# Multi-centre randomised controlled trial to compare the clinical and cost-effectiveness of a 'vein bypass first' with a 'best endovascular treatment first' revascularisation strategy for severe limb ischaemia due to infra-popliteal arterial disease

**B**ypass vs. **A**ngioplasty in **S**evere **I**schaemia of the **L**eg-2


**TRIAL PROTOCOL: Version 6.0 15 October 2019**

| | |
|---|---|
| **Sponsor:** | **University of Birmingham** |
| **Chief Investigator:** | **Professor Andrew Bradbury** |
| **Coordinating Centre:** | **Birmingham Clinical Trials Unit** |
| **Funder:** | **NIHR Health Technology Assessment programme** |
| **ISRCTN:** | **27728689** |
| **Main REC Ref. No.:** | **14/WM/0057** |

# TRIAL COMMITTEES AND CONTACT

| Trial Management Group | |
|---|---|
| **Chief Investigator**<br>**Professor Andrew Bradbury** | Sampson Gamgee Professor of Vascular Surgery<br>University of Birmingham<br>Email: andrew.bradbury@btinternet.com |
| **Co-Applicants** | **Southmead, Bristol:** Mr Hinchliffe;<br>**Imperial College, London:** Professor Davies;<br>**Oxford:** Mr Perkins; Dr Uberoi<br>**Birmingham:** Mr Claridge; Dr Ganeshan<br>**Leicester:** Dr Adair<br>**Hull:** Professor Chetter; Professor Ettles<br>**Leeds:** Professor Scott; Dr Patel<br>**Sheffield:** Dr Cleveland<br>**Newcastle:** Professor Stansby |
| **Birmingham Clinical Trials Unit** | |
| **Methodologist: Jon Deeks** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: j.deeks@bham.ac.uk |
| **Lead Statistician: Smitaa Patel** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: s.a.patel@bham.ac.uk |
| **Statistician: Catherine Hewitt** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: c.a.hewitt@bham.ac.uk |
| **Trial Management: Margaret Grant** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: m.r.grant@bham.ac.uk |
| **Trial Lead: Hugh Jarrett** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: h.jarrett@bham.ac.uk |
| **Trial Manager: Tina Griffin** | Birmingham Clinical Trials Unit, University of Birmingham<br>Email: t.griffin.1@bham.ac.uk |
| **Health Economist: Patrick Moore** | Health Economics Unit, University of Birmingham<br>Email: p.moore@bham.ac.uk |
| **Lead Research Nurse: Gareth Bate** | University Hospitals Birmingham NHS Foundation Trust<br>Email: gareth.bate@heartofengland.nhs.uk |

| Trial Steering Committee | |
|---|---|
| **Chair: Professor Jonathan Michaels** | Honorary Professor of Clinical Decision Science, Health Economics and Decision Science, ScHARR, University of Sheffield<br>Email: j.michaels@sheffield.ac.uk |
| **Mr James Griffin** | Medical Statistician, University of Warwick<br>Email: james.griffin@warwick.ac.uk |
| **Professor Jon Moss** | Consultant Vascular Interventional Radiologist, Southern General Hospital<br>Email: Jonathan.Moss@glasgow.ac.uk |
| **Mr Andrew Beech** | Chief Vascular Scientist, Nottingham University Hospitals<br>Email: Andrew.Beech@nuh.nhs.uk |
| **Professor Frances Game** | Consultant Diabetologist, University Hospitals of Derby and Burton NHS Foundation Trust<br>Email: frances.game@nhs.net |
| **Martin Fox** | Vascular Specialist Podiatrist, Huddersfield<br>Email: martin.fox@nhs.net |
| **Mr Peter Maufe** | PAD patient, Patient Representative<br>Email: pete.maufe@tiscali.co.uk |
| **Mr Barry Attwood** | PAD patient, Patient Representative<br>Email: barryattwood123@hotmail.com |
| **Dr Nick Latimer** | Senior Research Fellow in Decision Science, ScHARR, University of Sheffield<br>Email: n.latimer@sheffieldl.ac.uk |

| Data Monitoring Committee | |
|---|---|
| **Chair: Professor Charles McCollum** | Professor of Surgery, Division of Cardiovascular Sciences, University of Manchester<br>Email: charles.mccollum@manchester.ac.uk |
| **Dr Richard Jackson** | Acting Director of Statistics, Liverpool Cancer Research UK, Liverpool Cancer Trials Unit<br>Email: r.j.jackson@liverpool.ac.uk |
| **Dr Samin Chakraverty** | Locum Consultant Radiologist – Scottish NHS Trusts and Plymouth University Hospitals NHS Trust |

## BASIL-2 Trial Office

**For general protocol related queries and supply of trial materials:**

**Birmingham Clinical Trials Unit (BCTU), Institute of Applied Health Research, College of Medical & Dental Sciences, Public Health Building, University of Birmingham, Edgbaston, Birmingham B15 2TT**

**Telephone: 0121 415 84448444**
**Fax: 0121 415 91355**
**Email: basil-2@trials.bham.ac.uk**
**Website: www.birmingham.ac.uk/basil2**

## Randomisation

The randomisation procedure is described in section 44.3

**Telephone: 0800 953 0274**

**Website: www.trials.bham.ac.uk/BASIL2**

## Safety Reporting

Safety reporting is described in Section 55

**Fax SAE Forms to: 0121 415 9135**

## Chief Investigator and Sponsor Signatures

The Chief Investigator and Sponsor have discussed and agreed to abide by this this protocol and to conduct the trial in compliance with UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principals of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

This protocol has been implemented via IRAS and electronic signature constitutes approval of this document.

**Chief Investigator**

Professor Andrew Bradbury

_____

Signature Date

**Sponsor Representative**

David Law (Head of Research Support Group)

_____

Signature Date

**Sponsor Contact Details**

David Law

Room 121, Aston Webb, B Block

University of Birmingham

B15 2TT

Email: d.a.i.law@bham.ac.uk

Tel: 0121 414 2644

**Principal Investigator:**

I have read and agreed to the protocol, as detailed in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the Trial Steering Committee prior to seeking approval from the Health Research Authority (HRA).

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki and the trial protocol and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial.

**Principal investigator**

**<insert name>**

Signature Date

**Name of Institution**

**<insert name>**

**The Principal Investigator should sign this page and return a copy to the BASIL-2 Trial Office**

## Table of Contents

## List of Abbreviations

| | |
|---|---|
| **AATK** | At or Above the Knee |
| **ABPI** | Ankle to Brachial Pressure Index |
| **ACS** | Acute Coronary Syndrome |
| **AE** | Adverse Event |
| **AFS** | Amputation Free Survival |
| **AI** | Aorto-Iliac |
| **AKA** | Above Knee Amputation |
| **ATA** | Anterior Tibial Artery |
| **BA** | Balloon Angioplasty |
| **BASIL-1** | Bypass versus Angioplasty in Severe Ischaemia of the Leg-1 Trial |
| **BCTU** | Birmingham Clinical Trials Unit |
| **BET** | Best Endovascular Treatment |
| **BKA** | Below Knee Amputation |
| **BM** | Bare Metal Stent |
| **BMT** | Best Medical Treatment |
| **BP** | Blood Pressure |
| **BTK** | Below the Knee |
| **CABG** | Coronary Artery Bypass Graft |
| **CFA** | Common Femoral Artery |
| **CI** | Chief Investigator |
| **CKD** | Chronic Kidney Disease |
| **CLI** | Critical Limb Ischaemia |
| **CLTI** | Chronic Limb Threatening Ischaemia |

| | |
|---|---|
| **CRF** | Case Report Form |
| **CTA** | Computed Tomographic Angiography |
| **DCB** | Drug Coated Balloon |
| **DEB** | Drug Eluting Balloon |
| **DES** | Drug Eluting Stent |
| **DM** | Diabetes Mellitus |
| **DMC** | Data Monitoring Committee |
| **DPA** | Dorsalis Pedis Artery |
| **DSA** | Digital Subtraction Angiography |
| **DUS** | Duplex Ultrasound |
| **EQ-5D-5L** | European Quality of Life- 5 dimension- 5 level |
| **ET** | Endovascular Treatment |
| **FP** | Femoro-popliteal |
| **GA** | General Anaesthetic |
| **GCP** | Good Clinical Practice |
| **GFR** | Glomerular Filtration Rate |
| **GP** | General Practitioner |
| **GSV** | Great Saphenous Vein |
| **HADS** | Hospital Anxiety and Depression Scale |
| **HRQoL** | Health Related Quality of Life |
| **HTA** | Health Technology Assessment |
| **IC** | Intermittent Claudication |
| **ICECAP-O** | ICEpop CAPability measure for Older people |
| **ID** | Inflow Disease |
| **IG** | Infra-geniculate |

| | |
|---|---|
| **IMP** | Investigational Medicinal Products |
| **IP** | Infra-popliteal |
| **IR** | Interventional Radiologist |
| **ISF** | Investigator Site File |
| **ISRCTN** | International Standard Randomised Control Trial Number |
| **ITT** | Intention to Treat |
| **LA** | Local Anaesthetic |
| **MACE** | Major Adverse Cardiovascular Event |
| **MALE** | Major Adverse Limb Event |
| **MDT** | Multi-disciplinary Team |
| **MI** | Myocardial Infarction |
| **MRA** | Magnetic Resonance Angiography |
| **NHS** | National Health Service |
| **NHS R&D** | National Health Service Research & Development |
| **NICE** | National Institute of Clinical and Health Excellence |
| **NIHR** | National Institute of Health Research |
| **OS** | Overall Survival |
| **PA** | Popliteal Artery |
| **PAD** | Peripheral Artery Disease |
| **PBA** | Plain Balloon Angioplasty |
| **PCI** | Percutaneous Coronary Intervention |
| **PEDIS** | Perfusion Extent Depth Ischaemia Sensation |
| **PerA** | Peroneal Artery |
| **PI** | Principal Investigator |
| **PIS** | Patient Information Sheet |

