomitant medication check | X | X * | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Eligibility Assessment | X → | | | → Δ | | |
| Physical exam (if in person) | X | X * | X ** | X ** | X ** | X ** |
| Medical history | X | X * | X | X | X | X |
| Ultrasound Complex/Developmental/Contrast-Enhanced Ultrasound (if in person and if needed clinically) | X | | X ** | X ** | X ** | X ** |
| Vessel treatment | | X | | | | |
| CRF/eCRF completion including data transfer and query resolution | X | X | X | X | X | X |
| Review of participant Adverse Events (AEs) | | X | X | X | X | X |
| Follow-up (via telephone & remote data collection if not aligned with a clinical follow up per standard of care) | | | X | X | X | X |

***This data will be collected if available at baseline, as not all activities may be repeated following pre-op timepoint**
**** This data will be collected if the participant is seen in person due to clinical need at these timepoints, and the data is available**
**Δ Window +/- 14 days (2 weeks) does not apply (Note: where recruitment and enrolment takes place up to 90 days/3 months after the IVL L6 procedure, collection of data for 30 day follow up is not considered a protocol deviation)**
⊗ **Note:** Screening and informed consent may take place before the planned IVL L6 procedure or within three months (90 days) after the procedure. Where screening and consent are completed before the procedure, the participant must not be enrolled until the IVL L6 procedure has taken place.
Participants may only be enrolled if they undergo the IVL L6 procedure per the eligibility criteria, and enrolment must occur no later than 3 months (90 days) after the procedure. Participants who have not been enrolled on this basis within this period are not eligible to participate. Where screening takes place before the planned procedure, it is recommended that it occurs no more than six months in advance. However, the six-month period is not a strict requirement. If the procedure is subsequently delayed beyond six months after screening, this will not be considered a protocol deviation.

## 5.2 Recruitment

The recruitment phase will commence as soon as all necessary approvals have been received. Potential participants will be identified and contacted through the approaches described below.

## 5.3 Participant Identification

Potentially suitable participants for IVL L6 will be those with symptomatic PAD attending vascular clinics or vascular wards at the participating locations who have been referred for an IVL procedure. As such potentially suitable participants are those who are due to receive IVL as a primary treatment irrespective of this study.

Potential participants may be first identified and introduced to the study by a member of the patient's direct clinical care team at a hospital visit or over the phone ahead of the IVL procedure. Alternatively, they may be identified when listed on the operating theatre list by a member of the patient's direct healthcare team, or by a member of the research team screening the operating theatre list. They may also be identified after the IVL procedure has already taken place, within three months (90 days) from baseline/treatment.

Participants may be recruited either:

- Prospectively, where the participant is identified before their planned IVL procedure, receives the Participant Information Sheet before or around the time of treatment, and provides informed consent after the procedure but before study data collection commences; or
- Retrospectively, where the participant is identified after completion of the IVL procedure, up to 90 days following treatment. In these cases, written informed consent will be obtained retrospectively prior to collection, transfer or use of study data for research purposes.

In both recruitment pathways, IVL L6 treatment will have been delivered as part of routine clinical care independent of study participation. No research-specific interventions will occur before consent is obtained.

A member of the patient's direct clinical care team will aim to have a brief discussion about the study with the individual and provide them with the appropriate version of the PPI (Patient and Public Involvement) reviewed Participant Information Sheet (PIS). This may be provided in person or given the low risk of the study (in that patients would be referred for IVL as a primary treatment independent of this protocol), via post/email (depending on the method of approach and/or preferences of the patient). This process will be clearly documented in the patient's medical notes.

On many occasions the direct clinical care team may also be members of the research team. In the scenario where a member of the direct clinical care team has not been delegated the responsibility to undertake research tasks (as per the Delegation of Authority (DoA) and Signature Log) they will ask the potential participant if they agree to be contacted by a member of the research team to further discuss the study. The

patient's preferences will be clearly documented in the patient's medical notes. Where permission to be approached by a member of the research team has not been obtained, the initial introduction of the study will be done by a member of the direct clinical care team.

Staff involved in recruitment will be appropriately trained and documented on the DoA and Signature Log.

### 5.3.1 Screening and eligibility assessment

Potential participants will be adults (aged 18 years and above) attending a vascular clinic or ward at the one of the named study locations. They would have been diagnosed with symptomatic PAD and referred for primary treatment of calcified lesions in the iliac/aorto-

Iliac/femoral arteries with IVL (independently and irrespective of the protocol/study). The following inclusion criteria will be assessed by the patient's direct healthcare team:

- PAD classed as stages 3-5 according to the Rutherford classification
- Presence of calcified lesions in the aorta and/or iliac/femoral arteries which are to be treated using IVL

A member of the research team will confirm that the participant meets the eligibility criteria. This will include a review of the patient's medical notes to confirm the above inclusion criteria. The screening of patients for eligibility can take place at any point from pre-op, e.g. up to 6 months pre-treatment, up until 3 months (i.e. 90 days) after IVL treatment has taken place.

### 5.3.2 Informed consent

Following the provision of the correct version of the participant information sheet (PIS), the potential participant will be given as much time as they need to decide whether or not they would like to take part. They will be given the opportunity to ask questions regarding taking part and withdrawing and will have these answered. The process of obtaining informed consent will include a discussion between the potential participant and a member of the research team which will detail no less than; the exact nature of the study, the implications and constraints of the protocol, and any risks involved in taking part. It should be clarified by the study team that the research is separate to the procedure planned or has already taken place, i.e. the research does not affect their care in any way.

Participants may withdraw from the study at any time, for any reason, without prejudice to their current or future care and without affecting their legal rights. Participants may either withdraw from telephone follow-up only, while permitting continued collection of trial-related data from routine healthcare records and NHS digital sources, or withdraw from all study activities, after which no further study-specific data will be collected. Data collected prior to withdrawal will be retained and used in study analyses according to GDPR. All withdrawals, including the date, type of withdrawal, and reason (if provided), will be documented in the Participant Screening and Enrolment Log.