| | |
|---|---|
| **PTA** | Posterior Tibial Artery |
| **QALY** | Quality Adjusted Life Year |
| **QoL** | Quality of Life |
| **R&D** | Research and Development |
| **RCT** | Randomised Controlled Trial |
| **REC** | Research Ethics Committee |
| **RN** | Research Nurse |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SF-12** | Short Form 12 QoL Questionnaire |
| **SF-6D** | Short Form – 6 Dimension QoL Questionnaire |
| **SFA** | Superficial Femoral Artery |
| **SLI** | Severe Limb Ischaemia |
| **SSV** | Small Saphenous Vein |
| **TBPI** | Toe to Brachial Pressure Index |
| **TMG** | Trial Management Group |
| **TPT** | Tibio-peroneal Trunk |
| **TSC** | Trial Steering Committee |
| **UK** | United Kingdom |
| **US** | Ultrasound |
| **VAS** | Visual Analogue Scale |
| **VascuQoL** | Vascular QoL Questionnaire |
| **VB** | Vein Bypass |
| **VS** | Vascular Surgeon |
| **WIFI** | Wound, Ischaemia and Foot Infection |

| | |
|---|---|
| **+ / -** | With or Without |

# 1 Trial Summary

| | |
|---|---|
| **Title** | Multi-centre randomised controlled trial to compare the clinical and cost-effectiveness of a 'VB first' with a 'BET first' revascularisation strategy for SLI due to IP arterial disease. |
| **Short title/Acronym** | **B**ypass vs. **A**ngioplasty in **S**evere **I**schaemia of the **L**eg-2 Trial: **BASIL-2 Trial** |
| **Type of trial** | An individually randomised multi-centre pragmatic two-arm open trial of two alternative revascularisation strategies (VB *first* vs. BET *first*) for the management of SLI due to IP, with or without inflow disease, incorporating an internal pilot and within-trial economic evaluation. |
| **Outcome measures** | **Primary end-point:**<br>AFS, defined as the time to major limb (above the ankle) amputation of the index (trial) limb or death from any cause.<br>**Secondary end-points:**<br>• OS<br>• In-hospital and 30-day morbidity and mortality<br>• MALE defined as amputation (transtibial or above) of, or any major vascular re-intervention (thrombectomy, thrombolysis, BA, stenting or surgery) to, the trial leg<br>• MACE (SLI and amputation affecting the contralateral limb, ACS, stroke)<br>• Relief of ischaemic pain (VAS, medication usage)<br>• QoL using generic (EQ-5D-5L v2, SF-12 v2, ICECAP-O) and disease specific (VascuQoL) tools<br>• Re- and cross-over intervention rates<br>• Healing of tissue loss/damage (ulcers, gangrene) of arterial aetiology as assessed by the PEDIS and WIFi instruments<br>• Extent and healing of minor (toe and forefoot) amputations (also using PEDIS and WIFi) |

| | |
|---|---|
| | • Haemodynamic changes; absolute ankle and toe pressures ABPI, TBPI* |
| **Trial design** | Superiority RCT |
| **Trial duration per participant** | 24 – 96 months |
| **Total trial duration** | Approximately 96 months |
| **Trial sites** | Multicentre, UK and Europe |
| **Participants** | Patient recruitment will be terminated once 247 events (primary end-point) are achieved. |
| **Main inclusion and exclusion criteria** | **Inclusion criteria:**<br>- Have provided written informed consent;<br>- Have SLI due to IP +/- inflow disease;<br>- Have had no previous vascular intervention to the target crural artery within the previous 12 months (vascular interventions to the non-target crural arteries are permitted any time);<br>- Be judged by the responsible clinicians to require early IP +/- inflow revascularisation (in addition to BTM, foot and wound care);<br>- Have supra-inguinal 'inflow' adequate to support both trial revascularisation strategies;<br>- Be judged by two consultants to be suitable and medically fit for both VB and BET;<br>- Have an anticipated life expectancy >6 months;<br>- Are able to understand sufficient English or there are suitable translation services available at the relevant hospitals to ensure informed consent;<br>- Are able and willing to complete the QoL and health economic questionnaires, with help if required.<br><br>**Exclusion criteria:**<br>- Have tissue loss/damage considered to be primarily of venous aetiology. |

The BASIL-2 trial is a pragmatic trial that aims to collect data in line with current UK practice. Wherever possible, centres are requested to report toe and/or ankle pressures. However, since these are secondary outcomes, inability to collect haemodynamic data should not prevent randomisation.

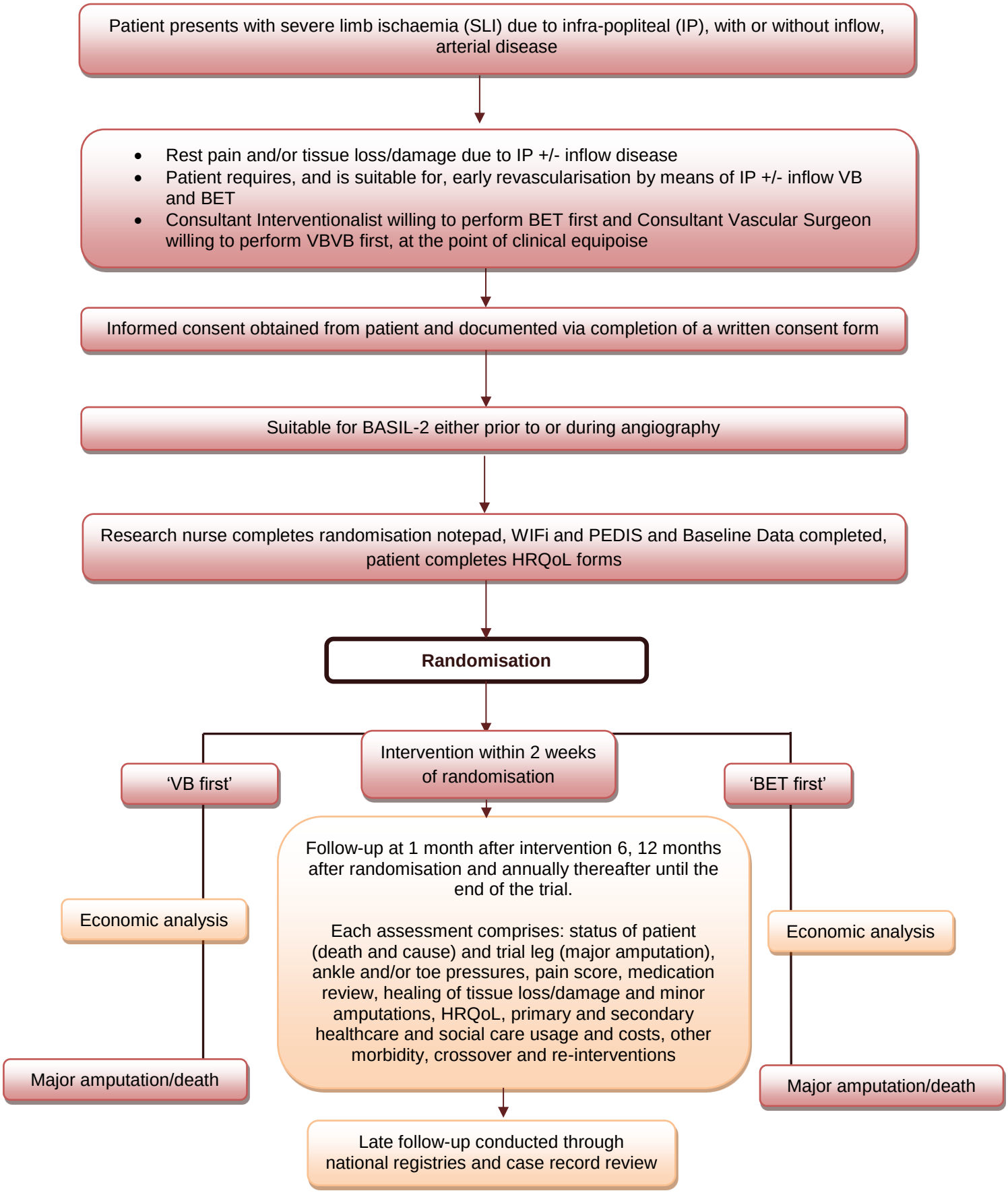



*Figure 1. Trial Schema*

# 2 Introduction

## 2.1 The problem of SLI

As a result of a combination smoking, DM, high BP, high cholesterol levels, CKD and the ageing process, some people develop atherosclerosis (*aka* 'hardening' of the arteries) in their legs; a condition known as PAD. PAD can narrow or block lower limb arteries so reducing the blood supply to people's legs and feet. In the early stages, such disease often causes pain in the leg only when walking, a condition termed IC. However, as the disease progresses, the blood supply to the leg can become so poor that people get severe pain (often requiring morphine) all the time (ischaemic rest pain), especially at night (ischaemic night pain). At this stage, even minor injuries to the foot can fail to heal, allowing infection to enter the tissues, resulting in the development of ulceration, even gangrene. The presence of rest / night pain, tissue loss/damage, or both, of presumed arterial aetiology is termed chronic limb threatening ischaemia (CLTI), critical limb ischaemia (CLI) or severe limb ischaemia (1).