Written informed consent will then be obtained by means of a participant dated signature and dated signature of the person who presented and obtained the informed consent on the latest approved version of the informed consent form (ICF) and the process documented in the medical notes. The person who obtains the consent will be suitably qualified and experienced and will have been authorised to do so by the Primary Investigator (PI) as detailed on the DoA and Signature Log for the study.

The informed consent procedure may take place in person or remotely. The delegated research team member undertaking the remote consent process will conduct the discussion with the potential participant by telephone or video link (e.g. Microsoft Teams). In this, potential participants will be able to have any questions answered and afterwards have sufficient time in private to consider the study before a further follow-up call (if requested). If the potential participant wishes to proceed, delegated research team member undertaking the remote consent process must document the consent process. The potential participant will be able to choose the method of consent in order to provide flexibility:

- **Verbally, by phone or video call:** During a follow-up call or video call, they can provide verbal consent to items on the consent form. A video or audio recording of the conversation will be made, and the recording retained to evidence consent along with completed consent form by the delegated research team member
  If audio or video recording of the consent process is not feasible, the informed consent discussion must be conducted in the presence of an independent witness. The independent witness must be present throughout the entire consent discussion and must confirm that the participant received and understood the study information, was given the opportunity to ask questions, and voluntarily agreed to participate in the study. The delegated member of the research team obtaining consent and the independent witness must sign and date the ICF to document the participant's verbal consent. This process must be completed before any study-specific procedures are undertaken.
- **Digitally, by return of consent form wording within email thread:** the email must be sent from a mailbox that only the consenting individual has access to. Confirmation for this must be sought prior to undertaking this method of consent.
- **Digitally, by e-signature software:** the link must be sent from a mailbox that only the consenting individual as access to. Confirmation of this must be sought prior to undertaking this method of consent.
- **Written, by return of scanned copy of the wet-ink completed consent form added as an attachment to an email**
- **Written, by return of wet-ink completed consent form via post**
- **Written, by visiting a member of the research team in person**

For participants identified after completion of the IVL L6 procedure, informed consent will be obtained retrospectively before any research activities are undertaken, including review, extraction, transfer or entry of identifiable study data into study records or databases. Data relating to the IVL procedure and routine clinical care that occurred before consent will be obtained and used for research purposes following provision of written informed consent.

The original signed consent form will be retained at the study site within the Investigator Site File (ISF). A copy of the signed ICF will be given to the participant and a further copy will be retained in the participant's medical notes. The participants will be required to give written informed consent prior to any study activities taking place. Once provided, the potential participant will be added to the 'Participant Screening and Enrolment Log' and given a Screening number. Participants will be considered enrolled after completion of the baseline intravascular lithotripsy procedure (i.e. after all parts of the procedure have taken place as planned by the clinical team) providing all other eligibility criteria are met and provided with a unique participant ID number which will also need to be added to the Participant Screening and Enrolment Log.

## 5.4 Randomisation

This is a non-randomised study. All participants will receive standard of care as per NHS and local practice at each site before, during, and after the index procedure. There are no additional scans or appointments taking place. There is no exposure to radiation or additional scans taking place as part of the research. All participants will be enrolled only after their lithotripsy procedure (the standard of care) has been completed and providing all other eligibility criteria have been met.

### 5.4.1 Blinding and code breaking

Not Applicable. All participants will be recruited after their lithotripsy treatment has taken place and will have already been made aware of this by their clinical team.

## 5.5 Study assessments

The following data will be obtained from the patient's medical records and from the patient themselves, by a member of the research team. The majority of this data is routinely collected as part of standard PAD care. The exception will be any information received from the patient during a follow-up telephone call at 30 days, and 3, 6 and 12 months post treatment made by a member of the research team. It should be noted that participants may be consented to the study up to 3 months (i.e. 90 days) post IVL treatment, and where this does occur close to the 3-month (i.e. 90 days) cut-off point, there may be some missing data for the pre-op, baseline, and 30-day timepoints. In this instance, this will not be a protocol deviation.

**Pre-op and baseline** (data collected at visit to vascular clinic or on the ward). Pre-operative data may be collected following consent during the screening process (e.g. This may occur 6 months pre-treatment. See schedule of events for further details.).

- Demographic information (e.g. age at time of recruitment, sex, ethnicity)
- PAD presentation including Rutherford stage
- Chronic kidney disease status
- Diabetes status, duration of diabetes history, and current diabetes medication(s)
- History of previous major cardiovascular events
- Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography
- Smoking status
- Previous operations, including a full surgical and vascular history

- All concomitant medications as reported by patients
- Degree of artery calcification on a three-point scale (low, medium, severe), based on the treating clinician at baseline
- TASC II classification of the main culprit lesion/affected segment (reported at site level) calculated at analysis

The data collected here will relate to information obtained at the time of the IVL procedure, including:

- Exact location of the lesion treated
- Exact length of the lesion treated
- Number and size(s) of intravascular lithotripsy catheters used
- Duration of intravascular lithotripsy application per arterial site in seconds
- Exact anatomy of the arterial lesions present on intra-operative angiography including degree of stenosis or occlusion, lesion length, vessel diameter, and degree of calcification including Peripheral Arterial Calcification Scoring System (PACSS)
- Nature of the additional surgical or endovascular treatments taking place including endovascular equipment used e.g. balloons, stents, guidewires
- Cost of catheters
- Duration of the whole procedure
- Immediate complications during the procedure and steps taken to address them (e.g. thrombectomy)
- Patency of the treated lesions upon completion of IVL use
- Lumen gain upon completion of IVL use (measured as degree of stenosis before and after use of IVL, reported as a binary outcome (lumen gain >50% or not) and as a continuous measure (based on immediate angiography)
- Use of any adjunct(s) after IVL and their exact nature
- Immediate patency of the lesion(s) treated on the completion angiogram
- Any residual stenoses and additional treatments delivered prior to completing the index procedure
- Level of most senior operator performing the procedure and duration of whole procedure (excluding Informed Consent)

### 5.5.1 Follow-up assessments

A review of participants' electronic medical records and clinical notes will be carried out, and a follow-up phone call will be made to the participant by a member of the research team. This will occur at 30 days and at 3, 6 and 12 months post IVL treatment (+/- 14 days (2 weeks)) to collect the following listed data, if available. Data will relate to the period between the previous and current timepoint. Information will be collected at a face-to-face assessment when clinically necessary (e.g. for additional scans). Causes for death and reasons for re-admissions as well as data relating to all re-interventions and clinical events will be collected via medical records and death certificates.

1. Hospital readmissions including nature and reason
2. Re-intervention(s) - nature and reasons why this occurred.
3. Amputation(s) - nature and reasons why this occurred.
4. PAD presentation including Rutherford stage
5. Adverse events of interest including any cardiovascular events (as per table in section 7)
6. Mortality including cause if applicable
7. Results of any cross-sectional imaging relating to the arterial vasculature e.g. arterial duplex or computed tomographic angiography (if needed clinically, not for research purposes)
8. Imaging timing and nature will be guided based on clinical judgment in order to ensure this remains a pragmatic cohort study reflecting real-world practice
9. Imaging will be used to capture patency during follow-up, based on whether an occlusion or stenosis of the index culprit lesion >=50% is present
10.

As this is a non-interventional observational cohort study, participant follow-up will be aligned with routine clinical care wherever possible and will not alter standard treatment pathways or scheduled clinical appointments. Clinical follow-up visits will occur according to local practice and the judgement of the treating clinician. Whilst routine clinical appointments may coincide with study follow-up timepoints, clinical appointments must not be scheduled, delayed, or amended to meet study requirements.

Study follow-up will be performed at approximately 30 days, 3 months, 6 months, and 12 months following IVL treatment. Follow-up data may be collected during routine clinical visits when these correspond with study timepoints, by telephone contact with the participant, and through review of relevant medical records.

A member of the research team will contact participants by telephone at the scheduled follow-up timepoints to ascertain participant status, collect outcome data, and identify any adverse events of interest. Where a routine clinical appointment occurs within the relevant follow-up window, study follow-up assessments may be completed in person during that visit.

If a participant cannot be contacted by telephone despite reasonable documented attempts, follow-up information may be obtained through review of hospital records, electronic healthcare records, or by contacting the participant's General Practitioner, where permitted. The participant's last known alive date and other relevant outcome information may be recorded in the Case Report Form (CRF).

Given that follow-up is aligned with routine clinical care and outcome data may be obtained through healthcare records, participants are not expected to become lost to overall study follow-up. Where a participant cannot be contacted directly for a follow up visit, the research team will seek outcome data through routine healthcare records and may re-attempt participant contact at subsequent follow-up timepoints. As a last resort the research team should liaise with the participant's direct clinical care team. However, participants may be classified as lost to follow up where repeated attempts to contact them directly have been unsuccessful, even by the direct clinical care team. Participants may withdraw from the study at any time. Withdrawal may occur at two levels:

1. **Withdrawal from telephone follow-up only:** Participants may discontinue telephone follow-up contacts while continuing to permit the study team to collect trial-related data from medical records and relevant NHS digital data sources.
2. **Complete withdrawal from the study:** Participants may withdraw fully from all study activities, after which no further study data will be collected. Withdrawal from the study will not affect the participant's standard clinical care pathway using IVL L6.

All participants who cannot be contacted directly, together with details of contact attempts and follow-up status will be documented in the patient's medical records and local study participant trackers. If eventually deemed lost to follow up this will be documented on the Sponsor's Participant Screening and Enrolment Log, CRF, and within the patient's medical records and local study participant trackers.

## 5.6 Study intervention(s) and comparator(s)

### 5.6.1 Description of study intervention

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

### 5.6.2 Description of comparator

Not applicable

## 5.7 Expenses and benefits

All visits to the vascular clinics or wards by participants will be required as part of standard care, and therefore no expenses associated with these visits will be reimbursed.

## 5.8 Early discontinuation/withdrawal of participants

Participants can withdraw from the study at any point and for any reason. They are not obliged to give the reason for withdrawal, and it will not prejudice their future care or affect their legal rights. After a participant provides consent for the study it may be that they do not receive IVL treatment and in which case, they will no longer meet the eligibility criteria and will be excluded from the study and not classed as enrolled. This will be recorded on the CRF. If a participant withdraws from the study, or loses the capacity to consent for themselves, data collected up until the point of withdrawal/loss of capacity will be retained and used in the study. The nature of the withdrawal and the reason, if known, will be recorded in the Withdrawal CRF and on the Participant Screening and Enrollment log.

## 5.9 Definition of end of study

The end of study is the date that it is confirmed all data queries are resolved and the database is locked for analysis.

# 6 Sample Handling

Not applicable

# 7 Safety Reporting

The IVL L6 Cohort Study is not an interventional study and therefore the usual monitoring of pharmacovigilance and associated terminology is not relevant. Serious Adverse Event (SAE) reporting is not applicable for this type of study.

This study follows established international guidance (including NHS and National Institute for Health and Care Excellence [NICE] guidance) as to what constitutes best medical therapy for PAD. Standard care (NHS within the UK) pathways will be followed.