One in every 1000-2000 people in the UK will be diagnosed with SLI each year. The incidence of SLI is rising principally as a result of our ageing population, the increasing numbers of people with DM, and continuing high rates of smoking. Unless the blood supply to the leg and foot is improved, many people affected by SLI will lose their limb and/or die within 12 months. SLI often affects both legs and bilateral amputation is not an uncommon outcome. Approximately 5-6,000 major lower limb amputations are carried out in the UK every year (NHS Choices http://www.nhs.uk/conditions/amputation) of which about 70% are for SLI. People with type 1 or 2 DM are 15 times more likely to need an amputation than the general population. As well as causing great suffering, SLI places a large economic burden upon health (NHS) and social care services. SLI is a growing global healthcare problem affecting every country in the world.

## 2.2 VB and BET for SLI

The two treatments currently available for SLI are:

1. VB, where a vein is used to bypass the blockage
2. BET, which involves opening up the diseased arteries with balloons and sometimes the use of small metal tubes called stents

Both treatments have pros and cons and there is considerable debate and uncertainty as to which is preferable, when, in which arteries, and in which patients (2). Those who favour a 'VB *first'* revascularisation strategy usually emphasise good long-term anatomic patency and clinical durability. Proponents of a 'BET *first'* strategy usually point to the potential for lower procedural morbidity and mortality, reduced costs, the speed with which the procedure can be

undertaken, and shortened hospital stay.

In recent years, a number of “advanced” endovascular technologies (BMS, DES, DEB) have become available. These devices are more expensive than PBA and, as yet, there is no evidence that they are more clinically effective, or that they are cost-effective, in patients with SLI (3).

The purpose of BASIL-2 is to determine which treatment is best at preventing amputation and death, getting the ulcers and gangrene to heal, and relieving pain, in people with SLI due to disease of the IP arteries; namely, the PTA, ATA (DPA) and PerA. We will invite people affected by SLI due to IP +/- inflow disease, and who are suitable for both VB and BET, to be randomly allocated, at the point of equipoise, to one or other of these revascularisation strategies *first*. If the allocated treatment doesn't work, then they can go on and have the other treatment. We will follow-up patients for a minimum of two years, during which they will be offered further medical, surgical, and endovascular treatment as required. Recovery time from surgery and endovascular intervention is often prolonged. SLI patients are frequently discharged to nursing and residential homes and those that return home often require significant support in the community as well as expensive adaptations to their homes. SLI is, therefore, extremely costly to NHS and social care services. For this reason, we will also study the costs of the two revascularisation strategies (VB *first* vs. BET *first*) to see which offers the best ‘value for money’ for the NHS.

## 2.3 BASIL-2 and NICE

In their Clinical Guideline 147 (http://guidance.nice.org.uk/CG147), NICE concluded that due to the lack of evidence supporting the use “advanced” endovascular interventions in patients with SLI due to IP disease, RCTs should be conducted to address the two following questions:

1. What is the clinical and cost effectiveness of a ‘bypass surgery first’ strategy compared with an ‘angioplasty first’ strategy for treating people with critical limb ischaemia caused by disease of the IP arteries?
2. What is the clinical and cost effectiveness of selective stent placement compared with angioplasty plus primary stent placement for treating people with critical limb ischaemia caused by disease in the IP arteries?

BASIL-2 directly addresses the first of these questions. If BASIL-2 supports BET as a clinically and cost-effective revascularisation strategy for this patient group then future trials comparing different forms of BET will be able to address question 2.

## 2.4 BASIL-2 and the HTA

The proposed research also directly addresses the research recommendations contained in the BASIL-1 trial HTA monograph (2):

1. Repeat the Delphi studies to determine whether there has been any convergence of views as to the relative merits of bypass surgery and balloon angioplasty in SLI
2. Confirm or refute the BASIL-1 findings and recommendations in further RCTs
3. Validate the BASIL-1 trial survival prediction model in a separate cohort of SLI patients
4. Examine the clinical and cost-effectiveness of new endovascular techniques and devices (such as stents and stent-grafts) in the management of SLI

## 2.5 Assessment and Management of Risk

All BASIL-2 patients would have been undergoing VB or BET in any event; and the proposed treatments are both current UK "standard of care". As such, there is no anticipated additional risk for trial participants. However, the assessment and management of risk will, of course, be reviewed throughout the trial based on a formal risk assessment document. This risk assessment will be used to develop and amend the trial monitoring plan. On-going evaluation of risk will continue throughout the recruitment period.

# 3 Trial Design

BASIL-2 is an individually randomised, multi-centre, pragmatic, two-arm, open trial of two alternative revascularisation strategies (VB *first* vs. BET *first*) for the management of SLI due to IP +/- inflow disease, incorporating an internal pilot phase and within-trial economic evaluation. BASIL-2 has been closely based on the successful HTA-funded BASIL-1 trial and the experience and expertise thereby gained by the CI and PIs.

SLI patients usually require frequent health care interventions in primary and secondary care after their primary revascularisation. To fully capture this activity, as well as the associated changes in QoL and health resource usage, patients will be closely followed up, especially during the first 12 months after randomisation.

In BASIL-1, the advantages of bypass over PBA were only observed after 1-2 years. For this reason, in BASIL-2, patients will be followed for a minimum of 24 months. Wherever possible follow-up visits will be conducted face-to-face in a clinical setting or in the patients' home (depending on local practice). Where this is not possible, patients may be followed-up remotely by telephone and/or post.

## 3.1 Trial Objective

To determine, at the point of equipoise, whether a 'VB *first'* or a 'BET *first'* revascularisation strategy represents the most clinically and cost-effective treatment for SLI due to IP arterial +/- inflow disease.

## 3.2 Primary Outcome Measure

AFS, defined as the time to major limb (above the ankle) amputation of the index (trial) limb or death from any cause.

## 3.3 Secondary Outcome Measures:

- OS
- In-hospital and 30-day morbidity and mortality
- MALE defined as amputation (transtibial or above) of, or any major vascular re-intervention (thrombectomy, thrombolysis, BA, stenting, or surgery) to, the trial leg
- MACE (SLI and amputation affecting the contralateral limb, ACS, stroke)
- Relief of ischaemic pain (VAS, medication usage)
- QoL using generic (EQ-5D-5L v2, SF-12 v2, ICECAP-O) and disease specific (VascuQoL) tools
- Re- and cross-over intervention rates
- Healing of tissue loss/damage (ulcers, gangrene) of presumed arterial aetiology as assessed by the PEDIS (4) and the WIFi (5) scoring and classification systems
- Extent and healing of minor (toe and forefoot) amputations (also using PEDIS and WIFi)
- Haemodynamic changes; absolute ankle and toe pressures, ABPI, TBPI[1]

[1] *The BASIL-2 trial is a pragmatic trial that aims to collect data in line with current UK practice. Wherever possible, centres are requested to report toe and/or ankle pressures. However, since these are secondary outcomes, inability to collect haemodynamic data should not prevent randomisation.*

## 3.4 Selection of Participants

A flowchart of the recruitment process is shown in the Trial Schema (Figure 1) together with the treatment and follow-up schedule. Where consent is given, baseline data and reasons for non-randomisation will be collected on the **BASIL-2 Screening Form**. Collecting these data on non-randomised patients is important so that judgements can be made regarding the generalisability of the BASIL-2 results to the overall population of patients presenting with SLI.

At all participating centres, patients thought to be potentially suitable for randomisation on the basis of clinical assessment and appropriate imaging will be discussed by a minimum of two consultants, at least one of whom is competent to do IP vein bypass and one of whom is competent to perform IP endovascular intervention. If there is agreement that the patient is or may be suitable for BASIL-2 then the patient will be approached by a delegated member of the clinical and/or research team, the BASIL-2 trial will be explained to the patient, and the patient will be provided with most up-to-date version of the **BASIL-2 Participant Information Sheet.** The patient must be allowed adequate time to consider this information before informed consent for trial entry is sought.

Depending on the patient pathway, the offer of consent to the patient may be after eligibility has been established or prior to eligibility being established during angiography.

In those willing to be randomised, written informed consent will be obtained by a trained member of the research team (with GCP training, knowledge of the trial protocol, and delegated authority from the local PI) who will be recorded on the **BASIL-2 Delegation and Signature Log**.

Consent will comprise a dated signature from the patient and the signature of the person who obtained informed consent. After consent has been received, and baseline QoL data collected, the patient will be randomised (1-to-1) at the point of clinical equipoise to either a 'VB *first'* or 'BET *first*' revascularisation strategy.

This study will include **optional consent** to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink; CPRD, The Health Improvement Network; THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that may appear in the future. This will allow us to double check the main outcomes against routine data sources, and extend the follow-up of patients in the trial and collect long-term outcome and

health resource usage data without needing further contact with the study participants. This is important as it will link a trial of treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data but which will not be collected during the follow-up period of the trial.

## 3.5 Inclusion Criteria

Patient will be considered for randomisation in BASIL-2, if he/she:

- Has provided written informed consent using the most up-to-date version;
- Has SLI due to IP +/- inflow disease;
- Has had no previous vascular intervention to the target crural artery within the previous 12 months[2];
- Is judged by two responsible clinicians to require early IP +/- inflow revascularisation[3];
- Has, or will have supra-inguinal 'inflow' adequate to support both trial revascularisation strategies[4];
- Is judged by two responsible clinicians to be suitable and medically fit for both VB and BET[5];
- Has anticipated life expectancy >6 months;
- Is able to understand sufficient English or there are suitable translation services available at the relevant hospitals to ensure informed consent;
- Is able and willing to complete the QoL and health economic questionnaires, with help if required.

## 3.6 Exclusion Criteria

Patient will be excluded from BASIL-2 if he/she:

- Has tissue loss/damage considered to be primarily of venous aetiology.

---

[2] *Vascular interventions to the non-target crural arteries are permitted any time.*
[3] *i.e. be judged by consultant VS, IR, diabetologists, to require early IP +/- inflow disease revascularisation in addition to BMT, foot and wound care.*
[4] *i.e. have inflow adequate to support IP VB and BET. Patients without adequate inflow can be randomised following a successful inflow procedure which can be either surgical or endovascular. The inflow procedure can be performed prior to, or at the same time, "hybrid procedure", as the allocated IP intervention.*
[5] *i.e. be judged as suitable for both VB and BET following diagnostic imaging and a formal (documented) discussion by two consultants, one of whom is competent to do IP vein bypass and one of whom is competent to perform IP endovascular intervention.*

# 4 Trial Procedures and Schedule of Assessments

### Bilateral SLI

Some patients may present with SLI in both legs; in the BASIL-1 trial this was the case in approximately 25% of the recruited patients. In such patients it is usually clinically obvious which is the 'worst' leg and thus in need of intervention (first); bilateral, simultaneous, intervention is rarely, if ever, necessary or performed in this patient group. The presence of bilateral SLI will not, therefore, be a contra-indication to recruitment and the 'worst' leg (as judged by the responsible consultant VS and IR) will become the "trial" leg. If treatment is required for the other leg then the responsible consultant VS and IR will be permitted to use whatever treatment they believe is most appropriate. Treatment to the second leg will be outside trial; in other words, each patient can only have one "trial" leg.

### Previous amputation

Prior unilateral amputation (a not uncommon scenario) will not be a contra-indication to randomisation of the remaining contralateral "trial" leg.

## 4.1 Informed Consent Procedure

Centres participating in screening or prospective cohort studies will formally assess patients for eligibility, followed with obtaining an informed consent for the randomisation and trial entry. Eligibility for randomisation must be assessed and documented following appropriate discussion by two consultants, one of whom is competent to do IP vein bypass and one of whom is competent to perform IP endovascular intervention.

Thereafter, the process of obtaining informed consent may be delegated to a suitably trained member of the local research team who is documented on the **BASIL-2 Delegation and Signature Log**.

The process by which consent is offered will vary according to the patient pathway in operation in each participating vascular centre;

- Where eligibility has already been confirmed by imaging patients will consent knowing that they are entering the BASIL-2 Trial
- Where eligibility has yet to be confirmed by imaging, usually but not always by angiography performed with a 'hybrid operating theatre' environment, patients will consent knowing that they may NOT NECESSARILY enter the BASIL-2 Trial (depending on the results of imaging)

The person obtaining informed consent will provide the patient with the REC approved PIS on NHS Trust headed paper. Adequate time will be given for consideration by the patient, and

where appropriate their family, before taking part. It will be explained to patients that there is no obligation for them to enter the trial, and that they can withdraw from the trial at any time, without having to give a reason. For all consented patients, a copy of the signed informed consent form will be given to the patient and a copy placed in the medical notes. For patients who are both consented and randomised to BASIL-2, a further copy will be sent to the BASIL-2 Trial Office and a copy held in the ISF at the site. With the BASIL-2 participant's prior consent, their GP will also be informed using a standard letter.

Informed consent will be obtained before any trial-related procedures are undertaken.

### 4.1.1 Time to consent

Ideally, potential participants will be approached and provided with a copy of the PIS a minimum of 24 hours prior to written informed consent being sought. However, in cases where the patient pathway does not allow this (e.g. should the revascularisation procedure be scheduled at short notice and there is a potential for harm in delaying), participants will be approached as early as possible prior to their procedure. Without defining a strict minimum time, this should be adequate for the patient to reflect on the implications of participating, to discuss the trial with friends/relatives (should they wish to), and to request any additional information. This should be judged on a case-by-case basis and should take into account the perceived level of understanding of the information provided by the patient as well as the patient's right to choose when they consent. In cases where less than 24 hours are given, the time of initial approach and consent should be recorded in the medical notes. Further guidance concerning time to consent is available from the HRA Guidance document "Applying a proportionate approach to the process of seeking consent" (6).

### 4.1.2 Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial at any time. A participant who withdraws from the trial does so completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis.

A participant who wishes to cease to participate in a particular aspect of the trial, will be considered as having changed their status within the trial. The responsible VS and IR may also withdraw a patient from the trial if their continued participation is not appropriate.

The changes in status within trial are categorised in the following ways:

• No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)

• No trial related follow-up: The participant would no longer like to receive the trial intervention AND does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

• No further data use: The participant would no longer like to receive the trial intervention AND is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

The details of either withdrawal or change of status within trial (date, reason and category of status change) should be clearly documented in the source data.

Patients who are either unable or unwilling to attend clinical assessments/home appointments/telephone follow-up and/or complete HRQoL forms are NOT withdrawn and, at the very least, primary endpoint data should continue to be available through routinely collected NHS data unless they indicate explicitly a withdrawal of consent as per the above criteria.

## 4.2 Baseline Assessments

All patients presenting to participating vascular units with SLI, and who are being considered for revascularisation (whether inside or outside trial), should have already undergone the following as part of their 'standard of care' prior to be being approached about BASIL-2. **Baseline assessment forms** are completed prior to randomisation and trial number allocation. The **Baseline Assessment Forms** will capture information on:

- History, enquiring into:
    - Risk factors: smoking, DM, hypertension hypercholesterolemia
    - Co-morbidity: previous stroke, angina, MI, and CKD
    - Previous PAD interventions to one or both legs

- Previous amputations
- Previous coronary intervention (CABG, PCI)

- Physical examination, including:
  - Assessment of functional status: ambulant, ambulant with walking aid, wheelchair bound, bed bound
  - Recording of peripheral pulses
  - Measurement of ankle and/or toe pressures (where it is part of the centre's standard practice)
- Imaging of their arteries by one or more of the following modalities: DUS, CTA, MRA or DSA
- Wound assessment (in those patients with tissue loss/damage)
- Assessment of ischaemic night/rest pain

In patients who have consented to take part in BASIL-2, these data will be transferred to the **Baseline Assessment Forms**.

Prior to randomisation, and after giving consent, participating patients will be asked to complete the **Baseline QoL Forms** (EQ-5D-5L v2, SF-12 v2, ICECAP-O).

At the end of the study a copy of the diagnostic imaging study on which the decision to randomise was taken will be forwarded to the BASIL Trial Office for angiographic scoring (7).

Patients with wounds on their feet will be assessed and scored according to the PEDIS and WIFi classification systems.

## 4.3 Randomisation Procedures and Minimisation

BCTU will provide a web-based randomisation service with a telephone option as back-up. Once eligibility criteria have been confirmed, consent has been obtained, minimisation variables have been determined and the baseline QoL instruments have been completed, randomisation will be performed.

The following 'minimisation' variables will be used:

- Age (≤60, 61-70, 71-80, >80 years)
- Gender (male, female)
- DM and CKD (DM, CKD*, DM *and* CKD or neither)
- Severity of clinical disease (rest / night pain only, tissue loss/damage only, or both, of

arterial aetiology)

- Previous (permissible) intervention to the trial leg (yes, no)
- Intention for hybrid procedure (yes, no)

*CKD will be defined as stage 3 or worse based on estimated GFR of < 60 (ml/min/1.73 m2) (http://www.nice.org.uk/nicemedia/live/12069/42117/42117.pdf)

### Telephone and online randomisation

Patients can be randomised into BASIL-2 via a secure 24/7 internet-based randomisation service (https://www.trials.bham.ac.uk/basil2) or by telephone (number **0800 953 0274**). Telephone randomisation is available Monday-Friday, 09:00-17:00. For the secure internet randomisation, each site and each researcher (delegated to perform randomisations) will be provided with a unique login username and password. Researchers are not permitted to share their password and must only login using their own account.

**Randomisation Forms** will be provided to investigators and should be completed and used to collate the necessary information *prior* to randomisation.

The inclusion, exclusion and minimisation criteria included on the **Randomisation Form** must be answered before a **Trial Number** can be given.

Once a **Trial Number** has been allocated, a confirmatory e-mail will be sent to the local PI and the named RN. With the participant's permission, the GP should be notified using the standard **Letter to GP** provided for this purpose.

### Back-up randomisation

If the internet-based randomisation service is unavailable for an extended period of time, a back-up paper randomisation service will be available from BCTU. In this instance, investigators should ring the BCTU randomisation service (**0800 953 0274**). The randomisation list will be produced using a random length block design.

## 4.4 Timing of Intervention

The allocated intervention (VB or BET) should be performed **within two weeks** of the date of randomisation where possible and clinically appropriate.

## 4.5 Best Endovascular Treatment

Patients randomised to BET will undergo the procedure that the responsible consultant VS or IR believes is the most appropriate given the individual patient's clinical and disease pattern characteristics. The options are PBA +/- 'bail-out' BMS, PBA +/- 'bail-out' DES, DEB +/- 'bail-out' BMS, DEB +/- 'bail-out' DES, primary BMS and primary DES. In the great majority of

cases, regardless of the exact technique / devices being used, the procedure will be performed under LA via an US-guided puncture of the CFA; occasionally intravenous sedation may be given and, rarely, a GA may be required. BET success will be established by post-intervention completion angiography, palpation of foot pulses and measurement of ABPI and TBPI (where it forms part of the centre's standard practice).