The below are considered as adverse events (AEs) of interest in this patient group with incident symptomatic severe PAD and should not be reported (only captured on CRFs as events):

| |
|---|
| Bowel obstruction |
| Acute kidney injury |
| Arterial dissection |
| Arterial pseudoaneurysm formation |
| Atrial fibrillation (new) |
| Bowel ischaemia |
| Chest infection |
| Diabetes (new diagnosis) |

| |
|---|
| Diabetic foot ulcer (new) |
| Diabetic ketoacidosis |
| Endovascular re-intervention (will have to be reported separately using the relevant form) |
| Failure of endovascular closure device |
| Fall |
| Fasciotomy |
| Haematoma (at site of surgery or percutaneous puncture) |
| Heart failure |
| Hernia |
| Hypertension (new diagnosis) |
| Ileus |
| Intermittent claudication (new diagnosis) |
| Laparotomy |
| Lower limb compartment syndrome |
| Lower limb oedema |
| Amputation (below the ankle joint) |
| Myocardial infarction |
| Need for open surgical access to an artery during the index endovascular procedure |
| Peripheral embolisation requiring re-intervention or additional endovascular treatment |
| Peripheral embolisation, not requiring surgery or re-intervention |
| Prescription of antibiotics for lower limb tissue loss (ulcer/gangrene) |
| Re-admission to hospital within 30 days of treatment |
| Requirement for catheterisation (urinary catheter) |
| Stent or graft occlusion |
| Stent or graft thrombosis |
| Stoma formation |
| Stroke |
| Surgical re-intervention (will have to be reported separately using the relevant form) |
| Transient ischaemic attack |
| Transient renal replacement therapy |
| Urinary retention |
| Urine infection |
| Use of additional stent or additional endovascular device |
| Venous thrombosis (deep and/or superficial) |
| Viral infection |
| Wound infection |

## 8.0 Statistics and Analysis

Descriptive statistics will summarise baseline characteristics, procedural details, and clinical outcomes. Continuous variables will be reported as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables will be presented as frequencies and percentages.

Primary and secondary outcomes, including procedural success, target lesion revascularisation (TLR), major adverse limb events (MALE), and adverse events, will be analysed using Kaplan-Meier methods for time-to-event data and compared across subgroups using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals will be calculated using Cox proportional hazards regression models.

Multivariate analyses will adjust for potential confounders identified a priori, including demographic, clinical, and procedural factors. Interaction terms will test for effect modification by key variables (e.g., lesion characteristics, vessel type). Predefined subgroup analyses will include comparisons by region, lesion complexity, and patient comorbidities. Sensitivity analyses will assess the robustness of results to variations in model assumptions.

All findings will adhere to CONSORT (Consolidated Standards of Reporting Trials) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines, with a focus on transparency and reproducibility. Results will be presented at international conferences and submitted to peer-reviewed journals.

### 8.1 Sample size calculation

A minimum of 60 participants would need to be recruited in order to demonstrate the primary study objectives. This assumes a 30% failure to reach the primary endpoint at 12 months, based on prior research, and a confidence interval width of 0.25 at 95% confidence level, assuming 5% loss to retention. It is therefore expected that a total of 80 patients would have to be contacted, to ensure we reach the target of 60 recruits.

### 8.2 Planned recruitment rate

The aim is to open at up to ten vascular locations – two in Europe (one each in Italy and Switzerland), and up to eight based in the UK. In a previous study in 2022 (SHOCC) that recruited from a very similar population of patients, we succeeded in recruiting 90 patients across eight UK locations in 16 months (average recruitment rate of 5.6 participants per month [0.7 per site per month]). At least four of the UK locations that we aim to open at were involved in SHOCC. Based on these factors, we would expect a similar recruitment rate in this study. Therefore, a recruitment target of 60 patients across up to 10 locations in 12 months (0.5 participants per location per month) is considered achievable.

## 8.3 Statistical analysis plan

### 8.3.1 Leads for Statistical analysis

The statistical analysis will be led by Mr Liam Musto and Professor Athanasios Saratzis (Leicester Vascular Research). Support will be sought where necessary from the NIHR (National Institute for Health and Care Research) Leicester Bioinformatics Hub.

### 8.3.2 Data Management

Data will be collected prospectively using a centralised electronic data capture system. Participating centres will adhere to standardised data collection protocols, ensuring consistency and comparability. Baseline characteristics, procedural details, and follow-up outcomes will be recorded. Data validation procedures will include automated and manual checks for completeness and accuracy. Missing data will be examined, and multiple imputation techniques may be employed if necessary, ensuring the robustness of the analysis.

### 8.3.3 Descriptive Statistics

Baseline characteristics will be summarised to describe the study cohort. Continuous variables will be presented as mean ± SD or median with IQR, depending on their distribution. Categorical variables will be reported as frequencies and percentages. Key procedural and clinical outcomes will also be summarised descriptively.

### 8.3.4 Outcomes Analysis

The primary outcomes of interest include procedural success, TLR and primary and secondary vessel patency, while secondary outcomes include freedom from amputation, MALE, and adverse events. Time-to-event data will be analysed using Kaplan-Meier survival curves, with comparisons between subgroups conducted using the log-rank test. Censoring will occur at the time of the last follow-up or event occurrence.

### 8.3.5 Multivariable Analysis

Cox proportional hazards regression will be used to calculate hazard ratios (HRs) with 95% confidence intervals for time-to-event outcomes, adjusting for potential confounders identified a priori. Covariates for adjustment may include demographic factors (e.g., age, sex), comorbidities (e.g., diabetes, smoking status), and lesion-specific characteristics (e.g., calcification severity, vessel size). Interaction terms will assess effect modification by key clinical and procedural variables.

### 8.3.6 Subgroup Analysis

Pre-specified subgroup analyses will examine outcomes based on factors such as geographic region, lesion complexity (simple vs complex), and patient characteristics (e.g., presence of diabetes or chronic kidney disease). Subgroup analyses will include tests for interaction to evaluate potential differential effects.

### 8.3.7 Reporting

Findings will be reported in accordance with international guidelines, including CONSORT and STROBE. Results will include comprehensive tables and figures summarising the study population, outcomes, and statistical analyses. Interim analyses, if conducted, will focus on descriptive summaries and safety outcomes.

## 8.4 Participant population

Participants will be adults with symptomatic PAD referred for primary treatment of calcified lesions in the iliac/aorto-iliac/femoral arteries with IVL, that meet the eligibility criteria as set out in section 4. All participants will be included in the final data analysis for the study.