The **BET Intervention Form** captures:

- If this is the primary (allocated) or a further (secondary, tertiary etc.) intervention
- Site of each intervention by arterial segment
- Nature of the intervention in each treated arterial segment
- Number and type of devices used
- Technical Success of the intervention in the opinion of the operator

## 4.6 Vein Bypass

VB will be performed using standard anaesthetic and surgical techniques and equipment. Pre-operative DUS-based vein mapping is UK 'standard of care' and will be performed in all cases to determine the presence of a suitable (optimal) venous conduit for VB. This conduit will normally be the ipsilateral or contralateral GSV but the use of SSV and arm vein will be permitted as they are recognised techniques forming part of current UK 'standard of care'. In the unlikely event that the surgeon discovers intra-operatively that prosthetic material will be required then this will, of course, be permitted (rather than abandon the surgery) and noted. Technical success will be judged by the operator at the end of the procedure. Pre-and post-operative investigations and management will be what is 'standard of care' in the participating unit and follow local and national (NICE CG 147) guidelines.

The **VB Intervention Form** captures:

- If this is the primary (allocated) or a further (secondary, tertiary etc.) intervention
- Type of graft: reversed vein, non-reversed vein, composite, prosthetic only
- Type of vein: GSV, other leg, arm
- Location of proximal anastomosis
- Location of distal anastomosis
- Technical Success of the intervention in the opinion of the operator

## 4.7 Amputation

In patients who require amputation, the **Amputation Form** will capture data on the level and type of amputation (digits, forefoot, BKA, and AKA) as well as complications.

## 4.8 In-patient Follow-up

The hospitalisations for each patient will be tracked for both trial and non-trial related causes. An **In-patient Form** will be completed every time a patient is admitted to the hospital for any reason. The **In-patient Form** will capture a summary of the hospital admissions details, verify if any complications occurred, and confirm or deny if a trial intervention occurred. The **In-patient Form** will also be completed at each intervention, if applicable, along with the Intervention Form.

## 4.9 Follow-up Visit

Patients will be followed-up at 1 month after intervention, 6 and 12 months after randomisation and annually thereafter until the end of the trial.

Wherever possible follow-up visits will be conducted face-to-face in a clinical setting or in the patients' home (depending on local practice). Where this is not possible, patients may be followed-up remotely by telephone and/or post. Clinical information may also be obtained from the patient's GP, practice nurse, district nurse or podiatrist etc. if necessary.

The first follow-up assessment will be one month after the allocated intervention / surgery; subsequent assessment will be timed from the date of randomisation

On each occasion a **Follow-up Form** will be completed that captures:

- Interventions since last visit
- Hospitalisations since last visit
- Other health problems requiring medical intervention in primary and secondary care
- Clinical status of trial leg and contra-lateral leg
- Haemodynamic status of trial leg[6]

[6] *The BASIL-2 trial is a pragmatic trial that aims to collect data in line with current UK practice. Centres are requested to report ABPI / TBPI if such measurements are part of their standard practice. However, since these haemodynamic data are secondary outcome measures, not performing ABPIs should not prevent randomisation.*

- Functional status
- Patient HRQL and resource use forms

## 4.10 Assessment Schedule

*Table 1. Assessment Schedule*

| | Completed Form | Screen | Baseline | Randomisations | Intervention (initial within 2 weeks) | Follow-up Month: 1, 6, 12 and annually thereafter until the end of the trial |
|---|---|---|---|---|---|---|
| **Informed Consent** | Patient | ☑ | ☑ | | | |
| **History** | Case notes/Patient | ☑ | ☑ | | | |
| **Physical Exam** | Case notes | | ☑ | | | ☑ |
| **Imaging** | Case notes | | ☑ | | | ☑ |
| **Wound Assessment** | Case notes | | ☑ | | | ☑ |
| **Ischaemic Pain (VAS)** | Patient | | ☑ | | | ☑ |
| **WiFI** | Case notes | | ☑ | | | ☑ |
| **PEDIS** | Case notes | | ☑ | | | ☑ |
| **EQ-5D-5L** | Patient | | ☑ | | | ☑ |
| **ICECAP-O** | Patient | | ☑ | | | ☑ |
| **VascuQoL** | Patient | | ☑ | | | ☑ |
| **Haemodynamic changes** | Case notes | | ☑ | | | ☑ |
| **Amputation assessment* If applicable complete Amputation Form** | Case notes | | | | ☑ | ☑ |
| **Randomisations** | Case notes | | | ☑ | | |
| **Vascular Re-intervention Review* If applicable complete an intervention form** | Case notes | | | | ☑ | ☑ |
| **Resource Usage** | Case notes/Patient | | | | | ☑ |
| **Pain Relief Medication Review** | Case notes/Patient | | ☑ | | | ☑ |
| **SAE Review** | Case notes/Patient | | | | ☑ | ☑ |

## 4.11 Trial Duration

Patient recruitment will be terminated once 247 events (primary end-points) are achieved. All patients will be followed up for a minimum of two years.

# 5 Recording and Reporting of Adverse Events

## 5.1 Definitions

*Table 2. Safety reporting definitions*

| Event | Acronym | Definition |
|---|---|---|
| **Adverse Event** | AE | Any untoward medical occurrence in a trial patient to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure. |
| **Related Event** | | An event which resulted from the administration of any of the research procedures. |
| **Serious Adverse Event** | SAE | An untoward occurrence that:<br>• Results in death<br>• Is life-threatening*<br>• Requires hospitalisation** or prolongation of existing hospitalisation<br>• Results in persistent or significant disability of incapacity<br>• Or is otherwise considered medically significant by the Investigator** |
| **Unexpected and Related Event** | | An event which meets the definition of both an Unexpected Event and Related Event |
| **Unexpected Event** | | The type of event that is not listed in the protocol as an expected occurrence. |

***** *The term "life-threatening" refers to an event in which the patient 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.*

******** *Patients must be formally admitted – waiting in outpatients or A&E does not constitute an SAE (even though this can sometimes be overnight). Similarly, planned hospitalisations that clearly are not related to the condition under investigation or hospitalisations/ prolongation of hospitalisation due to social reasons should not be considered as SAEs.*

*Hospitalisations that are brought forward due to worsening symptoms of SLI or in which patients are admitted for clinical observation of their SLI DO constitute SAEs.*

*Hospitalisations for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition are not considered SAEs.*

********* *Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.*

**Note: the primary endpoint is amputation-free survival and, as such, both amputation and surgery-related deaths do not require reporting as expected SAEs, the data will be collected via the appropriate CRFs.**

## 5.2 Adverse Event General Recording Requirements

The collection and reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA).

It is routine practice to record adverse events in the patient's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also for causality (relatedness) in relation to the interventions in accordance with the protocol.

Safety will be assessed continuously throughout the trial. Safety monitoring has been delegated by the Sponsor (University of Birmingham) to the BCTU. There are no Investigational Medicinal Products being used as part of BASIL-2 and all of the surgical techniques being tested in this trial are part of current UK 'standard of care'; therefore few (S)AEs are anticipated as a unique consequence of participation in BASIL-2.

## 5.3 Adverse Events (AEs) Reporting Requirements

The cohort of trial patients are likely to have significant co-morbidities and therefore the frequency of AEs is likely to be high, but not directly relevant to the clinical question being addressed by the BASIL-2 trial. Most of the AEs occurring in BASIL-2, whether serious or not, will therefore be 'expected' in the sense that they are recognised and accepted complications / consequences of SLI, VB and BET that do not represent 'sub-standard' care. Furthermore,

since both interventional arms are standards of care, the safety profiles of the interventions are established.

Whilst all AEs should be routinely recorded in the clinical notes as per standard clinical care, given that the trial uses established techniques, **BASIL-2 does not require formal notification of these events**.

## 5.4 Serious Adverse Events (SAEs) Reporting Requirements

An event identified as a SAE requires completion of an **SAE form.**

In the context of this trial serious adverse events occurring **more than 30 days after the trial intervention**, for any given patient, **do NOT require routine notification**, since they will be disease related morbidities, pre-existing conditions and new conditions unrelated to the interventions used in this trial. A PI can still choose to notify the BASIL-2 Trial Office of events occurring out of this 30 day period should they believe that they are due to the trial procedures, but this should be for exceptional circumstances rather than routine conditions.

When an SAE occurs at the same hospital at which the participant is receiving the trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless which department first becomes aware of the event, in an expedited manner.

On receipt of an SAE form, the BASIL-2 Trials Office will allocate each SAE a unique reference number and return this via fax or email to site as proof of receipt. The site and BASIL-2 Trials Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

If the site has not received confirmation of receipt of the SAE from the Trials Office or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the Trials Office.

**Note:** Arrangements must be made, as far as reasonably possible, to ensure that a member of the trial team is available to respond to SAE queries, Monday – Friday, 09:00 – 17:00.

### 5.4.1 Expected SAEs

There are many recognised and accepted SAEs (**expected SAEs**) associated with SLI, VB and BET which can be **excluded from expedited notification** (immediately on the Investigator becoming aware of the event) during the course of the trial.. **Expected SAEs**

which are excluded from expedited reporting for the purposes of this trial can be found in Table 3.

Events that meet the trial definition of an **expected SAE** only require part A, B and D of the SAE form to be completed. SAE forms for expected events should be sent to the BASIL-2 Trial Office as per any other CRF i.e. within 2 weeks of completion. Site Investigators should also notify their own institutions of any SAEs in accordance with their institutional policies.

These events should continue to be recorded in the medical records according to local practice and will still be collated by the BASIL-2 Trial Office, but will not require evaluation by the CI. All SAEs will be followed up until the final outcome is determined (even if that continues after the end of the planned follow-up period).