## 8.5 Procedure(s) to account for missing or spurious data

This study in an observational study of a treatment used within a standard care pathway for patients with symptomatic PAD. All data to be recorded will be routinely collected as part of standard of patient care. In the case of any missing or spurious data the coordinating study team will contact the relevant site research team to ensure that any missing data is supplied, and confirm that all data collected is correct. For patients consented to the study close to the end of the recruitment window (3 months post IVL treatment), it is possible that there may be missing data that it is not possible to obtain).

## 8.6 Other statistical considerations

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

## 8.7 Economic evaluation

There is limited health economic data to support the use of IVL as the primary treatment strategy, with the avoidance of stenting, for the treatment of symptomatic PAD.

### 8.7.1 Introduction

The economic evaluation plan outlines the approach to assessing the costs associated with IVL in the treatment of aortic and/or iliac and/or femoral PAD as part of this multicentre international prospective cohort study. The primary focus

will be on capturing procedural costs, re-admissions, and re-interventions to estimate the economic impact of IVL over one year.

### 8.7.2 Data Collection

The economic analysis will include the following cost components:

**Cost of IVL catheters:** The number of catheters used during the endovascular procedures will be recorded for each patient and the cost calculated at analysis.

**Cost of endovascular equipment:** Additional procedural equipment (e.g., balloons, stents, guidewires) will be captured and the cost calculated at analysis.

**Re-admissions:** The number of re-admissions within one year of the index procedure will be documented.

Costs will be reported in the currency of each participating centre, with adjustments made to reflect purchasing power parity for international comparisons.

### 8.7.3 Analysis of Procedural Costs

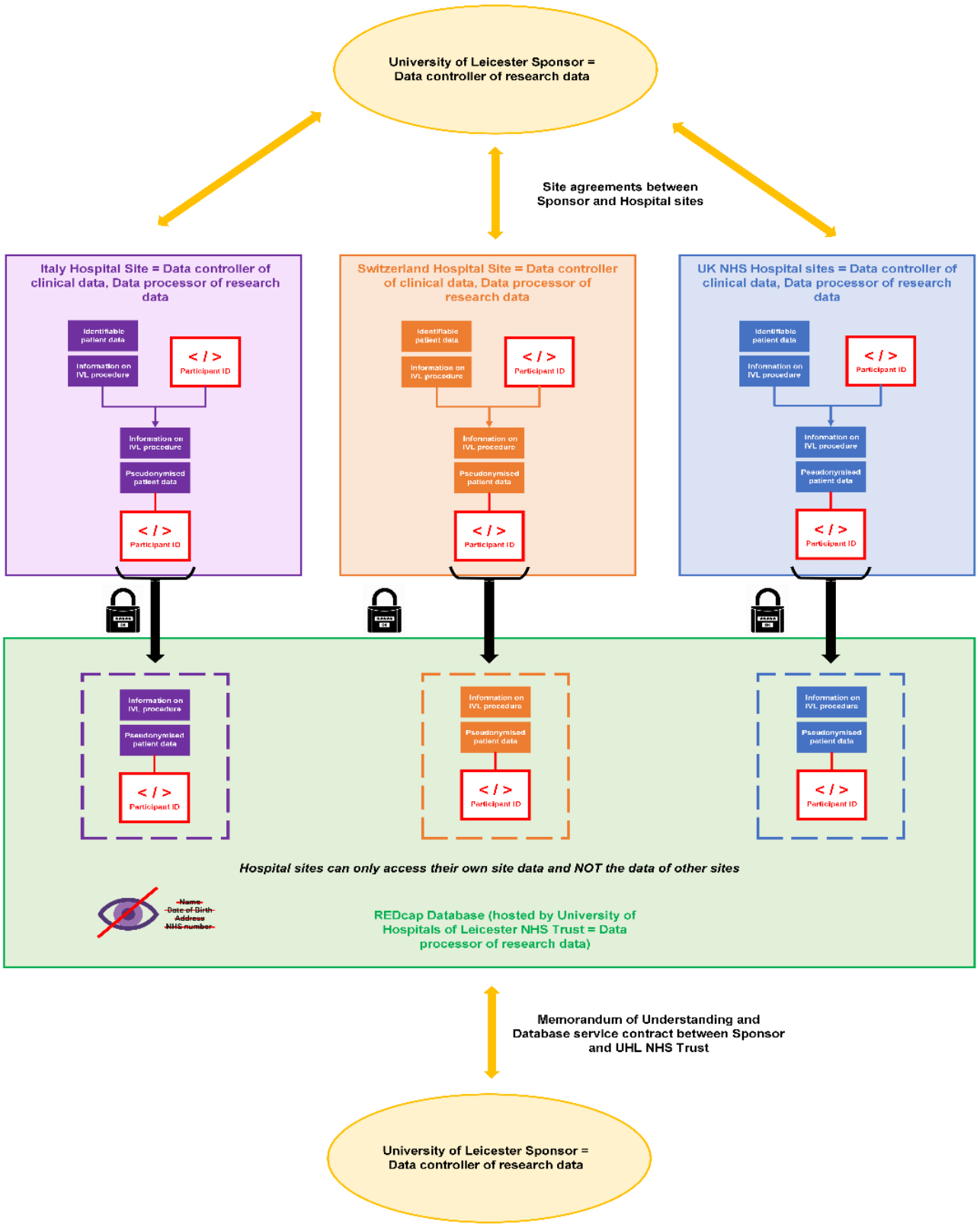
The mean and median costs of IVL catheters and endovascular equipment will be calculated per patient. Differences in procedural costs between subgroups (e.g., lesion complexity or geographic regions) will be analysed using descriptive and inferential statistics.

### 8.7.4 Reporting

Cost outcomes will be summarised as mean and total costs per patient for the index procedure and cumulative costs over one year. Results will be presented in tables and graphs, with stratification by patient subgroups where relevant. Sensitivity analyses results will also be reported to highlight uncertainty in the economic estimates.

# 9 Data Management

## 9.1 Data flow diagram



## 9.2 National data opt-out

In the UK the national data opt-out was introduced on 25th May 2018 enabling patients to opt out from the use of their data for research or planning purposes in line with the recommendations of the National Data Guardian in their review of Data Security, Consent and Opt-outs. As from 1st August 2022, all NHS Trusts are now compliant with the national data opt-out operational policy guidance document; for further information please visit https://digital.nhs.uk/services/national-data-opt-out/operational-policy-guidance-document. All study participants will have provided consent for the use of their data, specifically for the purposes of the research study. Therefore, this use falls within the general exemption from the national data opt-out. This rule applies even if the consent was given before the patient had set a national data opt-out.

## 9.3 Source data

The data required to answer the objectives of this study are routinely collected as part of the standard patient pathway within PAD care. The source data will be patients' medical records, and for the study locations in the UK these will be held in the NHS and documented via the Sponsor's Source Data Agreement.

## 9.4 Data collection tools, handling and record keeping

During screening potential participants will be provided with a unique screening number upon consent which will be captured on the relevant CRFs and Participant Screening and Enrolment Log. Each participant will also be assigned a unique participant identification number upon enrolment to the study. This number will be written on the ICF and then added to all study documents/data collection tools in place of the participant's name.

Data will be collected at pre-op and baseline/day of IVL treatment, with follow-ups completed at 30 days and at 3-, 6- and 12-months post IVL treatment (Please see Schedule of Events for details on applicable windows). Data in medical records will be accessed by a member of the patient's clinical care team, who will also be an appropriately trained member of the research named on the study DoA and Signature Log. Data retrieved from the source data will be entered into CRFs in REDCap (Research Electronic Data Capture). REDCap is a secure web application for building and managing databases, with a specific database designed and built for this study by the NIHR Leicester Bioinformatics Hub staff. REDCap will be located on the University Hospitals of Leicester NHS Trust server. Participants will be identified by a unique site-specific study identifier within the database, i.e. data will be pseudonymised. For individuals that do not hold a site's key for the study identifiers, data will be effectively anonymous. Identifying details such as name, date of birth and address will not be included in the database.

A contacts database (which contains participant contact details) will be held separately from the study database. Participant's contact details will be held securely in accordance with data protection regulations. This will be password protected, held on the relevant NHS Trust's/site's server and managed at the site by the research team. The patient's

contact details will also be entered onto the study Enrolment Log, which will be maintained within the ISF.

In order for data analysis to occur data will be exported from REDCap into Excel. This copy of the data will be stored within the University of Leicester's secure centralised storage facility (the Research File Store [RFS]). Data on the RFS is backed up automatically on a daily basis with backups held in a separate building for 28 days. Access to the area of the RFS where study data will be stored will be restricted to individuals named on the study DoA and Signature Log with access managed by UoL IT Services in conjunction with the CI and Study Coordinator.

The original signed and dated ICFs will be stored in the ISF. A copy will be retained in the participant's medical notes alongside a copy of the PIS, and a further copy given to the patient with a copy of the PIS. A sticker will be placed on the cover of the medical notes (or inside cover) detailing the study title, contact details of the PI and the fact that the notes should not be destroyed for 6 years from the end of the trial. All study visit summaries and AEs of interest will be recorded in the hospital notes.

All data handling and record keeping will be kept in adherence to University of Leicester's and relevant NHS Organisation(s)/site(s) policies. All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, The UK Policy for Health and Social Care Research and the Data Protection Act (for sites in the UK) and ICH-GCP and General Data Protection Regulation (GDPR) (for EU sites).

### 9.5 Access to data

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- in line with participant consent.

The Bioinformatics team will grant and manage REDCap database access rights in conjunction with the central Study Coordinator, through the use of assigned usernames and passwords. Members of site research teams will only be able to view data related to the participants at their own site. Only delegated individuals from the central coordinating team will be able to access all participant data. By consenting to participate in the study, participants will have agreed to have their data shared with individuals from the University of Leicester, i.e. the coordinating study team.

Study staff at participating sites will have access to additional data collected as part of this research, such as the participant contact database and the Enrolment Log. Access to these data will be restricted by role-based permission to authorised study personnel who will be suitably trained prior to being granted access. Individual user accounts will be password protected and will not be shared between members of the study team.

### 9.6 Archiving

Research data and archived files will be stored for a minimum of 6 years after the study has ended. Storage will comply with the University of Leicester archiving SOP. Details

can be found at: https://le.ac.uk/research/regi/standard-operating-procedures. Destruction of essential documents will require authorisation from the Sponsor. Archiving of source data and ISFs for participating sites will be arranged by the relevant participating sites. Archiving of the Sponsor TMF will be arranged by the central coordinating centre.

## 10 Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH-GCP, the principals of the Declaration of Helsinki, relevant regulations and SOPs. The site PI (or their delegate) will be responsible for maintaining the ISF (as appropriate) and ensuring it is kept 'inspection ready' at all times. The central coordinating centre will maintain the Sponsor TMF at the University of Leicester.

### 10.1 Monitoring, audit and inspection

The University of Leicester as Sponsor operates a risk-based monitoring programme which this study will be subject to.

## 11 Protocol Compliance

### 11.1 Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Planned deviations or waivers are not allowed however it is acknowledged that accidental protocol deviations may occur. Any deviations from the protocol will be documented in a protocol deviation form and filed in the ISF and the appropriate CRF completed.

If a protocol deviation occurs, then the CI (or delegate) will document this in accordance with the University's SOP Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol.

Deviations from the protocol which are found to frequently recur will be explored and where necessary an modification to the protocol will be made.

### 11.2 Serious breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC (Research Ethics Committee) and the relevant NHS host organisation within seven calendar days.

## 12. Ethical and Regulatory Considerations

### 12.1 Research ethics committee and regulatory review, approvals/permission/support, compliance and reports in the UK

Once the Sponsor Review process is complete, authorisation from the University of Leicester's Research Governance Office will be issued to book further regulatory review of the proposed research. An NHS REC and the Health Research Authority (HRA) will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will occur via the Integrated Research Application System (IRAS). The CI will ensure that all regulatory approvals, confirmation of capacity and capability from NHS sites and sponsor green light are in place before participants are approached.