*Table 3. Expected SAEs and codes for reporting.*

| Code | Description |
|---|---|
| **01** | **Events occurring during the surgical intervention: e.g. excessive bleeding** |
| **02** | **Wound / puncture site:** bleeding, infection, non-healing, debridement, haematoma, seroma, re-suturing, injection or repair of false aneurysm, requirement for further intervention |
| **03** | **Graft / endovascular device:** occlusion, infection |
| **04** | **Cardiac:** myocardial infarction, acute coronary syndrome, arrhythmia, sudden death of presumed cardiac aetiology |
| **05** | **Neurological:** stroke, transient ischaemic attack (TIA), amaurosis fugax, headache |
| **06** | **Lung:** infection, aspiration, pneumonia, pulmonary embolism, pneumothorax, requirement for ventilation, tracheostomy |
| **07** | **Leg:** deep vein thrombosis |
| **08** | **Urological:** urinary retention, urine infection, requirement for catheterisation, acute kidney injury, renal support |
| **09** | **Bowel:** bleeding, obstruction, ischaemia, formation of stoma, diarrhoea, nasogastric tube Bowel: bleeding, obstruction, ischaemia, formation of stoma, diarrhoea, nasogastric tube |

| | |
|---|---|
| **10** | **Anaesthesia:** nausea, vomiting, epidural haematoma, dental injury |

### 5.4.2 SAEs for Expedited Notification to the Trial Office

SAEs that occur **within 30 days of the trial intervention** and **do not meet the criteria of expected** (Table 3.), as above, must be notified to the BASIL-2 Trials Office **within 24 hours** of the Investigator becoming aware of the event. Unlike expected SAEs, the assessment of relatedness and expectedness to the trial intervention requires a clinical decision based on all available information at the time and therefore requires all pages of the SAE form to be completed.

Completed expedited SAE forms should be faxed or emailed to the BASIL-2 Trial Office. The sender should also confirm receipt by telephone.

**Fax: 0121 415 9135**

**Email: BASIL-2@trials.bham.ac.uk**

**Telephone: 0121 415 8444**

Expedited SAEs will immediately be referred to the CI or delegated deputy (Mr Martin Claridge, University Hospitals Birmingham) on receipt by the BASIL-2 Trial Office. The PI at each site will be required to respond to any related queries raised by the BASIL-2 Trial Office as soon as possible.

All SAEs will be followed up until the final outcome is determined (even if that continues after the end of the planned follow-up period). Site Investigators should also notify their own institutions of any SAEs in accordance with their institutional policies.

*Assessment of Relatedness*

When completing the SAE form, the PI will be asked to define the causality (relatedness) and the severity of the **expedited SAE** (Table 4)**.** In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which do not contribute to the event.

On receipt of an SAE form the Trials Office will forward it, with the unique reference number, to the CI (or delegate), who will independently review the causality of the SAE. An SAE judged by the PI or CI (or delegate) to have a reasonable causal relationship with the intervention will be regarded as a related SAE (Serious Adverse Reaction/ SAR). The causality assessment given by the PI will not be downgraded by the CI (or delegate). If the CI (or delegate) disagrees

with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Table 4. Point scale used when reviewing causality of an expedited SAE.*

| Category | Definition | Causality |
|---|---|---|
| **(1) Unrelated** | There is no evidence of any causal relationship. | Unrelated |
| **(2) Unlikely** | There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical; condition, other concomitant events or medication). | |
| **(3) Possibly** | There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events or medication). | Related |
| **(4) Probably** | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. | |
| **(5) Definitely** | There is clear evidence to suggest a causal relation, and other possible contributing factors can be ruled out. | |

*Assessment of Expectedness by the CI*

The CI (or delegate) will also assess all related SAEs for expectedness with reference to the following criteria (

Table 5).

The CI will not overrule the severity of causality assessment given by the site Investigator, but may add additional comment on these. If the event is unexpected (i.e. not defined in the protocol as an expected event), it will be classified as an Unexpected and Related SAE.

*Table 5. Criteria for expectedness assessment of related SAEs.*

| Category | Definition |
|---|---|
| **(1) Expected** | An adverse event that is consistent with known information about the trial related procedures. |
| **(2) Unexpected** | An adverse event that is not consistent with known information about the trial related procedures. |

### 5.4.3 Provision of Follow-up Information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the BASIL-2 Trials Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete the final version of the original SAE form completed at site must be returned to the BASIL-2 Trials Office and a copy kept in the Site File.

## 5.5 Reporting Serious Adverse Events to third Parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and Research Governance Team (RGT) within 15 days.

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the site file and TMF.

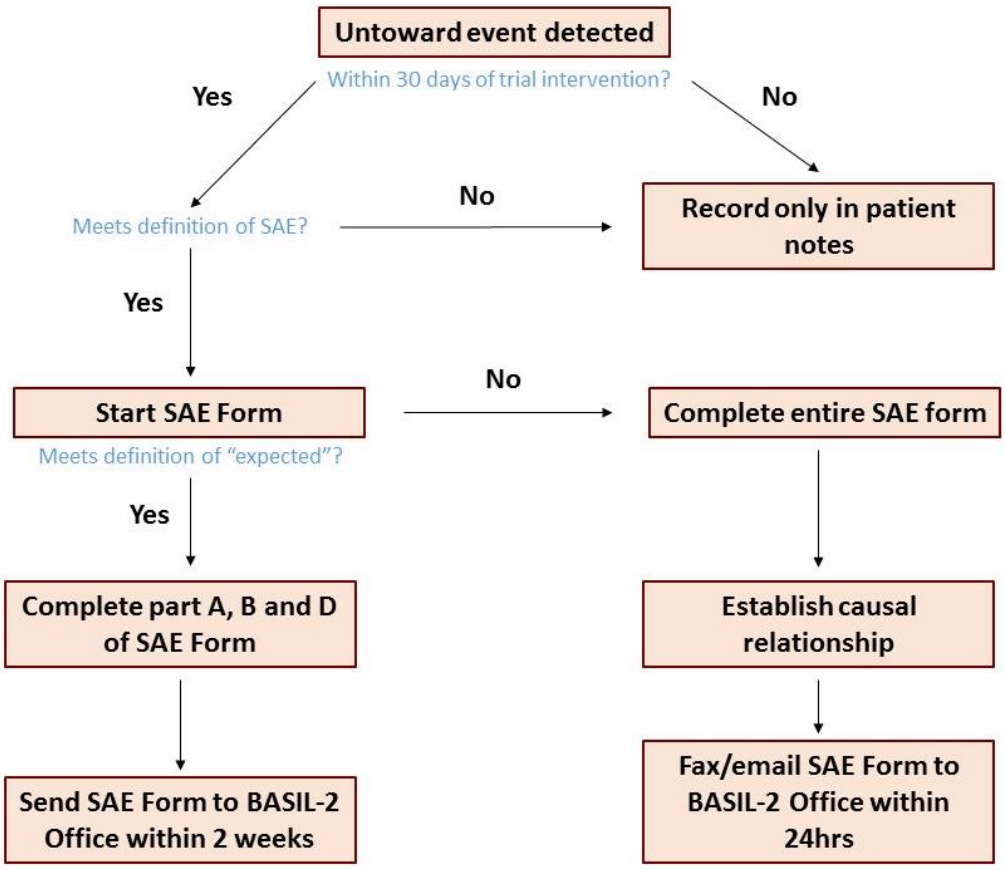
### 5.5.1 Related and Unexpected SAEs

SAEs categorised by a PI or the CI as both suspected to be related to trial participation and “unexpected” will be subject to expedited reporting to the REC. The CI (or delegated deputy) will undertake urgent review of such SAEs and may request further information immediately from the clinical team at site. The CI will not overrule the causality, expectedness or seriousness assessment given by the site PI but may add additional comment on these.

Related and Unexpected SAEs will be reported to the REC by the BASIL-2 Trial Office within 15 days of notification to the Trial Office. The BASIL-2 Trial Office (on behalf of the CI) will inform all PIs of relevant information about SAEs that could adversely affect the safety of participants.

In addition, at regular time points, the TSC and DMC will be provided with details of all SAEs.

## 5.6 Summary of Safety Reporting Procedure for BASIL-2




## 5.7 Annual Progress Reports

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

## 5.8 Reporting Urgent Safety Measures

If any urgent safety measures are taken, the CI / BCTU shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

## 5.9 Notification of Serious Breaches of GCP and/or the Protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial.

The BCTU on behalf of the Co-Sponsors shall notify the REC in writing of any serious breach of:

- the conditions and principles of GCP in connection with the trial; or
- the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

# 6 Data Management and Quality Assurance

## 6.1 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Source data is generally kept at the site in the participants' medical notes. However, patients are permitted to send their completed HRQoL forms directly to BCTU where they will be stored and a copy sent to the site.

## 6.2 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 20182018. CRFs, other than the **SAE Form**, will not bear the participant's name. The participant's initials, date of birth and trial number, will be used for identification.

## 6.3 Data Collection

The BASIL-2 patient population is likely, in the main, to be both elderly and infirm. Thus, all outcome assessments will be completed with assistance from the RN and, as far as possible, at face-to-face appointments in a clinical setting or in the patients' home (depending on local practice).) Where this is not possible, patients may be followed-up remotely by telephone and/or post. Outcomes will be assessed at baseline, 1 month after intervention, 6, 12 months after randomisation and annually thereafter until the end of the trial, as outlined in Tables & 61 6.

The CRFs will comprise, but will not necessarily be limited to, the following forms:

*Table 6. Form Table*

| Form Name | Schedule for Submission |
|---|---|
| Screening Form | Weekly |
| Randomisation Form | Collected at randomisation |
| Patient Contact Details | Collected at randomisation |
| Baseline Medical Status Form | Collected at randomisation |
| Baseline Clinical Assessment Form | Collected at randomisation |
| In-patient/daycase Form | Where applicable, as soon as possible after each hospitalisation |
| Surgical Bypass Form | Where applicable, as soon as possible after each intervention |
| Non-bypass Vascular Surgery Form | Where applicable, as soon as possible after each intervention |
| Best Endovascular Treatment Summary | Where applicable, as soon as possible after each intervention |
| Best Endovascular Segmental Treatment Form | For every segment identified in the above form, as soon as possible after the intervention |
| Amputation Form | Where applicable, as soon as possible after each intervention |
| Exit Form | Where applicable, as soon as possible after exit event |
| Follow-up CRFs | As soon as possible after each follow-up assessment point |
| Patient Completed Booklets | As soon as possible after each assessment point |
| Serious Adverse Event Form | If “unexpected”; Faxed within 24hrs of research staff becoming aware of event<br>If “expected”, as defined in the protocol, page 1 only, within 2 weeks. |

Outcomes will be collected by RNs and entered onto paper CRFs.. These must be completed, signed/dated and returned to the BASIL-2 Trial Office by the PI or an authorised member of the site research team (as delegated on the **BASIL-2 Trial Signature & Delegation Log**) within the timeframe listed in Table 3. above. Entries on paper CRFs should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change. Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All sections should be completed; all missing and ambiguous data will be queried. In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate.

The design of CRFs may be amended by the BASIL-2 Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately upon confirmation to do so by the BASIL-2 Trial Office.

# 7 Archiving

Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report. PIs are responsible for the secure archiving of essential trial documents (for their site) as per their NHS Trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

# 8 Statistical Considerations

## 8.1 Outcome Measures

These have been described above at Sections 3.2 and 3.3.

## 8.2 Sample Size and Recruitment

### 8.2.1 Original Sample Size

The sample size calculation for this trial is for a time-to-event analysis undertaken two-years after completion of recruitment. Recruitment will take place over 3 years with 20% recruited in Year 1, and 40% in each of Years 2 and 3, giving a mean follow-up of 3.3 years per patient.

Non-event rates for the primary outcome (AFS) are assumed to be 0.72, 0.62, 0.53, 0.47 and 0.35 at the end of Years 1-5 based on the original BASIL-1 trial.

Conservatively, allowing for 10% drop-out for the primary outcome (the lost of follow-up rate in BASIL-1 was around 1%) a trial of 600 patients will have 90% power to detect a reduction in AFS of one-third (HR=0.66 equivalent to a 12% absolute difference in AFS at Year 3) at the 5% significance level.

Revised Sample Size

In line with the original sample size calculation we require 247 events (see section 8.2.1) to have 90% power to detect a reduction in AFS of one-third (HR=0.66). However, observed recruitment rates in BASIL-2 were not as expected and therefore the median follow-up time has been extended in order for us to recruit enough patients to attain the required number of events, this is subject to recruitment rates.

## 8.3 Statistical Analysis

A separate **Statistical Analysis Plan** for the BASIL-2 trial provides a detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

### 8.3.1 Primary Outcome Analysis

Differences in the primary outcome (AFS) will be assessed by comparing time from randomisation to major limb amputation or death from any cause between randomised groups, assessed up until the end of the follow-up period.

The primary, adjusted analysis will be presented using Kaplan-Meier plots and a hazard ratio will be produced from a cox model adjusting for the minimisation variables as listed in section 4.3. Data will be censored when individuals reach the end of follow-up or are lost to follow-up before incurring the primary outcome. Further analysis of the primary outcome will be an unadjusted analysis and involve fitting flexible parametric survival models to estimate both the relative and absolute differences in the hazard of the primary outcome, to model the underlying differences in hazard, and to allow for non-proportional hazards. These models will allow examination of differences in effect for short, medium and longer term follow-up. The primary analysis of AFS will be undertaken on an ITT basis according to allocated first intervention, regardless of whether the intervention was delivered and whether repeat and cross-over interventions were subsequently undertaken. A sensitivity analysis will explore whether effectiveness estimates vary when analysed according to treatment received rather than treatment allocated.

### 8.3.2 Secondary Outcome Analysis

Secondary outcome measures that are based on a continuous scale (pain VAS, EQ-5D-5L, etc.) will be analysed using a repeated measure, multilevel model to examine any differential effect over time. Where necessary, data transformations will be made to fulfil modelling assumptions. Categorical data will be presented using frequency and percentages, and a risk ratio will be produced from the log binomial model. Time to event outcomes will be analysed as per the primary outcome.

All analyses will be performed using the ITT principle in the first instance with effect sizes presented as point estimates, 95% confidence intervals and associated p-values.

### 8.3.3 Repeat and Cross-over Interventions

Further intervention is possible in both arms of the trial, even when the initial intervention has been successful. This may be either with the same (re-intervention) or the alternative (cross-

over intervention) technique, and may be repeated more than once.

Based on clinical experience, and data from the original BASIL trial, we anticipate that further intervention:

- will be required in up to 20% of participants
- is most likely to be required within 12 months of randomisation
- is more likely after randomisation to BET

The decision to undertake further interventions, and nature of those interventions, depends upon the individual patient's clinical and disease pattern characteristics and will be left to the discretion of the responsible consultant VS and IR. During the trial we will collect data on all further repeat and crossover interventions and as in BASIL-1, we will specifically examine whether failed BET appears to impact negatively upon the success of subsequent VB (and vice-versa).

The trial addresses the question of the choice of the *first* revascularisation strategy at the point of clinical equipoise. This is answered by the planned ITT analysis for the primary outcome, where participants are analysed according to the *first* intervention they were allocated to, regardless of subsequent interventions received, or whether they actually receive the allocated intervention (a small proportion may not receive their allocated intervention).

Like BASIL-1, BASIL-2 focuses on addressing the important pragmatic question faced by VS and IR in selecting which revascularisation strategy to recommend to patients and their families *first*; at the point of clinical equipoise. Patients can have had previous interventions in the non-target crural vessels at any point in the past and can have had a previous vascular intervention in the target crural vessel provided it was at least 12 months prior to the planned trial intervention. In a secondary analysis we will compare re-intervention rates between groups (the trial is powered at 90% to detect a two-fold difference of 10% vs. 20%), measure resource usage associated with re-intervention, and assess QoL throughout the patient journey.

All of these metrics will capture the impact of failure of the first procedure and the need for subsequent re- and cross-over intervention(s). In this way, we will be able to assess how any substantial difference in re- and cross-over intervention rates between the groups adversely or beneficially impacts on AFS and QoL.

### 8.3.4 Planned Sub-group Analysis

Variation in the treatment effect between subgroups will be limited to pre-specified variables and investigated using appropriate tests for interaction. Variables likely to be considered will

include rest / night pain only vs. tissue loss/damage only vs. both; presence of DM, CKD, and haemodynamic measurements (ABPI, TBPI) (some of which will also be contained within the minimisation algorithm).

### 8.3.5 Pilot Phase

BASIL-2 contained an internal pilot phase. After the first year recruitment, retention, patient burden and completeness of QoL data were assessed against several criteria.

- less than 2/3rds of centres are recruiting
- less than 60 patients have been randomised
- less than 2/3rds of centres are recruiting 2 per month from month 4 onwards
- less than 80% of patients have received their allocated treatment

The original aim was to have just 11 regional centres and to achieve the calculated sample size of 600 patients over 3 years, each of the 11 regional centres was expected to recruit on average 2 patients per month with all 11 centres recruiting by the end of the first year. Although the pilot phase succeeded in randomising 60 patients, had 2/3 of the regional centres recruiting and 80% of patients had their allocated treatment, the regional centres were not able to recruit at 2 patients per month. Therefore the trial is now open to any centres that wish to participate throughout the UK, with the estimate of in excess of 50 centres being opened to recruitment.

The QoL data completeness and the burden of the portfolio of HRQoL instruments to patients, will continued to be monitored. In the event of evidence to suggest that the burden of HRQoL is such that it is preventing patients from either entering the study, or continuing to complete the instruments, then use of the ICECAP-O instrument will be discontinued. HADS data will no longer be collected.

### 8.3.6 Interim Analysis

Interim analyses of efficacy and safety are planned annually. The Haybittle-Peto approach will be used whereby all interim analyses use a difference of 3 standard errors (approximately p=0.002) as a stopping guideline. These interim analyses will be reviewed by the independent DMC on an annual basis or more frequently if required by the DMC or TMG.

### 8.3.7 Final Analysis

The final analysis for the BASIL-2 trial will occur once the last randomised patient reaches the 24 months follow-up assessment.

# 9 Health Economic Analysis

There is considerable uncertainty around the cost-effectiveness of VB and BET in this patient group. Determining the most cost-effective revascularisation strategy (VB *first* vs. BET *first*) will enable the NHS to ensure that care provided to patients represents the most appropriate use of the available public resources.

The economic analysis will comprise two components: a 'within-study' analysis, which will be based on data obtained within the study end points, and, conditionally on the availability of relevant data, a 'model-based' analysis, which will capture long-term costs and effects likely to accrue beyond the study follow-up period.

Results of the analysis will be presented in terms of cost per year of AFS and cost per additional QALY gained. In line with existing recommendations, the base-case analysis will adopt a health care system (payer's) perspective by considering costs incurred by the NHS and personal social services (8). If plausible, additional analyses will be undertaken from a wider societal perspective, by considering private (patient-incurred) and productivity costs. Costs and benefits accruing in the future will be discounted to reflect the impact of positive time preference.

## 9.1 Within Study Analysis

The 'within-study' analysis will be carried out with a view to determining the cost-effectiveness of VB and BET on the basis of the patient-level data obtained during the study period.