For any required modification(s) to the study, modification(s) will be submitted to the Sponsor in the first instance for review and approval to submit the modification for external regulatory approval. Modification(s) must be implemented following all required ethical, competent authority, site and Sponsor approvals and in line with Sponsor SOPs.

The Research Governance Office's SOPs will be followed for the duration of the study.

The CI will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying REC.

A study TMF will be maintained for the duration of the study and will be stored for a minimum of 6 years after the study has ended.

### 12.2 Considerations and requirements for Italy and Switzerland

In line with local processes, ethics and other appropriate approvals will be obtained. The Sponsor and central coordinating centre will liaise with key contacts at the sites for guidance on obtaining local approvals. All sites in Italy and Switzerland will provide their own sponsorship.

### 12.3 Peer review

This protocol has been reviewed by two experts in performing IVL on Iliac vasculature as a primary treatment. They are also external to UoL. The peer-review therefore meets the NIHR's criteria to be adopted on the portfolio as reviewers are also not affiliated with any of the study sites or delivery in any way.

## 12.4 Patient and public involvement (PPI)

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| **Who was involved?** | We have not specifically involved patients in the initial concept and design of this study because IVL L6 is already used in many hospital centres as a primary treatment of calcification in the Iliac vasculature and the study is not influencing the treatment that patients would receive. However though IVL is already approved for use, we know through conducting the procedure in Leicester and via personal communications, that the longer-term efficacy and safety is important to patients.<br><br>PPI input will be sought into the design and wording of the PIS. |
| **How and when have they been involved?** | Our PPI group will be involved at the beginning of the study when patient-facing materials are being developed to ensure that the study design is appropriately conveyed to potential participants. They will also be involved during the study if any amendments are needed. Finally, our PPI group will be involved in the dissemination strategy. |

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| **How has the input of the people you involved made the study ethically acceptable?** | The involvement of our PPI group in the design of the PIS will hopefully make the studying of IVL as a primary treatment of the Iliac vasculature and the use of patient's data for research more acceptable to the people that agree to take part in the study so that the results can benefit wider populations.<br><br>From a clinical perspective, the studying of this procedure as part of a study protocol presents no additional risk to patients participating in the study because they would be receiving the treatment anyway and clinical consent will be separately obtained for this, as per usual clinical practice. Additional scans and procedures will only be carried out if clinically required as part of a patient's normal, standard care. As such, in this case, clinical follow up will occur in person. If no further procedures are clinically needed (as no procedures/interventions are specifically needed to answer the research question) then all clinical follow up will be conducted remotely and via phone to minimise the burden from a patient perspective, separate to a participant perspective.<br>To give flexibility to the potential participant, the direct clinical care team, and to the research team, a variety of options and approaches have been provided to recruit and provide study information. With respect to the minimal risk of studying the procedure and follow up, informed consent may also take place remotely. |

## 12.5 Assessment and management of risk

This study is a PMS, observational prospective, cohort study of IVL as a primary treatment of the Iliac vasculature. The study is considered low risk for the following reasons:

- The device is CE marked and used within its intended purpose for peripheral arteries which include the iliac/aorto-iliac/femoral arteries. Please see: https://evtoday.com/device-guide/euro/intravascular-lithotripsy-1 for further information.
- This protocol does not determine the treatment patients will receive and is entirely observational.
- The study is not an interventional study: IVL as a primary treatment of the Iliac vasculature would have already been identified by the direct clinical care team as the next step for an individual's clinical care (independent of this protocol)
- IVL as a primary treatment of the Iliac vasculature will only be conducted in centres that already offer this treatment and by experienced clinical operators per local location procedures.

A formal risk assessment will be undertaken if determined necessary during Sponsor review, in accordance with standard UoL Sponsor processes.

## 12.6 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the relevant legislation in their country. In the UK, the Common Law Duty of Confidentiality, UK GDPR, and UK Data Protection Act 2018 will be adhered to. In Italy and Switzerland EU GDPR applies. All information collected in the study will be kept strictly confidential and restricted to those that need access in order to deliver the study in accordance with the ICF.

The personal information that is collected will be kept secure and maintained by:

- The creation of a unique screening identification number for each upon consenting to the study
- The creation of a unique participant identification number for each upon enrolment into the study
- Secure maintenance of the data, in both electronic and paper forms and the linking code in separate locations.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.
- Any paper-based pseudonymised trial records will be stored in locked filing cabinets within a locked office, with access limited to those on the DOA and Signature Log.

- Electronic pseudonymised records will be stored on secure University of Leicester and/or University Hospital of Leicester NHS Trust server systems where the database is hosted.
- Identifiable information and trial data will be retained by the clinical teams at the sites electronically and/or in paper-based medical records in line with local processes.
- The database will be password protected and access granted only to researchers collecting/checking/cleaning data and the Sponsor (including the central coordinating centre) for monitoring and audit purposes.
- All data collected during the trial and entered onto the study database by participating sites will be stored on the database pseudonymised (linked to Screening Number/Participant ID). No identifiable details will be held in the trial database(s) at all. Therefore, members of the University of Leicester coordinating team will not have access to identifiable information from external sites
- Analysis of the data generated will be undertaken by the CI (or delegate) on University of Leicester premises.
- Pseudonymised research data will be stored for six years after the study has ended.
- At site, participant contact details will be held separate to the trial visit data and will be used by the research team or direct care team to arrange the delivery of clinical care and/or data collection visits on local systems.
- While participants are taking part in the study their contact details will be available to the researchers so that they can contact the participant to arrange the details of their research involvement. These will be deleted once they have been used for their agreed purpose. Where individuals have consented to receive a copy of the research findings, contact details will be retained until this has taken place. Contact details will be stored securely and separately from participant's research data and clinical information.
- Where a participant has provided additional consent for their contact details to be held on a central database (in order to invite them to participate in future research or invite them to help with dissemination of the research or PPI), this information will be held securely on University of Leicester server systems, e.g. the Research

File Store and have the highest level category of restriction for storage, access, and permissions verifiable authorisation before access is granted according to University of Leicester IT service SOPs.