### 9.1.1 Resource Use and Costs

Data collection will be carried out prospectively for all trial participants so that a stochastic cost analysis can be undertaken. Data will be collected on:

(a) procedure-related resource use for the primary interventions and any secondary procedures, including amputations;

(b) hospital stay associated with each procedure;

(c) resource use and hospital stay due to readmissions and serious adverse events

(d) any day-case admissions, out-patient visits and appointments with general practitioners and nurses

In order to consider the wider cost implications of the interventions to patients, a tailored resource use questionnaire will be administered to all trial patients at the suggested time-points. The questionnaire will contain questions to determine out of pocket expenses incurred (e.g. transport costs) when attending for treatment, as well as private costs including time lost from work. To obtain a total per-patient cost, resource use will be weighted by unit cost values

taken from up-to-date national sources and tariffs, including the Unit Cost of Health and Social Care report (9), the British National Formulary (10) and the NHS Reference Cost Schedules (11). Variations in the unit cost of items and services across settings will be explored in sensitivity analyses.

### 9.1.2 Outcomes

QoL will be derived from the EQ-5D-5L (v2) instrument as well as by means of the EQ-5D VAS which records the patient's self-rated QoL on a range from 0 to 100. Each patient's health status descriptions obtained from the EQ-5D-5L will be translated into a single, preference-based (utility) index using a UK specific value set (12). QALYs will be calculated as the area under the curve connecting utility scores reported at different time points from baseline to month 36 after randomisation. Deceased patients will be allocated a utility of zero from the date of death. In addition to EQ-5D-5L, patients' QoL will be measured through the Short Form 12 (SF-12 v2) and ICECAP-O instrument. The SF-12 is a shorter and more practical version of the widely used Short Form 36 (SF-36) generic health status measure (13). Responses to SF-12 can be converted into single preference-based index values, and subsequently into QALYs, by using the SF-6D classification system (14). The ICECAP-O is developed with a view to measuring wellbeing and capabilities in older people, and comprises five attributes (attachment, security, role, enjoyment and control) (15, 16). The time points at which quality of life instruments will be collected are: baseline, 1 month after intervention, 6, 12 months after randomisation and annually thereafter until the end of the trial.

### 9.1.3 Analysis

The analysis will be conducted on an ITT basis. Missing data will be accounted for by using appropriate techniques, such as multiple imputation, depending on the extent and type of missing items (17). As the distribution of costs is usually skewed by the existence of patients with very high costs, mean per-patient cost will be given alongside confidence intervals obtained through non-parametric bootstrap methods (18). Incremental analysis will be undertaken to calculate the difference in costs and the difference in benefits between the two revascularisation strategies. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the extra cost for an additional unit of outcome. To account for the inherent uncertainty due to sampling variation, the joint distribution of differences in cost and effect (QALYs) will be derived by carrying out a large number of non-parametric bootstrap simulations (Willan, 2006) (19). The simulated cost and effect pairs will be depicted on a cost-effectiveness plane and will be plotted as cost-effectiveness acceptability curves (CEACs). CEACs show the probability of the 'VB *first*' and 'BET *first*'

revascularisation strategies being cost-effective across a range of possible values of 'willingness to pay' for an additional QALY (17).

### 9.2 Model Based Analysis

In addition to the 'within-trial' evaluation, a 'model-based' analysis will be conducted to consider costs and benefits likely to accrue over a lifetime time horizon. A decision analytic model, possibly in the form of a Markov model, will be built to serve as a framework for quantifying long-term costs and outcomes.

The model will be populated with data from various sources, including patient-level data obtained from the trial, evidence from the preceding BASIL trial and information from a pragmatic literature review.

Relevant data required for the model will include:

- the probability of a patient requiring a limb amputation
- the cost and resource use associated with post-treatment care
- the cost and resources use associated with care received after amputation
- estimates of the quality of life after amputation

Given the long-time horizons being considered, much of the data on costs (and benefits) will be incurred (and experienced) in future years. Using discounting, adjustments will be made to reflect this differential timing. Both deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and plausible variations in key assumptions and employed analytical methods (20). The broader issue of the generalizability of the results will also be considered.

If appropriate, value of information analysis (expected value of perfect and parameter information (21) will be also conducted to infer the benefits from obtaining further information for all or a subset of the parameters affecting the choice of treatments.

## 10 End of Trial

For the purposes of REC approval, the study end date is deemed to be the date of last data capture.

## 11 Direct Access to Source Data

The investigator(s)/institution(s) will permit trial-related monitoring, audits and REC review, providing direct access to source data/documents.

Trial participants will be informed of this during the informed consent discussion and will consent to provide access to their medical notes.

# 12 Ethics

The Sponsor will ensure that the trial protocol, PIS, consent form, GP letter and submitted supporting documents have been approved by the REC, prior to any participant recruitment. The protocol, and all substantial amendments, will be documented and submitted for ethical approval prior to implementation.

Before a site can enrol participants into the trial, the PI or designee must apply for and be granted NHS permission from their Trust (R&D).

It is the responsibility of the PI (or designee) at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the REC within one year after the end of the trial.

# 13 Monitoring Requirement for the Trial

Monitoring of BASIL-2 will ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of BASIL-2 will be adopted and outlined in the trial-specific risk assessment.

# 14 Oversight Committees

## 14.1 TMG

The TMG will comprise the CI, other lead investigators (clinical and non-clinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of BASIL-2. The TMG will convene typically once a month, or as otherwise deemed necessary by the members.

### 14.2 TSC

An independent TSC will provide overall supervision for the BASIL-2 and advice to the CI. The ultimate decision regarding the feasibility of the trial lies with the TSC. The composition of the TSC can be found on page 2 of the protocol. Further details of TSC functioning are presented in the TSC Charter.

### 14.3 DMC

The role of the DMC is to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, ensure the trial collects the necessary information to address the trial question, and monitor the overall conduct of the clinical trial. The DMC will operate in accordance with the DMC charter.

An independent DMC will meet approximately 6 months after the trial opens; the frequency of further meetings will be dictated in the DMC charter. More frequent meetings may be required for a specific reason and will be recorded in minutes. The composition of the DMC can page found on page 3 of the protocol.

The DMC will consider data using the statistical analysis plan and will advise the TSC. Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

## 15 Finance

The NIHR HTA Programme is funding this trial under reference 12/35/45.

## 16 Indemnity

This is a clinician-initiated study. The Sponsor (University of Birmingham) holds Public Liability (negligent harm) and Clinical Trial (negligent harm) insurance policies, which apply to this trial. Participants may be able to claim compensation, if they can prove that the University of

Birmingham has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to the patients being treated. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. University of Birmingham does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. Participants *may* also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University of Birmingham or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

Hospitals selected to participate in this trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to University of Birmingham, upon request.

# 17 Dissemination and Publication

The CI will coordinate dissemination of data from BASIL-2. All publications and presentations, including abstracts, relating to the main trial will be authorised by the BASIL-2 TMG. The results of the analysis will be published in the name of the BASIL-2 Collaborative Group in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified. Trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper. All applications from groups wanting to use BASIL-2 data to undertake original analyses will be submitted to the TMG for consideration before release. To safeguard the scientific integrity of BASIL-2, trial data will not be presented in public before the main results are published without the prior consent of the TMG.

# 18 Statement of Compliance

This trial will be conducted in compliance with UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principals of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive.

# 19 References


1. Available from: https://vascular.org/research-quality/guidelines-and-reporting-standards/global-vascular-guidelines.

2. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health technology assessment (Winchester, England). 2010;14(14):1-210, iii-iv.

3. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. Circulation. 2013;128(6):615-21.

4. Karthikesalingam A, Holt PJ, Moxey P, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of scoring systems for diabetic foot ulcers. Diabetic medicine : a journal of the British Diabetic Association. 2010;27(5):544-9.

5. Mills JL, Sr., Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). Journal of vascular surgery. 2014;59(1):220-34.e1-2.

6. HRA Guidance. Applying a proportionate approach to the process of seeking consent v1.01 17.01.2017 FINAL/ Policy and Public Affairs Directorate. 2017.

7. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A description of the severity and extent of disease using the Bollinger angiogram scoring method and the TransAtlantic Inter-Society Consensus II classification. Journal of vascular surgery. 2010;51(5 Suppl):32s-42s.

8. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2013. London, NICE. .

9. Curtis L. Unit costs of health and social care. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2012/ 2012 [

10. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: http://bnf.org/bnf/bnf/current/ 2013.

11. DOH. National Schedule of Reference Costs 2011-2012. Department of Health. Available from: https://www.gov.uk/government/news/financial-year-2011-to-2012-reference-costs-published. 2012.

12. van Hout B JM, Feng YS, Kohlmann T, Busschbach J, Golicki D et al. ,. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health; 15(5):708-715. 2012.

13. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996;34(3):220-33.

14. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.

15. Coast J, Flynn TN, Natarajan L, Sproston K, Lewis J, Louviere JJ, et al. Valuing the ICECAP capability index for older people. Social science & medicine (1982). 2008;67(5):874-82.

16. Coast JI-O. http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/HE/ICECAP/ICECAP-O/index.aspx 2012 [

17. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing.... presumed at random: cost-analysis of incomplete data. 2003;12(5):377-92.

18. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Statistics in medicine. 2000;19(23):3219-36.

19. Willan AR. Statistical analysis of cost-effectiveness data from randomized clinical trials. Expert review of pharmacoeconomics & outcomes research. 2006;6(3):337-46.

20. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making. Health technology assessment (Winchester, England). 2009;13(29):iii, ix-xi, 1-61.

21. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. Health economics. 1996;5(6):513-24.