- Any data transferred will be done securely in approved University of Leicester methods following consultation with the University of Leicester's Legal and Information Assurance Services (IAS) as part of the necessary completion of the Record of processing activities (ROPA) assessment and Data Protection Impact Assessment (DPIA), if applicable, and will consider site processes as part of the assessment where any special category data is required to be transferred. Any data transferred will be done in accordance with the DPIA and Sponsor SOPs, e.g. encryption and password protection in order to comply with all relevant laws and protect the rights of trial participants according to ICH-GCP.
- The Sponsor TMF will be kept in a folder in a locked cabinet, in a secured room, in a secure office environment office at the University of Leicester by the central coordinating centre.
- The ISFs at participating sites will be kept at the relevant participating hospital site and will be stored in a secure environment. Storage will adhere to each organisational policy on storage and ICH-GCP.
- Consent forms, enrolment logs and details of record linkage* (i.e., participant ID numbers/pseudonyms) will be kept for a minimum of 6 years after the study has ended as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data. At the end of this period approval from the Sponsor will be requested for the destruction of the data.
- Long-term storage will comply with the University of Leicester archiving SOP.

### 12.7 Access to the final trial dataset

The CI and their appointed deputies will have access to the analysed trial dataset following execution of the Statistical Analysis Plan and completion of the End of Trial Report.

## 12 Finance and Insurance

### 13.1 Funding

The research costs are funded by ShockWave Medical, Inc. In the UK, as it is planned that the study will be portfolio adopted, service support costs would be funded by the Department of Health and Social Care (DHSC). A contribution will be made from the research budget to support equivalent service support costs in Italy and Switzerland.

## 13.2 Indemnity

Sponsorship and insurance for study design and management will be provided by the University of Leicester.

Due to the nature of the study being observational, it is highly unlikely that a participant would be harmed due to negligence and/or conduct of the study as the study involves following up and collecting data for up to 12 months, following their IVL treatment that they would have received if they hadn't participated in the study. However, if a participant is harmed due to negligence and/or the conduct of the study, this will be covered by the local Trust(s) indemnity arrangements for all UK participants in clinical studies. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard NHS complaint system will be available to them. Details of this are made available to participants in the PIS.

Insurance, indemnity, and sponsorship will be provided by each Italian and Swiss site separately.

## 13.3 Contractual arrangements

The contractual arrangements that will be required are as follows:

- University of Leicester Sponsor with The Funder, Shockwave
- University of Leicester Sponsor and University Hospitals of Leicester NHS Trust for database provision
- Site agreements

# 13 Dissemination and Publication

## 14.1 Dissemination Policy

We will aim to disseminate the results from IVL L6 as widely as possible, involving national and international groups, expert groups, and lay people, supported by our research team members and existing links with patient groups and professional societies globally. The overall dissemination strategy will be kept under review and is subject to change to include additional avenues/groups for dissemination as necessary.

## 14.2 Academic publication and dissemination strategy

Our academic publication strategy will be led by the CI. 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. All publications will quote the clinical trials registration number and will acknowledge the participating investigator sites, the Sponsor, and the Funder. Prior to publication the manuscript will be submitted to the funder. The Funder will have no role in preparing the publication.

In addition to final results being published in medical journals, results will also be shared at conferences, and sent to relevant professional societies worldwide. Our key research team / co-applicants include members and chairs of several professional societies such as the British Society for Interventional Radiology, Vascular Society of Great Britain and Ireland (VSGBI), European Society for Vascular and Endovascular Surgery (ESVS), the James Lind Alliance, the Vascular and Endovascular Research Network (presence in 53 countries), NICE, and the NIHR. Our team includes key opinion leaders in peripheral arterial disease (globally) and some of the highest volume users of Shockwave and similar technologies in the UK as well as Europe. We represent key radiology and vascular surgery groups nationally and internationally. We will use these networks to disseminate in a variety of forums and methods, including personal communications and email.

### 14.3 Public dissemination strategy

Our public dissemination strategy will be led by the study manager and coordinated by our joint Trust/University/BRC (Biomedical Research Centre) communications team. Input from the University of Leicester's Vascular PPI Registry and/or the NIHR/DHSC infrastructure such as the The Patient Research Ambassadors Initiative (PRAI) will be sought.

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).

During the study, progress updates will be provided by email. At the end of the study, access to findings of the study will be made available in a contemporary and user-friendly way and full details of the results (excluding identifiable information) provided if the participant requests them. We will prepare plain English summaries and summaries in Italian, French, German, and Romansh (e.g. videos and/or infographics) when the study is completed for dissemination.

In previous research we have found that conventional, traditional media is the most effective method to reach members of the public and patients and we will adopt the same approach here. We will supplement this with social media engagement and websites in addition. We will also make use of other communication strategies and infrastructure of charitable groups such as the British Heart Foundation (BHF), the Circulation Foundation, and the funder, Shockwave Medical Ltd. To ensure a broader reach, findings will be disseminated via the University Hospitals of Leicester and University of Leicester press offices targeting generic and specialist publications.

### 14.4 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be ultimately determined by the CI, according to contribution to the study and delivery after discussion and agreement with the TMG, and according to the guidelines of leading medical journals, based on the latest version of the criteria published by the International Committee of Medical Journals Editors (ICMJE): 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 research team members who uploaded at least 80% of data points for at least 5 patients at 12 months i.e. completion of follow-up. The group will be collectively named "The IVL L6 Cohort Study collaborators". Authors will acknowledge that the study was funded by ShockWave Medical, Inc and sponsored by the University of Leicester. Other contributors will be appropriately acknowledged.

### 14.5 Outputs

- Peer-reviewed publication
- National/international conference publication

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# IVL L6 Protocol_v2.0_2026-08-11

Final Audit Report 2026-08-14

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